RSC Advances

REVIEW

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Cite this: *RSC Adv.*, 2020, **10**, 30314

Applications of alkyl orthoesters as valuable substrates in organic transformations, focusing on reaction media

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In this review we focus on applications of alkyl orthoesters as valuable and efficient substrates to perform various classes of two-component and multi-component organic reactions. The article has classified them according to two aspects, which are: (i) a focus on the reaction medium (solvent-free conditions, aqueous media, and organic solvents); and (ii) an examination of product structures. Reaction accomplishment under solvent-free conditions is an eco-friendly process with the absence of volatile toxic solvents, which puts it in line with green chemistry goals. Water is an interesting choice in organic transformations due to its inexpensiveness and safety. The authors hope their assessment will help chemists to attain new approaches for utilizing alkyl orthoesters in various organic synthetic methods. The review covers the corresponding literature up to the beginning of 2020.

Received 16th June 2020
Accepted 27th July 2020

DOI: 10.1039/d0ra05276k

rsc.li/rsc-advances

1. Introduction

Orthoester (1,1,1-triorganyloxyalkane) (**1**) is the general name for a functional group containing three alkoxy groups attached to one central carbon atom, with the general formula $RC(OR')_3$. In fact they are the esters of orthoacids which do not exist in a free state.[1,2] Orthoesters were first synthesized *via* nucleophilic the substitution reaction of chloroform (**2**) with alkoxides (**3**) by Williamson and Kay in 1854 (Scheme 1).[3] There are several examples of acyclic alkylorthoesters such as:[4]

(a) Trimethyl orthoformate (TMOF) is the simplest orthoester in organic chemistry, which is also called trimethoxymethane, 2-methoxyacetaldehyde dimethyl acetal, methoxymethylal, and methyl orthoformate. This colorless liquid with a pungent odor is soluble in ethanol and ether ($(CH(OMe)_3$, **4**), bp = 100.6 °C, and d = 0.9676 g mL^{-1}).

(b) Triethyl orthoformate (TEOF, $CH(OEt)_3$, **5**), also called diethoxymethoxyethane, triethoxymethane, and ethyl orthoformate a colorless volatile liquid with bp = 146 °C and d = 0.891 g mL^{-1}, is the orthoester of formic acid.

(c) Triethyl orthoacetate (TEOAc, $CH_3C(OEt)_3$, **6**) 1,1,1-triethoxyethane, (bp = 142 °C, d = 0.885 g mL^{-1}), is an oily yellow to colorless liquid with a pungent odor.

(d) Triethyl orthopropionate ($CH_3CH_2C(OEt)_3$, **7**), also called 1,1,1-triethoxypropane and orthopropionic acid triethyl ester, is a clear colorless liquid (bp = 155–169 °C, d = 0.886 g mL^{-1}) which is soluble in alcohol, chloroform, ethyl acetate, and ether and hydrolyzes slowly in water.

(e) 3,3,3-Triethoxy-1-propyne ($HCC(OEt)_3$, **8**).

Orthoesters may be considered to be products of the exhaustive alkylation of unstable orthocarboxylic acids and it is from these that the name "orthoester" is derived. Orthoesters are highly reactive owing to the electron-deficient central carbon atom caused by the –I effect of the electronegative groups OR.[1] Among the ortheosters introduced above, TEOF involved maximal exploitation in the reactions based on our literature survey (109 reports) followed by TMOF (54 reports), TEOAc (21 cases), TMOAc (4 items), and triethyl orthopropionate (2 cases), and other kinds of alkyl orthoesters (1 case) (Fig. 1a). Several orthoesters were applied in various domains as dehydrating agents,[5–18] alkylating agents,[19–24] dialkoxymethylation agents,[25] esterification agents,[26] methoxy sources,[27] additives,[28–30] solvents,[31–33] and protecting groups.[34–36] This functional group is also necessary for some conversions such as the Johnson–Claisen rearrangement.[37] Fig. 1b demonstrates the assorted applications mentioned *vs.* the type of orthoester. As specified, TMOF and TEOF are the most commonly used in different processes, except for the case of rearrangements where TMOAc is the most abundant.

Different kind of orthoesters also have many applications in several branches of science, such as polymers,[38–43] liquid-crystalline compounds,[44] biochemistry,[45–49] medicine[50–56] and medicinal organic chemistry,[57–60] inorganic chemistry,[61,62] organometallic chemistry,[63] dynamic covalent chemistry,[64] supramolecular chemistry,[65–68] and crystal structure analysis.[69] Orthoesters have also been used in the synthesis of natural products, *e.g.* loganin is a monoterpene glucoside occupying a central position in the generation of secoiridoids and alkaloids, obtained from orthoesters biosynthetically. Because of this, in 1973, Buechi and co-workers described the total

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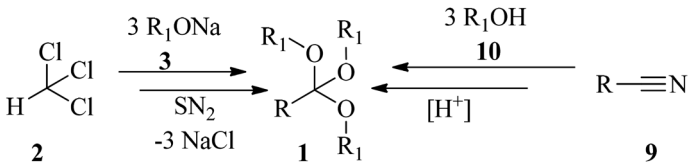


Scheme 1 The Pinner reaction for orthoester synthesis.

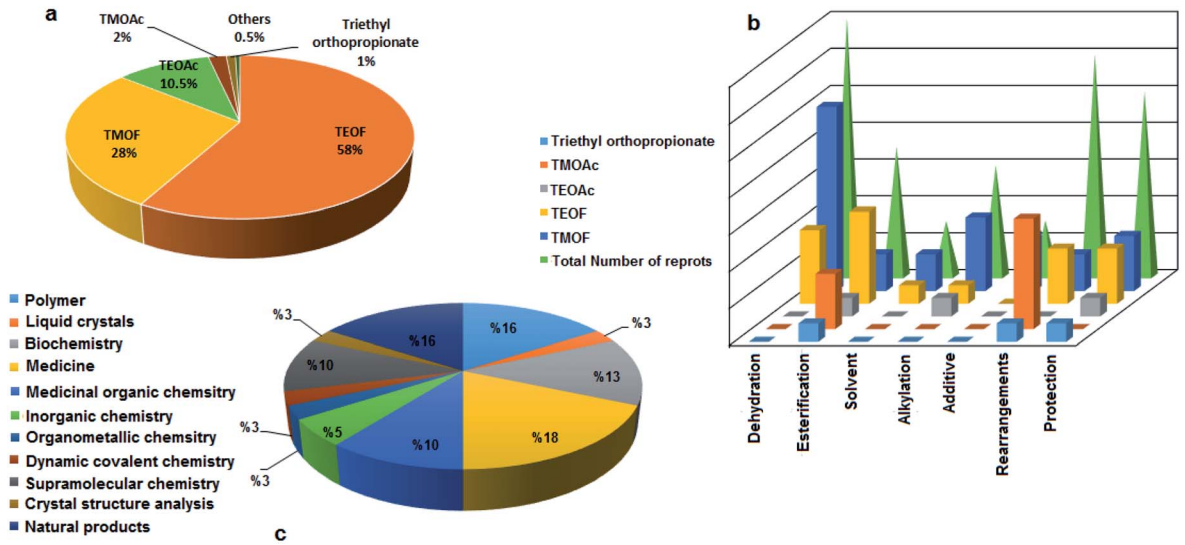
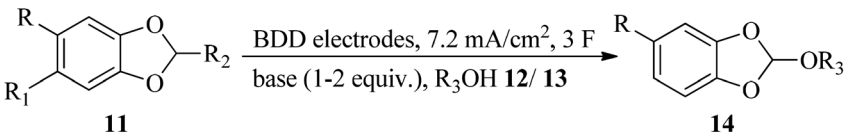


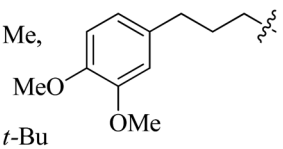
Fig. 1 The abundances of different orthoesters as substrates in organic transformations (a), assorted applications of different kinds of orthoesters in some processes (b), and the classification of their utilization in various domains of science and technology (c).

synthesis of loganin. It should be noted that trimethyl orthoformate was employed in some of the steps in the preparation of loganin,[70] and the total synthesis of (−)-monomorine,[71] and (±)-vernolepin.[72] It has been reported that TEOF is exploited in the total synthesis of palytoxin, as a marine natural product.[73] In 1976, Greenlee and Woodward reported the total synthesis of marasmic acid, one of the many fungal metabolites obtained from the Basidiomycetes, in which trialkyl orthoformates were applied in some of the syntheses.[74] Chan and Koide utilized orthoesters for the first total synthesis of the stresgenin B



R= H, Me, *t*-Bu, OMe, CH_2OMe, Cl, CN, CH_2CO_2Me, OCH_2CO_2Me, CH_2CHCH_2

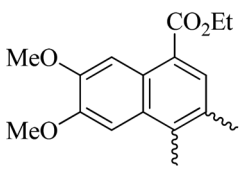
R_1= H, Me,



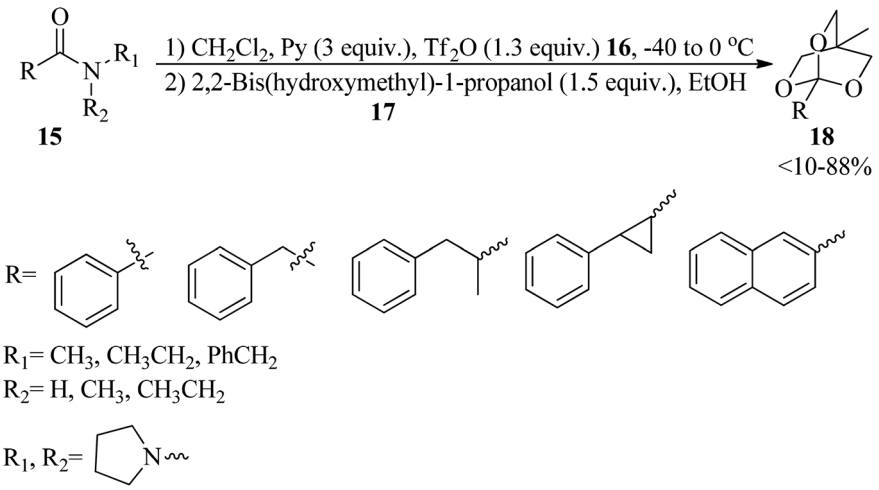
R_2= H, *t*-Bu

R_3OH= **12**, **13**

R, R_1=

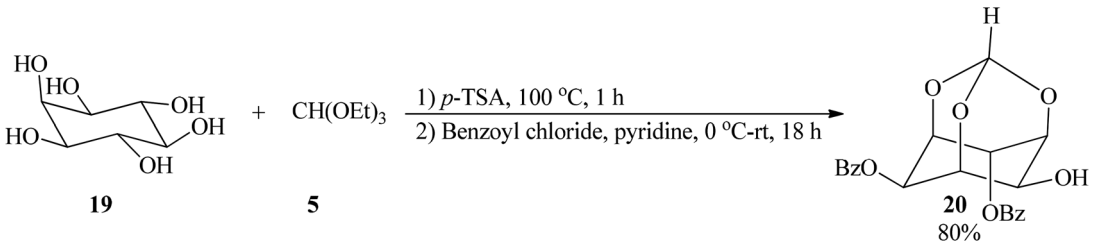


Scheme 2 The electrochemical synthesis of highly fluorinated orthoesters.

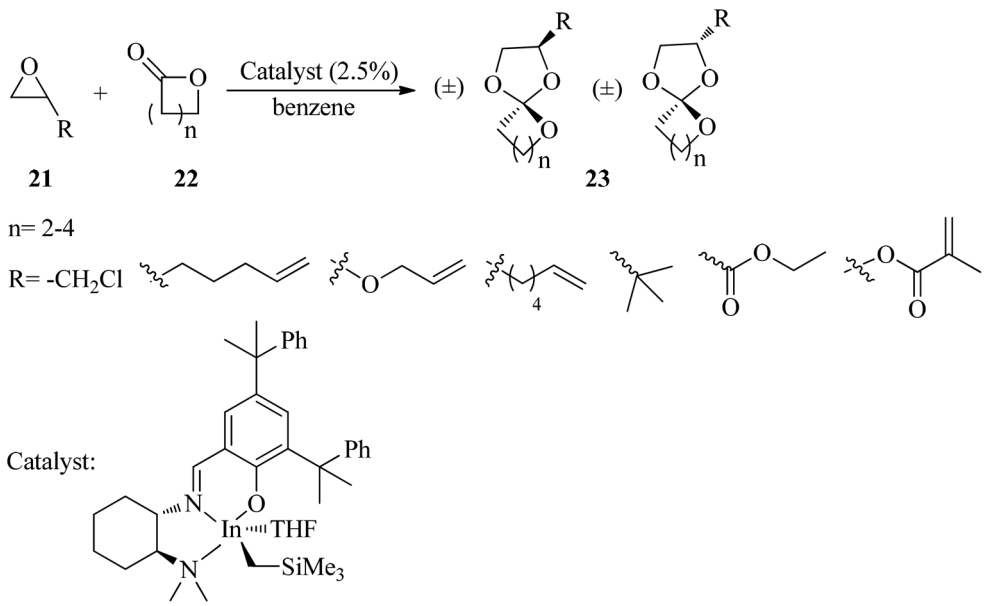


Scheme 3 A synthetic approach to 2,6,7-trioxabicyclo[2.2.2]octane orthoesters.

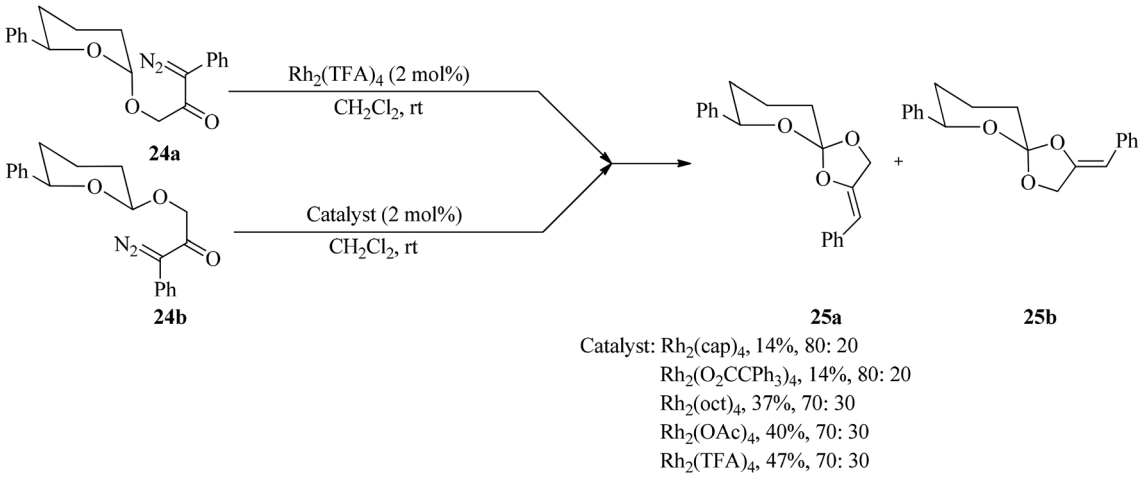
scaffold as a heat shock protein expression inhibitor.[75] The application of orthoesters in the synthesis of condensed carbon-cage organics was investigated in the preparation of twistane as a cycloalkane and also the simplest diamondoid. In 1967, Gauthier and Deslongchamps obtained twistane *via* a multi-step process started by TEOF as one of the substrates.[76] The diagram in Fig. 1c illustrates the vast range of applications of different kinds of orthoesters in various sciences. The results



Scheme 4 The preparation of 2,4-di-*O*-benzoyl-*myo*-inositol 1,3,5-orthoformate.



Scheme 5 The synthesis of spiro orthoesters.

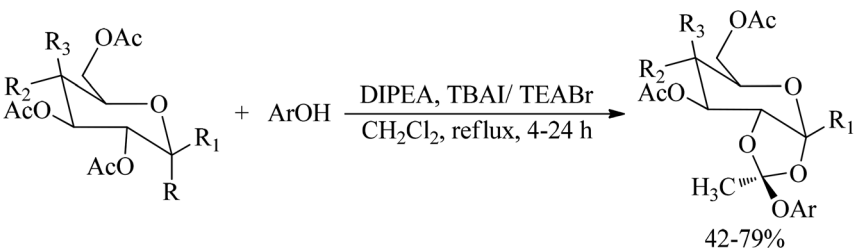


Scheme 6 The Rh(II)-catalyzed synthesis of spirocyclic orthoesters.

indicate the comprehensive use of orthoesters in many domains of science and technology.

In addition to the Williamson and Kay method, there are various procedures for the preparation of orthoesters. The Pinner reaction of nitriles (**9**) with alcohols (**10**) in the presence of strong acids generated orthoesters (Scheme 1).[77] Electrochemical approaches[78–81] are also employed for the synthesis of these compounds, *e.g.*, new highly fluorinated orthoesters (**14**) were synthesized through the functionalization of 1,3-benzodioxoles (**11**) in the 2 position with diverse fluorinated alcohols (such as 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP, **12**) or 2,2,2-trifluoroethanol (TFE, **13**)) in an undivided cell and in the presence of *N*,*N*-diisopropylethylamine or 1,8-diazabicyclo-[5.4.0]undec-7-ene (DIPEA/DBU) as basic electrolytes by boron-doped diamond (BDD) electrodes under a constant current density of 7.2 mA cm^{-2} until a catalytic quantity of 3.0 F mol^{-1} of electricity has passed (Scheme 2).[82]

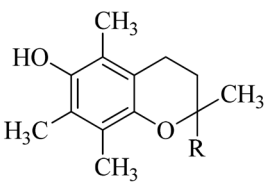
Secondary and tertiary amides (**15**) were reacted with triflic anhydride (**16**) by pyridine in CH_2Cl_2 at low temperatures to form imino and iminium triflates within 4 h, which on treatment with 2,2-bishydroxymethyl-1-propanol (**17**) utilizing pyridine buffered solution attained 2,6,7-trioxabicyclo[2.2.2]octane orthoesters (**18**) (Scheme 3).[83]

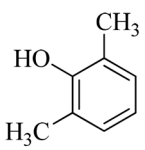


26α: R= I, R_1, R_2= OAc, R_3= H
27α: R= I, R_1, R_2= H, R_3= OAc
28α: R= Br, R_1= H, R_2= OAc, R_3= H
28β: R= H, R_1= Br, R_2= OAc, R_3= H
29α:R= Cl, R_1= H, R_2= OAc, R_3= H
29β: R= H, R_1= Cl, R_2= OAc, R_3= H

33: Ar= 1, R= OAc, R_1= H
34: Ar= 1, R= H, R_2= H, R_1= OAc
35: Ar= 2, R= OAc, R_2= OAc, R_1= H
36: Ar= 3, R= OAc, R_2= OAc, R_1= H

ArOH:

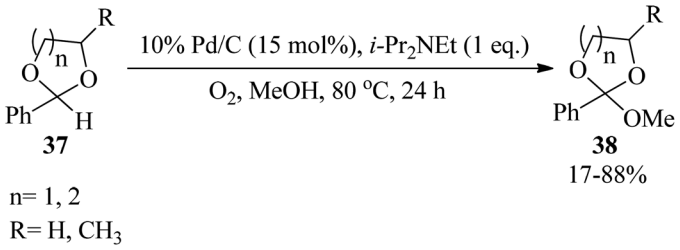




30: R= $C_{16}H_{33}$
31: R= CH_3

32

Scheme 7 Synthetic procedure for peracetylated orthoester.



Scheme 8 The synthesis of orthoesters *via* the methoxylation of cyclic acetals.

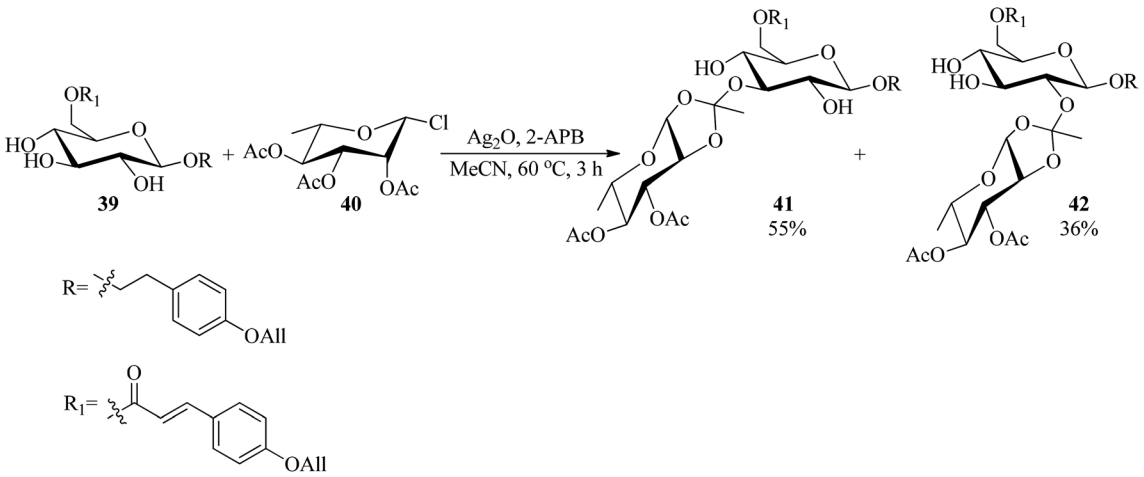
2,4-Di-*O*-benzoyl-*myo*-inositol 1,3,5-orthoformate (**20**), a cyclic alkyl orthoester, was obtained from successive treatment of *myo*-inositol (**19**) with TEOF (**5**) and benzoyl chloride by Shashidhar and Praveen in 2001 (Scheme 4).[84]

The reaction of epoxides (**21**) and lactones (**22**) in the presence of a cationic indium catalyst under heating with benzene resulted in spiro orthoesters (**23**) (Scheme 5).[85]

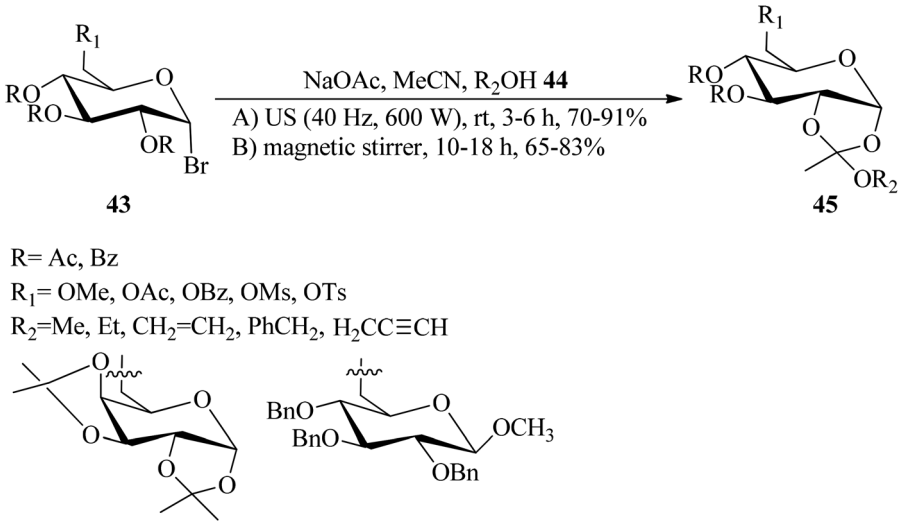
Tetrahydropyranyl acetals containing a phenyl diazoketone substituent (**24**) underwent Rh(II)-catalyzed C–H insertion through an unusual C–O bond generation to give spirocyclic orthoesters (**25**) (Scheme 6).[86]

3,4,6-Tri-*O*-acetyl-1,2-*O*-(1-tocopheroxyethylidene)-α-D-glucopyranose (vitamin E sugar 1,2-orthoester) (**33–36**) with *exo*-type stereoselectivity were synthesized through the reaction of sugar halides (**26–29**) with various phenols, such as α-tocopherol (**30**), chroman-6-ol (**31**), and 2,6-dimethylphenol (**32**) by *N*,*N*-diisopropylethylamine (DIPEA) and tetrabutylammonium iodide (TBAI) or tetraethylammonium bromide (TEABr) in refluxing CH_2Cl_2 for 4–24 h. The obtained peracetylated orthoesters (**33–36**) were deprotected by utilizing aminolysis (NH_3/MeOH) or by reduction in the presence of DIBAL-H (Scheme 7).[87]

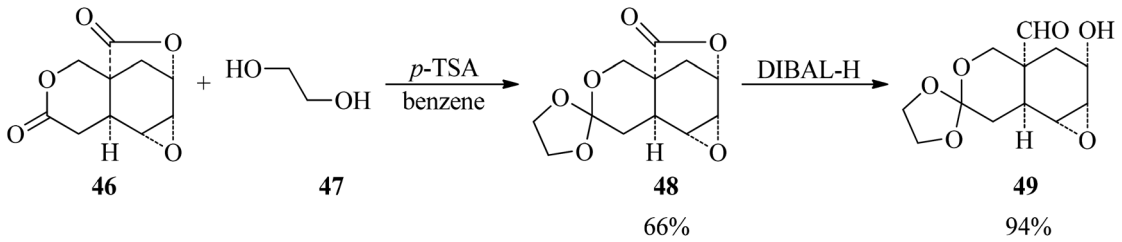
Palladium on carbon (Pd/C) catalyzed the straightforward methoxylation of the benzylic positions of cyclic acetals (**37**) by i-Pr_2NEt in refluxing methanol under atmospheric oxygen as a green oxidant to obtain orthoesters (**38**) (Scheme 8).[88]



Scheme 9 The preparation of orthoesters *via* the Koenigs–Knorr glycosylation reaction.



Scheme 10 The synthetic route to sugar 1,2-orthoesters.



Scheme 11 The preparation of a crystalline ethylene orthoester possessing an aldehydic moiety.

The Koenigs–Knorr glycosylation reaction of glucopyranoside (**39**) with rhamnosyl chloride (**40**) as a glycosyl donor was accomplished using a catalytic amount of 2-aminoethyl diphenylborinate (2-APB, 5 mol%)[89] and silver(I) oxide (Ag_2O) in acetonitrile at 60 °C to obtain the mixture of 3- and 2-orthoesters (**41**) and (**42**) in 55% and 36% yields, respectively within 3 h (Scheme 9).[90]

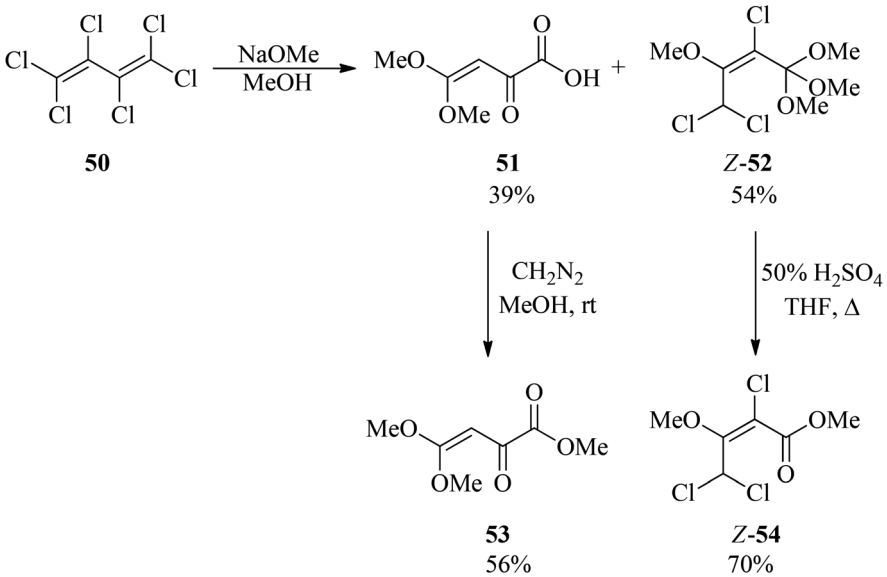
Zhao *et al.* prepared sugar 1,2-orthoesters (**45**) *via* the reaction of peracetylated mannopyranosyl bromides (**43**) with alcohol derivatives (**44**) and anhydrous sodium acetate (NaOAc) as a base in acetonitrile at room temperature under ultrasound irradiation (40 KHz and 600 W) (method A), and the traditional reaction under high-speed magnetic stirring (method B). The results confirmed that an ultrasound-assisted reaction proceeded much better than the traditional method (70–91% yields, 3–6 h) (Scheme 10).[91]

The reaction of dilactone (**46**) with ethylene glycol (**47**) by *p*-toluenesulfonic acid (*p*-TSA) in the presence of magnesium sulfate in refluxing benzene obtained the crystalline ethylene orthoester (**48**) in 66% yield within 4.5 h, which underwent a reduction reaction with diisobutylaluminum hydride as a reducing agent in combined dimethoxyethane/toluene (1 : 2) media at −76 °C to room temperature to afford the hydroxy aldehyde (**49**) in 94% yield (Scheme 11).[92]

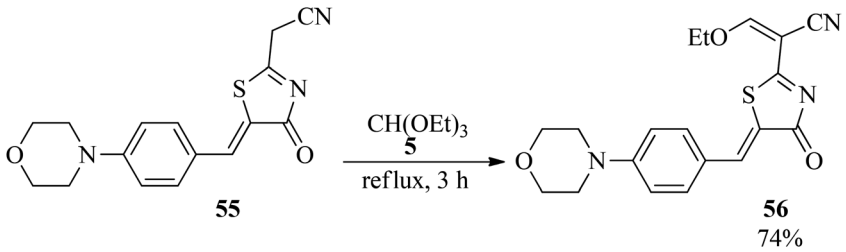
Hexachlorobuta-1,3-diene (**50**) was refluxed with sodium methoxide in methanol for 12 h to obtain a mixture of 4,4-dimethoxy-2-oxobut-3-enoic acid (**51**) and (*Z*)-2,4,4-trichloro-1,1,1,3-tetramethoxybut-2-ene (**52**) in 39% and 54% yields, respectively in which for easy identification, compound (**51**) was reacted with diazomethane (CH_2N_2) in methanol at room temperature to produce methyl (*Z*)-4,4-dimethoxy-2-oxobut-3-enoate (**53**) in moderate yield (56%), while orthoester *Z*-**52** was converted into methyl (*Z*)-2,4,4-trichloro-3-methoxybut-2-enoate (*Z*-**54**) in good yield (70%) *via* acid hydrolysis in THF at 50 °C for 2 h (Scheme 12).[93]

In 2018, a review entitled "Synthesis and biological activity of oxazolopyrimidines" was published. In some parts of it, orthoesters were used to prepare oxazolo[4,5-*d*]pyrimidines and 7-aminooxazolo[5,4-*d*]pyrimidines.[94]

Perillo *et al.* presented a review article entitled "Synthesis and properties of seven- to nine-membered ring nitrogen heterocycles. Cyclic amidines and cyclic amidinium salts" which pointed to the application of orthoesters in synthetic methods.[95] In 2011, Lavigne's research group published a review article about the route yield from N-heterocyclic carbene precursors. They introduced trialkylorthoesters as the pre-carbenic unit.[96] In 2013, A. Elassar and co-workers published a review article about diaminomaleonitrile (DAMN) in which



Scheme 12 The synthesis of some *Z*-orthoester structures.



Scheme 13 The synthesis of 3-ethoxy-2-[5-(4-(morpholin-4-yl)benzylidenyl)-4-oxo-4,5-dihydro-thiaol-2-yl]acrylonitrile by TEOF.

the mentioned synthon reacted with various orthoesters to prepare different kinds of biologically active heterocycles.[97]

Numerous review papers have reported on different applications of orthoesters;[98,99] for example, a 1986 review article entitled "Alkyl orthoesters and their applications in organic synthesis", by Pavlova and co-workers, focused on a systematic account of data describing the chemical properties of alkyl esters of orthocarboxylic acids. The proposed reaction mechanisms were discussed and the scope of utility of the orthoesters in the solution of diverse problems in organic synthesis was shown.[100] Moreover, a 1988 article entitled "Carbon–carbon bond formation and annulation reactions using trimethyl and triethyl orthoformates", by Ghosh and Ghatak, focused on the annulation reactions by orthoformates and also the introduction of a formylation–cyclization method for the production of functionalized polycyclic bridged-bicyclo[3.3.1]nonanes, cyclopentenones, and other isolated products to develop the synthetic potential of carbon–carbon bond formation reaction *via* orthoformates.[98] In 2007, a review of "Recent studies on reaction pathways and applications of sugar orthoesters in synthesis of oligosaccharides", was published by Kong.[101] In 2009, Liao and co-workers presented a focused literature survey on plant orthoesters.[102] In 2014, a review article with the title "The orthoester Johnson–Claisen rearrangement in the synthesis of bioactive molecules, natural products, and synthetic intermediates-recent advances", was published with 211 ref. 103. In 2016, another review was also published with the title "Recent development in the orthoester Johnson–Claisen rearrangement and application", by the Alam group.[99] In 2009, a spotlight titled "Alkyl orthoformate: a versatile reagent in organic synthesis", was compiled by Frizzo.[104] It should be noted that, during the preparation of this review article, a paper was published entitled "Orthoesters: multiple role players in organic synthesis", by Nazarian and Dabiri.[105]

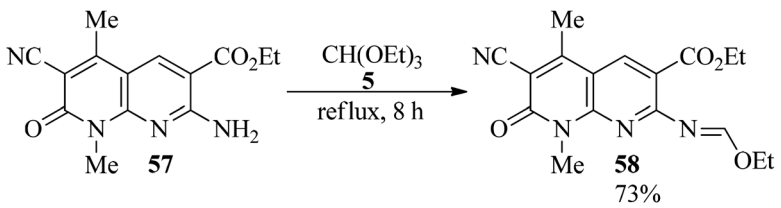
Due to the central role of orthoesters and their comprehensive applications, the authors considered the literature reports of usage of orthoesters according to several classes of organic transformations. The initial classification is based on the reaction media: solvent-free conditions, aqueous medium and organic solvents. Each part is also subdivided according to the structures of the achieved products. This dual classification demonstrates the importance of the reaction media in progressing the preparation of each class of organics, because the nature of the solvent and its interaction with the reaction components and reagents (orthoesters and other participants) affect the route of the process and may change it seriously. The authors hope the review will highlight the significant role of orthoesters in organic and pharmaceutical chemistry as well as in biosciences and be a proper guide to designing new procedures and approaches to obtain new organics to reach a better life.

2. Orthoester reactions under solvent-free conditions

Performing organic reactions under solvent-free conditions has been notable recently for chemists due to its individual eco-environmental and economical features. In fact, in the absence of solvents the substrates are closer, allowing the right effectual contacts to let the reaction happen. This process, that elevates the reactivity of the substrates, diminishes the reaction time and energy usage, and performs the procedures more selectively in a safe and clean manner. In addition, the absence of hazardous solvents is in line with the rules of green chemistry, turning the transformation into an eco-friendly process. So, because of the importance of the reaction being accomplished under solvent-free conditions, below we focus on reports of utilizing orthoesters in various classes of organic synthesis. The presence of about 150 references in this area confirmed the significance of this method.

2.1. Synthesis of ethoxymethylenes

In 2004, Lamphon *et al.* synthesized 3-ethoxy-2-[5-(4-(morpholin-4-yl)benzylidenyl)-4-oxo-4,5-dihydro-thiaol-2-yl]acrylonitrile



Scheme 14 The synthesis of ethoxymethyleneamino derivatives.

containing an ethoxymethylene moiety (**56**) in 74% yield *via* the condensation of TEOF (**5**) with 2-cyanomethyl-5-[4-(morpholin-4-yl)benzylidenyl]-4,5-dihydro-4-thiazolinones (**55**) under reflux conditions within 3 h (Scheme 13).[106]

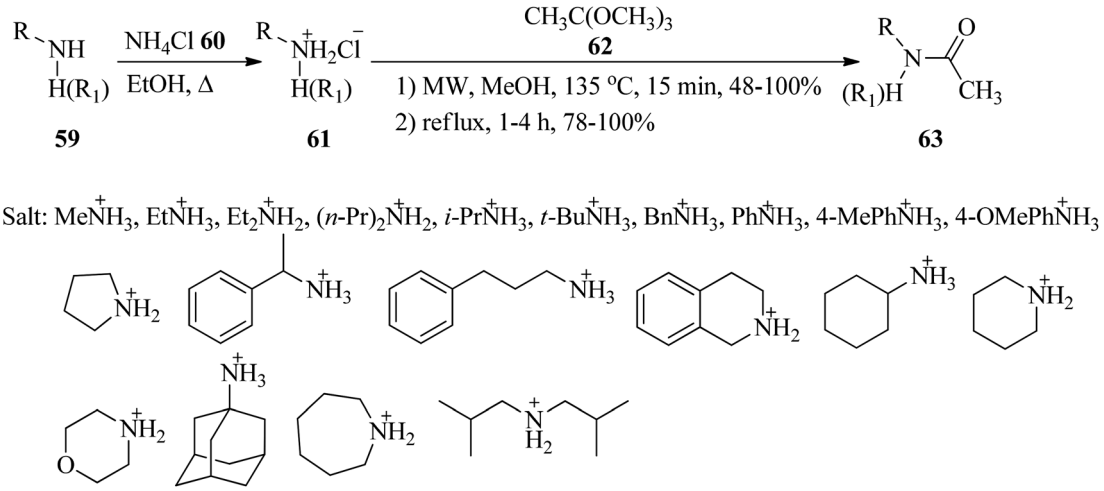
2.2. Synthesis of ethoxymethylene amino derivatives

In 2001, Mekheimer presented a novel technique for the synthesis of ethoxymethyleneamino derivative (**58**)[107–110] in high yield (73%) *via* the condensation of a 1,8-naphthyridin-2-one ring system (**57**) with TEOF under reflux conditions within 8 h.[109] Condensation of TEOF[111] with 3-amino-5-bromo-4,6-dimethylthieno[2,3-*b*]pyridine-2-carbonitrile[112] also generated a Schiff base (Scheme 14).[113]

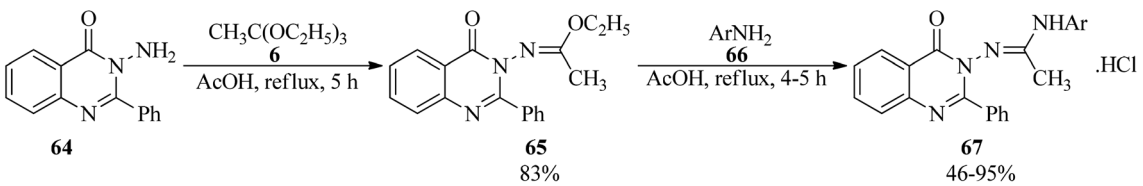
2.3. Synthesis of acetamides

In 2015, Grandi *et al.* presented an efficacious, fast and high-yielding method for the conversion of amine hydrochloride salts (**61**) to acetamides (**63**). Initially, the reaction between equimolar amounts of the primary and secondary amines (**59**) with ammonium chloride (**60**) under heating in ethanol obtained amine hydrochloride salts (**61**) in a 2 h period with excellent yields (>90%)[114] which were transformed into their corresponding acetamides (**63**) *via* the acetylation reaction with trimethyl orthoacetate (**62**)[115,116] by two different pathways: (a) using microwave irradiation (Biotage Initiator™ Sixty EXP) at 135 °C in methanol, and (b) under conventional heating conditions through refluxing. The results demonstrated that MW-assisted reaction promotion with shorter reaction times (15 min) than conventional heating (1–4 h) (Scheme 15).[116]

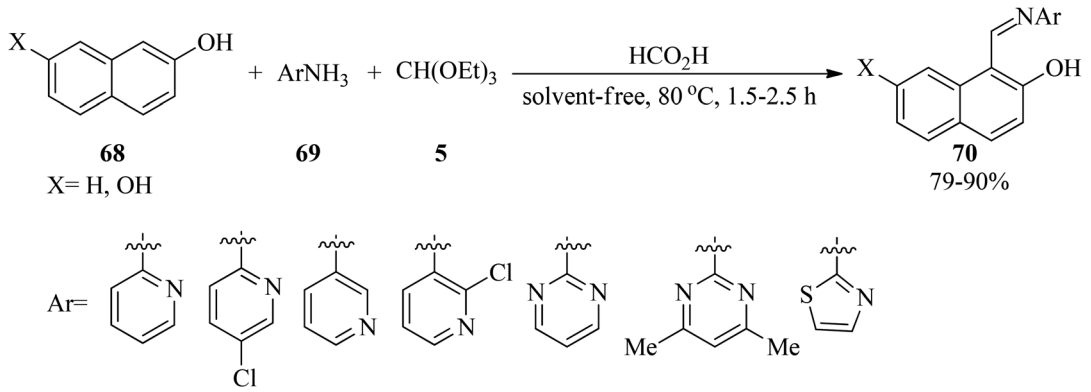
In 2010, Khan *et al.* presented a simple methodology for the synthesis of unsymmetrical *N*,*N*′-disubstituted acetamidines (**67**).[117,118] In this paper, ethyl(1*E*)-*N*-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)ethanimidoate (**65**) was first prepared *via* the condensation reaction of 3-amino-2-phenyl-4(3*H*)-quinazolinone (**64**) with TEOAc (**6**) using acetic acid under reflux conditions. After completion of the reaction, the mixture was poured into ice-cold water. The resultant precipitation was filtered, washed with water and recrystallized from ethanol to produce (**65**) as a white crystalline solid in 83% yield within 5 h.[119] In the next step, *N*-(4-oxo-2-phenyl-3(4*H*)-quinazolinoyl)-*N*-(aryl)acetamidines (**67**) were obtained through the condensation reaction of (**65**) with substituted aromatic amines (**66**) by glacial acetic acid at reflux condition in moderate to excellent yields (46–95%) for 4–5 h (Scheme 16). It was found that electron-donating aromatic amines gave the corresponding acetamidines in good yields while the reaction failed with electron-withdrawing aromatic amines. The reaction proceeded selectively with just primary aromatic amines, including electron-donating substituents.[118] On the other hand, symmetrical *N*,*N*′-disubstituted acetamidines were produced by a microwave-assisted (850 W) condensation reaction of triethyl orthoacetate with the anilines in acetic acid within very short reaction times (5–7 min). High



Scheme 15 The synthesis of acetamides from amine hydrochloride salts and trimethyl orthoacetate.



Scheme 16 The preparation of *N*-(4-oxo-2-phenyl-3(4*H*)-quinazolinoyl)-*N*-(aryl)acetamidines begins by forming amino quinazolinone and TEOAc.



Scheme 17 Anil-like product formation utilizing TEOF.

yields and high purity of the product were obtained by the removal of ethanol as a by-product, *via* placing a receiver between the round-bottom flask and the condenser under heating by microwave irradiation at 850 W for 2–3 min.[120]

2.4. Synthesis of imines

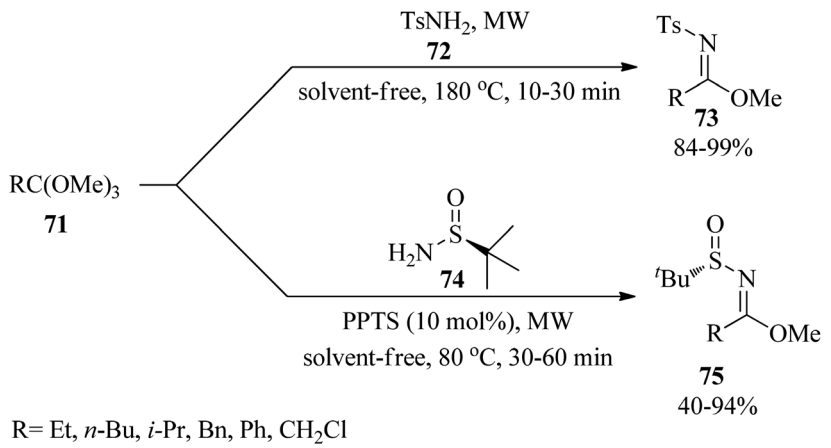
In 2012, Olyaei *et al.* synthesized novel anil-like products (**70**)[121,122] *via* the one-pot three-component condensation reaction of naphthols (**68**), TEOF (**5**), and heteroaryl amines (**69**) by formic acid as catalyst under solvent-free conditions at 80 °C in high yields (79–90%) within 1.5–2.5 h (Scheme 17). Investigation of ^{1}H NMR and FT-IR exhibited that the products are in tautomeric equilibrium between the enol–imine and keto–enamine forms. Moreover, intramolecular hydrogen bonds were observed in the synthesized Schiff bases. In this research, 14-(2-hydroxynaphthyl)-14*H*-dibenzo[*a*,*j*]xanthene was also prepared through the treatment of 2-naphthol with TEOF in the absence of heteroaryl amines under solvent-free conditions at 80 °C.[122]

2.5. Synthesis of imidates

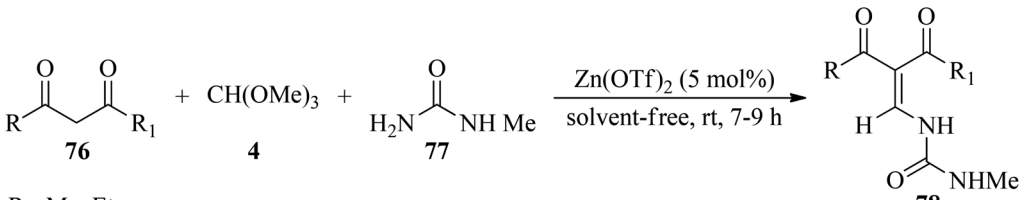
In 2018, Verrier *et al.* reported metal and solvent-free microwave-assistance for the convenient preparation of *N*-sulfonyl and *N*-sulfinyl imidate derivatives by a leaky septum filled up with 4 Å MS which was placed 3 cm above the top of the microwave-tube. The treatment of trimethylorthoesters (**71**) with 4-methylbenzenesulfonamide (**72**) under solvent-free conditions at 180 °C afforded *N*-sulfonylimidates (**73**) within 10–30 min. Replacing (**72**) with *tert*-butanesulfinamide (**74**) in the presence of pyridinium *p*-toluenesulfonate (PPTS) (10 mol%) at 80 °C yielded *N*-sulfinyl imidates (**75**) within 30–60 min (Scheme 18). The design of an efficient apparatus with the ability to use molecular sieves to trap methanol, short reaction times, easy purification and isolation of the compounds, and excellent conversion and yields are some advantages of this strategy.[123]

2.6. Synthesis of enamines

Majee *et al.* developed an improved method of the Miyashita protocol[124] for the synthesis of enamine derivatives (**78**)[125,126] by the three-component condensation reaction of 1,3-dicarbonyls (**76**), *N*-methylurea (**77**) and TMOF (**4**) using zinc triflate [$Zn(OTf)_2$, (5 mol%)] under solvent-free conditions at room temperature within 7–9 h in good yields (56–85%) (Scheme 19).[126]



Scheme 18 Imidate synthetic procedure to form trimethyl orthoesters.



Scheme 19 Enamine synthesis by TMOF.

2.7. Synthesis of formamidines

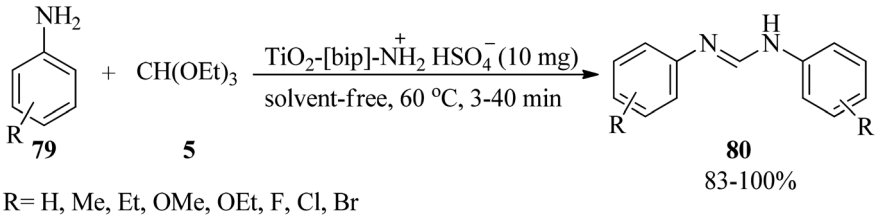
Mazloumi *et al.* originated and characterized TiO_2-[bip]-NH_2^{+}-HSO_4^{-} as an effective and eco-friendly catalyst through the modification of nanoporous TiO_2 with bis-3-(trimethoxysilylpropyl)-ammonium hydrogen sulfate and then its catalytic activity was investigated for the generation of *N*,*N*′-diarylformamidines (**80**)[127,128] *via* the *N*-formylation reaction of anilines (**79**) with TEOF (**5**) under solvent-free conditions at 60 °C in very short reaction times (3–40 min) in high to excellent yields (83–100%) (Scheme 20). In this research, the formation of the unsymmetrical diarylformamidines or aliphatic formamidines was unsuccessful.[128]

2.8. Synthesis of lactones

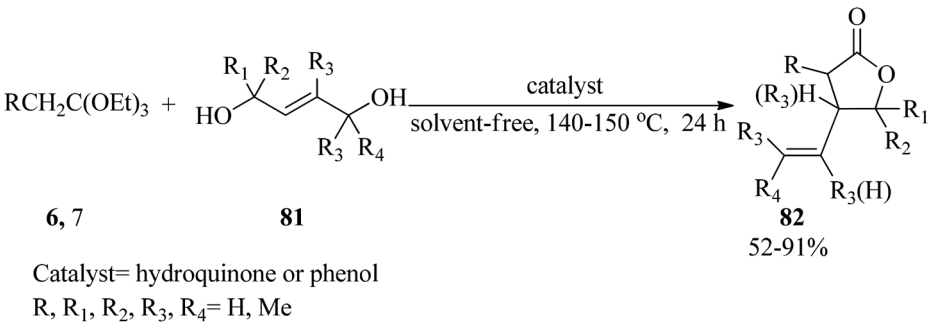
The condensation reaction of *trans*-2-alkene-1,4-diols (**81**) with triethyl orthoesters (**6**, **7**) in 1 : 2 molar ratio was accomplished by utilizing catalytic amounts of hydroquinone or phenol under solvent-free conditions at 140–150 °C to give γ-lactones containing a vinylic substituent on the β-position (**82**) in 52–91% yields within 24 h (Scheme 21).[129]

2.9. Synthesis of aminomethylene bisphosphonates

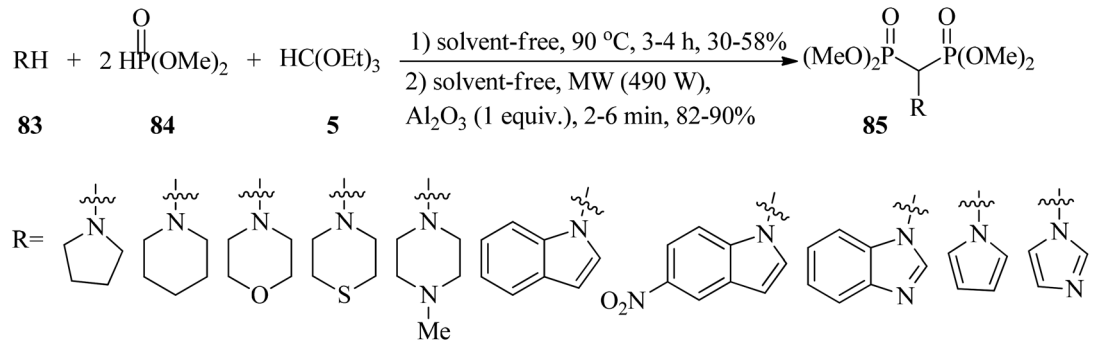
In 2011, Reddy *et al.* designed an easy, efficient, and green procedure for the synthesis of amino methylene bisphosphonates (**85**)[130–135] *via* the one-pot three-component condensation reaction of amines (**83**), TEOF (**5**), and dimethyl phosphite (**84**) using an alumina solid support (Al_2O_3) by microwave irradiation (490 W) in excellent yield (82–90%) for 12 min in two intervals. In addition to the microwave irradiation manner, the reaction was also performed under conventional thermal heating (90 °C, 3–4 h, 30–58%) (Scheme 22). The results revealed shorter reaction times and higher yields using microwave-assistance.[135] A similar transformation occurred *via* the treatment of primary amines, diethyl phosphite, and TEOF using amberlyst-15 under solvent-free conditions at room temperature within 90 min in good to excellent yields (70–95%). All compounds were screened for *in vitro* antioxidant (by nitric



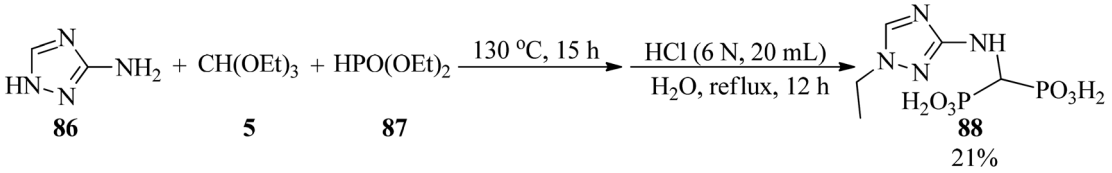
Scheme 20 The generation of *N*,*N*′-diarylformamidines with TEOF.



Scheme 21 The preparation of some classes of γ-lactones.



Scheme 22 A three-component route to obtain amino methylene bisphosphonates.



Scheme 23 The synthesis procedure for biologically active aminomethylenebisphosphonic acid.

oxide, DPPH radical scavenging, H_2O_2 methods),[136–139] and antimicrobial activities.[140]

2.10. Synthesis of aminomethylenebisphosphonic acids

In 2017, some aminomethylenebisphosphonic acids (**88**) were prepared by Miszczyk *et al.* through the reaction of 3-amino-1,2,4-triazole (**86**) with diethyl phosphite (**87**) and TEOF (**5**), in a 1 : 2 : 4 molar ratio (Scheme 23). The products are powerful inhibitors of the activity of J774E cells. So they can be used in antiosteolytic therapy, and are equipotent to the popular drug zoledronate and exhibit higher activity than the drug incadronate.[141,142]

2.11. Synthesis of indole derivatives

Zirconium(IV) chloride ($ZrCl_4$, 5 mol%) catalyzed the electrophilic substitution reaction of indole (**89**) with TEOF (**5**) in a 3 : 1 molar ratio under solvent-free conditions at 50 °C to obtain tris(indolyl)methane (**90**)[143] in a short reaction time (22 min) in excellent yield (95%) (Scheme 24).[144]

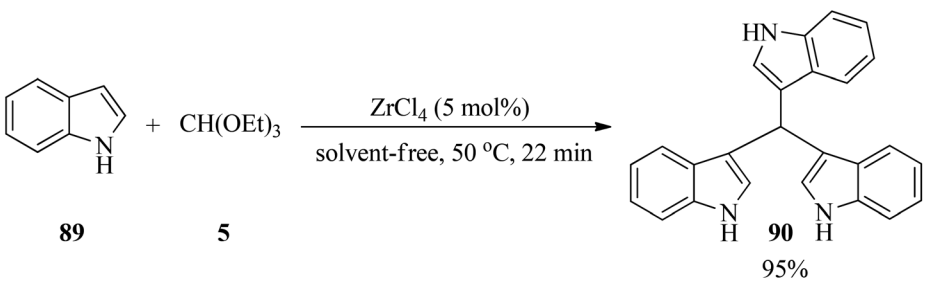
The regioselective reaction of carbazole (**91**) with TEOF (**5**) using *p*-TSA under solvent-free conditions at 80 °C gave 9-(diethoxymethyl)carbazole (**92**) in 65% yield in 48 h. On the other hand, 4-methoxycarbazole (**93**) was regioselectively functionalized at the C_1 position *via* reaction with (**5**) in the presence of trichloroacetic acid in dichloromethane at room temperature to furnish various carbazole derivatives, such as 4-methoxycarbazole-1-carboxaldehyde (**94**), bis[4-methoxycarbazol-1-yl]methylium trichloroacetate (**95**), tricarbazolylrnethane (**96**) according to the reaction conditions (Scheme 25).[145]

2.12. Synthesis of triaroyl methanes

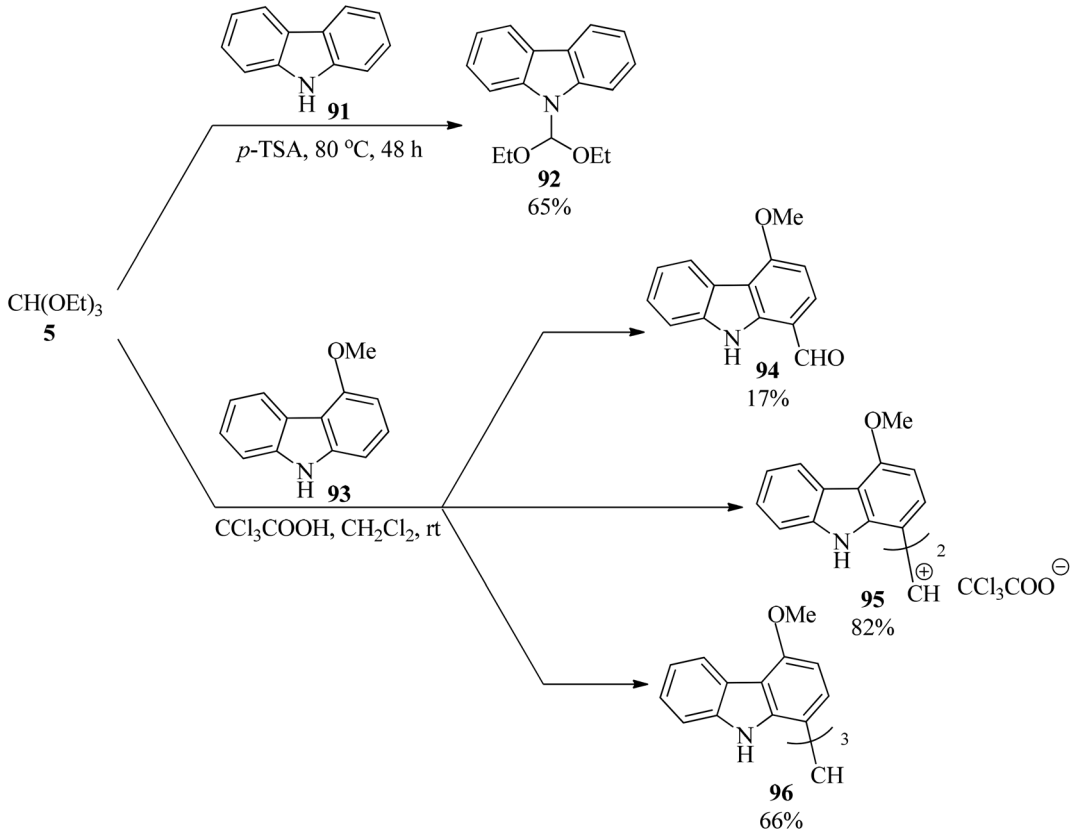
Boron trifluoride etherate liquid ($BF_3 \cdot OEt_2$, 0.05 mol) catalyzed the condensation reaction of aryl ketones (**97**) with TEOF (**5**) under microwave irradiation to obtain triaroyl methanes (**98**) in 55–85% yields for 8–10 min. It was found that a substrate containing a bulky group such as (**99**) afforded a fused cyclopentenone ring product (**100**) in 79% yield within 8 min (Scheme 26).[146]

2.13. Synthesis of 5,15-diphenyl-10,20-dimethyl porphyrins

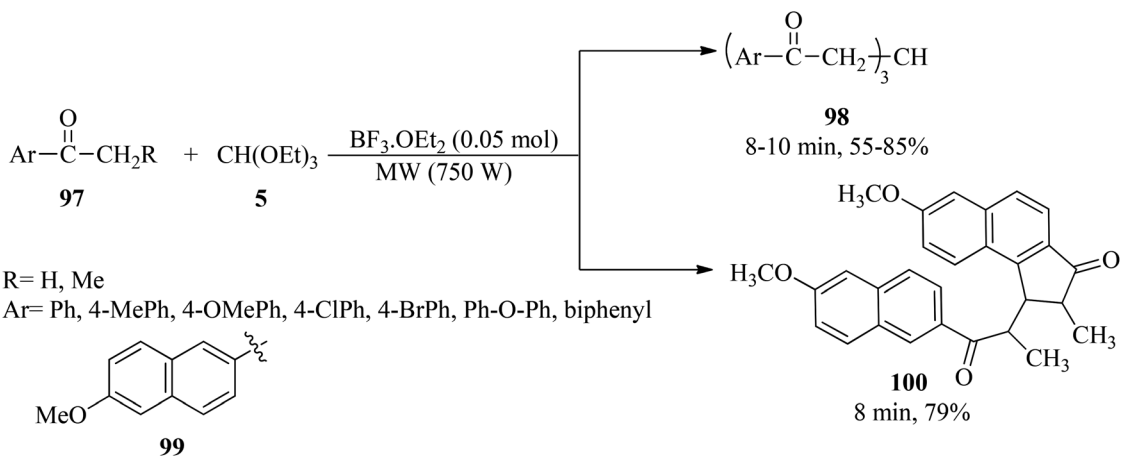
In 2003, the reaction of 5-phenyldipyrromethanes (**101**) with orthoesters (**102**) was presented for the generation of 5,15-diphenyl-10,20-dimethyl porphyrins (DPPs) (**103**) by trichloroacetic acid (TCA) (Scheme 27). Notably, trimethyl



Scheme 24 Tris(indolyl)methane synthesis.



Scheme 25 The preparation of various heterocycles containing an indole moiety using TEOF.

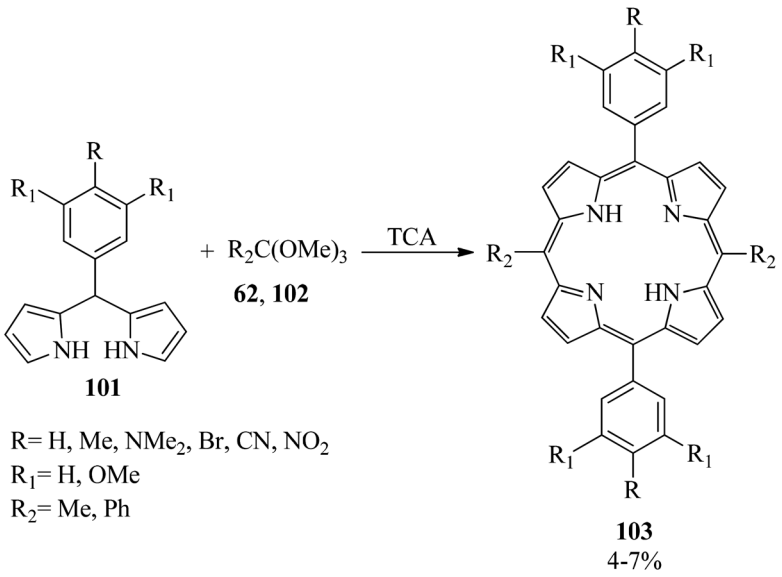


Scheme 26 The triaroyl methane synthetic procedure.

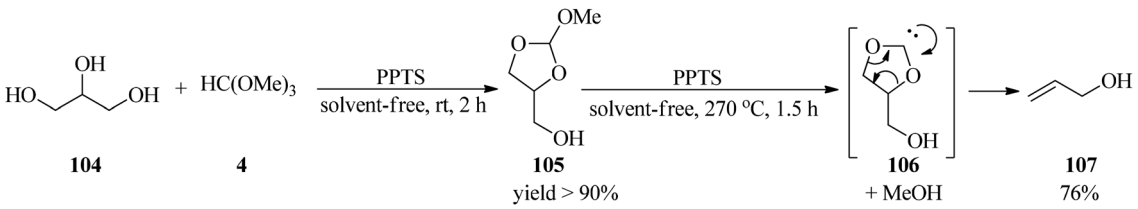
orthobenzoates as the bulky orthoesters produced scrambled products. Also, the 5-phenyldipyrromethane, including strong electron-withdrawing substituents on the phenyl ring, improved the scrambled products.[147]

2.14. Synthesis of allyl alcohol

In 2019, Wormann and Maier presented an integrated procedure for the conversion of glycerol (**104**) to the cyclic orthoester (**105**) in high yield through the reaction with TMOF (**4**) by a catalytic amount of PPTS at room temperature for 2 h, which was converted into allyl alcohol (**107**) under pyrolysis conditions at 270 °C using PPTS under solvent-free conditions. This reaction progressed *via* the disintegration of the orthoester (**105**) into carbene (**106**) and recoverable methanol, which was followed by decarboxylation to produce the mentioned product (**107**) in high yield (76%) within 1.5 h (Scheme 28).[148]



Scheme 27 Obtaining 5,15-diphenyl-10,20-dimethyl porphyrins (DPPs).



Scheme 28 Allyl alcohol preparation from glycerol and TMOF.

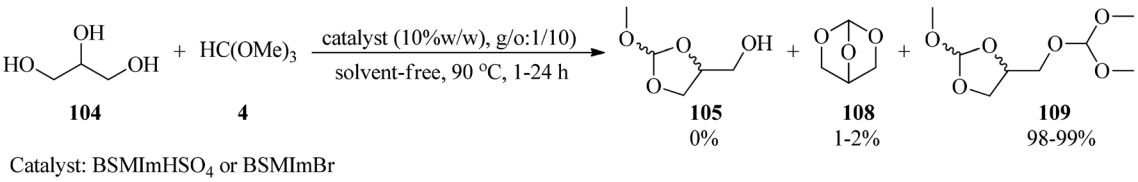
2.15. Orthoester exchange reaction

Calmanti *et al.* investigated the reactivity of glycerol (**104**) with TMOF (**4**) with the purpose of developing a credible synthetic strategy for glycerol valorization. It was found that the treatment of glycerol with TMOF under various conditions provided a mixture of compounds (**105**), (**108**), (**109**). Hence, in order to synthesize 4-(dimethoxymethoxy)methyl)-2-methoxy-1,3-dioxolane (**109**), different parameters, such as different molar ratios of TMOF, temperature, and the absence or presence of various catalysts, were examined. Significantly among different amounts of glycerol and TMOF, the best result was obtained in a molar ratio of 1 : 10 at 90 °C. Moreover, product (**109**) was selectively synthesized in the presence of a catalyst as well as in catalyst-free conditions, taking advantage of the thermodynamically controlled equilibrium between intermediates. To probe the effect of a catalyst, various catalysts, such as basic catalysts (K_2CO_3, ($[P_{1888}]CH_3OCO_2^-$) or Brønsted and Lewis acid catalysts were employed in which both Brønsted and Lewis acid catalysts progressed this reaction, and specifically Brønsted acidic ionic liquids ($BSMImHSO_4$ and BSMImBr) were the most efficient catalysts (Scheme 29).[149]

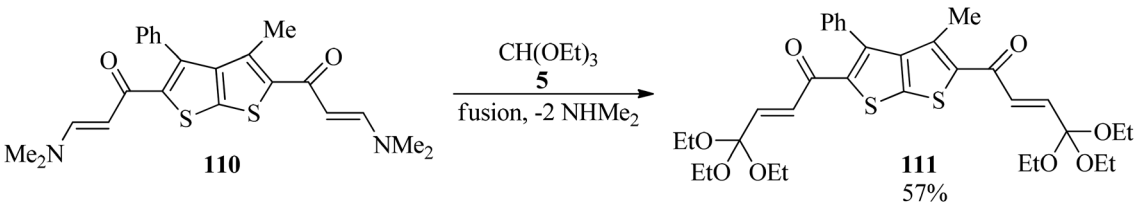
In 2012, the one-pot fusion reaction of bis(enaminone) derivative (**110**) with TEOF (**5**) under solvent-free conditions was reported to obtain 1,1′-(3-methyl-4-phenylthieno[2,3-*b*] thiophene-2,5-diyl)bis(4,4,4-triethoxybut-2-en-1-one) (**111**) as pale red crystals in relatively high yield (57%) (Scheme 30).[150]

2.16. Synthesis of 1,2-dimethyltetramethoxydisilane

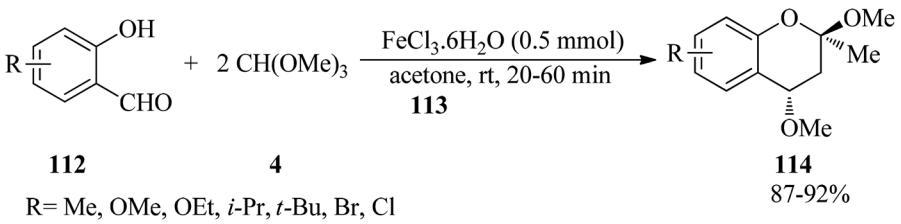
The reaction of methyldichlorosilane with TMOF at room temperature afforded dimethoxymethylsilane overnight[151,152] in 61% yield. Then, photolysis of dimethoxymethylsilane in the presence of a drop of mercury in the gas phase resulted in 1,2-dimethyltetramethoxydisilane in 81% yield within 8 h.[153]



Scheme 29 The synthesis of 4-(dimethoxymethoxy)methyl-2-methoxy-1,3-dioxolane.



Scheme 30 Preparing 1,1′-(3-methyl-4-phenylthieno[2,3-*b*]thiophene-2,5-diyl)bis(4,4,4-triethoxybut-2-en-1-one).

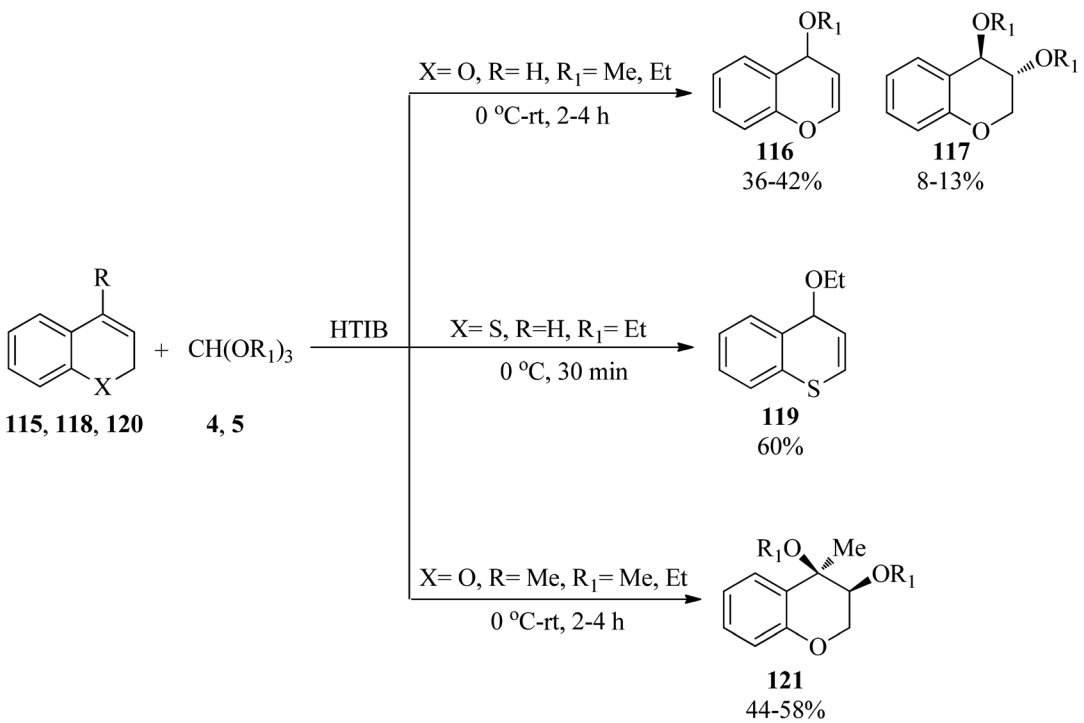


Scheme 31 The synthesis of 2,4-dimethoxy-2-methyl-2*H*-1-benzopyrans.

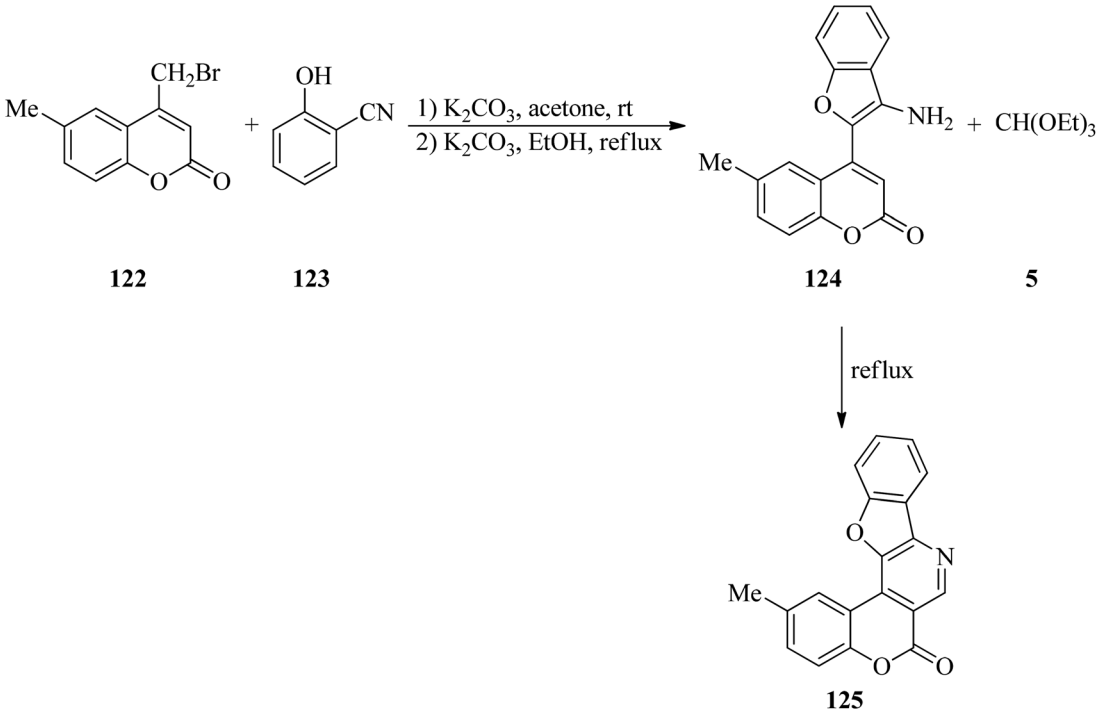
2.17. Synthesis of chromanes, chromenes, and thiochromene

In 2002, Yadav *et al.* interpreted the highly diastereoselective synthesis of 2,4-dimethoxy-2-methyl-2*H*-1-benzopyrans (**114**) *via* the three-component reaction of *o*-hydroxybenzaldehydes (**112**), acetone (**113**), and trimethyl orthoformate (**4**) utilizing a catalytic amount of ferric chloride hexahydrate ($FeCl_3 \cdot 6H_2O$, 0.5 mmol) at room temperature in excellent yields (87–92%) for 20–60 min. The only diastereomer bore a *trans*-relationship between two methoxy groups at the 2- and 4-positions (Scheme 31). Mild reaction conditions, experimental simplicity, easily available substrates, short reaction times, and excellent yields are some of the advantages of this process.[154]

In 2012, Ahmad and Silva Jr investigated the oxidation of different oxygen-containing benzo-fused cycloalkenes with various trialkyl orthoformates (**4**, **5**) in the presence of hypervalent iodine reagent [[hydroxy(tosyloxy)iodo]benzene, HTIB] under solvent-free conditions. It was found that 2*H*-chromenes (**115**) generated alkoxy-substituted 4*H*-chromenes (**116**) as the main product, along with the *trans*-addition product (**117**). On the other hand, 2*H*-thiochromene (**118**) and 4-methyl-2*H*-chromene (**120**) obtained 4*H*-thiochromene (**119**) and *cis*-3,4-



Scheme 32 The synthesis of different chromenes using trialkyl orthoformates.



Scheme 33 The synthesis of fused polycyclic heterocycles utilizing TEOF.

dialkoxy-4-methyl-3,4-dihydro-2*H* chromenes (**121**), respectively (Scheme 32).[155]

2.18. Synthesis of coumarin derivatives

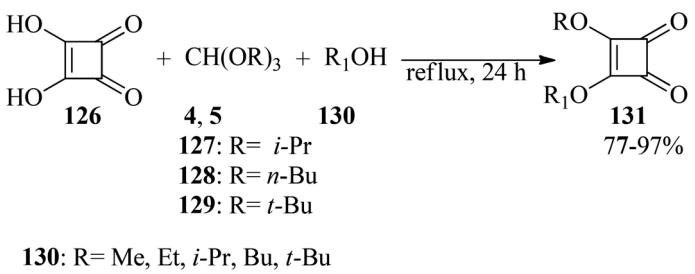
Kulkarni and Sun's research group investigated a three-step sequence, as an array to obtain angularly fused polycyclic heterocycles with coumarin, benzofuran and pyridine rings (**125**). They started from 4-bromomethylcoumarins (**122**) and salicylonitrile (**123**) followed by the addition of TEOF (**5**) (Scheme 33). Several of these exhibited promising inflammation-inhibiting and anti-microbial properties.[156]

2.19. Etherification and esterification reaction, and Johnson–Claisen rearrangement

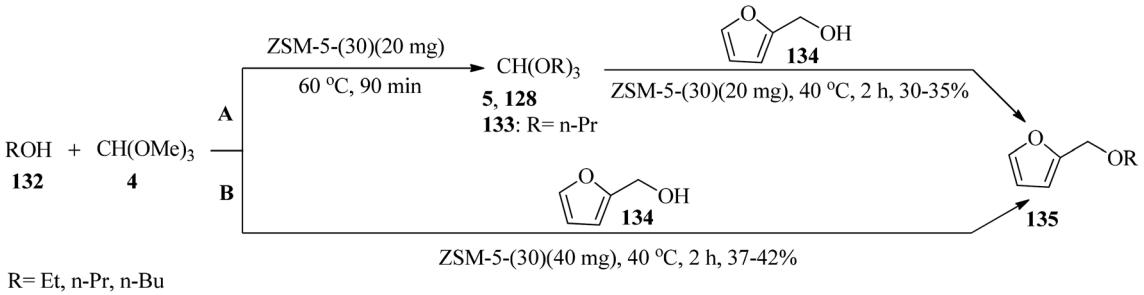
In 1997, Liu and co-workers described a simple and efficient process for the preparation of alkyl squarates (**131**) through the reaction of squaric acid (**126**), orthoformates (**4**, **5**, **127–129**), and appropriate alcohols (**130**) under reflux conditions in 77–97% yields (Scheme 34).[157]

Furfuryl ethers (**135**) as bio-renewable fuel could be synthesized *via* two pathways: (a) a sequential reaction method was used in which the appropriate orthoester (**5**, **128**, **133**) was synthesized upon treatment with TMOF (**4**) and an alcohol (**132**) in the presence of ZSM-5 zeolite (Si/Al ratio = 30 : 1, ZSM-5-(30)) catalyst (40 mg) at 60–40 °C, followed by the addition of furfuryl alcohol (**134**) to obtain furfuryl ether (**135**) bio-fuels. (b) The mentioned products were synthesized through a tandem etherification condensation reaction of (**4**), an excess amount of alcohol (**132**), and furfuryl alcohol (**134**) at 40 °C by ZSM-5-(30) (40 mg) in good yield and good to high selectivity (Scheme 35). It must be mentioned that the low temperature applied improved selectivity by decreasing the production of hydrolysis products, and the competing polymerization reactions resulting in humin by-products.[158]

In 2015, Zhang *et al.* utilized ZrO_2 supported $Pd(OH)_2$ ($Pd(OH)_2/ZrO_2$) as a new catalytic system for the synthesis of aryl ethers (**137**) *via* the reaction of substituted cyclohexanones (**136**) with orthoesters (**4**, **5**, **127**) as both dehydrating and nucleophilic reagents under an atmospheric pressure of oxygen (0.5



Scheme 34 Preparation method of alkyl squarates.

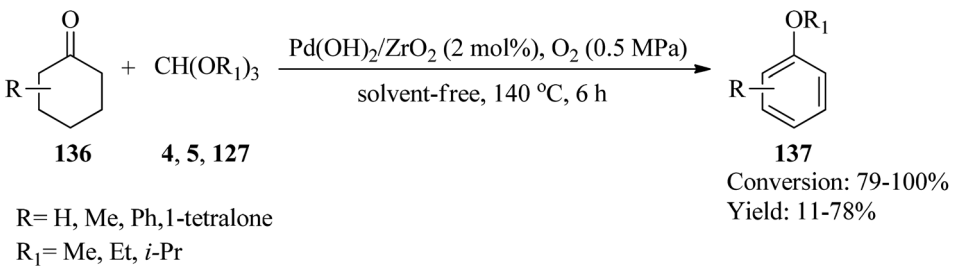


Scheme 35 The synthesis of furfuryl alcohols.

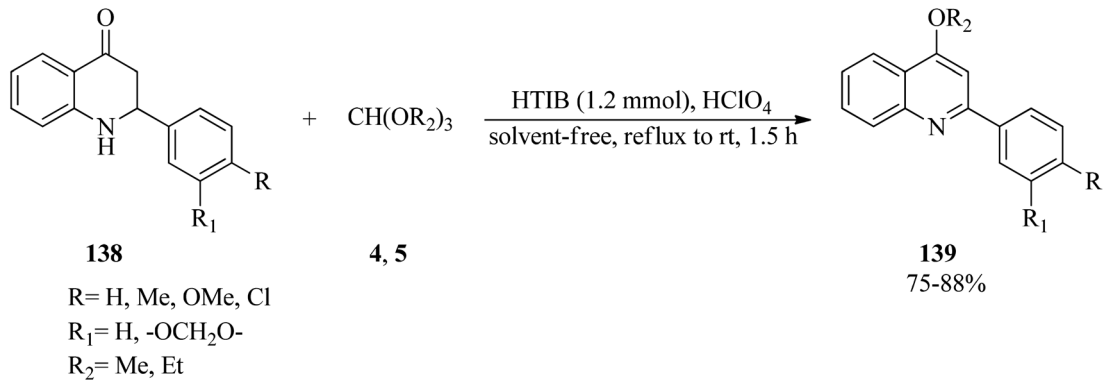
MPa) at 140 °C for 6 h (Scheme 36). It was found that in the presence of TMOF (**4**) reagent, the corresponding aryl ethers were obtained in moderate to good yields. Additionally, replacing other orthoester reagents, such as TEOF (**5**) and triisopropyl orthoformate (**127**) with (**4**) furnished the relevant products in low yields. Comparatively, the weak yields of the products compared to their high conversion were because of the generation of phenols as by-products. Due to the lower reactivity of TIPOF (**127**) to attain the related product than TMOF (**4**) or TEOF (**5**), this orthoester was employed as a dehydrating reagent in the reaction of cyclohexanones with alcohols to provide aryl ethers without forming isopropoxybenzene.[159]

In 1998, Varma and Kumar developed an applicable oxidative method for the synthesis of 4-alkoxy-2-arylquinolines (**139**) through the reaction of readily available 2-aryl-l,2,3,4-tetrahydro-4-quinolones (**138**) with orthoformates (**4**, **5**) using the hypervalent iodine oxidative reagent, HTIB, in the presence of a few drops of perchloric acid under solvent-free conditions at reflux to room temperature within 1.5 h in good yields (75–88%) (Scheme 37).[160]

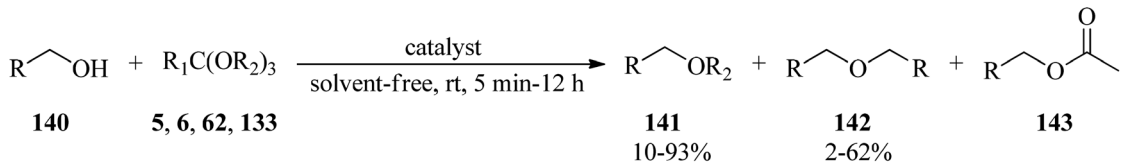
Unsymmetrical ethers (**141**) were obtained *via* the reaction of allylic and benzylic alcohols (**140**) with orthoesters (**5**, **6**, **62**, **133**) using acidic catalysts such as montmorillonite KSF and K10, $BF_3 \cdot Et_2O$, SiO_2, amberlyst-15 at room temperature under an N_2 atmosphere. It is noteworthy that the change in the catalyst was accompanied by an important change in the yields and the type of products obtained, such as dimerized ethers (**142**) and *O*-acetylated (**143**) *via* competitive reactions (Scheme 38). This reaction was general due to the presence of varied orthoesters, but selective with regard to different allylic and benzylic alcohols. On the other hand, Johnson–Claisen orthoester rearrangement[161–164] of allylic alcohols (**144**) with TEOAc (**6**) by



Scheme 36 The synthesis of aryl ethers.

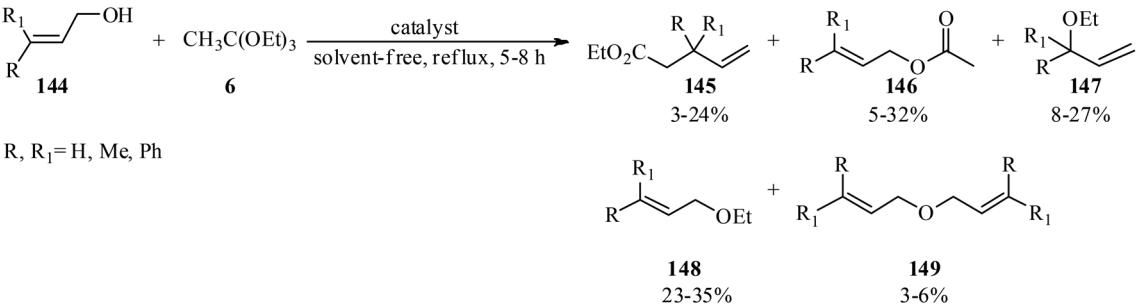


Scheme 37 The synthesis of 4-alkoxy-2-arylquinolines.



Catalyst= MMKSF, MMK10, SiO_2, SiO_2(MW), $BF_3.OEt_2$, Amberlyst-15
R= *n*-Bu, Vinyl, Ar
R_1= H, Me
R_2= Me, Et, *n*-Pr

Scheme 38 The reaction of allylic and benzylic alcohols with orthoesters.



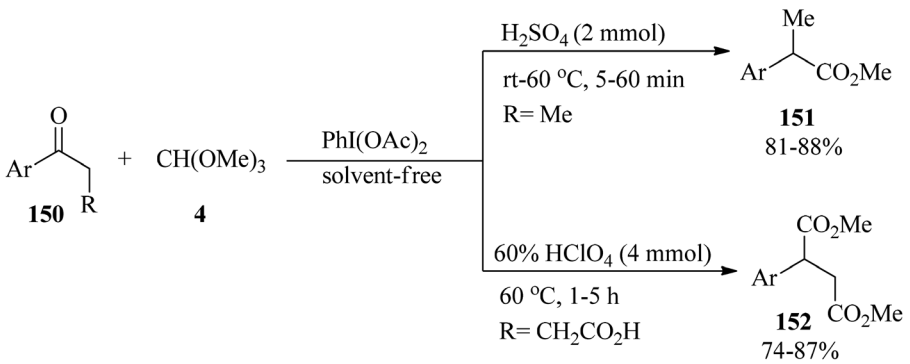
R, R_1= H, Me, Ph

Scheme 39 The Johnson–Claisen orthoester rearrangement of allylic alcohols.

MMKSF, MMK10, and SiO_2 under reflux conditions and N_2 atmosphere produced a mixture of Claisen ester (**145**), acetylated product (**146**), ethyl ether (**147**), unsymmetrical terminal ether (**148**), and dimeric ether (**149**) in which *O*-acetylation and *O*-alkylations were significant side reactions (Scheme 39).[164]

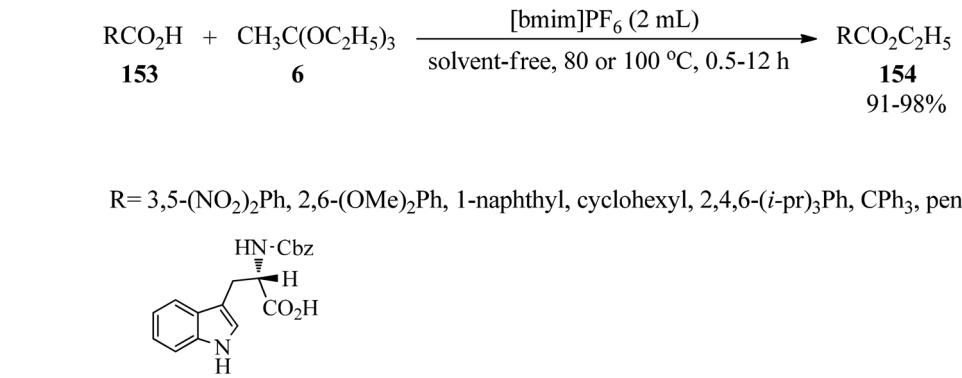
Tamura and co-workers prepared 2-arylalkanoates (**151**, **152**) *via* oxidative 1,2-aryl migration of alkyl aryl ketones (**150**) with diacetoxyphenyliodine, as oxidizing reagent, in TMOF (**4**) under acidic conditions at room temperature or 60 °C in high yields (74–88%) (Scheme 40).[165]

In 2004, Yoshino and Togo introduced a green, easy, inexpensive, and highly efficient system for the esterification of carboxylic acids (**153**) with TEOAc (**6**) by a typical room-temperature ionic liquid, 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF_6), at 80–100 °C under neutral and solvent-free conditions in good yields (Scheme 41). The proposed method greatly facilitated the formation of the desired ethyl esters (**154**), especially for less acidic carboxylic acids, and it could also be used for sterically hindered carboxylic acids, like 2,4,6-triisopropylbenzoic acid or 2,2,2-triphenylacetic acid, and for amino acid without any racemization. Notably, replacement of trimethyl orthoacetate with TEOAc exhibited similar reactivity. On the other hand, the utilization of [bmim]BF_4 instead of [bmim]PF_6, as an ionic liquid, revealed the same results.[166]

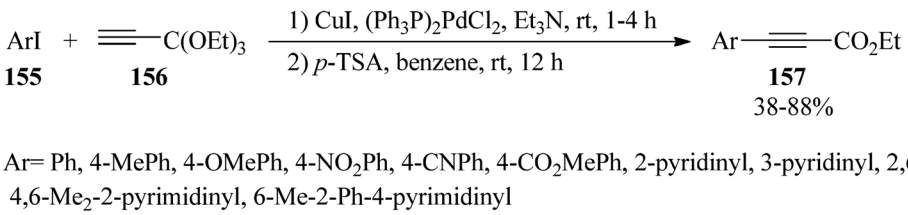


Ar= Ph, 4-MePh, 4-OMePh, 4-*i*-BuPh, 4-FPh, 4-BrPh, 4-cyclohexylphenyl, 2-naphthyl, 9,10-dihydrophenanthrene

Scheme 40 2-Arylalkanoate preparation.



Scheme 41 The esterification of carboxylic acids with TEOAc.

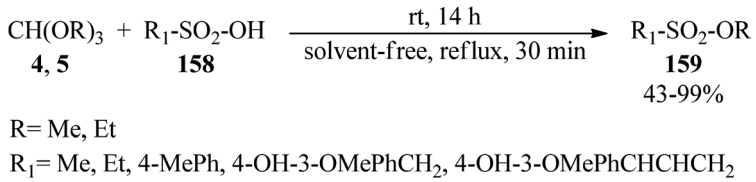


Scheme 42 The synthesis of ethyl arylpropiolate.

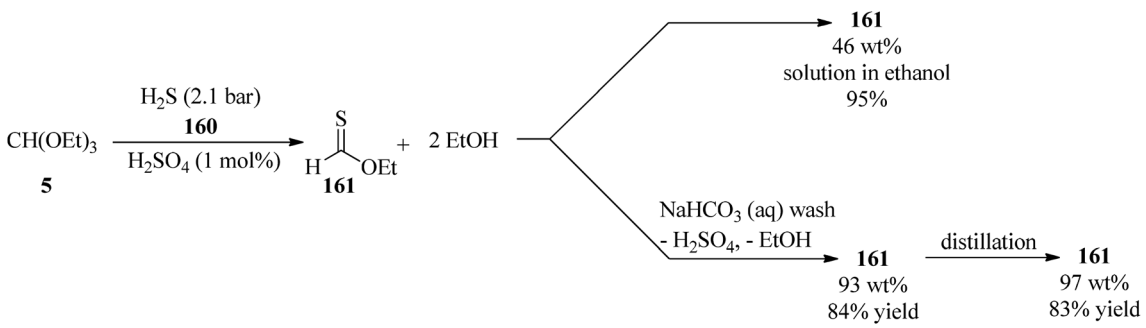
The cross-coupling reaction of aryl iodides (**155**) with 3,3,3-triethoxy-1-propyne (**156**) using dichlorobis(-triphenylphosphine) palladium [$(PPh_3)_2PdCl_2$] and cuprous iodide (CuI) in triethylamine (Et_3N) at room temperature led to the production of 3,3,3-triethoxy-1-aryl-1-propyne within 1–4 h, which after isolation was subsequently reacted with a catalytic amount of *p*-TSA in benzene at room temperature for 12 h to yield the ethyl arylpropiolates (**157**) (Scheme 42).[167]

Padmapriya and co-workers reported the alkylation of sulfonic acids (**158**) by trialkyl orthoformates (**4**, **5**) to generate the alkyl sulfonates (**159**) under solvent-free conditions at room temperature for 14 h or under reflux conditions in a 30 min period in 43–99% yields (Scheme 43).[168]

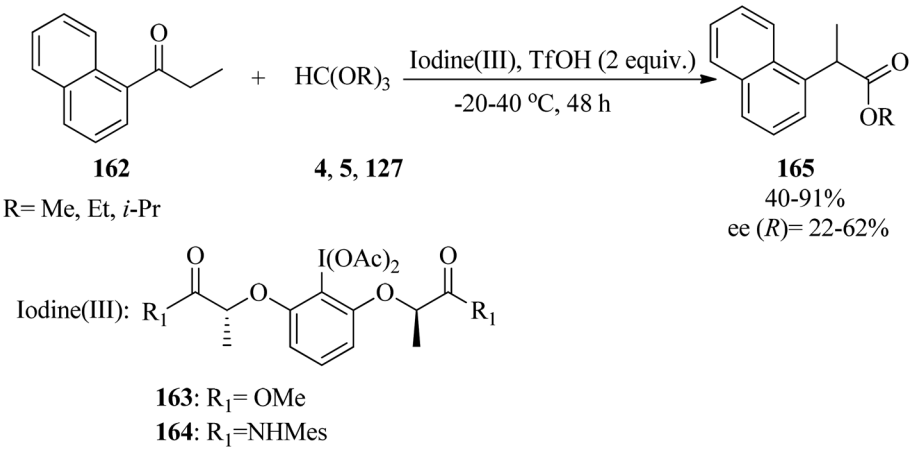
In 2009, Borths *et al.* synthesized *O*-ethyl thioformate (**161**) *via* the condensation reaction of TEOF (**5**) with hydrogen sulfide gas (H_2S) (**160**) at 2.1 bar in the presence of sulfuric acid (H_2SO_4, 98%, 1 mol%) as a Brønsted acid catalyst under solvent-free



Scheme 43 The alkylation of sulfonic acids by trialkyl orthoformates.



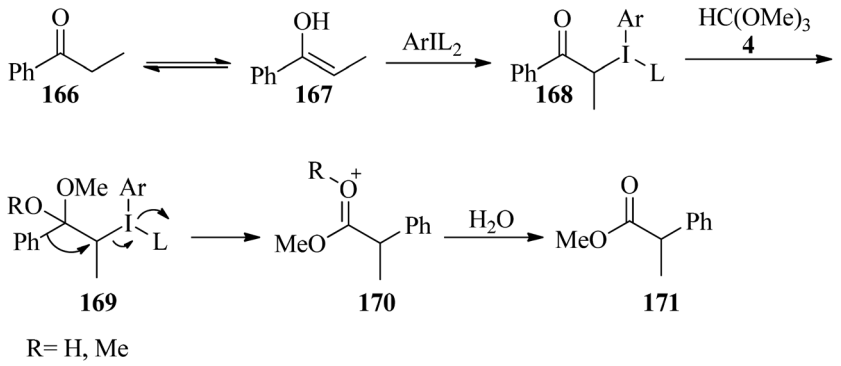
Scheme 44 The condensation of TEOF with H_2S to obtain *O*-ethyl thioformate.



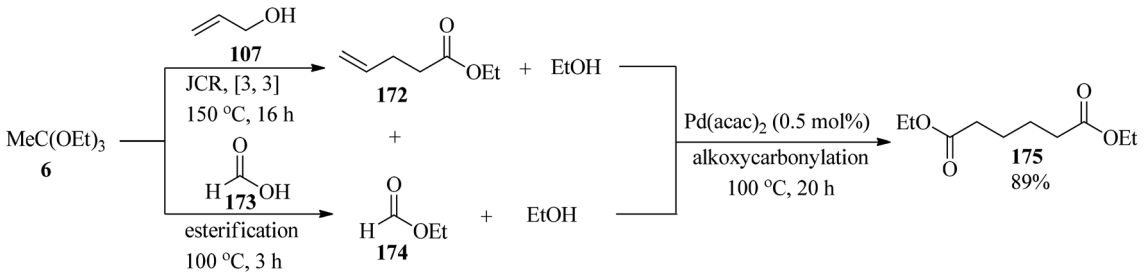
Scheme 45 The preparation of alkyl 2-(naphthalen-1-yl)propanoates.

conditions. The 46 wt% ethanolic *O*-ethyl thioformate solution was obtained in 95% assay yield and could be purified initially by washing with basic aqueous sodium hydrogen carbonate ($NaHCO_3$) to eliminate the sulfuric acid and ethanol and then by distillation at atmospheric pressure to remove the residual ethanol to provide 97 wt% of *O*-ethyl thioformate as a yellow oil in 83% yield, which could be utilized as a thioformylating agent for amines (Scheme 44).[169]

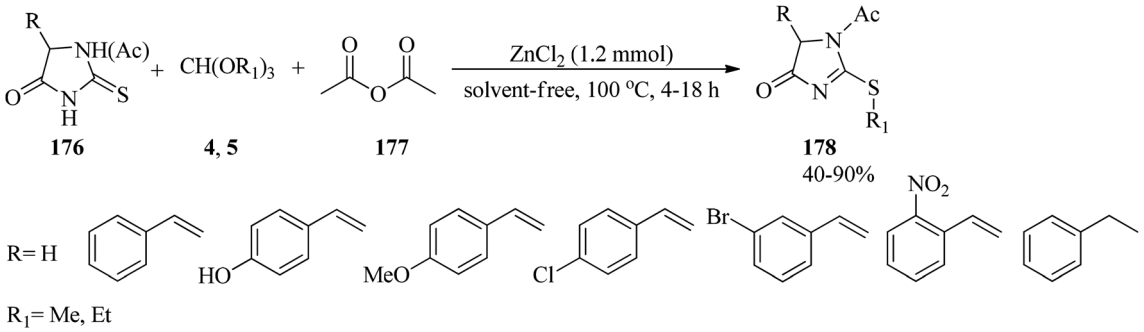
In 2016, Malmedy and Wirth developed a stereoselective reaction to access 2-aryl alkanoates (**165**) in good enantioselectivity *via* the rearrangement reaction of 1-(naphthalen-1-yl) propan-1-one (**162**) with orthoesters (**4**, **5**, **127**) by iodine(III) reagent (**163**, **164**) and triflic acid (TfOH) at −20 to 40 °C, yielding the corresponding alkyl 2-(naphthalen-1-yl)propanoate (**165**) (Scheme 45). In this reaction the effect of different parameters, such as the type of catalyst, catalytic amounts of Lewis acid, the nature of the orthoester, and temperature were investigated. It was found that a reaction with too high a bulkiness of the triisopropyl orthoformate (**127**) did not result in any rearranged compound. Also, acceptable results were obtained in the presence of 2 equivalents of TfOH. A plausible mechanism for the rearrangement is shown in Scheme 46.[170] The reaction was promoted through the reaction of the enolic form (**167**) of ketone (**166**) with the iodine(III) moiety to produce the



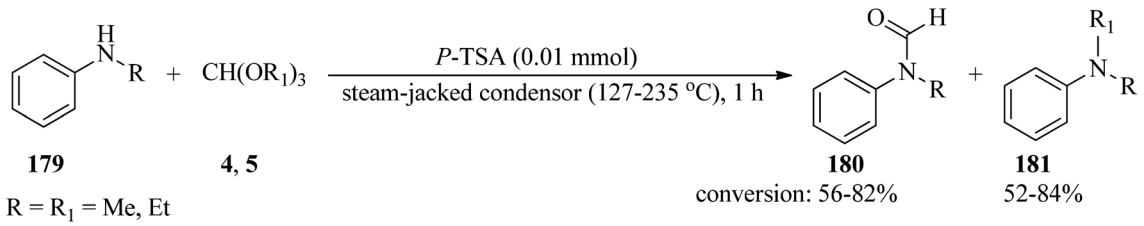
Scheme 46 Reaction mechanism for the reaction of ketones with TMOF.



Scheme 47 The synthesis of linear diester diethyl adipate by the Johnson–Claisen rearrangement and alkoxycarbonylation.



Scheme 48 *S*-Alkylation and *N*-acylation of 2-thiohydantoins.



Scheme 49 The synthesis of *N*-alkylformanilides and *N*,*N*-dialkylanilines.

intermediate (**168**), which provided the ketal (**169**) by TMOF (**4**). The elimination of aryliodide was accompanied with 1,2-aryl migration to form the intermediate (**170**); which was followed by hydrolysis in water to afford the rearranged product (**171**).[171]

The linear diester diethyl adipate (**175**) was synthesized by the merger of Johnson–Claisen rearrangement and alkoxycarbonylation *via* a one-pot procedure. This reaction proceeded through Johnson–Claisen rearrangement (JCR) of allyl alcohol (**107**) with TEOAc (**6**, 2 equiv.) to afford ethyl 4-pentenoate (**172**), which was followed by quenching the excess of (**6**) by the addition of formic acid (**173**) to obtain ethyl formate (**174**). Then, the alkoxycarbonylation of ethyl 4-pentenoate (**172**) with ethyl formate (**174**) using the palladium catalytic system such as palladium(II)acetylacetonate ($Pd(acac)_2$, 0.5 mol%) and 1,2-bis((di-*tert*-butylphosphino)methyl)benzene (2 mol% 1,2-DTBPMB) and methanesulfonic acid (MSA, 8 mol%) produced the linear diester diethyl adipate (**175**) in good yield (89%) (Scheme 47).[172]

2.20. Alkylation reactions

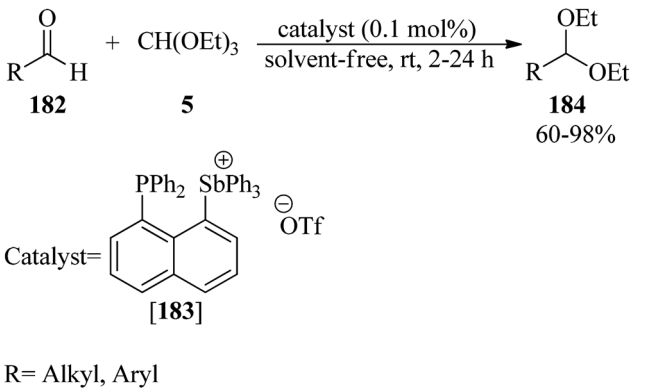
In 2008, the one-pot chemoselective *S*-alkylation and *N*-acylation reaction of 2-thiohydantoins (**176**) utilizing alkyl orthoformates (**4**, **5**) and acetic anhydride (**177**) was presented for the synthesis of the products (**178**) by zinc chloride ($ZnCl_2$, 1.2 mmol) at 100 °C within 4–18 h in 40–90% yields (Scheme 48).[173]

In 1980, Swaringen *et al.* discovered that the reaction of *N*-alkylanilines (**179**) and ortho formats (**4**, **5**), in a 2 : 1 molar ratio, gave high yields of *N*-alkylformanilides (**180**) and *N*,*N*-dialkylanilines (**181**) in the presence of *p*-TSA (Scheme 49). In addition, aliphatic cyclic amines (such as morpholine or piperidine) and orthoformates gave the corresponding orthoamides.[174]

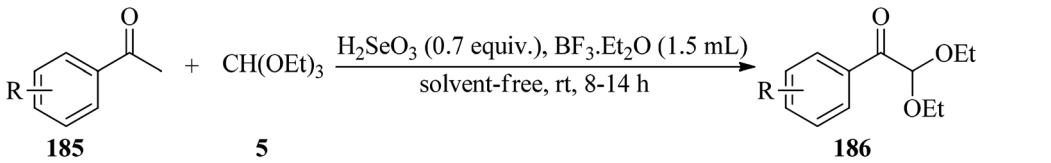
2.21. Acetalization reaction

In 2017, Ugarte and Hudnall presented a highly selective, environmentally friendly, rapid, and solvent-free procedure for the protection of carbonyls to acetals (**184**)[175–182] *via* the reaction of aldehydes (**182**) with TEOF (**5**) in equimolar amounts using the tetraarylstibonium salt, 1-diphenylphosphinonaphthyl-8-triphenylstibonium triflate ([**183**][OTf], 0.1 mol%), at room temperature (Scheme 50). Notably, the rate of the reactions increased in the presence of aliphatic aldehydes. This catalyst was recycled and reused for up to 6 runs without losing activity. Furthermore, the tetraarylstibonium salt could catalyze the deprotection of the acetals into their corresponding aldehydes in aqueous media.[182]

In 2009, Kharkongor and Myrboh presented a convenient and efficient one-pot method for the synthesis of α-ketoacetals

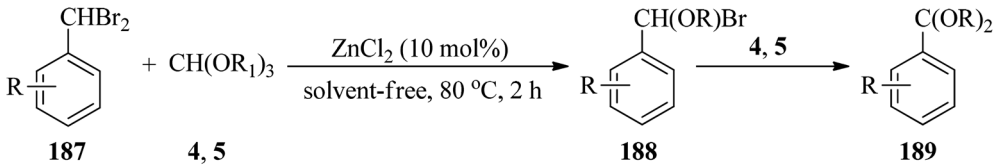


Scheme 50 Acetalization with TEOF in the presence of tetraarylstibonium salt.



R= Ph, 4-ClPh, 4-BrPh, 4-NO_2Ph, 3-NO_2Ph, 3-OH-Ph, 4-OHPh, 4-MePh, 4-OMePh, 3-NHCOMePh, 4-NHCOMePh, 2-furanyl, 5-Me-2-furanyl, 2-thiophenyl, 2-naphthyl

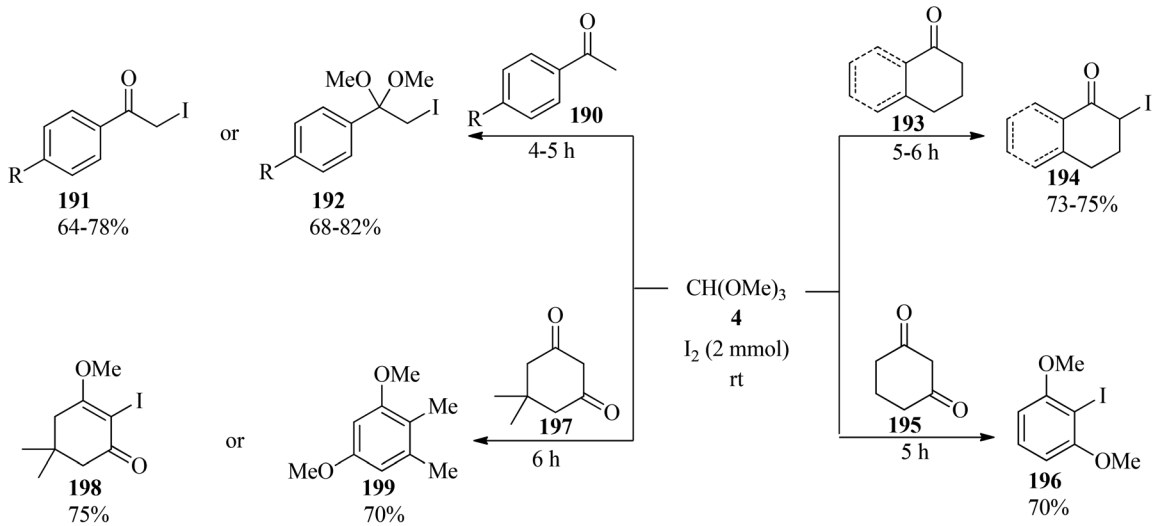
Scheme 51 Acetalization with TEOF in the presence of selenous acid.



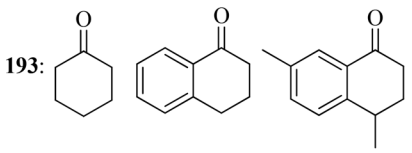
R= 4-$CH(OMe)_2$, 4-$CH(OEt)_2$, 4-CO_2Me, 4-CO_2Et, 3-OAc, 4-$CHBr_2$, 4-CHO
R_1= Me, Et

Scheme 52 Acetalization *via* the double debromoalkoxylation of dibromomethylarenes.

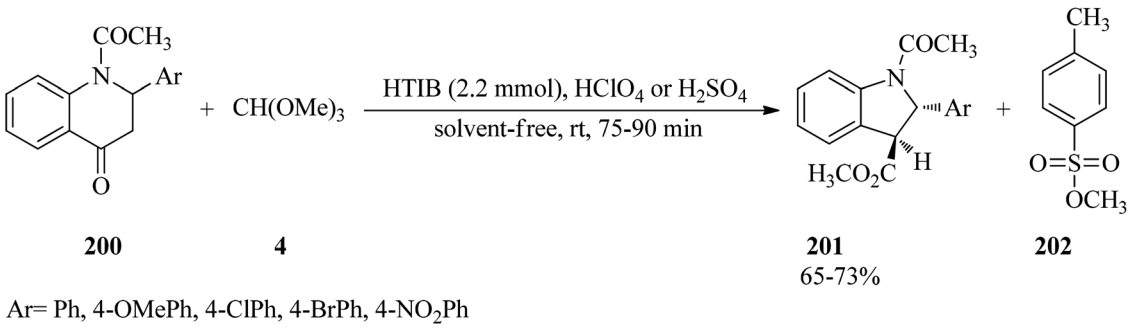
(**186**) from substituted acetophenones (**185**) and TEOF (**5**) by selenous acid (H_2SeO_3, 0.7 equiv.) and $BF_3 \cdot Et_2O$ (1.5 mL) as a catalyst under solvent-free conditions at room temperature in moderate to excellent yields (55–90%) within 8–14 h (Scheme 51).[183] Acetals could be also synthesized *via* the reaction of various acidic methines such as cyanoesters and 3,4,5-trimethoxybenzylmalononitrile with orthoformates under heating and solvent-free conditions. The reaction has been shown to be useful for the production of protected aldehydes and 2,4-diamino-5-benzylpyrimidines.[184]



R= H, OH, Me, F, OTBS, OAc, OBn



Scheme 53 The synthesis of iodo ketones and iodo dimethyl ketals.



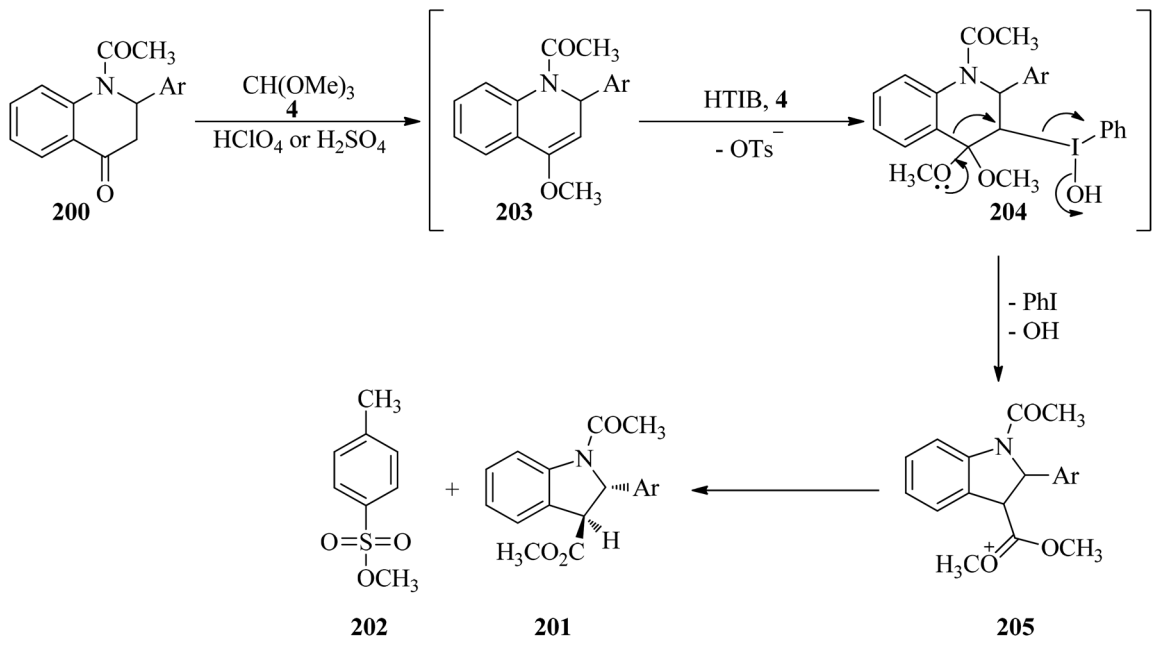
Scheme 54 The ring contraction of *N*-acetyl-2-aryl-1,2,3,4-tetrahydro-4-quinolones with TMOF.

Aromatic aldehyde acetals (**189**)[185,186] were synthesized *via* double debromoalkoxylation of dibromomethylarenes (**187**) with trialkyl orthoformate (**4**, **5**) using $ZnCl_2$ (10 mol%) under solvent-free conditions at 80 °C (Scheme 52). This reaction was promoted by the reaction of dibromomethylarenes (**187**) with an excess of (**4**, **5**) to form α-brominated ether intermediates (**188**) which underwent a second debromoalkoxylation in the presence of an excess of (**4**, **5**) to provide acetal (**189**) and the removal of 2 moles of alkyl bromide and 3 moles of formate ester.[186]

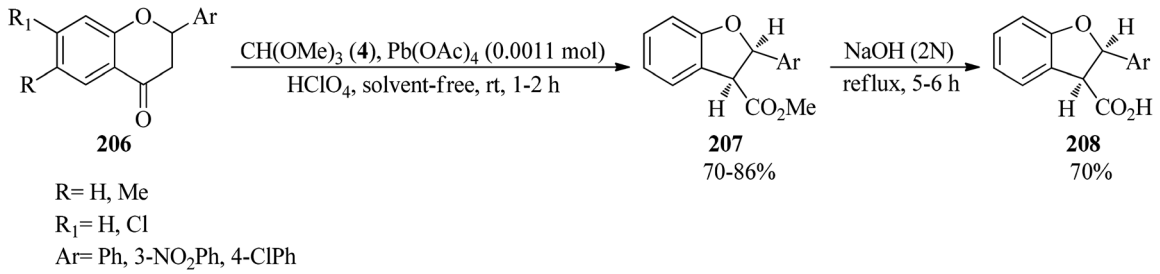
In 2006, Gazizov *et al.* investigated the reaction of TEOF with 1,1,2,2-tetrabromoethane with different molar ratios at 180 °C under solvent-free conditions within 10 h. It was found that dehydrobromination reaction took place *via* the reaction of triethyl orthoformate with 1,1,2,2-tetrabromoethane in 1 : 2 molar ratios to obtain tribromoethylene, ethyl formate, ethyl bromide, and ethanol as the main products along with low amounts of ethyl acetate and dibromoethylene. On the other hand, the debromination reaction was accomplished *via* the reaction of substrates in a 2 : 1 molar ratio to give ethyl formate, ethyl bromide, dibromoethylene, ethyl hypobromite, and acetal.[187]

2.22. Synthesis of α-iodo ketones and α-iodo dimethyl ketals

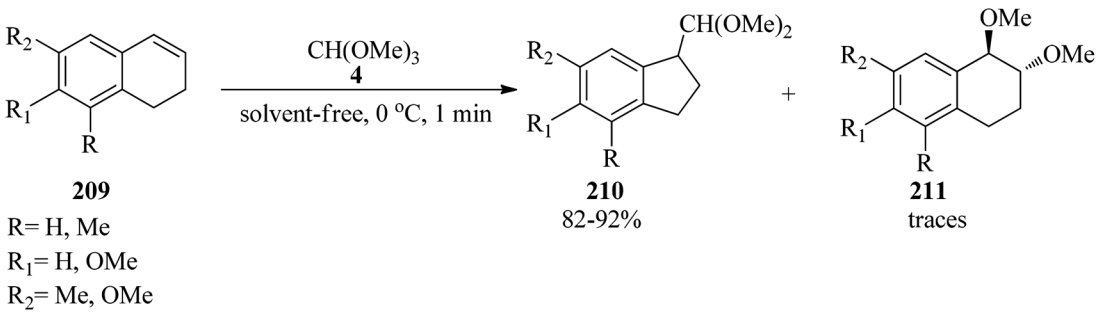
In 2008, Yadav *et al.* presented a new, effective, and simple protocol for the synthesis of α-iodo ketones (**191**) and α-iodo dimethyl ketals (**192**) *via* the reaction of substituted acetophenones (**190**), TMOF (**4**) and iodine at room temperature under solvent-free conditions (Scheme 53). It must be mentioned that the selectivity of the obtained products from acetophenones was attributed to the workup procedures. It was found that, after completion of the reaction, if the reaction mixture was quenched in the presence of aqueous saturated $Na_2S_2O_3$ and then extracted by dichloromethane, the α-iodinated dimethoxy ketal was obtained as the main product, but when the reaction mixture was stirred in the presence of water before washing with aqueous saturated $Na_2S_2O_3$, the α-iodo ketones were afforded as the main products. In this conversion, the ring-directed iodination or α,α-diiodination products were never



Scheme 55 A mechanistic approach for the ring contraction of *N*-acetyl-2-aryl-1,2,3,4-tetrahydro-4-quinolones with TMOF.



Scheme 56 The oxidative reaction of flavanones with TMOF using $Pb(OAc)_4$.

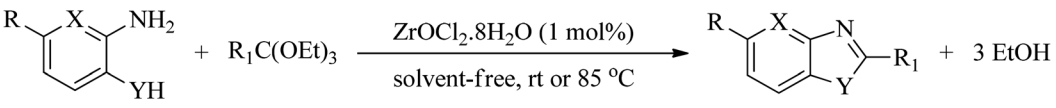


Scheme 57 The reaction of 1,2-dihydronaphthalenes with TMOF.

obtained. It is significant that this transformation in the presence of cyclohexanones (**193**) as a starting material resulted in the α-iodo ketos (**194**) as the only product, but 1,3-cyclohexadione (**195**) and substituted 1,3-cyclohexadione such as dimedone (**197**) yielded the α-iodinated products (**196**, **198**) and the aromatized compound (**199**)[188] in good yields.[189]

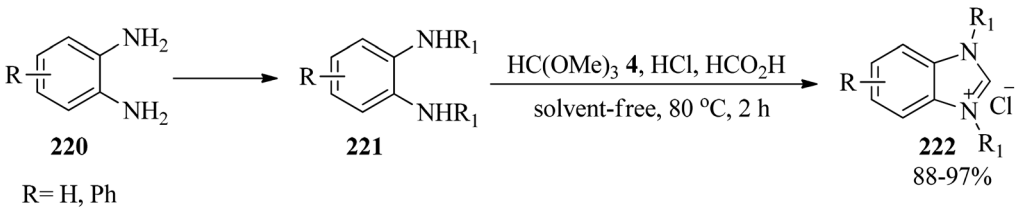
2.23. Ring-contraction reactions

In 2007, Kumar *et al.* described a stereoselective method for the synthesis of *trans*-methyl *N*-acetyl-2-aryl-2,3-dihydroindol-3-carboxylates (**201**) *via* the ring contraction of *N*-acetyl-2-aryl-1,2,3,4-tetrahydro-4-quinolones (**200**) with TMOF (**4**) by HTIB as oxidizing agent in the presence of a few drops of either $HClO_4$ or H_2SO_4 at room temperature in high yields (65–73%) for appropriate times (75–90 min) (Scheme 54). This reaction was accompanied by the formation of methyl *p*-toluenesulfonate (**202**) as a by-product in small quantity. The proposed mechanism, shown in Scheme 55, was begun through the ketalisation of (**200**) with (**4**) using either $HClO_4$ or H_2SO_4 to form intermediate enol ether (**203**). Then the electrophilic attack of HTIB on the double bond of enol ether (**203**) led to the iodine(III) complex (**204**), from which the elimination of iodobenzene from (**204**) with concurrent migration of aryl residue from the C_4 to the C_3 position gave intermediate carbocation (**205**), which on hydrolysis obtained the ring-contracted product (**201**) together with (**202**). To accomplish greater stability of the resultant carbocation, the migration of aryl residue was preferred over the C_2 position aryl ring. Eventually, (**201**) was afforded by ring contraction of compound (**200**), and meanwhile by-product



212, **213**: X= C, Y= NH, 85 °C, 4-10 min, 83-97%
214, **215**: X= C, Y= O, rt or 85 °C, 4-10 min, 85-95%
216, **217**: X= C, Y= S, rt, 4-6 min, 93-97%
218, **219**: X= N, Y= O, 85 °C, 12 min, 88-89%
R= H, Me, Cl
R_1= H, Me, Et

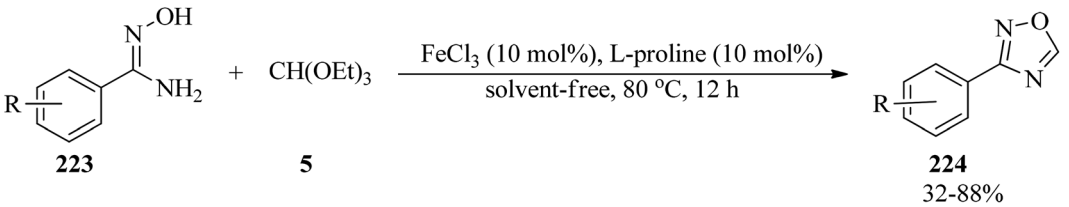
Scheme 58 The synthesis of benzimidazoles through the condensation of trialkyl orthoformates with diamines.



R= H, Ph

R_1= Ph, 4-MePh, 4-FPh, Py, 3-Me-2-pyridyl, 2-naphthyl

Scheme 59 The synthesis of benzimidazole-based N-heterocyclic carbenes.



R = H, 4-Cl, 3-Cl, 4-NO_2, 4-Br, 2,4-Cl_2, 4-OMe, 3-OMe

Scheme 60 The preparation of 3-substituted 1,2,4-oxadiazoles.

(**202**) was produced, probably through the *in situ* condensation of methanol with *p*-TSA.[190]

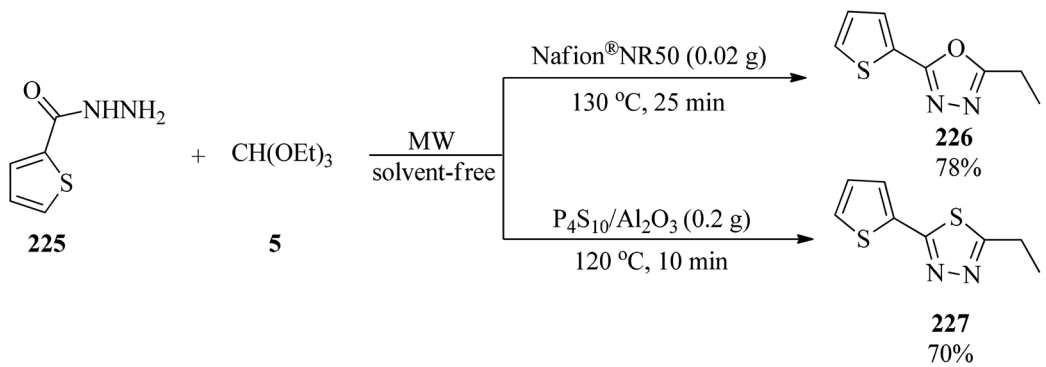
Flavanones (**206**),[191–193] through the oxidative reaction with TMOF (**4**) using lead tetraacetate ($Pb(OAc)_4$, 0.0011 mol) and 70% perchloric acid under solvent-free conditions at room temperature, were converted into *cis*-methyl-2,3-dihydro-2-arylbenzofuran-3-carboxylates (**207**) in high yields (70–86%) within 1–2 h. Subsequent alkaline hydrolysis of the product (**207**) by aqueous NaOH solution under reflux conditions obtained the corresponding acids (**208**) within 5–6 h in 70% yields (Scheme 56).[193]

Thallium(III) trinitrate [$Tl(NO_3)_3 \cdot 3H_2O$] catalyzed the oxidation of various olefins[194] such as 1,2-dihydronaphthalenes (**209**) with TMOF (**4**) at 0 °C to obtain indans (**210**) in good yields (82–92%) within a very short 1 min period (Scheme 57).[195] It was found that 1,2-dihydronaphthalenes (**209**) without an alkyl substituent at the double bond produced mainly the ring-contraction products (**210**) in high yields,[194–204] while the substrates containing an alkyl group because of their lower reactivity gave the addition products (**211**) in the presence of methanol,[197,198,205] although there are some exceptions.[200,206]

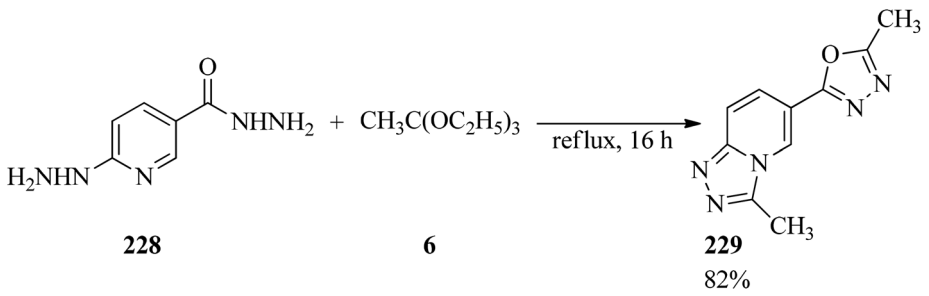
2.24. Synthesis of benzimidazoles, benzoxazoles, benzothiazoles, and oxazolo[4,5-*b*]pyridines

In 2007, the Mohammadpoor-Baltork group presented a green and efficient protocol for the preparation of a new library of benzimidazoles (**213**), benzoxazoles (**215**),[207,208] benzothiazoles (**217**),[128,209] and oxazolo[4,5-*b*]pyridines (**219**)[210–212] *via* the condensation reactions of orthoesters (**5**, **6**, **7**) with *o*-substituted aminoaromatics such as *o*-phenylenediamine (**212**), *o*-aminophenol (**214**), *o*-aminothiophenol (**216**), and 2-amino-3-hydroxypyridine (**218**), respectively, by catalytic amounts of $ZrOCl_2 \cdot 8H_2O$ under solvent-free conditions at room temperature or 85 °C for short reaction times (4–12 min) and moderate to excellent yields (83–97%) (Scheme 58).[212]

In 2018, $ZrOCl_2 \cdot 8H_2O$@nano SiO_2 as a new catalyst was originated and characterized and subsequently its catalytic



Scheme 61 The microwave-assisted synthesis of 1,3,4-oxadiazoles and 1,3,4-thiadiazoles.



Scheme 62 Double [4 + 1] cyclocondensation of 6-hydrazinonicotinic acid hydrazide hydrate with TEOAc.

activity (0.01 g) has been investigated for the preparation of benzimidazoles[213,214] *via* the condensation reaction of trialkyl orthoformates with diamines under solvent-free condition at 60 °C within reaction times of 1.5–5.5 h and 70–90% yields. High yields (70–90%), recyclability, and reusability of the synthesized catalyst are some of the main advantages of this method.[214] Nano-Ni(II)/Y zeolite, as a non-toxic heterogeneous catalyst, at 60 °C under solvent-free conditions also accelerated this transformation within 46–122 min in good to excellent 79–99% yields.[215]

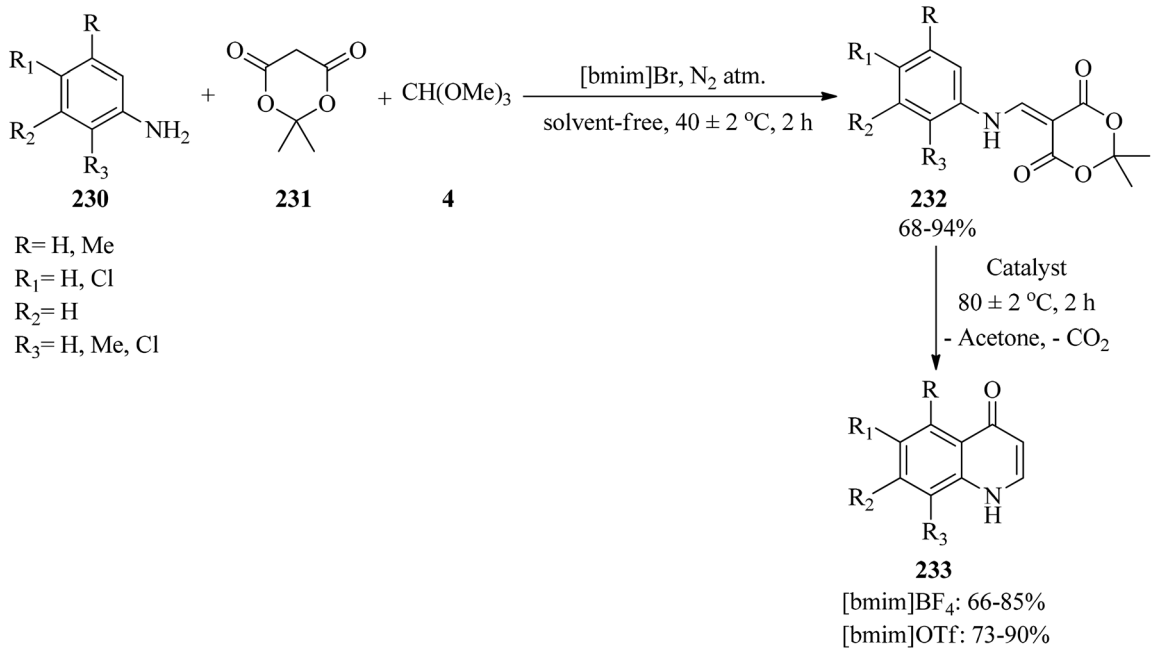
In 2013, Wang and co-workers developed a simple and efficacious process for the synthesis of benzimidazole-based N-heterocyclic carbenes (**222**) *via* the cyclization of *N*,*N*′-diarylaryldiamines (**221**), arising from aryldiamines (**220**), with TMOF (**4**) using concentrated HCl and formic acid at 80 °C for 2 h in 88–97% yields (Scheme 59). Notably, the reaction was unsuccessful with diamines containing strong electron-withdrawing substitutions.[216]

2.25. Synthesis of oxadiazoles and thiadiazoles

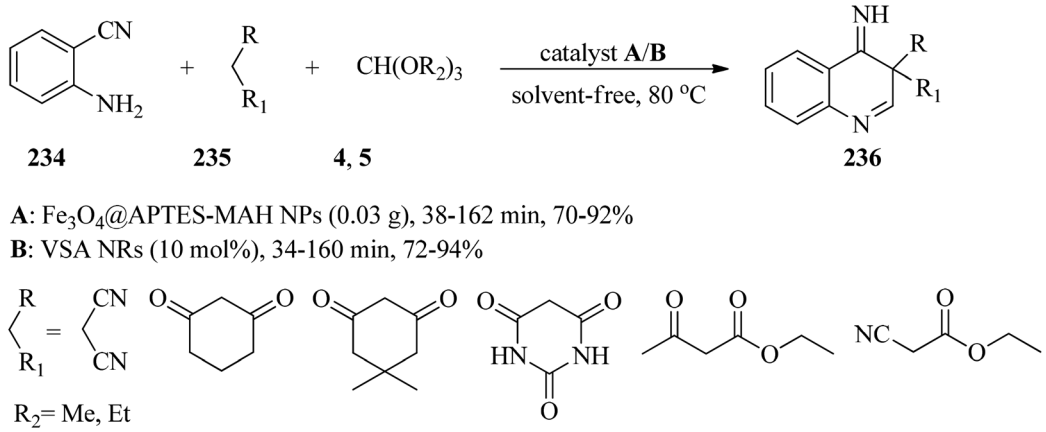
In 2016, Kaboudin *et al.* investigated iron(III) chloride/L-proline as an efficient catalytic system for the synthesis of 3-substituted 1,2,4-oxadiazoles (**224**) from amidoximes (**223**) and TEOF (**5**) (Scheme 60).[217]

Polshettiwar and Varma performed the solvent-free synthesis of 1,3,4-oxadiazoles (**226**)[218–223] and 1,3,4-thiadiazoles (**227**) by the condensation of acid hydrazide (**225**) and triethyl orthoalkanates (**5**) under microwave irradiation (40–140 W). According to Scheme 61, the condensation of hydrazide and TEOF were successfully undertaken in two catalytic systems which were solid supported Nafion® NR50 and P_4S_{10}/Al_2O_3.[223]

The double [4 + 1] cyclocondensation reaction of 6-hydrazinonicotinic acid hydrazide hydrate (**228**) containing two dinucleophilic centers[224] with TEOAc (**6**) obtained oxadiazolyltriazolopyridine (**229**) in 82% yield within 16 h under reflux conditions (Scheme 62). In this transformation, the hydrazine and the hydrazide moieties exhibited similar reactivity, whereas in the presence of aldehyde as one other carbon



Scheme 63 The synthesis of 4(1*H*)-quinolones.



Scheme 64 The synthesis of new 4-iminoquinolines.

donor moiety the hydrazine and the hydrazide groups were treated chemoselectively and regioselectivly.[225]

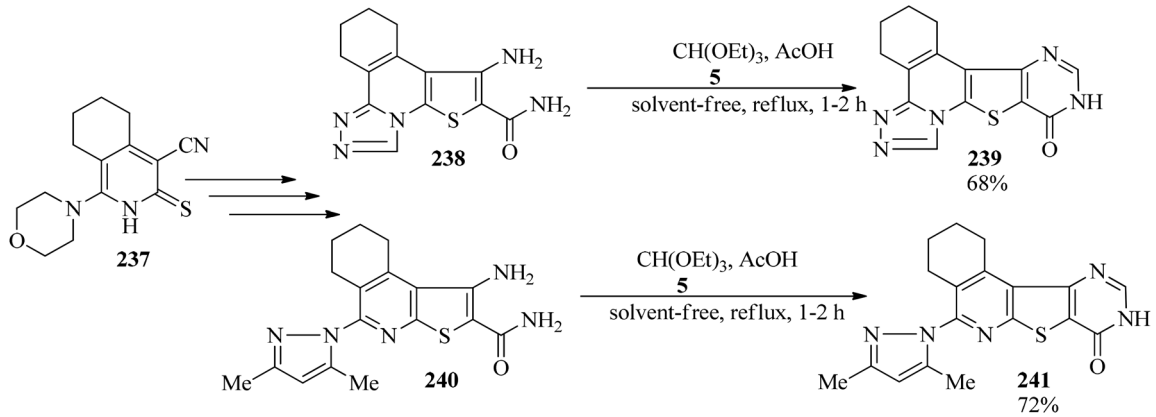
2.26. Synthesis of quinolones

In 2012, Yadav *et al.* developed a simple and green method for the synthesis of 4(1*H*)-quinolones *via* a two-step reaction. At first, the one-pot three-component condensation reaction of arylamines (**230**), Meldrum's acid (**231**), and TMOF (**4**) by 1-butyl-3-methylimidazolium bromide [bmim]Br as ionic liquid catalyst at 40 ± 2 °C obtained arylaminomethylene-1,3-dioxane-4,6-dione (**232**) in 68–94% yield in 2 h. After purifying, the resulting products underwent a cyclization reaction along with the elimination of acetone and CO_2 using [bmim]BF_4 or [bmim]OTf at 80 ± 2 °C in a 2 h period to afford 4(1*H*)-quinolones (**233**) (Scheme 63). The results revealed the better utility of [bmim]OTf in comparison with [bmim]BF_4.[226]

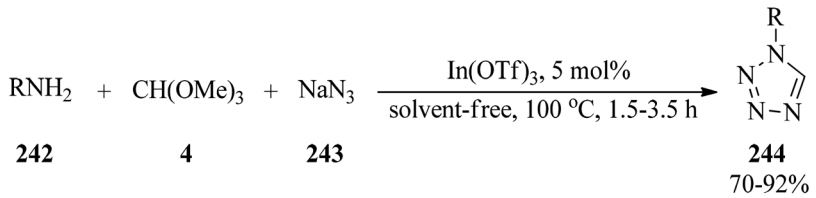
In 2018, Kanaani and Nasr-Esfahani prepared and characterized maleic anhydride coated magnetite nanoparticles (Fe_3O_4@APTES-MAH NPs) and nanorod vanadatesulfuric acid (VSA NRs) as Brønsted acid nanocatalysts. Subsequently, their catalytic activity was examined for the synthesis of new 4-iminoquinolines (**236**) *via* the one-pot three-component reaction of equimolar amounts of 2-aminobenzonitrile (**234**), orthoesters (**4**, **5**), and active methylenes (**235**) under solvent-free conditions at 80 °C. In this reaction the influence of different parameters, such as the type of catalyst and orthoesters, was examined. It was found that both VSA NRs and Fe_3O_4@APTES-MAH NPs catalysts yielded the corresponding 4-iminoquinolines (**236**) in good to excellent yields. VSA NRs in comparison with Fe_3O_4@-APTES-MAH NPs slightly improved the reaction times and yields (Scheme 64). They discovered that, among different orthoesters, TEOF was more effective. Short reaction times, high yields, simple purification of the products, the inexpensiveness, stability, recyclability and reusability of the catalysts are some of the advantages of this method.[227]

2.27. Synthesis of isoquinoline derivatives

1,2,3,4-Tetrahydro-10-oxopyrimido[4′,5′:4,5]thieno[2,3-*c*][1,2,4]triazolo[3,4-*a*]isoquinoline (**239**, 68%) and 5-(3,5-dimethylpyrazol-1-yl)-1,2,3,4-tetrahydropyrimido[4′,5′:4,5]thieno[2,3-*c*]isoquinolin-8(9*H*)-one (**241**, 72%) were synthesized *via* the ring closure of triazolo and pyrazolothienotetrahydroisoquinoline (**238**, **240**), derived from key precursors beginning from 4-cyano-1-morpholin-4-yl-5,6,7,8-tetrahydroisoquinoline-3(2*H*)thione

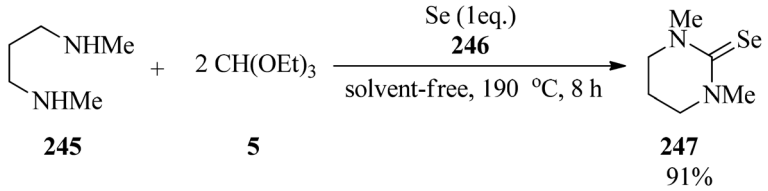


Scheme 65 The synthesis of isoquinolines with the aid of TEOF.



R= Bn, *n*-Bu, *t*-Bu, cyclohexyl, Ph, 4-MePh, 2-OMePh, 2,3-Me_2Ph, 4-FPh, 2-ClPh, 2-Cl-3-FPh, 3-NO_2Ph, 4-CO_2EtPh, 4-vinylaniline, 2-pyridyl, furfurylamine, (*S*)-1-phenylethylamine

Scheme 66 The preparation of substituted-1*H*-1,2,3,4-tetrazoles.



Scheme 67 Selenourea synthesis by the condensation of amines, TEOF, and Se.

(**237**), with TEOF (**5**) using a few drops of glacial acetic acid under reflux conditions for 1–2 h (Scheme 65). The synthesized products were examined and evaluated as antimicrobial agents.[228]

2.28. Synthesis of 1-substituted-1*H*-1,2,3,4-tetrazoles

Indium triflate [$In(OTf)_3$, 5 mol%] as a highly efficient Lewis acid catalyst, catalyzed the one-pot three-component condensation reaction of amines (**242**), TMOF (**4**), and sodium azide (**243**) under solvent-free conditions at 100 °C to furnish 1-substituted-1*H*-1,2,3,4-tetrazoles (**244**)[229–245] in good to excellent yields (70–92%) within 1.5–3.5 h. Both electron-donating and electron-withdrawing anilines yielded the products in high yields. The catalytic system also proceeded well with heterocyclic amine and aliphatic amines (Scheme 66).[245] On the other hand, the reaction of substituted anilines, TEOF, and trimethylsilyl azide[209,246] also afforded **244** using $FeCl_3$ (20 mmol%) under solvent-free conditions at 70 °C within 5–7 h in 87–95% yields.[246]

2.29. Synthesis of selenoureas

Selenoureas (**247**) were obtained by a novel three-component condensation reaction from primary or secondary amines (**245**), TEOF (**5**) and metallic selenium (**246**) (Scheme 67).[247]

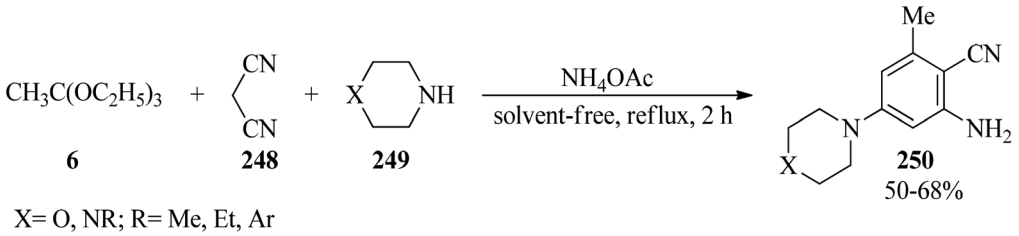
2.30. Synthesis of piperazinyl pyridines

In 2000, Rao *et al.* described a new simple method for the synthesis of 2-amino-3-cyano-5-*N*-substitued piperazinyl pyridines (**250**) *via* the condensation reaction of TEOAc (**6**), malononitrile (**248**), and *N*-substituted piperazine (**249**) in a 2 : 1 : 1 molar ratio in the presence of excess of ammonium acetate (5 moles) under reflux conditions at 90–92 °C for 2 h in moderate yields (50–68%) (Scheme 68). The products were obtained by a simple filtration and recrystallization from ethylacetate/*n*-hexane. Elemental and spectral data (FT-IR, PMR) confirmed the structures of the isolated compounds.[248]

2.31. Synthesis of pyrimidine derivatives

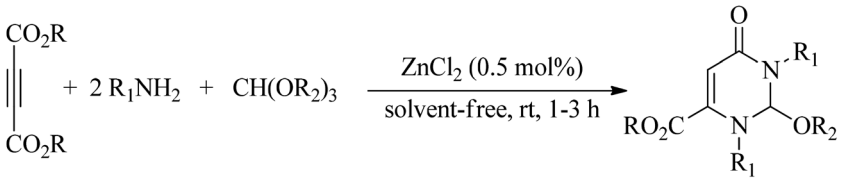
In 2010, Nagarajan and Reddy prepared substituted pyrimidine derivatives (**253**) *via* the one-pot three-component condensation reaction of acetylenedicarboxylates (**251**), amines (**252**), and orthoformates (**4**, **5**) with a molar ratio of 1 : 2 : 1 in the presence of $ZnCl_2$ (0.5 mol%) under solvent-free conditions at room temperature in 27–80% yields within 1–3 h (Scheme 69).[249]

In 2006, Toche *et al.* presented a two-step procedure for the synthesis of 4-amino-5-(4-bromobenzoyl)-3-ethyl-2(1*H*)-pyrimidone (**257**). First, the domino three-component condensation reaction of 4-bromobenzoylacetonitrile (**254**), mono-



X= O, NR; R= Me, Et, Ar

Scheme 68 Synthetic route to substituted piperazinyl pyridines.



251 **252** **4, 5** **253**
27-80%

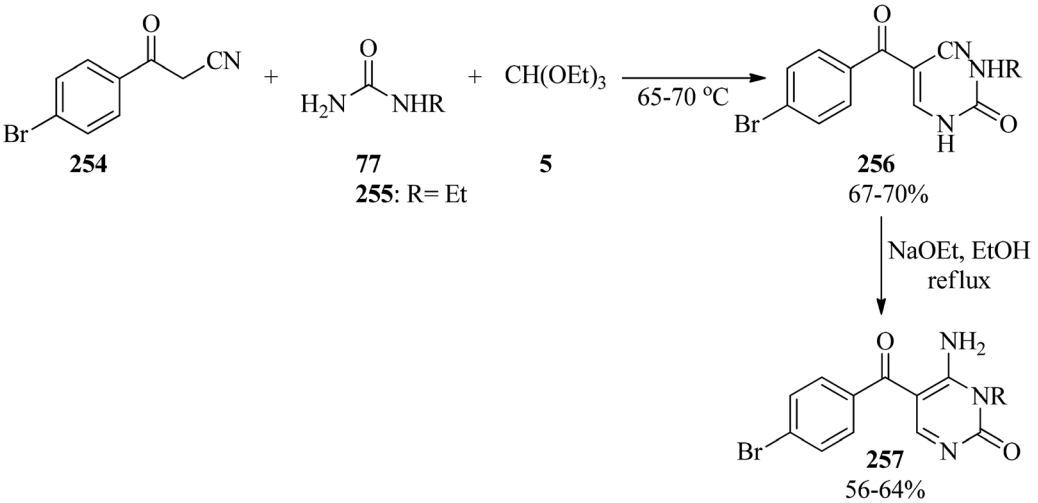
R, R_2= Me, Et
R_1= Et, *n*-Pr, 4-OMePh, 4-NO_2Ph, 2-OMe-5-MePh, 2,5-Et_2Ph, 3,4-F_2Ph, 2-Cl-4-BrPh, 2-Br-4-FPh, 2-Cl-4-BrPh, 2,4,6-Me_3Ph, 2,4,6-Br_3Ph, 2,6-Br_2-4-MePh, 2,6-Br_2-4-MePh

Scheme 69 The synthesis of substituted pyrimidine derivatives.

alkylated ureas (**77**, **255**), and TEOF (**5**) at 65–70 °C yielded enamine intermediates (**256**). Subsequently, the resultant precipitate (which dissolved in EtOH/NaOEt under reflux conditions) underwent an intramolecular cyclization reaction and dissolved in refluxing ethanol to produce **257** in 56–64% yield (Scheme 70). The compounds were evaluated for their insect repellent activity against *Sitophilus oryzae* (Coleoptera, Curculeonidae).[250]

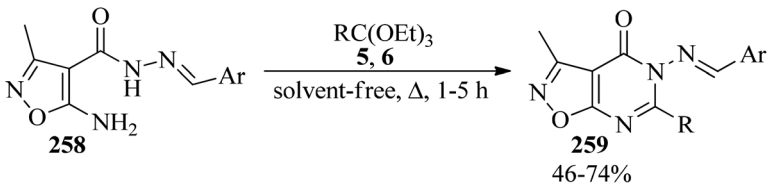
1,2-Oxazolo[5,4-*d*]pyrimidin-4(5*H*)-ones (**259**) were obtained in 46–74% yields *via* the ring-closure reaction of 1,2-oxazole-4-carbohydrazides (**258**) with boiling orthoesters (**5**, **6**) under solvent-free conditions within 1–5 h (Scheme 71). The *in vitro* mycobacterial and cytotoxicity activities of the products were screened against *Mycobacterium fortuitum* in an MABA test, and lung (A549) and fibroblasts (L929) cell lines, respectively.[251]

Ethyl-substituted 2-(4-bromo-phenyl)amino-3-amino-pyrazolo[3,4-*d*]pyrimidin-4-one (**260**) was refluxed in the presence of TEOF (**5**) and *p*-TSA, as catalyst, in order to obtain 2-ethyl-8-(4-bromophenyl)-pyrazolo[3,4-*d*][1,2,4]8*H*-triazolo[2,3-*a*] 4*H*-pyrimidin-4-one (**261**) in 95% yield (Scheme 72).[252] The



254 **77** **5** **256**
255: R= Et
67-70%
257
56-64%

Scheme 70 The domino synthesis of 4-amino-5-(4-bromobenzoyl)-3-ethyl-2(1*H*)-pyrimidones.



258 **259**
46-74%

Ar= Ph, 4-OHPh, 4-OMePh, 4-MePh, 4-CF_3Ph, 4-ClPh, 2,4-Cl_2Ph, 3,4-Cl_2Ph, 4-NO_2Ph
R= H, Me

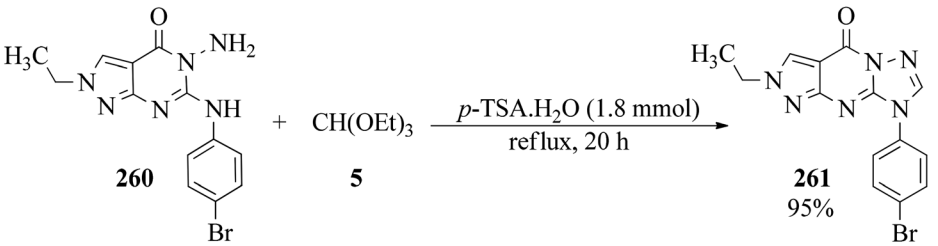
Scheme 71 Ring closure of 1,2-oxazole-4-carbohydrazides with orthoesters.

products have previously been reported as potential anti-inflammatory–analgesic agents.[253]

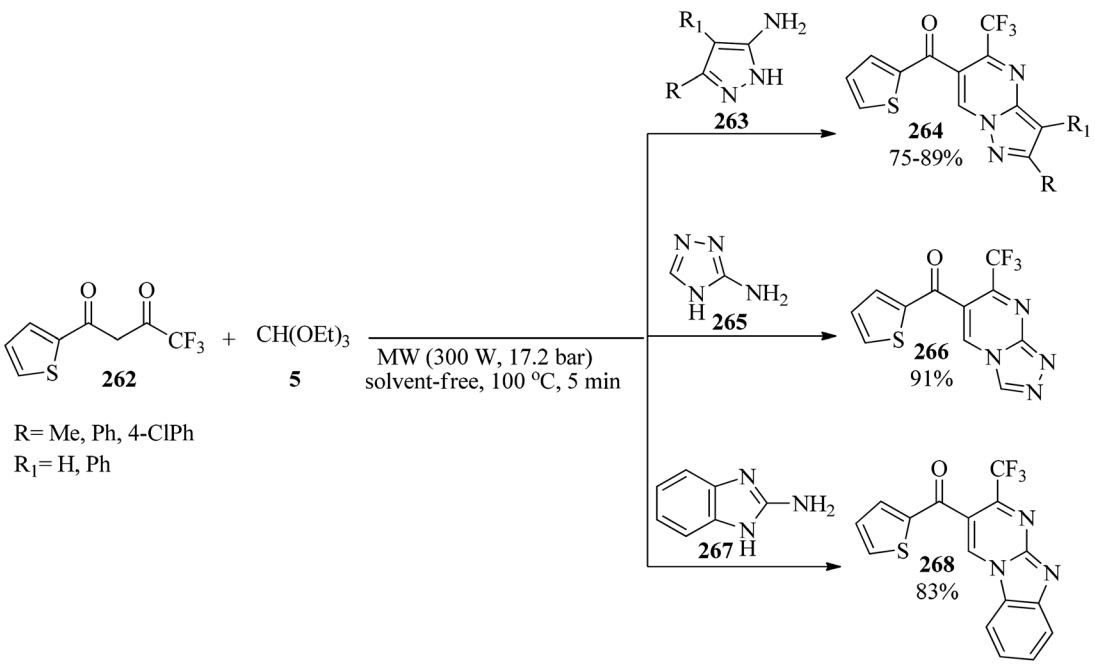
Due to the key role of fluorine-containing heterocyclic products in biological and pharmacological activities,[254–256] and also the development of new functional groups,[257–263] in 2008, 5-(trifluoromethyl)-pyrazolo[1,5-*a*]pyrimidines (**264**), 6-thienoyl-7-(trifluoromethyl)-[1,2,4]triazolo[4,3-*a*]pyrimidine (**266**) and 6-thienoyl-7-(trifluoromethyl)benzimidazo[1,2-*a*]pyrimidine (**268**) were synthesized *via* the condensation reaction of 4,4,4-trifluoro-1-(thien-2-yl)butane-1,3-dione (**262**), TEOF (**5**) and the appropriate heterocyclic amines, such as aminopyrazoles (**263**), 3-amino-l,2,4-triazole (**265**), and 2-aminobenzimidazole (**267**), respectively, by pressurized microwave irradiation (300 W, 17.2 bar) at 100 °C under solvent-free conditions for 5 min (Scheme 73).[264]

In 2000, 2-amino-4,5-di-(2-furyl)furan-3-carbonitrile (**269**)[265] was utilized as a key starting material for the synthesis of furo[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines (**273**). At first, the condensation of (**269**) with TEOAc (**6**) under reflux conditions for 5 h obtained the corresponding 2-ethoxyimine (**270**) in good yield (65%) which upon treatment with hydrazine hydrate (**271**) was converted into (**272**). Eventually, the cyclocondensation of (**272**) with TEOF (**5**) under reflux conditions for 8 h achieved (**273**) in 73% yield (Scheme 74). The products were purified by simple filtration and crystallization and were finally characterized by their correct analyses and spectroscopic data (IR and ^{1}H NMR).[266]

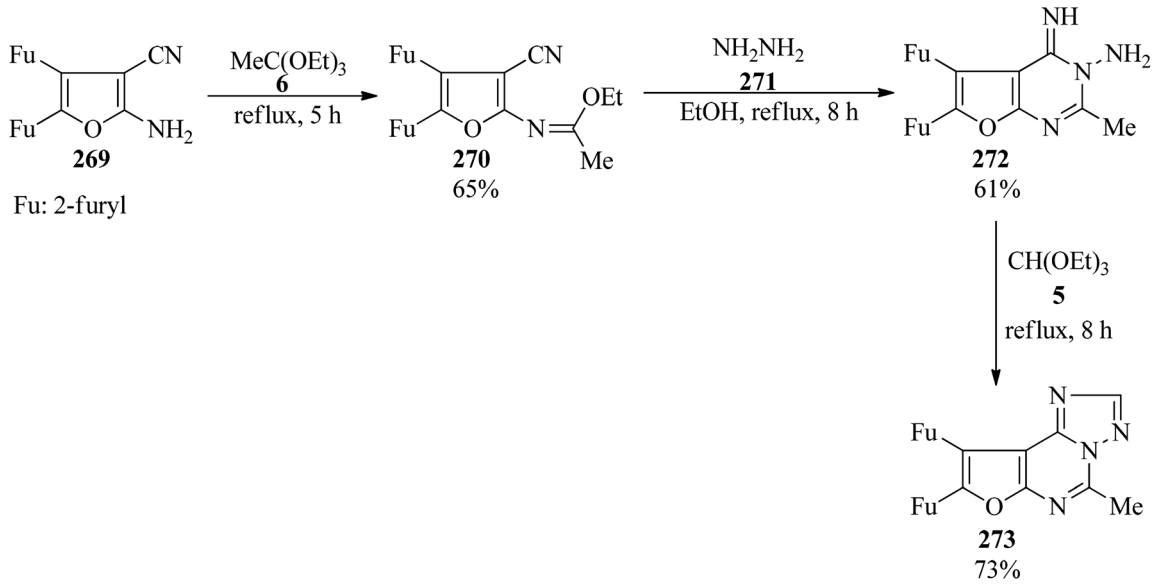
In 2000, Dave and Shah synthesized 7*H*-1,2,4-triazolo[1,5-*c*]pyrrolo[3,2-*e*]pyrimidines (**277**) *via* the domino multicomponent reaction of 1,4-disubstituted 2-amino-3-cyanopyrroles (**274**),[267] TEOF (**5**), and hydrazine hydrate (**271**) under reflux conditions. This reaction proceeded through the condensation of **274** with **5** under reflux conditions to generate 1,4-disubstituted *N*-ethoxymethylene-2-amino-3-cyanopyrroles (**275**) in 3–4 h in good yields (70–88%) which led to 5,7-disubstituted 3-amino-4-imino-7*H*-pyrrolo[2,3-*d*]pyrimidines (**276**) (60–88%) on hydrazinolysis with **271** within 3.5–4 h. Finally, the cyclocondensation reaction of **276** with one carbon donor moiety, such as **5**, afforded product (**277**)[268,269] in 6–7 h in weak to high yields (42–70%) (method A). On the other hand, the similar reaction of 4-hydrazino-7*H*-pyrrolo[2,3-*d*]pyrimidines (**278**)[270] with **5** and **271** (method B) obtained the [4,3-*c*] isomers (**279**),



Scheme 72 The synthesis of 2-ethyl-8-(4-bromophenyl)-pyrazolo[3,4-*d*][1,2,4]8*H*-triazolo[2,3-*a*]4*H*-pyrimidin-4-ones.



Scheme 73 The preparation of some fluorinated pyrimidines.



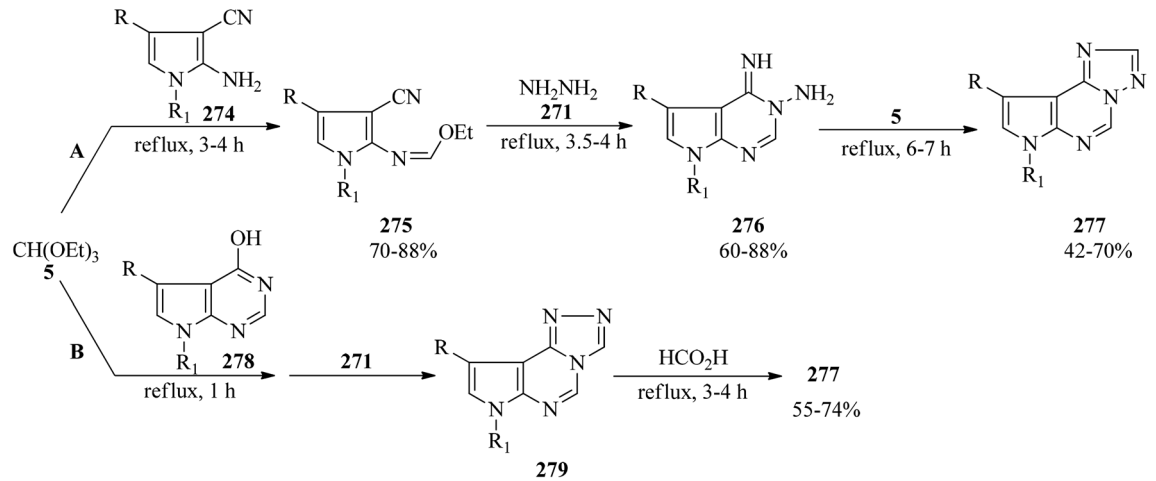
Scheme 74 Preparation procedure of furo[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines.

which using formic acid were isomerized to the thermodynamically more stable [1,5-*c*] isomers (**277**) through Dimroth rearrangement (Scheme 75). Notably, the latter procedure was faster and more efficient.[269]

In 2005, Rashad *et al.* prepared several derivatives containing thieno[2,3-*d*]pyrimidine systems with potent anti-inflammatory properties: *e.g.* 11-hydrazino-5,6-dihydronaphtho[1′,2′:4,5]-thieno[2,3-*d*]pyrimidines were refluxed with triethyl orthoesters for 10 h to obtain 8,9-dihydronaphtho[1′,2′:4,5]thieno[3,2-*e*][1,2,4]triazolo[4,3-*c*]pyrimidines[271,272] in 72–86% yields; which were isomerized to the thermodynamically more stable triazolo[1,5-*c*]pyrimidines under heating in either acid or basic media.[272] Thieno[2,3-*b*]-pyridine-2-carbohydrazide (**280**) was refluxed with TEOF (**5**) for 4 h to form 3-aminopyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidines (**281**) in 73% yield (Scheme 76).[273]

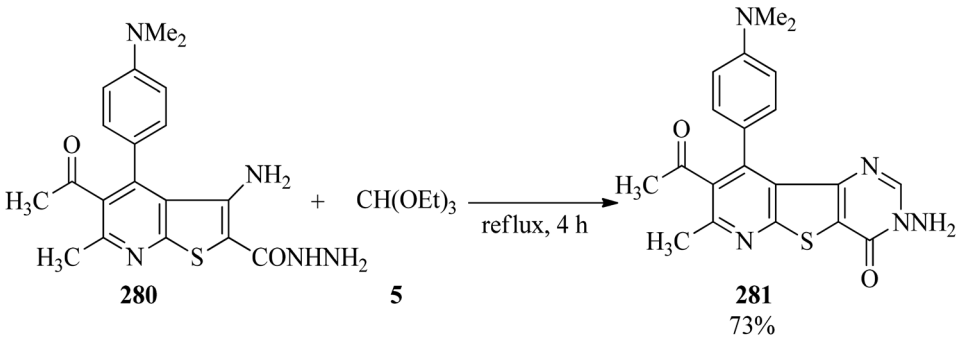
2,4-Dimethyl-7-benzyledineamino-8-oxopyrimido[4′,5′:4,5]-seleno[2,3-*b*]pyridine (**283**) was synthesized upon cyclo-condensation of benzylidene carbohydrazone (**282**) with TEOF (**5**) by a few drops of acetic acid under reflux conditions for 1 h in 51% yield (Scheme 77).[274]

In 2004, three pathways were presented for the synthesis of pyrido[2,3-*d*]pyrimidines (**286**) through the one-pot three-component condensation reaction of equimolar amounts of 6-aminouracils (**284**), alkyl nitriles (**285**), and TEOF (**5**) in (a)

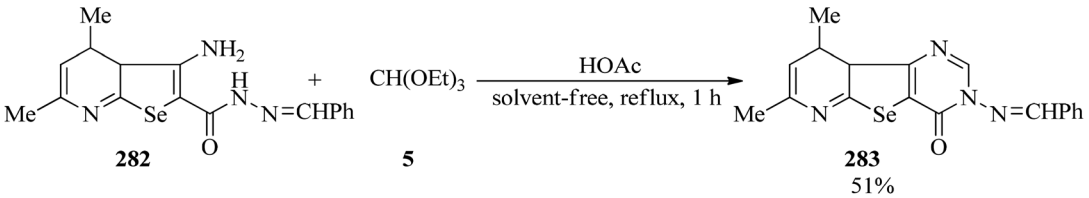


R= Ph, 4-OMePh, 4-ClPh, 4-OClPh
R_1= 4-OMePh, 4-OClPh, 4-BrPh, 4-IPh

Scheme 75 The synthesis of 7*H*-1,2,4-triazolo[1,5-*c*]pyrrolo[3,2-*e*]pyrimidines.



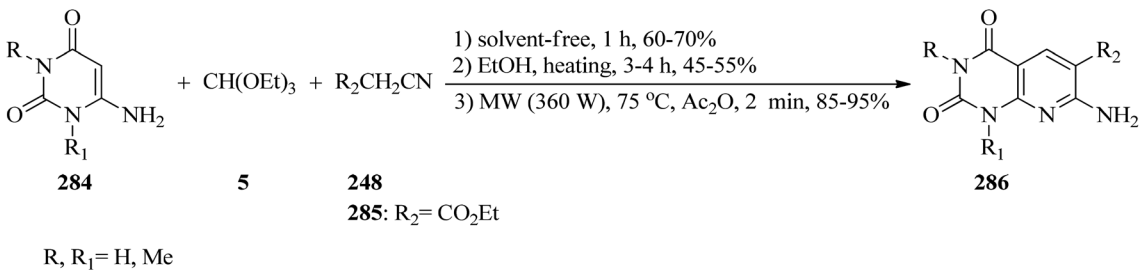
Scheme 76 Formation of 3-aminopyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidines.



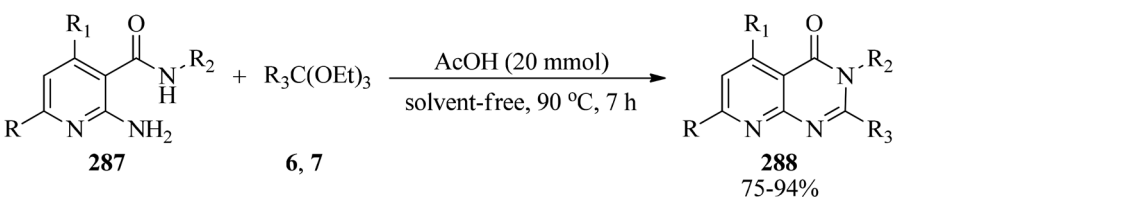
Scheme 77 Synthetic approach for 2,4-dimethyl-7-benzyledineamino-8-oxopyrimido[4′,5′:4,5]-seleno[2,3-*b*]pyridine.

solvent-free conditions, (b) using ethanol as a solvent under heating thermal conditions, and (c) under microwave irradiation with 360 W power at 75 °C utilizing acetic anhydride (Scheme 78), for which the third method had a great effect on decreasing the time and increasing the yield.[275] Some compounds have different pharmacological activities, such as antibacterial,[276] antitumor,[277] cardiotonic, hepatoprotective, and antihypertensive,[278] and antibronchitic effects.[279]

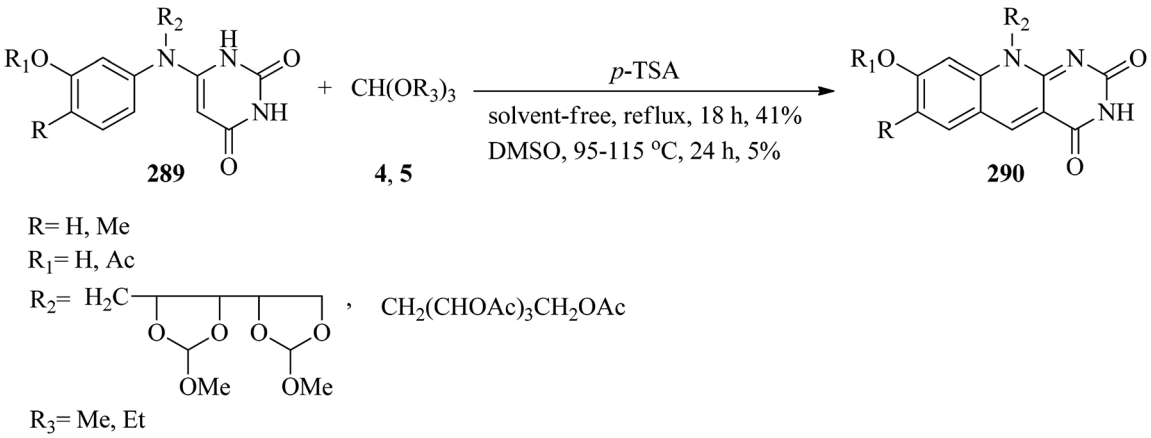
2,3,5,7-Substituted-pyrido[2,3-*d*]pyrimidin-4(3*H*)-ones (**288**) were synthesized in good to excellent yields (75–96%) from the cyclocondensation reaction of 2-amino-*N*,6-substituted phenyl-4-substituted nicotinamides (**287**) with orthoesters (**6**, **7**) by



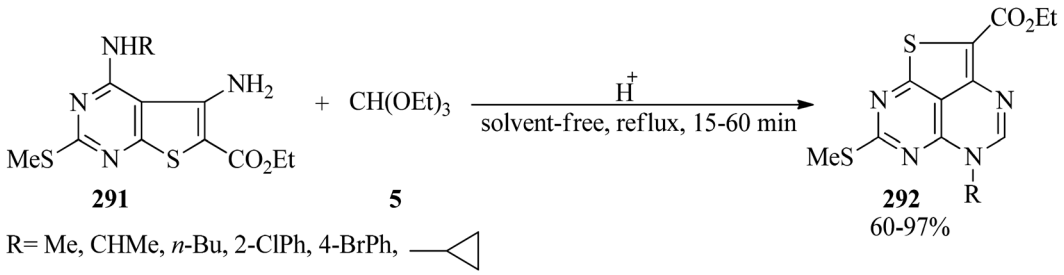
Scheme 78 Pyrido[2,3-*d*]pyrimidine synthetic routes under three sets of conditions.



Scheme 79 The formation of substituted-pyrido[2,3-*d*]pyrimidin-4(3*H*)-ones.



Scheme 80 Cyclization by TEOF to obtain *N*-containing heterocycles.



Scheme 81 The preparation of 7-(methylthio)-5*H*-1-thia-3,5,6,8-azaacenaphthylene-2-carboxylates.

catalytic amounts of glacial acetic acid at 90 °C for 7 h (Scheme 79). All the resultant compounds (**288**) were examined for antibacterial activity against Gram +ve and Gram −ve bacteria.[280]

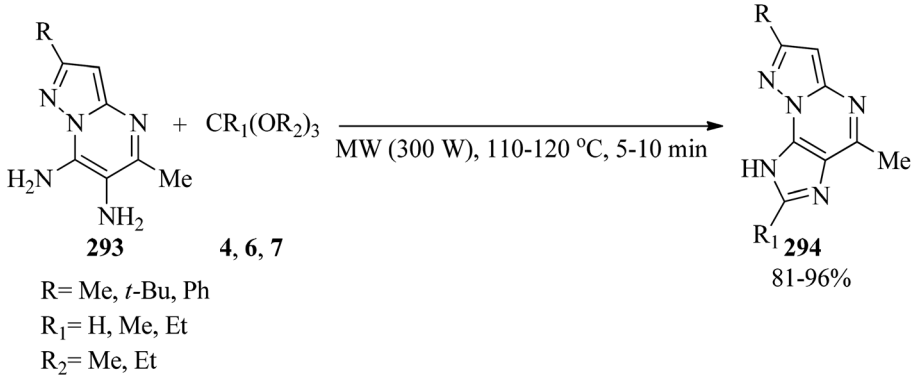
The cyclization of compounds (**289**) with excess amounts of trialkyl orthoformates (**4**, **5**) resulted in products (**290**) using catalytic amounts of *p*-TSA under reflux conditions or in DMSO as solvent at 95–115 °C in 5–41% yields within 18–24 h (Scheme 80).[281]

Acid-mediated cyclocondensation of ethyl 5-amino-4-(substituted amino)-2-(methylthio)thieno[2,3-*d*]pyrimidine-6-carboxylates (**291**) with TEOF (**5**) resulted in ethyl 5-substituted 7-(methylthio)-5*H*-1-thia-3,5,6,8-azaacenaphthylene-2-carboxylates (**292**) in 60–97% yields within 15–60 min (Scheme 81).[282]

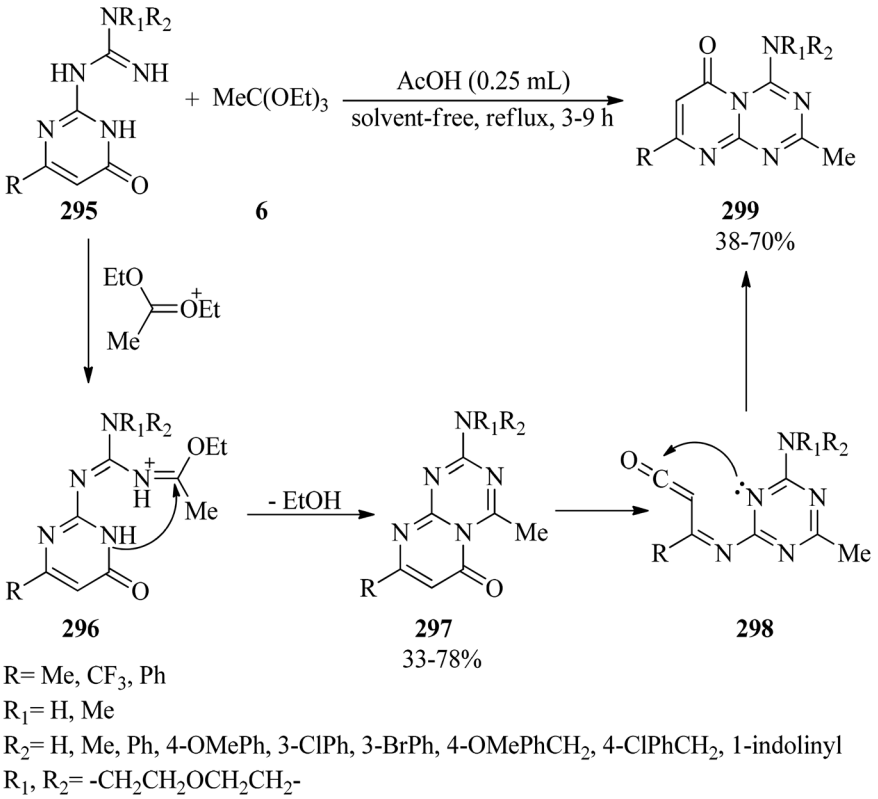
In 2016, Castillo and co-workers developed pyrazolo[5,1-*b*]purines (**294**) by a microwave-assisted (300 W) cyclocondensation of pyrazolo[1,5-*a*]pyrimidine-6,7-diamines (**293**) with orthoesters (**4**, **6**, **7**) at 110–120 °C under solvent-free conditions in good to excellent yields (81–96%) within 5–10 min (Scheme 82).[283]

2.32. Synthesis of triazin derivatives

In 2012, Sachdeva and co-workers synthesized 2-amino-4-methylpyrimido[1,2-*a*][1,3,5]triazin-6-ones (**297**) and 4-amino-2-

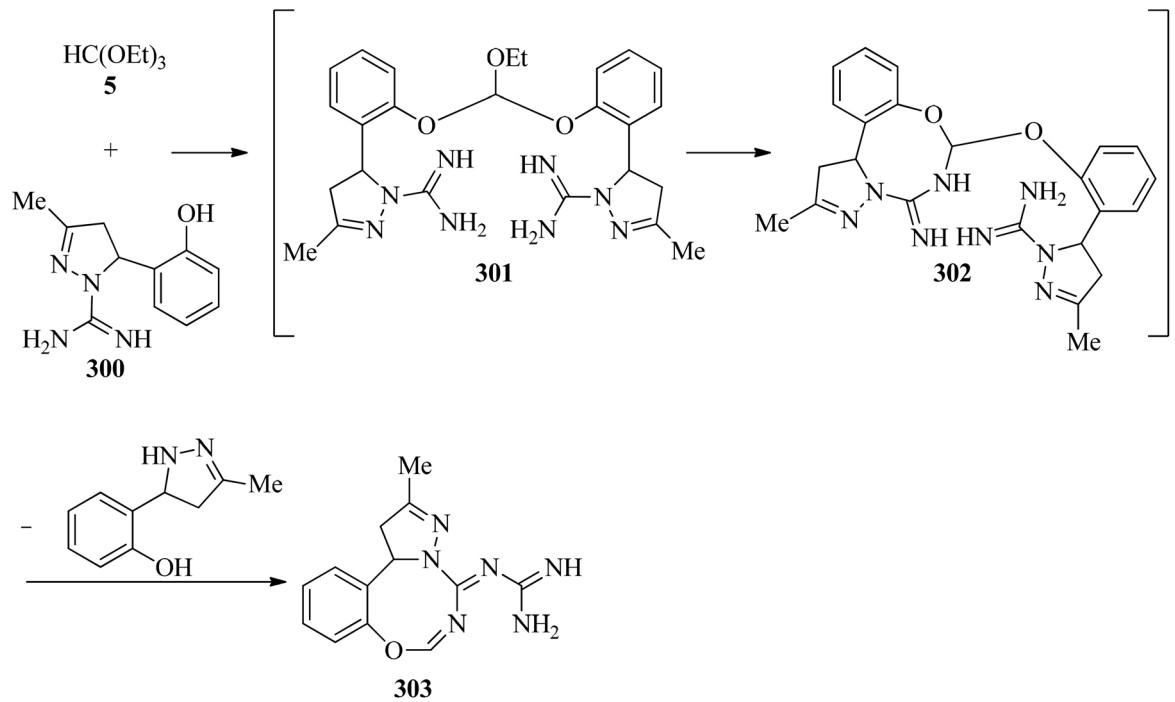


Scheme 82 The microwave-assisted synthesis of pyrazolo[5,1-*b*]purines.

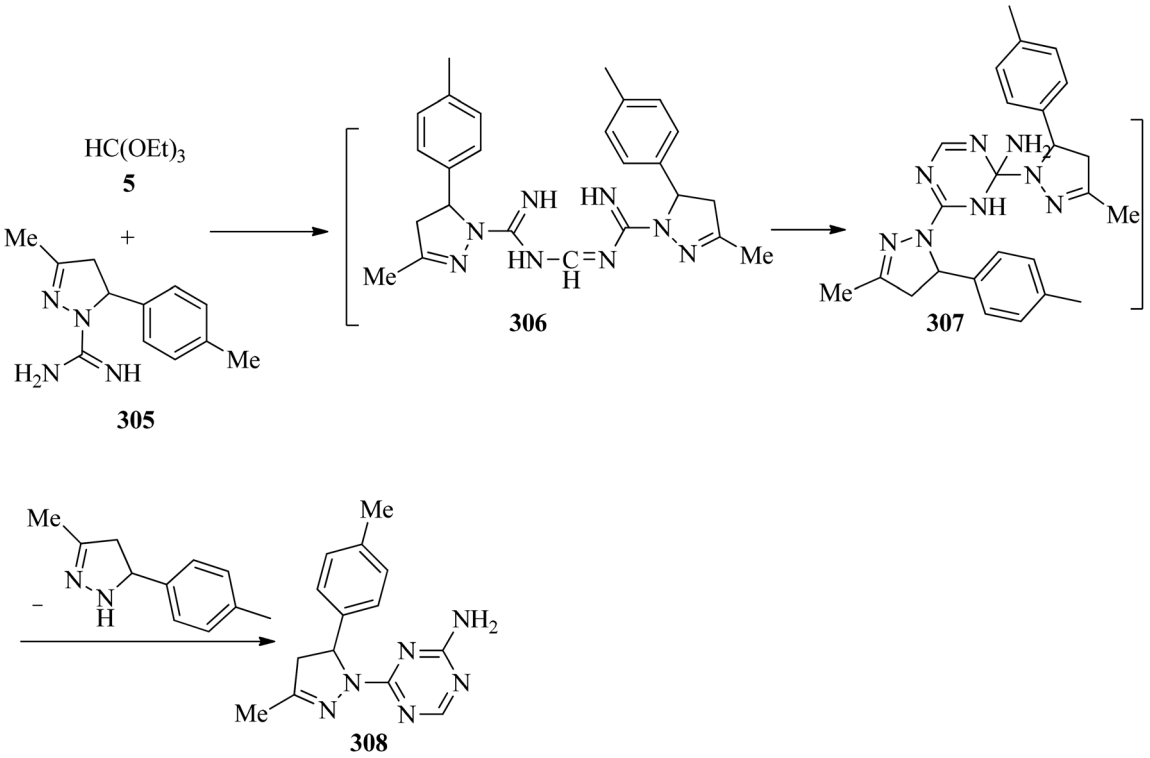


Scheme 83 The synthesis of 4-amino-2-methylpyrimido[1,2-*a*][1,3,5]triazin-6-ones.

methylpyrimido[1,2-*a*][1,3,5]triazin-6-ones (**299**) utilizing 1-(6-oxo-1,6-dihydropyrimidin-2-yl)guanidines (**295**) as starting materials. Firstly, the guanidines (**295**) were condensed with triethylorthoacetate (**6**) in glacial acetic acid under reflux conditions to form an iminium ion intermediate (**296**). Subsequent intramolecular cyclization along with the elimination of



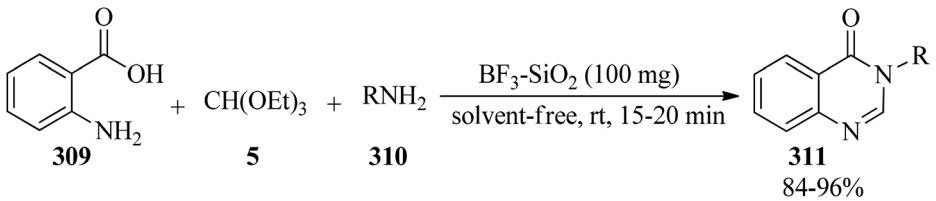
Scheme 84 The synthesis of dihydro-pyrazolo benzoxadiazocin-5-ylidene guanidines.



Scheme 85 Formation procedure for 2-amino-4-[4,5-dihydro-3-methyl-5-(4-methylphenyl)-1*H*-pyrazol-1-yl]-1,3,5-triazine.

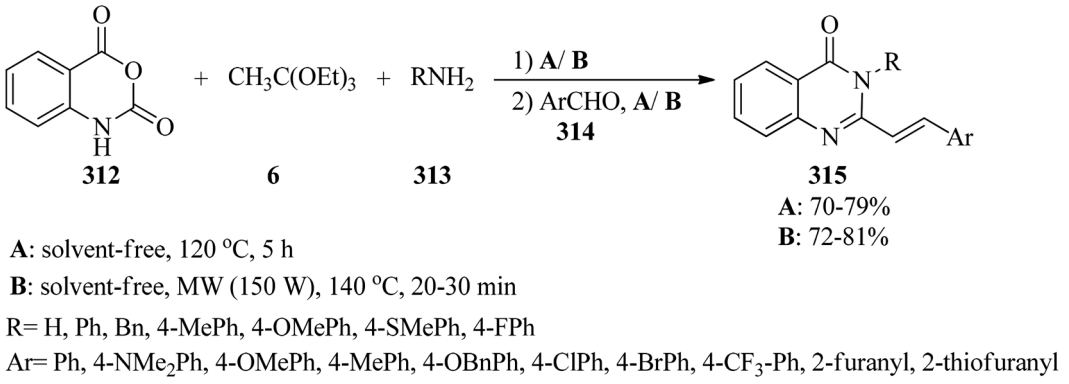
ethanol yielded product (**297**); which was followed by thermal rearrangement for unsubstituted (NH_2), alkyl-substituted ($NHCH_3$), and aralkyl guanidines ($NHCH_2Ph(R)$) *via* ring opening of pyrimidine at the amide moiety to produce the ring-open triazine carbenone (**298**). Finally, intramolecular nucleophilic attack of the N-1 nitrogen of 1,3,5-triazine on the carbonyl functional group and annulation, respectively, achieved product (**299**) (Scheme 83). It is noteworthy that the guanidines (**295**) containing a tertiary amino group such as $-N(CH_3)_2$, $-N(CH_2CH_2)_2O$, indolino and or aryl secondary amino substituent groups, *e.g.* –NHPh, NHPh(3-Br), NHPh(3-Cl), NHPh(4-OMe) produced mainly the corresponding product **297**.[284]

In 2002, Světlík and Liptaj synthesized new heterocyclic ring systems including a pyrazole moiety, such as *N*-[(5*E*)-1,12-*b*-dihydro-substituted-5*H*-pyrazolo[1,5-*e*][1,3,5]-benzoxadiazocin-5-ylidene]guanidine (**303**) or 2-amino-4-[4,5-dihydro-3-methyl-5-(4-methylphenyl)-1*H*-pyrazol-1-yl]-1,3,5-triazine (**308**). The products (**303**) were obtained *via* the re-esterification of TEOF (**5**) with phenolic hydroxys of two equivalents of 4,5-dihydro-3-methyl-5-(2-hydroxyphenyl)-1*H*-pyrazole-1-carboximidamide (**300**) to produce orthoester (**301**) which underwent a cyclization reaction with the vicinal amidine moiety to form an oxadiazocine system (**302**). Then, the nucleophilic attack of the adjoining exocyclic imine nitrogen on the carbon atom of the other amidine group enabled C1-transfer, which was followed by loss of the disubstituted pyrazoline component to obtain (**303**) (Scheme 84). On the other hand, the condensation reaction of 4,5-dihydro-3-methyl-5-(4-methylphenyl)-1*H*-pyrazole-1-carboximidamide acetate (**305**) with **5** under reflux conditions gave intermediate (**306**) which was followed by a cyclization reaction to get (**307**). The reaction was completed by the formation of 2-amino-4-[4,5-dihydro-3-methyl-5-(4-methylphenyl)-1*H*-pyrazol-1-yl]-1,3,5-triazine (**308**) for 1 h in 65% yield through the elimination of the disubstituted pyrazoline component (Scheme 85).[285]

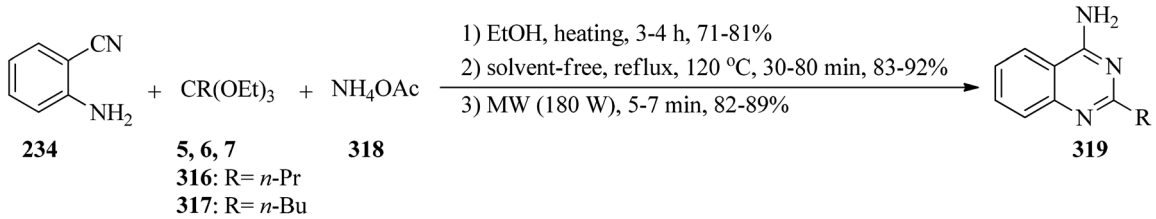


R= Ph, 2-MePh, 4-MePh, 4-OMePh, 4-BrPh, 4-ClPh, 4-NO_2Ph, 3,4-Br_2Ph, 2,4-Br_2Ph, Bn, *n*-Bu, *t*-Bu

Scheme 86 The preparation of 4(3*H*)-quinazolinones.



Scheme 87 Tandem preparation route for (*E*)-3-substituted-2-styrylquinazolin-4(3*H*)-ones.



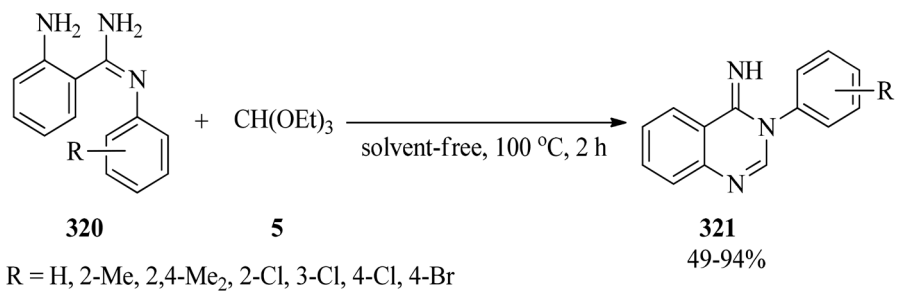
Scheme 88 The synthesis of 2-substituted 4-aminoquinazolines.

2.33. Synthesis of quinazoline derivatives

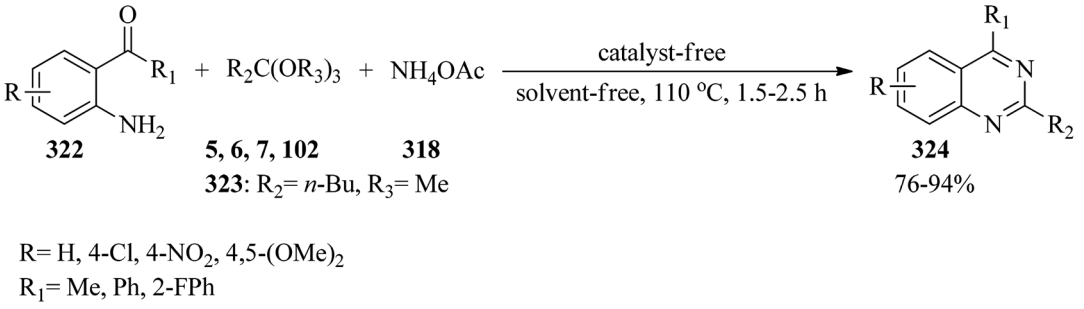
In 2010, Wu *et al.* prepared 4(3*H*)-quinazolinones (**311**) in excellent yields (84–96%) and very short reaction times (15–20 min) *via* the one-pot three-component condensation reaction of anthranilic acid (**309**),[286–293] TEOF (**5**) and primary amines (**310**) under solvent-free conditions at room temperature by silica-supported boron trifluoride (BF_3–SiO_2, 100 mg) as a green, recyclable and reusable heterogeneous catalyst (Scheme 86).[293] Microwaves (210 W) accelerated the formation of 4(3*H*)-quinazolinones in the absence of solvent *via* the one-pot three-component condensation reaction of anthranilic acid, orthoesters, and ammonium acetate using a catalytic amount of antimony(III) chloride ($SbCl_3$, 1 mol%) in excellent yields (89–93%) within 5 min. According to the results, both aliphatic and aromatic substituents on orthoesters indicated no significant effect on the reaction times and the yields, but generally, the presence of a substituent on orthoesters prolonged the reaction times.[294] Quinazolin-4(3*H*)-ones could also be obtained from the condensation of anthranilic amide with orthoesters using ionic liquids under ultrasound irradiation in 20–25 min in 82–91% yields.[209]

The catalyst/solvent-free one-pot three-component reaction of isatoic anhydrides (**312**), TEOAc (**6**), and various amines (**313**) in equimolar amounts obtained 4(3*H*)-quinazolinones (**311**) through two different pathways: (a) utilizing microwave irradiation (150 W) at 140 °C, and (b) under conventional heating at 120 °C. This method developed through the Knoevenagel condensation reaction of 4(3*H*)-quinazolinones with aromatic aldehydes (**314**) by a tandem four-component condensation reaction to achieve (*E*)-3-substituted-2-styrylquinazolin-4(3*H*)-ones (**315**).[295,296] The results affirmed that MW assisted the reaction progression much better than conventional heating (Scheme 87).[296]

In 2006, three pathways were presented for the synthesis of 2-substituted 4-aminoquinazolines (**319**) *via* the uncatalyzed one-pot three-component condensation reaction of 2-



Scheme 89 The synthesis of 3-arylquinazolin-4(3*H*)imines.



Scheme 90 The synthesis of 2,4-disubstituted quinazolines.

aminobenzonitrile (**234**), orthoesters (**5**, **6**, **7**, **316**, **317**), and ammonium acetate (**318**) in (a) ethanol as solvent under heating conditions, (b) under reflux conditions without a solvent, and (c) microwave irradiation in the absence of a solvent. The results showed that, in comparison with the two premier routes, microwave irradiation has an important influence on decreasing the reaction time (5–7 min) (Scheme 88).[297]

In 2015, a catalyst and solvent-free one-step method was reported for the synthesis of 3-arylquinazolin-4(3*H*)imines (**321**) by heating 2-amino-*N*′-arylbenzamidines (**320**) with TEOF (**5**) (Scheme 89).[298]

In 2015, Bhat and co-workers, presented an efficient and eco-friendly method for the synthesis of 2,4-disubstituted quinazolines (**324**) in high yields (76–94%) *via* the catalyst/solvent-free one-pot three-component reaction of 2-aminoaryl ketones (**322**), trialkyl orthoesters (**5**, **6**, **7**, **102**, **323**), and ammonium acetate (**318**) in a 1 : 1.5 : 1.5 molar ratio at 110 °C within 1.5–2.5 h (Scheme 90). In this study, in order to investigate the scope and limitations of the presented procedure, the reaction was carried out by diverse substituted 2-aminoaryl ketones and trialkyl orthoesters. The reaction was performed by 2-aminobenzophenones and 2′-aminoacetophenones. It was found that the transformation with 2′-aminoacetophenones proceeded faster, which may be ascribed to the steric effect resulting from the aryl substitution, which decreases the reactivity of the carbonyl group. Remarkably, 2-aminobenzophenones containing both electron-withdrawing and electron-donating groups on the aniline ring provided good results. However, 2′-aminoacetophenones including a strong electron-donating substituent on the aniline ring obtained poor yield. It was also found that the reactivity of aliphatic orthoesters was better than orthobenzoate as an aromatic orthoester, which could probably be attributed to the steric effect of different substituents on the orthoester functional group. It was found that the chain length of the orthoalkylates did not have a significant influence on the reaction results.[299]

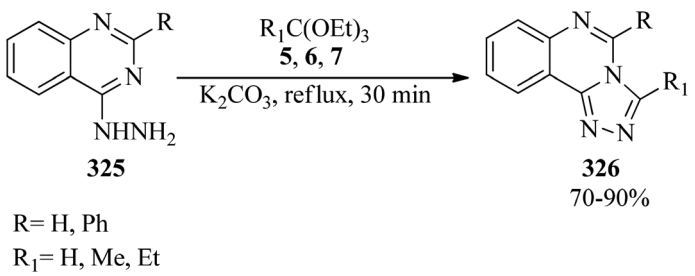
In 1970, Potts and Brugel synthesized 3-substituted-triazolo[4,3-*c*]quinazolines (**326**) in good yields (70–90%) *via* the cyclization reaction of 4-quinazolylhydrazine (**325**) with orthoesters (**5**, **6**, **7**) using potassium carbonate under reflux conditions for 30 min (Scheme 91).[300]

2.34. Synthesis of macrocycles

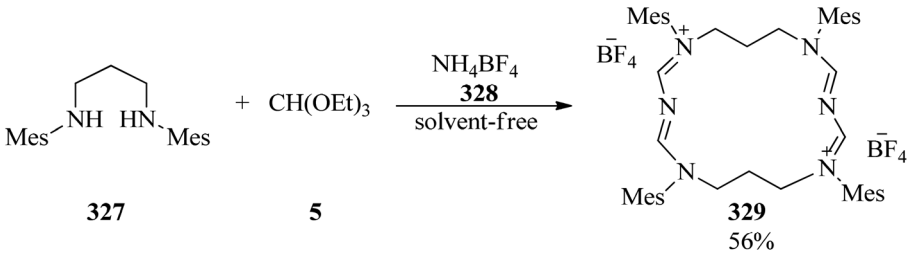
The three-component cyclocondensation of *N*,*N*′-dimesitylpropane-1,3-diamine (**327**), TEOF (**5**), and ammonium tetrafluoroborate (**328**) was accomplished to produce the main product macrocycle (**329**) under solvent-free conditions (Scheme 92) and 1,3-dimesityl-3,4,5,6-tetrahydropyrimidin-1-ium tetrafluoroborate in the presence of ethanol as solvent.[301]

3. Orthoester reactions in aqueous media

One of the most interesting challenges to chemists is the reaction performance in water media as a cheap, readily available, safe, and non-toxic solvent. This effective and completely green medium causes the ready hydrolysis of some substrates and/or products, such as orthoesters. In fact, reports of the transformation of orthoesters in aqueous media are very rare (8 references) that are discussed below.

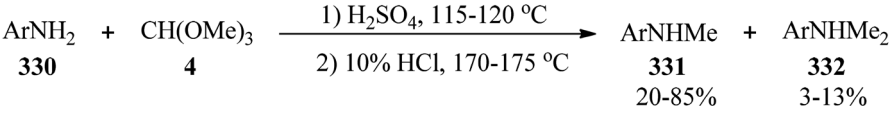


Scheme 91 Formation procedure of 3-substituted-triazolo[4,3-*c*]quinazolines.



327 5 329 56%

Scheme 92 *N*-Bearing macrocycle synthesis.



Ar= 3-IPh, 4-OMePh, 3-SMePh, 3,4,5-$(OMe)_3$Ph, 4-NO_2Ph, 2,4-Cl_2Ph

Scheme 93 The aqueous alkylation of amines.

3.1. Synthesis of formamidines

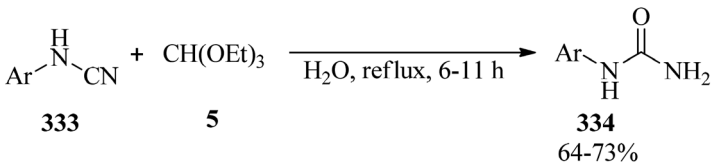
In 2013, a simple, eco-friendly, and catalyst-free methodology was reported for the *N*-formylation of amines by TEOF under ultrasound irradiation in water.[302] Symmetric formamidines could be also prepared *via* the *N*-formylation reaction of amines with TMOF using tin(II) chloride–choline chloride ($ChCl/SnCl_2$, 30 mol%), as catalyst and reaction media, in water at 70 °C for 20–160 min in 30–80% yields.[127]

3.2. Alkylation reactions

The treatment of anilines (**330**) with TMOF (**4**) utilizing sulfuric acid at 115–120 °C resulted in the formation of an *N*-methylformanilide intermediate; which without isolation was hydrolyzed by aqueous hydrochloric acid (10%) at 170–175 °C to obtain *N*-methylated anilines (**331**) in weak to good yields (20–85%) and in some cases along with dimethylated derivatives (**332**) in minor yields (3–13%) as by-products (Scheme 93).[303]

3.3. Synthesis of *N*-arylureas

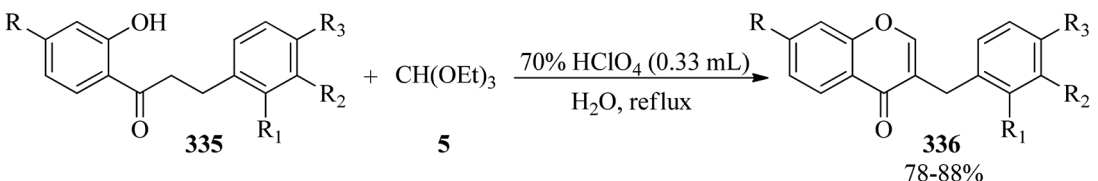
In 2014, a facile and green procedure was presented for the preparation of *N*-arylureas (**334**) through the hydration of various aromatic cyanamides (**333**) with TEOF (**5**) in refluxing water in 64–73% yields within 6–11 h (Scheme 94). It should be noted that the cyanamides including electron-withdrawing groups prolonged reaction times.[304]



333 5 334 64-73%

Ar= Ph, 4-MePh, 4-OMePh, 2-MePh, 3-BrPh, 4-ClPh, 4-NO_2Ph, 1-naphthyl

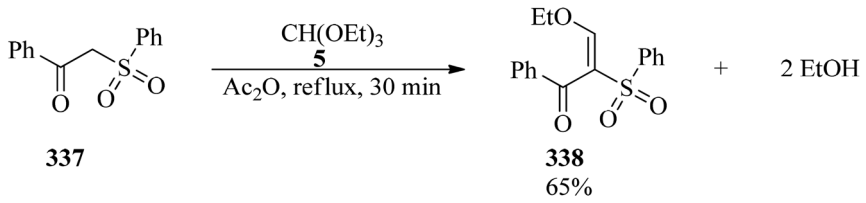
Scheme 94 The water-mediated synthesis of *N*-arylureas.



335 5 336 78-88%

R= H, OH, OMe, OBn
R_1, R_2= H, OMe
R_3= H, OMe, Cl

Scheme 95 The preparation of homoisoflavones.



337 338 65%

Scheme 96 The synthesis of ethoxymethylenes.

3.4. Synthesis of homoisoflavones

In 2008, Rao *et al.* described a process for the preparation of homoisoflavones (**336**)[305] in good yields (78–88%) *via* the ring closure of TEOF (**5**) with 1-(2-hydroxyphenyl)-3-phenylpropane-1-ones (**335**) in the presence of 70% perchloric acid, which was followed by aqueous hydrolysis of the intermediate perchlorates (Scheme 95). The *in vitro* antioxidant and anti-fungal activities of the products were examined using the superoxide (NBT) and agar cup methods, respectively.[306]

3.5. Synthesis of benzoxazoles

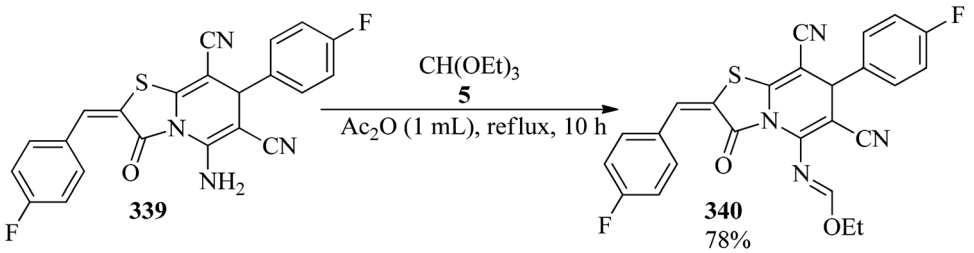
Maleki *et al.* synthesized and characterized Ag (1.5%)@TiO_2 (0.1 mL) as a heterogeneous, hazardless, eco-friendly, and reusability nanocatalyst. Then its catalytic activity was examined for the preparation of benzoxazole[214,307] *via* the condensation reaction of orthoesters with 2-amino phenol in water at room temperature within very short reaction times (4–10 min) and at excellent yields (82–93%).[307]

3.6. Synthesis of 1-substituted-1*H*-1,2,3,4-tetrazoles

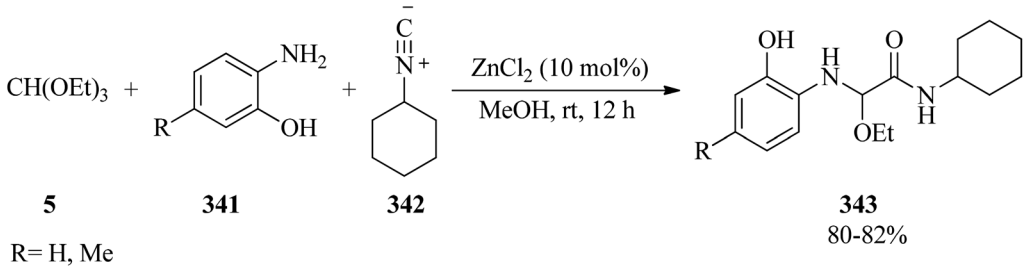
In 2018, Sharghi *et al.* synthesized iron-doped acidic multi-walled carbon nanotubes (Fe@acidic-MWCNs). The characterization by inductively coupled plasma (ICP), X-ray diffraction (XRD), scanning electron microscopy (SEM), atomic force microscopy (AFM), Raman, and FT-IR analysis confirmed that the iron nanoparticles were supported on the acidic multi-walled carbon nanotubes (MWCNs). Subsequently their catalytic activity was probed for the preparation of 1-substituted-1*H*-tetrazoles *via* the one-pot three-component reaction of substituted anilines, TEOf, and sodium azide in water at 50 °C within 1–3.5 h with excellent yields (80–95%). This reaction was carried out faster in the presence of electron-donating anilines than with electron-withdrawing analogs.[308] Copper(II) nanoparticles loaded on magnetic core (Fe_3O_4@SiO_2/aza-crown ether–Cu(II)) as a new and highly effective magnetic nanocomposite catalyst in water at 100 °C also facilitated this transformation within 40–70 min in excellent yields (87–98%).[309]

4. Orthoester reactions in organic solvents

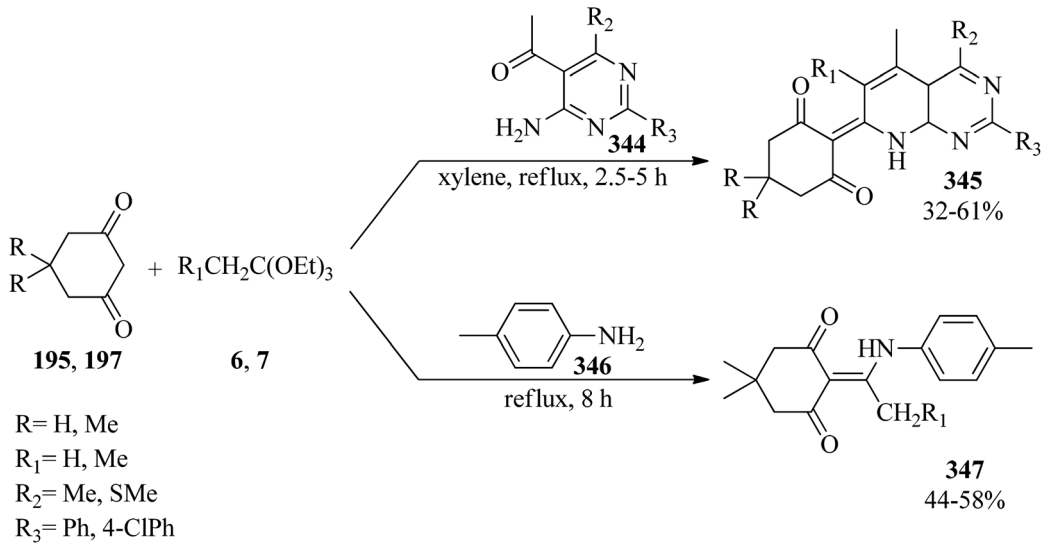
Organic solvents, as carbon-based liquids, are conventional common media to accomplish organic transformations. There are too many organic liquids categorized as solvents. The subdivision of the vast list of solvents could be based on polarity, melting point range, volatility, chemical inertness towards substrates and reagents, or solubility of the existing components



Scheme 97 The synthesis of an anti-*Staphylococcus aureus* heterocycle.



Scheme 98 The Ugi reaction to obtain acetamides.

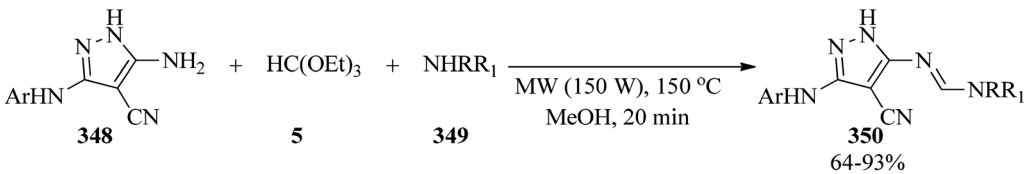


Scheme 99 The synthesis of enamine-bearing heterocycles.

in the reaction. In addition to the solvent characteristics, the chemical and physical nature of each reaction member, and the effective relationship between components and solvents determines the choice of reaction media. According to the detailed data below, most solvents utilized in orthoester-participating transformations are alcohols that dissolve many organic compounds as well as most orthoesters (20 reports). The subsequent grades belong to CH_2Cl_2 (16 cases), acetic anhydride (15 items), benzene and its halogen and alkyl substituted analogs (such as chlorobenzene, xylenes, and toluene, 11 cases), acetic acid (10 items), CH_3CN (8 cases), THF (5 points), ether and DMF (each with 3 cases), and dioxane (2 items). The other solvents reported in the literature survey are DMSO, pyridine, CCl_4, and ionic liquid that each appeared in just one study.

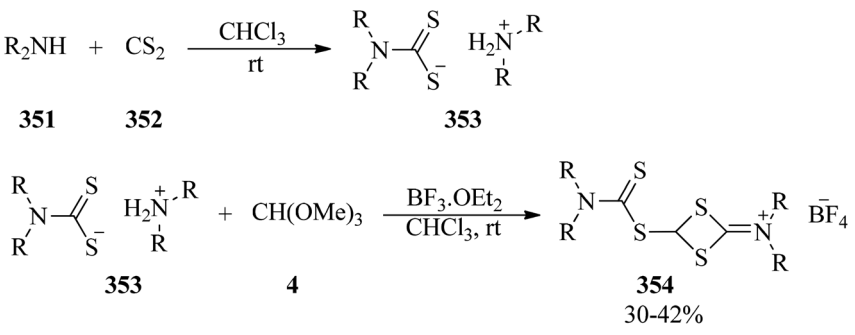
4.1. Synthesis of ethoxymethylenes

In 2000, Elkholy *et al.* reported the synthesis of 1-benzoyl-1-phenylsulfonyl-2-ethoxyethene containing an ethoxymethylene group (**338**),[310–315] as yellow crystals, by the reaction of 1-phenyl-2-(phenylsulfonyl)ethanone (**337**) with TEOF (**5**) in refluxing acetic anhydride. In this reaction 2 moles of ethanol were removed (Scheme 96).[315]



Ar= Ph, 3-MePh, 4-MePh, 4-EtPh, 2-OMePh, 4-OMePh, 2-OEtPh, 4-OEtPh, 3-CF_3Ph, 4-FPh, 4-ClPh, 3-BrPh, 4-BrPh
R, R_1= -$CH_2CH_2OCH_2CH_2$-, -$CH_2(CH_2)_2CH_2$, -$CH_2(CH_2)_3CH_2$, -$CH_2CH_2NMeCH_2CH_2$-

Scheme 100 Preparing novel *N*-pyrazolylformamidines.



R= Et, -$CH_2(CH_2)_4CH_2$-, -$CH_2(CH_2)_3CH_2$-

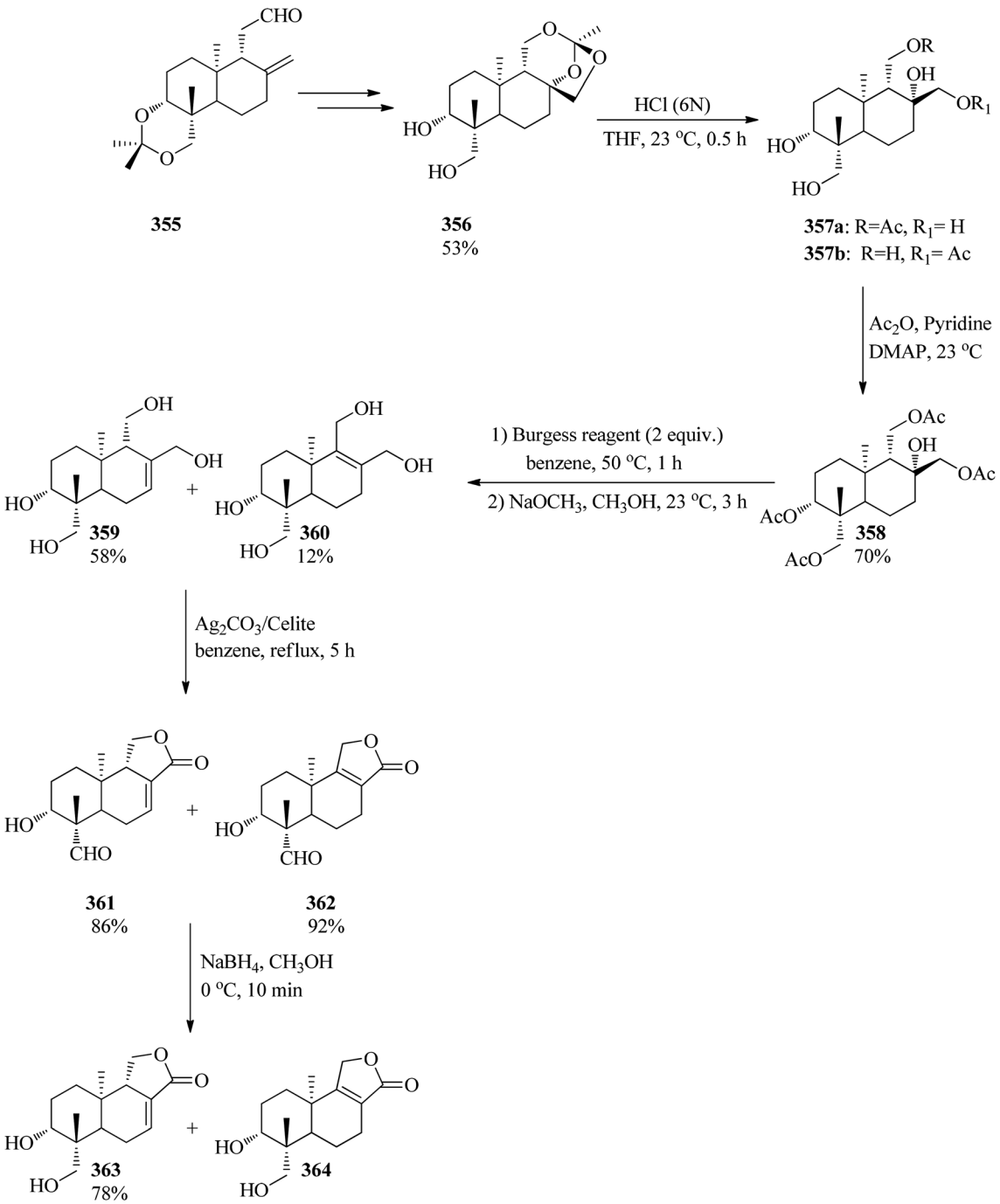
Scheme 101 Dithiocarbamic acid salt synthetic approach.

4.2. Synthesis of ethoxymethylene amino derivatives

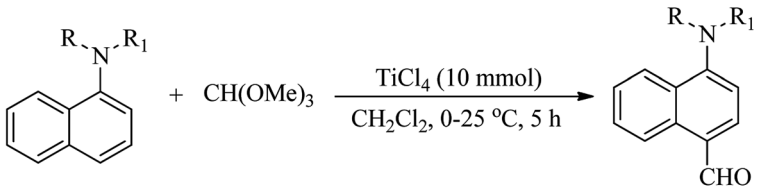
In 2002, 2-(4-fluorophenyl)methylidene-7-(4-fluorophenyl)-2,3-dihydro-5-ethoxymethyleneamino-7*H*-3-oxo-thiazolo[3,2-*a*]-pyrimidin-6,8-dicarbonitrile containing an ethoxymethylene amino motif (**340**)[316–328] was synthesized *via* the condensation of 5-amino-2-(4-fluorophenyl)methylidene-7-aryl-6,8-dicyano-3-oxo-2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyridine (**339**) with TEOF (**5**) in refluxing acetic anhydride (10 mL) (as catalyst and solvent) (Scheme 97). Pure (**340**) was obtained from recrystallization from cold water in 78% yield. Compound (**340**) exhibited highly antimicrobial activity against *Staphylococcus aureus* (NCTC-7447).[328]

4.3. Synthesis of acetamides

The three-component Ugi reaction of 2-aminophenols (**341**), cyclohexyl isocyanide (**342**), and TEOF (**5**) in equimolar amounts was accomplished using $ZnCl_2$ (10 mol%) in methanol at room temperature to construct *N*-cyclohexyl-2-(2-hydroxyphenylamino)-2-ethoxyacetamides (**343**) for 12 h in high yields (80–82%) (Scheme 98).[329]



Scheme 102 The asymmetric total synthesis of (+)-iresin and (−)-isoiresin.



365 **4** **366**
75-89%

ArNRR$_1$: Ar= Ph, 1-naphthyl, R= Me, Et, -C_5H_{10}-; R_1= Me, Et, *n*-Bu, -C_5H_{10}-

Scheme 103 The formylation of *N*,*N*-dialkylarylamines by TMOF.

4.4. Synthesis of enamines

In 2006, Komkov *et al.* investigated the reaction of cyclohexane-1,3-diones (**195**, **197**) and orthoesters (**6**, **7**) with various amines (**344**, **346**). It was found that the one-pot three-component condensation reaction of cyclohexane-1,3-dione (**195**) and orthoesters with 5-acetyl-4-aminopyrimidines (**344**) under reflux in *p*-xylene obtained a novel series of 7-(1,3-dioxocyclohex-2-ylidene)-7,8-dihydropyrido[2,3-*d*]pyrimidines (**345**) in 32–61% yields in 2.5–5 h, while the condensation of dimedone (**197**) and orthoesters with *p*-toluidine (**346**) progressed to generate enamine derivatives (**347**)[330–335] under reflux conditions within 8 h in 44–58% yields (Scheme 99).[336]

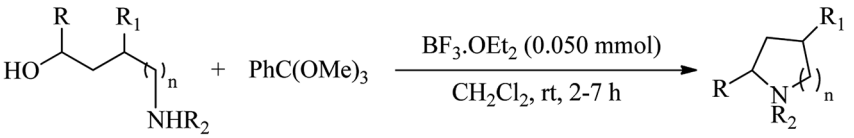
4.5. Synthesis of formamidines

Lim *et al.* designed the catalyst-free one-pot three-component condensation reaction of polysubstituted 5-aminopyrazoles (**348**), TEOF (**5**),[337] and cyclic secondary amines (**349**)[338] under microwave irradiation (150 W) at 150 °C in methanol in order to prepare novel *N*-pyrazolylformamidines (**350**) in 20 min in 64–93% yields (Scheme 100). Some of the synthesized products were found to inhibit interleukin-17 secretion in phenotypic *in vitro* evaluations.[339]

1,3-Bis-arylcarbamylformamidines were prepared *via* the reaction of *N*-arylureas with TEOF in boiling acetic anhydride in 85–90% yields.[340]

4.6. Synthesis of substituted 2-dialkyliminio-1,3-dithietane tetrafluoroborates

In 2015, a facile and straightforward methodology was presented for the synthesis of 4-(*N*,*N*-dialkyldithiocarbamato)-2-dialkyliminio-1,3-dithietane tetrafluoroborates (**354**) in 30–42% yields. In this paper, the condensation reaction of secondary aliphatic amines (**351**) with carbon disulfide (**352**) in $CHCl_3$ at room temperature first afforded dithiocarbamic acid salt (**353**) which upon treatment with TMOF (**4**) using $BF_3 \cdot OEt_2$ as catalyst in $CHCl_3$ at room temperature furnished (**354**) (Scheme 101). This reaction failed with some orthoesters, such as orthovalerate and trimethyl orthobenzoate.[341]



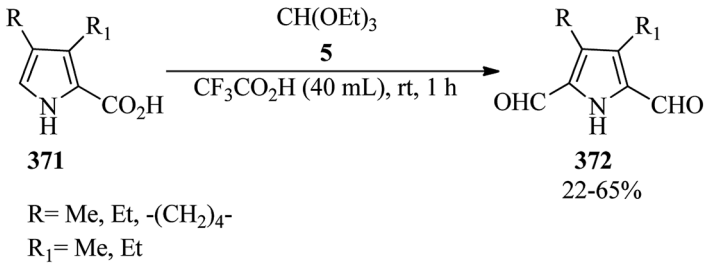
367 **102** **368**
62-87%

or or

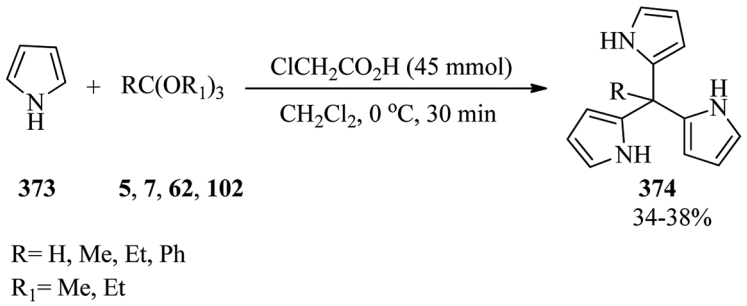
369 **370**
87-94%

n= 1, 2
R= CH_2Br, CH_2OTs, -$CH_2(CH_2)_3CH_2$-
R_1= H, Ph
R_2= Boc, Fmoc, Cbz
R_3= H, C_5H_{11}

Scheme 104 The synthesis of pyrrolidines and piperidines.



Scheme 105 The preparation of disubstituted pyrrole-2,5-dicarbaldehydes.



Scheme 106 Synthetic procedure for tri-(pyrrol-2-yl)alkanes.

4.7. Synthesis of lactones

In 2015, Wang and co-workers described the asymmetric total synthesis of (+)-isoiresin (**363**) and (−)-isoiresin (**364**) from (3*S*,5*aR*,7*aS*,8*R*,9*R*,11*aR*,11*bR*)-8-(hydroxymethyl)-3,8,11*a*-trimethyldecahydro-1*H*-3,5*a*-epoxynaphtho[1,2-*e*][1,3]dioxepin-9-ol (**356**) derived from readily available aldehyde (**355**). This transformation occurred *via* acidic hydrolysis (HCl, 6 N) of the orthoester (**356**) in THF at 23 °C for 30 min to form a mixture of monoacetate compounds (**357a** and **357b**) which underwent acetylation to produce the tetrakis-acetate (**358**). Subsequent regioselective dehydration of (**358**) by various dehydrating agents and then deacetylation resulted in (**359**) and (**360**) in different molar ratios, which upon the regioselective oxidative lactonization reaction using Fétizon reagent obtained (**361** and **362**). Finally, the reduction of the aldehyde functional group by $NaBH_4$ at 0 °C in methanol yielded (**363**) and (**364**) (Scheme 102).[342]

4.8. Synthesis of aminomethylene bisphosphonates

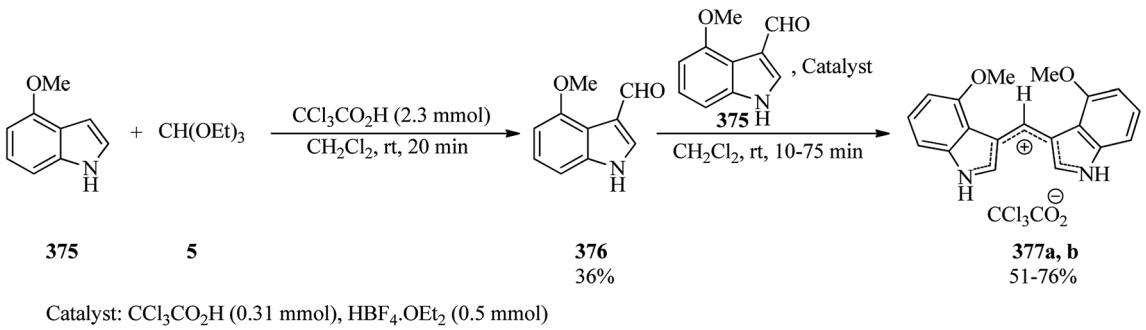
In 2012, Reddy *et al.* presented an effective, rapid and green method for the synthesis of aminomethylene bisphosphonates *via* the one-pot three-component reaction of amines, diethyl phosphite and TEOF in a 1 : 2 : 1 molar ratio using $Yb(PFO)_3$ (10 mol%) in the presence of ionic liquid [bmim][Cl] at 100 °C for 15–25 min in good to excellent yields (70–93%).[343]

4.9. Synthesis of 4-dialkylarylamino-1-naphthaldehyderivatives

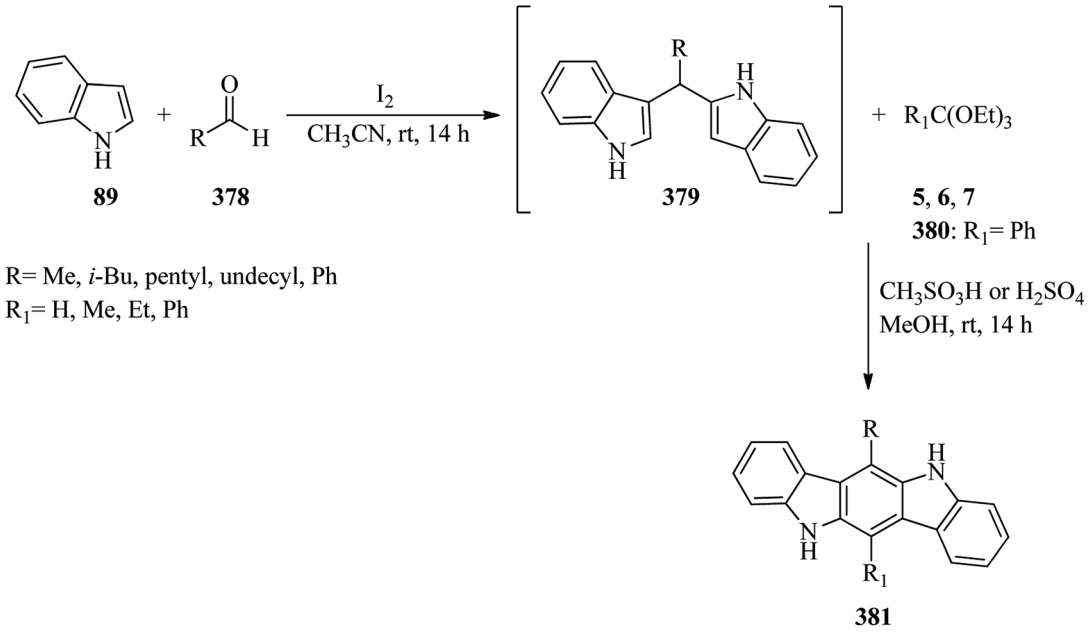
The reaction of *N*,*N*-dialkylarylamines (**365**) with TMOF (**4**) was accomplished using $TiCl_4$ (10 mmol) in CH_2Cl_2 at 0–25 °C to obtain the corresponding formyl derivatives (**366**) in 75–89% yields (Scheme 103).[344]

4.10. Synthesis of pyrrolidines and piperidines

Boron trifluoride diethyl etherate ($BF_3 \cdot OEt_2$, 0.050 mmol) catalyzed the cyclodehydration of *N*-carbamate-protected amino



Scheme 107 The synthesis of bis(indolyl)methane salts.



Scheme 108 The synthesis of substituted dihydroindolo[3,2-*b*]carbazoles.

alcohols (**367**) with trimethyl orthobenzoate (**102**) in CH_2Cl_2 at room temperature to get azaheterocycles such as pyrrolidines and piperidines within 2–7 h, in high yields (62–87%) (**368**). Replacing (**367**) with *N*-carbamate-protected amino vicinal diols (**369**) in refluxing CH_2Cl_2 yielded regio- and stereoselective prolinol derivatives (**370**) in excellent yields (87–94%) (Scheme 104).[345]

4.11. Synthesis of pyrrole derivatives

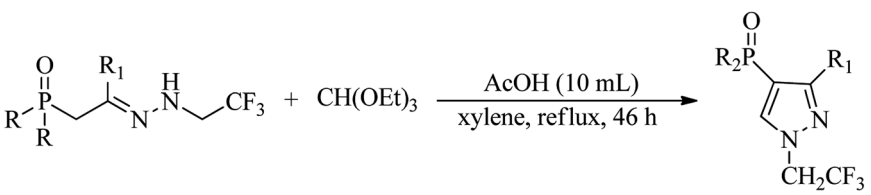
In 1998, Tardieux and co-workers presented a simple and mild one-step route for the synthesis of 3,4-disubstituted pyrrole-2,5-dicarbaldehydes (**372**) *via* the diformylation[346,347] reaction of β-substituted pyrrole-2-carboxylic acids (**371**) with TEOF (**5**) in trifluoroacetic acid, in a dual role of catalyst and solvent, at room temperature for 1 h in 22–65% yields (Scheme 105).[347]

Tri-(pyrrol-2-yl)alkanes (**374**) could be synthesized *via* the reaction of pyrrole (**373**) with orthoesters (**5**, **7**, **62**, **102**) using chloroacetic acid (45 mmol) in CH_2Cl_2 at 0 °C within 30 min, in 34–38% yields (Scheme 106). 5-Phenyl-4,6-dipyrrin has also been prepared in comparatively good yield (51%) through the reaction of pyrrole with trimethyl orthobenzoate by dichloroacetic acid (38 mmol) under similar conditions.[348]

4.12. Synthesis of indole derivatives

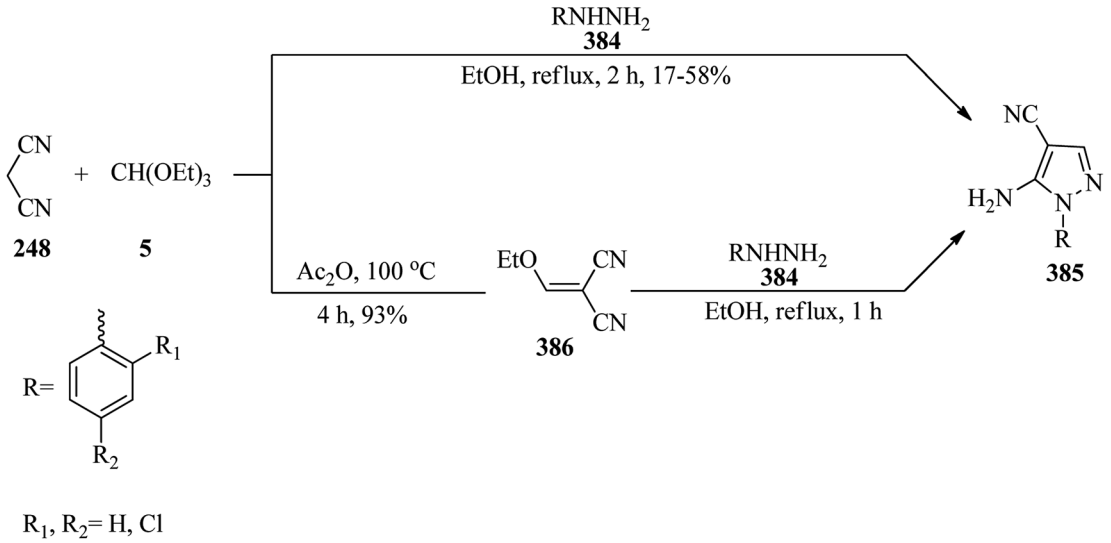
In 1990, indole-3-carbaldehyde (**376**) as pale yellow crystals was synthesized upon treatment of 4-methoxyindole (**375**) with TEOF (**5**) using trichloroacetic acid in CH_2Cl_2 at room temperature within 20 min in 36% yield. On the other hand, bis-benzo-annellated pentamethine cyanines such as bis(4-methoxyindol-3-yl)methyliumtrichloroacetate (**377a**) and bis(4-methoxyindol-3-yl)methyliumtetrafluoroborate (**377b**) were also synthesized in 51 and 76% yields under similar conditions using trichloroacetic acid and tetrafluoroboric acid diethyl ether ($HBF_4 \cdot OEt_2$), respectively (Scheme 107).[349]

In 2012, Khaksar and co-workers prepared symmetrical tris(indolyl)methanes[349,350] *via* a catalyst-free reaction of indoles with orthoesters in the presence of hexafluoro-2-propanol



R= Ph, $-OCH_2C(Me)_2CH_2O-$, $-OCH_2C(Me)(n\text{-}Pr)CH_2O-$
R_1= Me, *i*-Pr, Ph

Scheme 109 The formation of novel 1-fluorinated-4-phosphopyrazoles.



Scheme 110 The formation of substituted 5-aminopyrazole-4-carbonitriles.

(HFIP) at room temperature within 15–60 min in excellent yields (88–98%).[350]

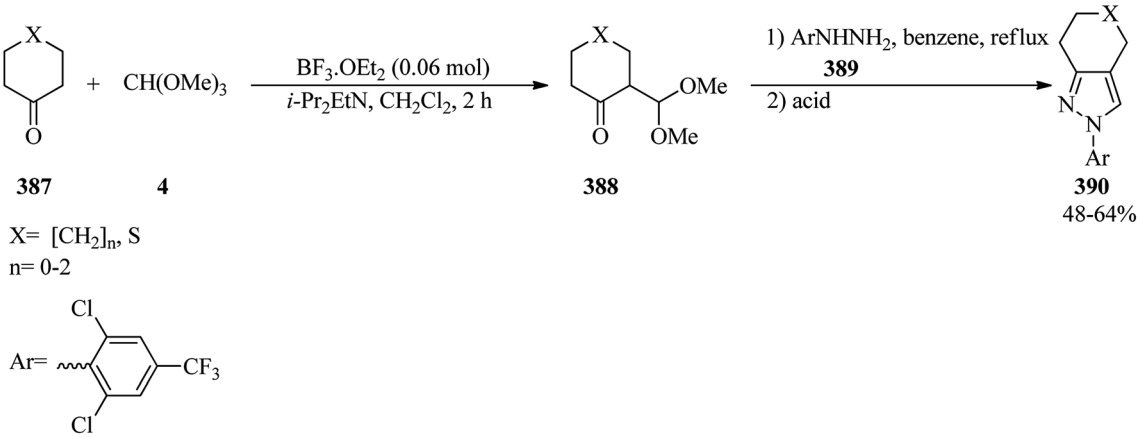
6-Monosubstituted and 6,12-disubstituted 5,11-dihydroindolo[3,2-*b*]carbazoles (**381**) were synthesized in 20–50% yields *via* the one-pot three-stage condensation reaction of indole (**89**) and aldehydes (**378**) using a catalytic amount of iodine; which underwent an acid-mediated intramolecular ring-closure reaction by orthoesters (**5**, **6**, **7**, **380**) in methanol at room temperature for 14 h (Scheme 108).[351]

4.13. Synthesis of pyrazole derivatives

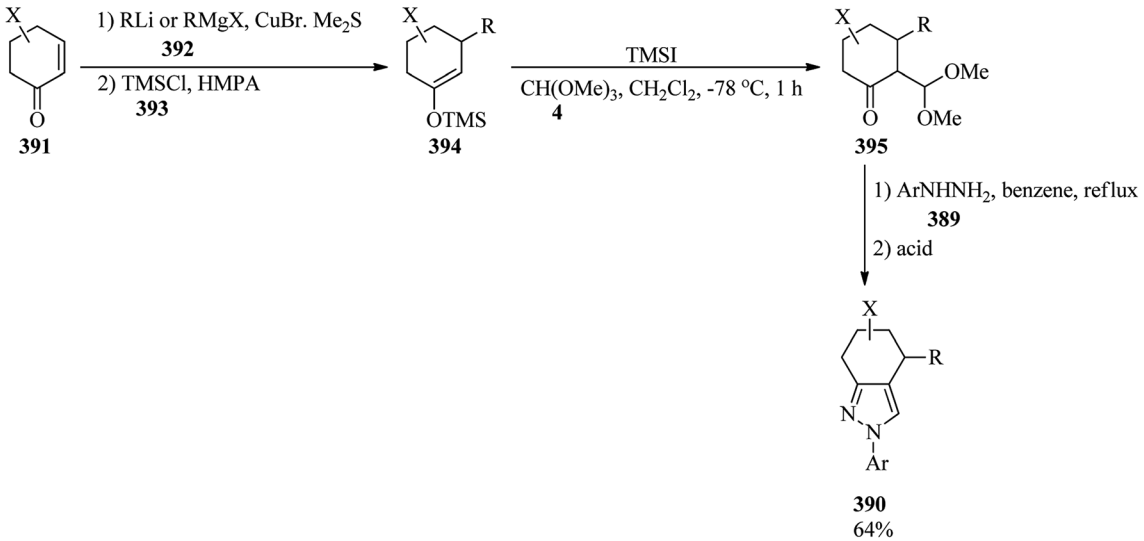
In 2003, Hassen *et al.* described that *N*-(2′,2′,2′-trifluoroethyl) phosphonyl β-hydrazones (**382**) on cyclization with TEOF (**5**) in the presence of acetic acid in refluxing xylene resulted in novel 1-fluorinated-4-phosphopyrazoles (**383**) in 46 h, in moderate to excellent yields (60–94%) (Scheme 109).[352]

1-Substituted 5-aminopyrazole-4-carbonitriles (**385**) could be prepared *via* two pathways: (a) The products were produced through the one-pot three-component reaction of 1-substituted hydrazines (**384**), malononitrile (**248**), and TEOF (**5**), in refluxing ethanol within 2 h in low to moderate yields (17–58%). (b) The reaction of malononitrile (**248**) with TEOF (**5**) in acetic anhydride at 100 °C which got ethoxymethylenemalononitrile (**386**) in 93% yield within 4 h. After completion of the reaction, 1-substituted hydrazines (**384**) were added under similar conditions to afford the desired product (**385**) in 42–78% within 1 h (Scheme 110).[353]

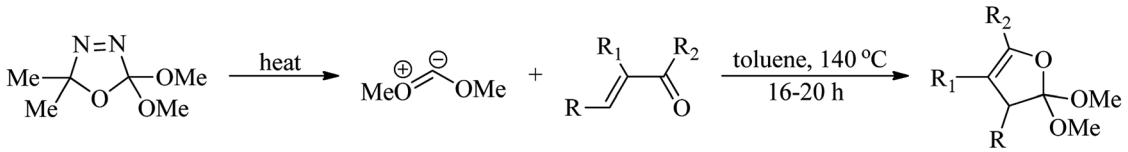
In 2002, an effective, useful, and versatile synthetic approach was introduced for the regiospecific synthesis of 3,4-fused-cycloalkyl-1-arylpyrazoles (**395**) in 48–64% yields *via* two pathways A and B. In pathway A, BF_3-progressed alkylation of symmetric ketones (**387**) with TMOF (**4**) in dichloromethane by Hunig's base formed an α-(dimethoxymethyl)ketone intermediate (**388**), and after isolation, the cyclocondensation of intermediate (**388**) with arylhydrazine (**389**) under acidic conditions in refluxing benzene produced product (**390**) (Scheme 111). In pathway **B**, the kinetic enolates were first regiospecifically



Scheme 111 The regiospecific synthesis of 3,4-fused-cycloalkyl-1-arylpyrazoles (method A).



Scheme 112 The regiospecific synthesis of 3,4-fused-cycloalkyl-1-arylpyrazoles (method B).



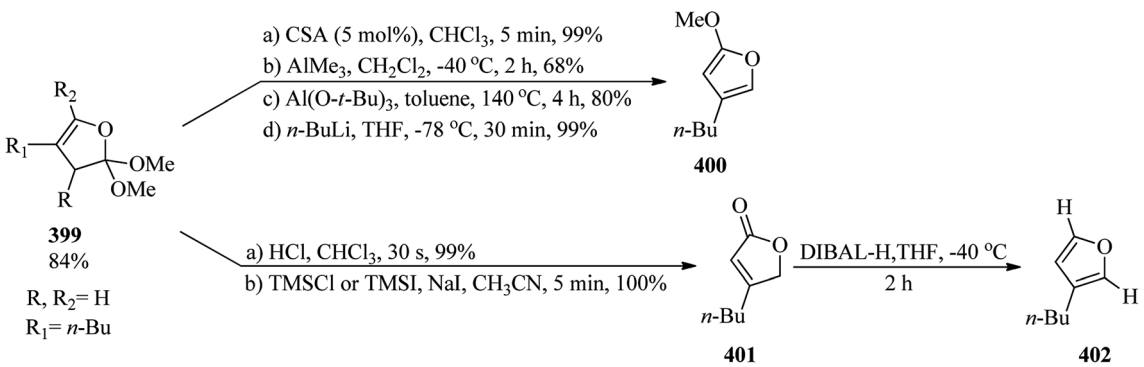
R= H, Me, Et, Ph, CO_2Me, $-(CH_2)_3Br$, $-(CH_2)_3OTBS$
R_1= H, Me, *n*-Bu
R_2= H, Me, Ph
R, R_1= $-CH_2(CH_2)_2CH_2-$
R_1, R_2= $-CH_2(CH_2)_2CH_2-$

Scheme 113 Synthesizing O-heterocycles containing methoxyfurans, furanones, and furans.

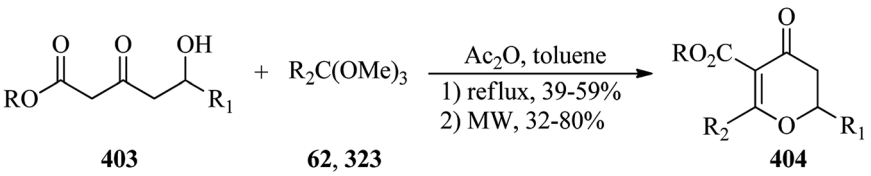
obtained *via* the condensation of α,β-unsaturated cycloalkanones (**391**) with organolithium/Grignard reagents (**392**) by a copper(I) bromide dimethyl sulfide complex ($CuBr \cdot Me_2S$) which was followed by trapping of the above-mentioned enolate utilizing chlorotrimethylsilane (**393**) as silyl enol–ethers (**394**). Then, the reaction of the crude enol–ethers (**394**) with TMOF (**4**) utilizing catalytic amounts of iodotrimethylsilane (TMSI) in CH_2Cl_2 at −78 °C for 1 h achieved intermediate (**395**) regiospecifically, which on cyclocondensation with arylhydrazine (**389**) resulted in the product (**390**) (Scheme 112).[354]

4.14. Synthesis of methoxyfurans, furanones, and furans

In 2018, Croisetière and Spino devised a rapid and effective sequence of reactions to synthesize O-heterocycles, containing methoxyfurans, furanones, and furans. Initially, the [4 + 1]-



Scheme 114 The synthesis of some novel methoxyfurans and furans.



403 62, 323 404

R= Me, *i*-Pr
R_1= Pr, *i*-Pr, Ph, CH_2OBn, cyclohexyl, 2-furyl
R_2= Me, Bu

Scheme 115 The synthesis of highly functionalized dihydropyran-4-ones.

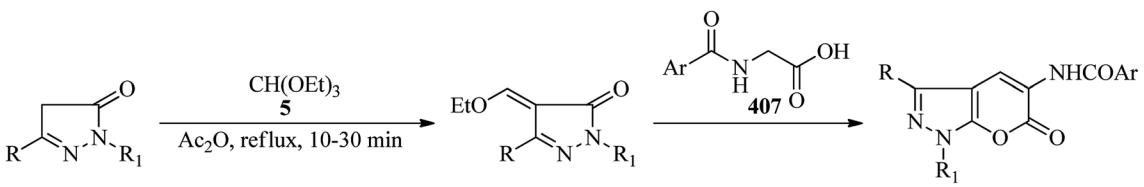
annulation reaction of dimethoxycarbene (**397**),[355] arising from Warkentin's oxadiazoline (**396**), with readily available α,β-unsaturated carbonyls (**398**) gave cyclic orthoesters (**399**) (Scheme 113), which were applied as key precursors for the synthesis of methoxyfurans (**400**), furanones (**401**), and furans (**402**). The synthetic methoxyfurans in this report were classified in four parts: first, by a catalytic amount of camphorsulfonic acid in $CHCl_3$; secondly, trimethylaluminum in CH_2Cl_2 at −40 °C; third, using a weaker Lewis acid aluminum tris(*tert*-butoxide) in toluene at 140 °C; finally, in the presence of *n*-BuLi in THF at −78 °C. Furanone (**401**) could be prepared from the acid hydrolysis of orthoester by concentrated HCl in $CHCl_3$ (method A). Also, utilizing a mild Lewis acid such as TMSCl/TMSI in the presence of NaI iodide in CH_3CN furnished furanones (method B). Furan (**402**) was achieved from the reduction of the resultant furanone by DIBAL-H at −40 °C in THF[356] (Scheme 114).[357]

4.15. Synthesis of dihydropyran-4-ones

In 2015, Clarke *et al.* utilized a novel modification Maitland–Japp cyclization reaction for the synthesis of highly functionalized dihydropyran-4-ones (**404**) *via* the reaction of δ-hydroxy-β-ketoesters (**403**) with two easily available orthoesters (**62, 323**) in the presence of acetic anhydride as a dehydrating agent in dry toluene under heating conditions through refluxing and microwave irradiation. It was found that replacing conventional heating with microwave irradiation reduced the large excess amount of orthoesters from 10 equivalents to only 2 equivalents and also the reaction progressed in a few minutes (Scheme 115).[358]

4.16. Synthesis of pyrano[2,3-*c*]pyrazoles

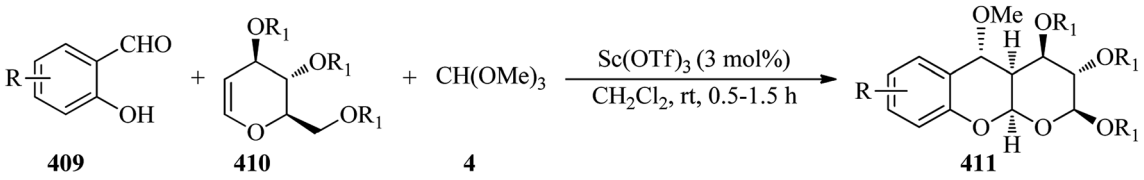
3-Substituted pyrazolin-5-ones (**405**) were condensed with TEOF (**5**) in refluxing acetic anhydride to give the intermediate (**406**) which was then cyclized *via* Michael addition with hippuric



405 406 408
75-94%

Ar= Ph, 4-MePh, 4-OMePh, 4-ClPh
R= Me, NH_2
R_1= Ph, COMe

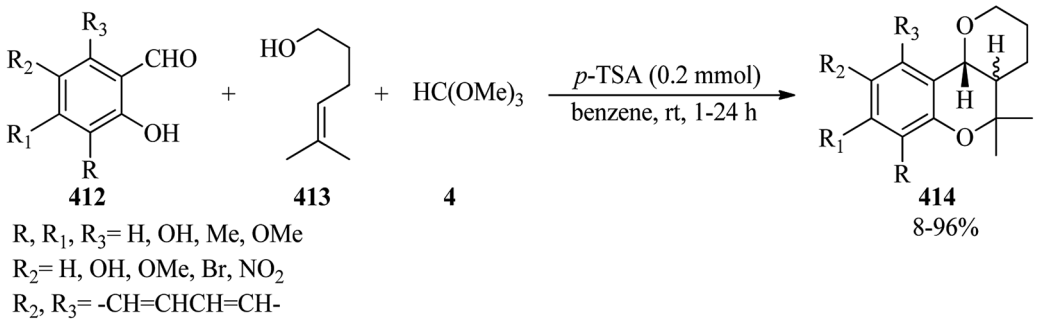
Scheme 116 Pyrano[2,3-*c*]pyrazoles achievement route.



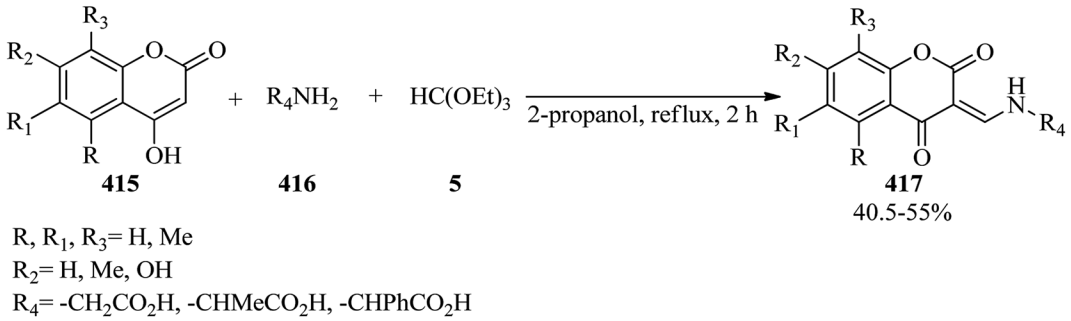
409 410 4 411
74-83%

R= H, OMe, OEt, OBn
R_1= Allyl, Me, Bn

Scheme 117 The formation of *cis*-fused pyranobenzopyrans.



Scheme 118 The stereoselective synthesis of *trans*-tetrahydropyrano[3,2-*c*]benzopyrans.



Scheme 119 The synthesis of 2-[(substituted-2,4-dioxochromane-3-ylidene)methyl]amino acetic acids.

acids (**407**) together with ethanol elimination and acetylation of the ring nitrogen to achieve pyrano[2,3-*c*]pyrazoles (**408**) for 10–30 min in good to excellent yields (75–94%) (Scheme 116).[359]

4.17. Synthesis of chromane derivatives

Scandium triflate [$Sc(OTf)_3$, 3 mol%] catalyzed the diastereoselective reaction of *o*-hydroxybenzaldehydes (**409**), glycals (**410**), and TMOF (**4**) in dichloromethane at room temperature to furnish *cis*-fused pyranobenzopyrans (**411**) within 0.5–1.5 h in good yields (74–83%) with high diastereoselectivity (Scheme 117).[360] This transformation was also accomplished with various other alkenes, such as indene, styrene and allyltrimethylsilane under similar conditions to give substituted benzopyrans within 2–6 h in 78–90% yields with high selectivity.[361]

In 1999, Miyazaki *et al.* reported a novel, effective, and stereoselective procedure for the synthesis of *trans*-tetrahydropyrano[3,2-*c*]benzopyrans (**414**) in 8–96% yields in 1–24 h *via* the one-pot three-component reaction of *o*-hydroxybenzaldehydes (**412**), TMOF (**4**), and unsaturated alcohols (**413**) utilizing a catalytic amount of *p*-TSA (0.2 mmol) in benzene at room temperature (Scheme 118).[362]

In 2003, the one-pot three-component reaction of 4-hydroxy coumarins (**415**),[363,364] carbamates (**416**), and TEOF (**5**) was presented for the synthesis of 2-[(substituted 2,4-dioxochromane-3-ylidene)methyl]amino acetic acids (**417**)[365] in refluxing 2-propanol within 2 h in moderate yields (40.5–55%) (Scheme 119). All the products were screened for their biological activity but only a few molecules were active against *B. subtilis*, *S. aureus*, *E. coli* and *P. aeruginosa* at minimum inhibitory concentrations (MIC) of 100, 300, 500 μg mL^{-1} compared to streptomycin (CAS 57-92-1) and kanamycin (CAS 59-01-8).[366]

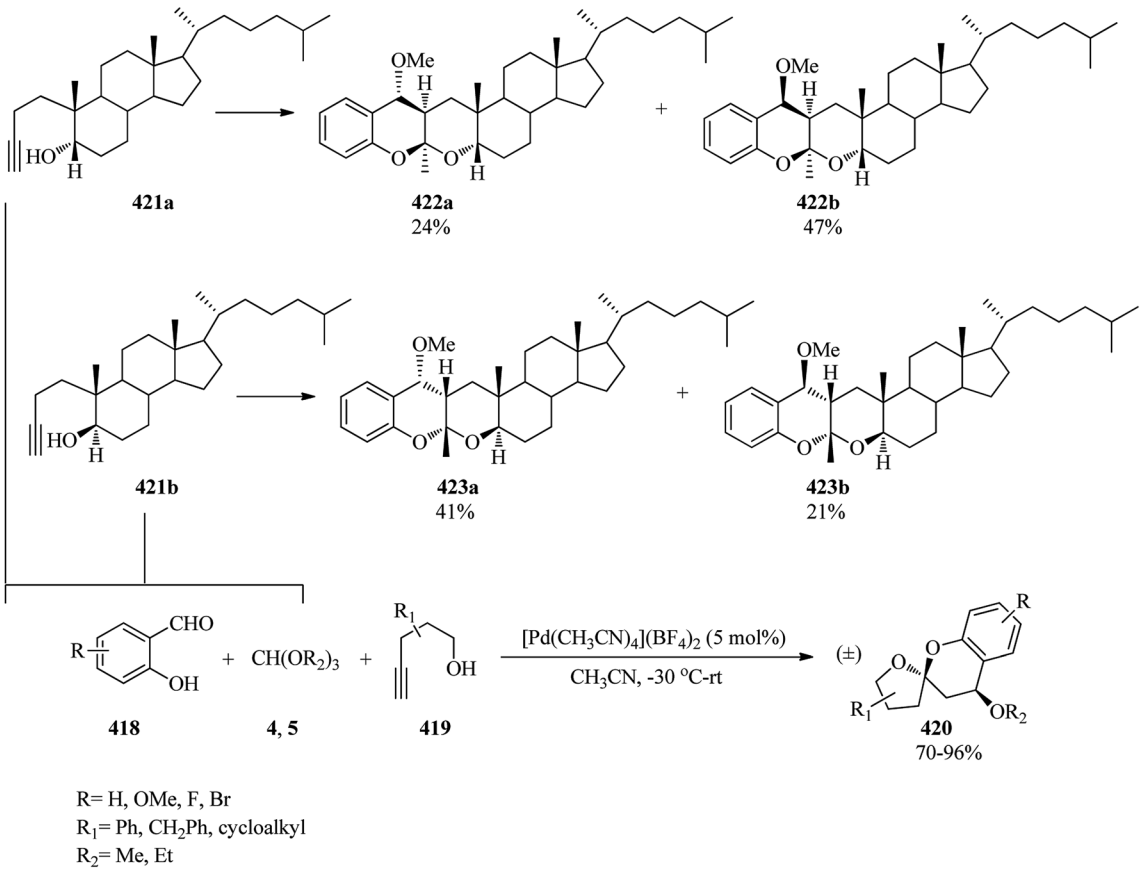
Pd(II) catalyzed the one-pot cascade three-component coupling reaction of *o*-hydroxybenzaldehydes (**418**), 4-pentyn-1-ols (**419**), and orthoesters (**4**, **5**) in CH_3CN at −30 °C to room temperature achieved a direct diastereoselective synthetic method for chromane spiroacetals (**420**).[367–369] It was found that replacing 4-pentyn-1-ols (**419**) with the 5α- and 5β-epimers of 4,5-secocholestan-5-ol (**421a**, **b**) yielded the corresponding steroid chroman spiroketals (**422a**, **b** and **423a**, **b**) (Scheme 120).[368]

4.18. Synthesis of chromene derivatives

Various 2,2-dimethyl-2*H*-chromenes (**426**)[370–374] could be prepared in 42–67% yields through a two-step $Yb(OTf)_3$-catalyzed reaction of *o*-hydroxybenzaldehydes (**424**), TMOF (**4**), and 2-methylpropene (**425**) in CH_2Cl_2 at room temperature for 60 h, which was followed by refluxing toluene in the presence of a catalytic amount of *p*-TSA (0.03 g) for 1 h to eliminate the methanol from the reaction mixture (Scheme 121). Notably, the reaction failed with salicylaldehydes containing methoxy substituents at the 2- and 4-positions. On the other hand, aldehydes including hydroxyl functional groups at the 3- and 5-positions could not be fully isolated because other unidentified compounds were formed with similar polarity that prevented a complete purification.[374]

4.19. Synthesis of coumarin derivatives

The synthesis of substituted 3-benzoylamino-5-oxo-5,6,7,8-tetrahydrocoumarins (**427**) from 1,3-cyclohexanediones (**195**,

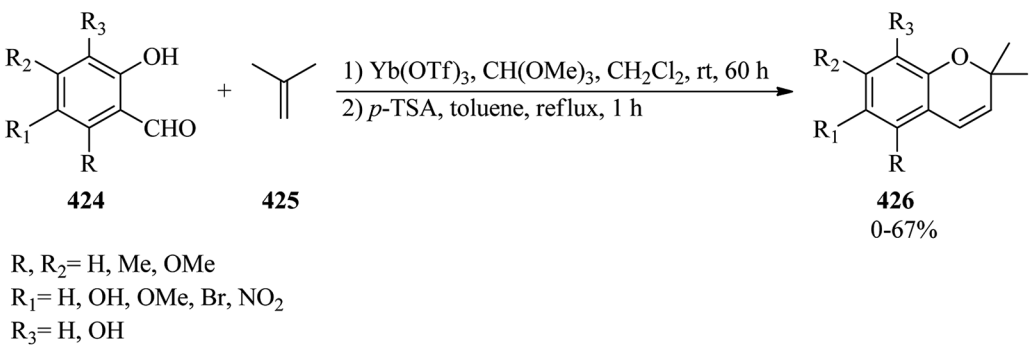


Scheme 120 A synthetic method for chromane spiroacetals.

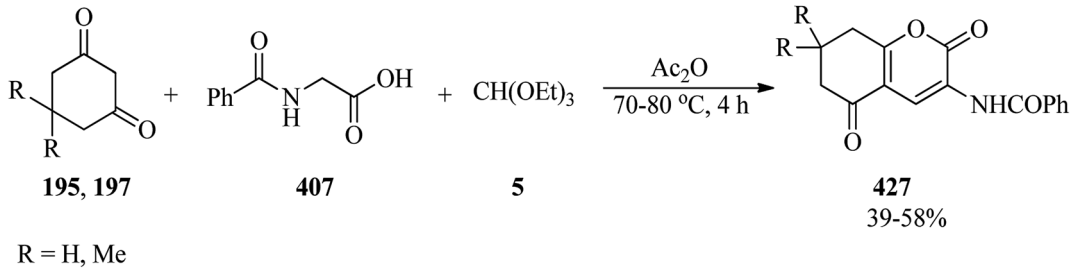
197), hippuric acid (**407**), and TEOF (**5**) (or other one-carbon synthetic equivalents, such as diethoxymethyl acetate or *N*,*N*-dimethylformamide dimethyl acetal) in acetic anhydride has been described (Scheme 122).[375]

In 2003, 8-amino-7-(*p*-bromophenyl)-10-hydroxypyridino [3′,2′-6,5]4*H*-pyrano[3,2-*c*][1]benzopyran-6-one (**429**) was prepared *via* the cyclocondensation of 2-amino-4-(4′-bromophenyl)-3-cyano-4*H*,5*H*-pyrano[3,2-*c*][1]benzopyran-5-one (**428**) with TEOF (**5**) in refluxing acetic anhydride within 2 h in 55% yield (Scheme 123). The resultant product exhibited antibacterial and antifungal activities.[376]

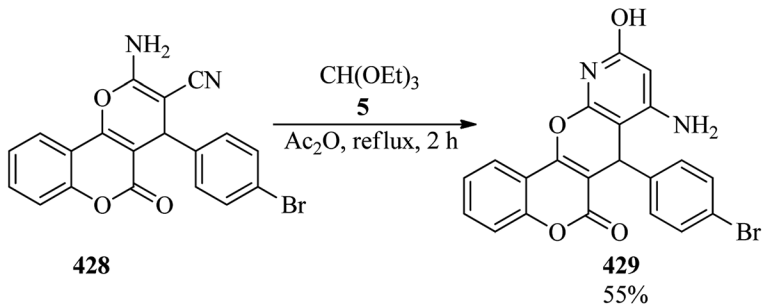
In 2000, the El-Agrody group synthesized 14-methyl-13,14*H*-[1]benzopyrano[3′,4′:5,6]-pyrano[3,2-*e*][1,2,4]triazolo[1,5-*c*]-pyrimidine-13-one as colorless crystals in 87% yield *via* the ring-closure reaction of 9-amino-8,9-dihydro-8-imino-7-methyl-6*H*,7*H*-[1]benzopyrano[3′,4′:5,6]-pyrano[2,3-*d*]-pyrimidine-6-one with TEOF in refluxing benzene within 3 h.[377] In 2001, they also reported the preparation of antibacterial and antifungal active 11-bromo-14-(*p*-methoxyphenyl)-14*H*-naphtho[1′,2′:5,6]pyrano [3,2-*e*][1,2,4]triazolo[2,3-*c*] pyrimidine through the cyclo-condensation of 10-amino-3 -bromo-12-(*p*-methoxyphenyl)-11-imino-10,11-dihydro-12*H*-naphtho[1′,2′:5,6]-pyrano[2,3-*d*]



Scheme 121 A synthetic approach to various 2,2-dimethyl-2*H*-chromenes.



Scheme 122 The synthesis of substituted 3-benzoylamino-5-oxo-5,6,7,8-tetrahydrocoumarins.



Scheme 123 The formation of amino-7-(*p*-bromophenyl)-10-hydroxypyridino[3′,2′-6,5]4*H*-pyrano[3,2-*c*][1]benzopyran-6-ones.

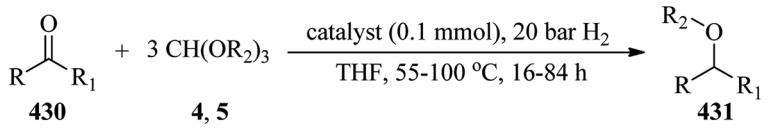
pyrimidine with TEOF under similar condition for 6 h in 79% yield.[326]

4.20. Etherification and esterification reactions

Bakos *et al.* reported that a single frustrated Lewis pair catalyst $B(C_6Cl_3H_2)(C_6F_4H)_2$ could progress the tandem reductive etherification reaction of aldehydes/ketones (**430**) with trialkyl orthoformate (**4**, **5**), as alkylating agent, to produce ethers (**431**) under 20 bar H_2 pressure in THF at 55–100 °C, for 16–84 h with high selectivity (98–99%) and weak to good yields (35–92%) (Scheme 124).[378]

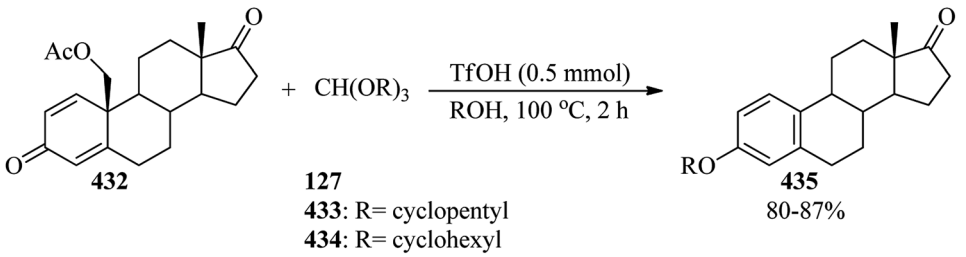
In 2016, estrone 3-secondary ethers (**435**) were made through the eco-friendly etherification/aromatization reaction of readily accessible dienone (**432**) with trialkyl orthoformates (**127**, **433**, **434**), as alkylating agent, in a 1 : 5 molar ratio by triflic acid (TfOH, 0.5 mmol) in the corresponding alcohol (5 mL) at 100 °C for 2 h in 80–87% yields (Scheme 125). The above-mentioned procedure was applied for the generation of three marketed 3-etherified estrogen drugs, quinestrol, quinestradol, and nilestriol, utilizing 19-hydroxyandrost-4-ene-3,17-dione as a commercially available precursor.[379]

Scandium triflate [$Sc(OTf)_3$, 10 mol%] catalyzed the one-pot three-component condensation of aldehydes, allylsilane and TMOF in dichloromethane to produce homoallyl ethers[380,381] at room temperature. Mild reaction conditions, good yields (70–90%), high selectivity, recyclability, and reusability of the catalyst are some important advantages of this procedure.[381] On the other hand, the reaction of equimolar amounts of homoallyl alcohol (**436**) with TMOF (**4**) using Lewis acids such as $InCl_3$ (3 mmol) in CH_2Cl_2 at room temperature obtained homoallyl ethers (**437**) and homoallyl chlorides (**439**) in good yields. Notably, homoallyl alcohols with aryl moieties with electron-

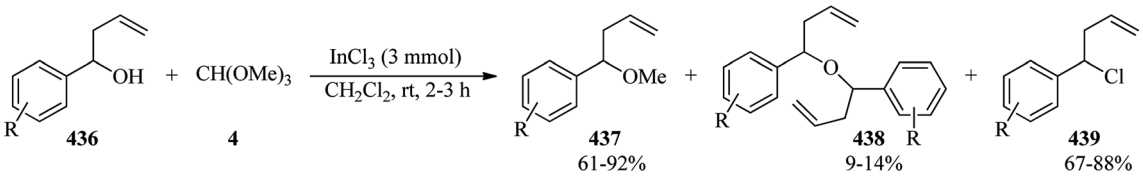


Catalyst: $B(C_6Cl_3H_2)(C_6F_4H)_2$
R= H
R_1= $PhCH_2$, 4-OMe$PhCH_2$, 4-Cl$PhCH_2$, 4-CO_2Me$PhCH_2$, 4-Br$PhCH_2$, 2-Cl$PhCH_2$, 3,4-$(OMe)_2PhCH_2$, 3-OMe-4-OH$PhCH_2$, 3-OEt-4-OH$PhCH_2$, $CH_2CH{=}CHCH{=}CHCH_2$, $Me(CH_2)_6CH{=}CHCH_2$, $PhCH{=}CHCH_2$
R_2= Me, Et

Scheme 124 Tandem reductive etherification reaction of aldehydes/ketones.



Scheme 125 Etherification/aromatization reaction of dienone.



R= H, 2-Me, 3-Me, 4-Me, 2,5-Me_2, 4-F, 4-Cl, 4-Br, 4-CF_3, 4-CN, 4-NO_2, Pentafluoro

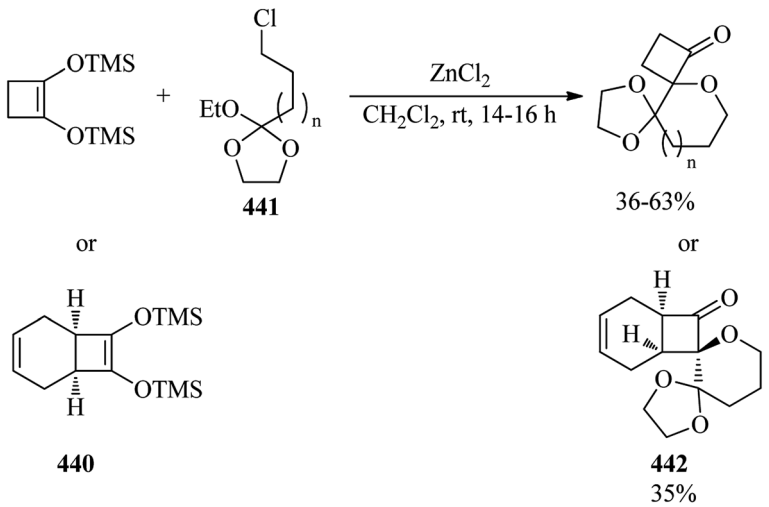
Scheme 126 The preparation of some homoallylic compounds.

donating substituents furnished exclusively homoallyl ethers (**437**) in 84–92% yields. Homoallyl alcohol including halogen atoms as the substituents resulted in homoallyl ethers (**437**, 61–72%) along with bishomoallyl ethers (**438**) (9–14%) as by-products. The homoallyl alcohols containing several halogen atoms or an electron-withdrawing substituent produced only the homoallyl chlorides (**439**) in 67–88% yields (Scheme 126). Similarly, this transformation was accomplished using $BiCl_3$ at room temperature and $BF_3 \cdot OEt_2$ at −78 °C, while treatment utilizing $TiCl_4$ at −78 °C afforded exclusively the homoallyl chloride (**439**) in 92% yield. Hence, the type of product could be controlled through the selection of the desired Lewis acid.[382]

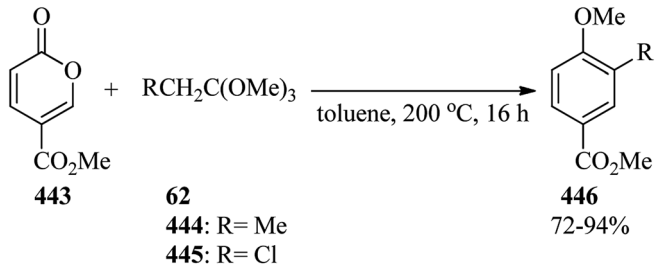
Maulide and Markó synthesized spirocyclic ethers (**442**) in 35–63% yields *via* the Mukaiyama aldol reaction of the silylated acyloins (**440**) with functionalized orthoesters (**441**) by $ZnCl_2$ in dichloromethane at room temperature, which was followed by desilylation of the resultant adducts using TBAF in THF, and finally annulation in the presence of *t*-BuOK (Scheme 127).[383]

In 2013, Lee and Kraus presented a new technique for the synthesis of substituted benzoates (**446**) in 72–94% yields *via* the one-step one-pot inverse electron-demand Diels–Alder reaction of methyl coumalate (**443**) with orthoesters (**62**, **444**, **445**) as an electron-rich dienophile in toluene at 200 °C for 16 h (Scheme 128).[384]

In 1998, Fletcher co-workers reported a facile and inexpensive process for the formation of alkoxy/aryloxycyclopropanes (**448**) with preference for the generation of the more hindered *cis*-isomers through the reaction of TMOF (**4**) with alkenes (**447**) in the presence of zinc amalgam and Me_3SiCl in refluxing diethyl ether for 24 h (Scheme 129).[385]



Scheme 127 Mukaiyama aldol reaction of silylated acyloins.



Scheme 128 The synthesis of substituted benzoates.

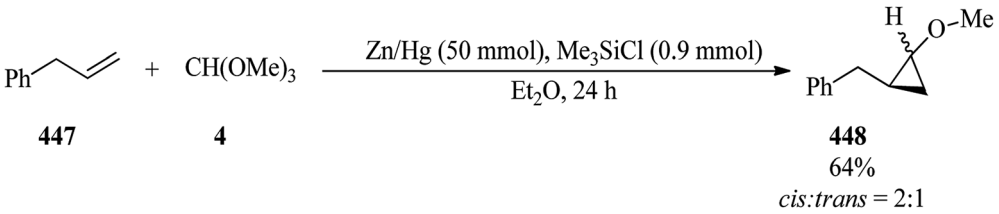
In 2018, Bunse *et al.* synthesized ethoxycarbonyl-substituted 1-alkylidenephthalanes (**451**) from the reaction of orthoester (**449**) arising from triethyl orthopropanoate (**7**). This reaction was prompted *via* halogen–metal exchange of the orthoester (**449**) with *n*-butyllithium (*n*-BuLi) in THF at −78 °C for 15 min which was followed by the nucleophilic addition reaction with diverse carbonyl compounds (**450**) along with regioselective 5-*exo*-dig cyclization of the corresponding intermediate lithium alcoholate and eventually hydrolysis to produce the products (**451**) as mixtures of (*Z*)- and (*E*)-configured diastereomers with an approximate range of 90 : 10 to 95 : 5 (Scheme 130). Notably, the aromatic aldehyde benzaldehyde was unsuccessful in getting the phenyl-substituted derivative.[386]

In 2018, Sempere and Carreira prepared β-substituted γ,δ-unsaturated esters (**453**) *via* an iridium-catalyzed enantioselective allylic alkylation reaction of trimethyl orthoacetate (**62**), as an acetate enolate source, with racemic allylic carbonates (**452**), utilizing $ZnBr_2$ as an additive in 1,4-dioxane at room temperature (Scheme 131). Significantly, halogenated and electron-rich substrates yielded the relative products with high yields and excellent enantioselectivity. Notably, the meroterpenoid (+)-conicol has been synthesized through employment of this new procedure in a formal enantioselective synthesis.[387]

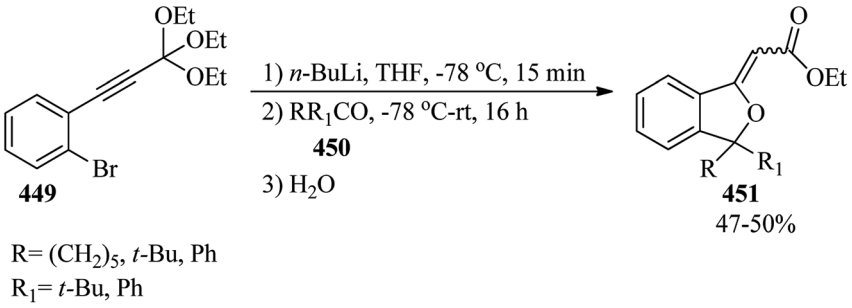
Brodzka and co-workers probed the enzymatic kinetic resolution (EKR) of Novozym 435 as a biocatalyst for the synthesis of enantiomerically pure carboxylic acid esters (**456**) *via* the esterification of racemic 3-phenyl-4-pentenoic acid (**454**) with trialkyl orthoesters (**4**, **5**, **6**, **62**, **102**, **323**, **380**, **444**, **455**) as alkoxy group donors in toluene at 40 °C (Scheme 132). Based on the resulting data, trialkyl orthoesters including bulky alkyl groups, such as trialkyl orthobenzoate, obtained excellent results for both yield and enantioselectivity (50% yield, >99% ee). It was found that the enantioselectivity of EKR is highly dependent on the structure of an alkoxy group donor.[388]

In 2015, Koszelewski *et al.* described a novel method of kinetic resolution based on irreversible enzymatic esterification of *rac*-3-hydroxy-3-(aryl)propanoic acids (**457**) with triethyl orthobenzoate (**380**) using Novozym 435 tandem metal-enzyme dynamic kinetic resolution (DKR) in toluene at 40 °C to access enantiomerically active β-hydroxy ester (**458**) with low enantioselectivities in low yields (<1–45%) for 48 h (Scheme 133).[389]

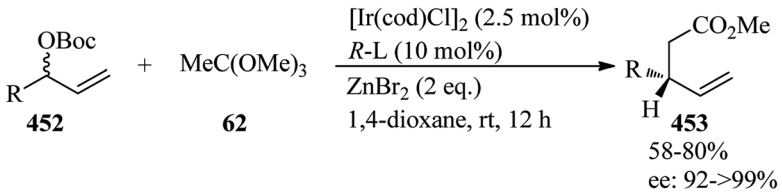
In 1993, Trujillo and Gopalan used triethylorthoacetate as an ideal reagent for the transformation of sulfonic acids into their ethyl esters under a catalyst-free mode in dichloromethane (CH_2Cl_2) at room temperature in high to excellent yields (69–97%) for 30 min. The uncatalyzed esterification reaction of carboxylic acids using this reagent was also conveniently performed in refluxing toluene within 24 h in high yields (81–92%). Replacing trimethylorthoacetate with triethylorthoacetate resulted in the desired methyl esters. According to the resulting data, the utilization of TEOF instead of triethylorthoacetate was unsuccessful.[390]



Scheme 129 The formation of alkoxy/aryloxycyclopropanes.

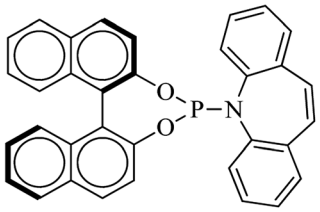


Scheme 130 The preparation of ethoxycarbonyl-substituted 1-alkylidenephthalanes.

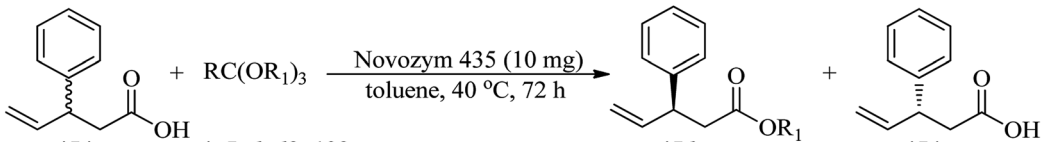


R= Ph, 4-BrPh, 4-FPh, 2-OMePh, 3-OMePh, 4-CO_2MePh, 3-CF_3Ph, 4-NO_2Ph, 2-naphthyl

(*R*)-L:



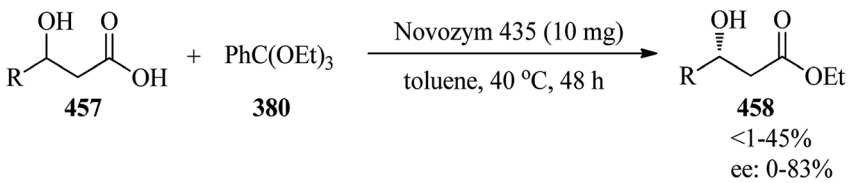
Scheme 131 The preparation of β-substituted γ,δ-unsaturated esters.



Scheme 132 The synthesis of enantiomerically pure carboxylic acid esters.

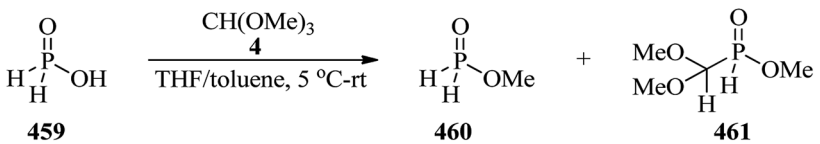
In 1996, Schwabacher and Stefanescu designed a useful and convenient method for the generation of methyl phosphinate (**460**) together with the elimination of methyl formate and methanol *via* the reaction of phosphinic acid (**459**) with TMOF (**4**) in a combined dry THF/toluene (1 : 1) medium at 5 °C to room temperature. This reaction was accompanied by the formation of a by-product (**461**), which was assumed to form through the attack of the dimethoxymethyl cation on the phosphorus(III) tautomer of (**459**) or (**460**) (Scheme 134).[391]

In 1994, King introduced a convenient method for the formation of ester–ethers (**463**) in 61–95% yields *via* the reaction of lactones (**462**) with orthoformates (**4, 5, 133**) using sulfuric acid in the desired alcohol as solvent at 50 °C within 3–8 h (Scheme 135).[392]

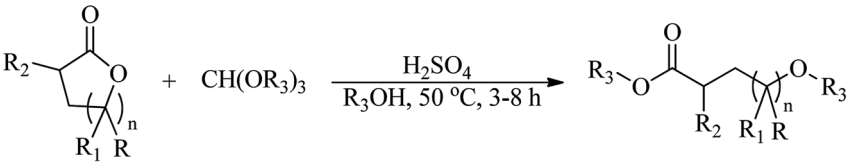


R= Ph, 4-OMePh, 2-FPh, 2-BrPh, 4-CF_3-2-NO_2Ph, 4-F-2-NO_2Ph,2,4-$(NO_2)_2$Ph, 4-CNPh

Scheme 133 The synthesis of enantiomerically active β-hydroxy ester.



Scheme 134 The generation of methyl phosphinate.



462 **4, 5, 133** **463**
61-95%

n= 0-2
R= H, Me
R_1= H, Me, pentyl
R_2= H, Me
R_3= Me, Et, *n*-Pr

Scheme 135 The formation of ester–ethers from lactones and orthoformates.

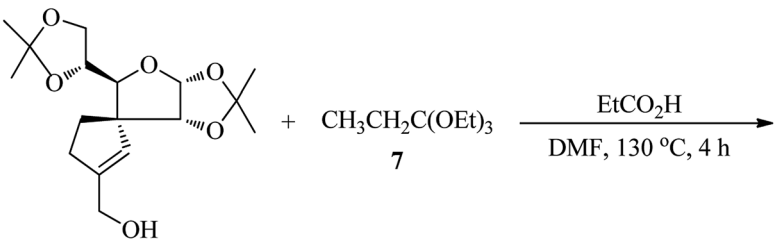
4.21. Johnson–Claisen rearrangement

In 2001, Takao *et al.* showed that the Claisen rearrangement of the substrate (**464**)[393,394] derived from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, with triethyl orthopropionate (**7**) by a catalytic amount of propanoic acid in DMF at 130 °C for 4 h obtained an inseparable mixture of the rearrangement products (**465**, **466**, and **467**) as a 1 : 2.5 : 10 diastereomeric mixture in a combined yield of 87% (Scheme 136). Under similar conditions, the reaction of (**464**) with trimethyl orthobutyrate (**455**) by powdered molecular sieves 4A (MS-4 Å) afforded an inseparable mixture of the rearrangement products (**468** and **469**) as a 1 : 3 diastereomeric mixture in a combined yield of 46% (Scheme 137). In both reactions, the σ-bond formation progressed prevalently from the β-side. This resultant stereochemical was opposite to the observed rearrangement of (**464**) with TEOAc.[395]

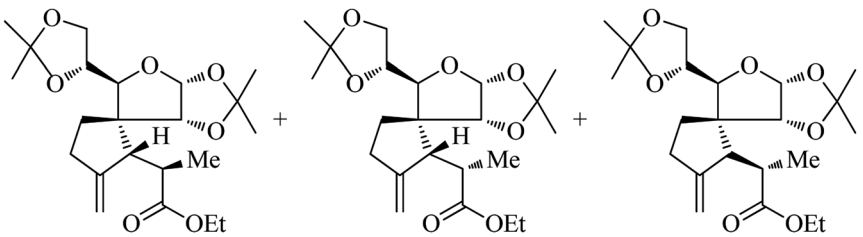
4.22. Acetalization reaction

In 2003, Ma *et al.* presented an efficient and chemoselective method for the preparation of diethyl acetals in good to excellent yields (63–96%) *via* the acetalization[178,396–408] of aldehydes/ketones with TEOF using TiO_2/SO_4^{2-} in refluxing ethanol for 25 min to 3 h. It was found that, in competitive reactions, aldehydes and cyclic aliphatic ketones revealed excellent chemoselectivity.[408] The reaction of enamines (**470**) with trialkyl orthoformates (**4**, **5**) was also accomplished in the presence of $BF_3 \cdot OEt_2$ in CH_2Cl_2 to give α-dialkoxymethyl carbonyl compounds (**471**), after hydrolysis, in 61–85% yields within 1 h (Scheme 138).[409]

In 1999, Martins *et al.* reported the regioselective reaction of 2-acylcycloalkanones (**472**) with TMOF (**4**) using *p*-TSA (0.78 mmol) in methanol at room temperature to afford the corresponding acetals within 24 h (Scheme 139). It was found that

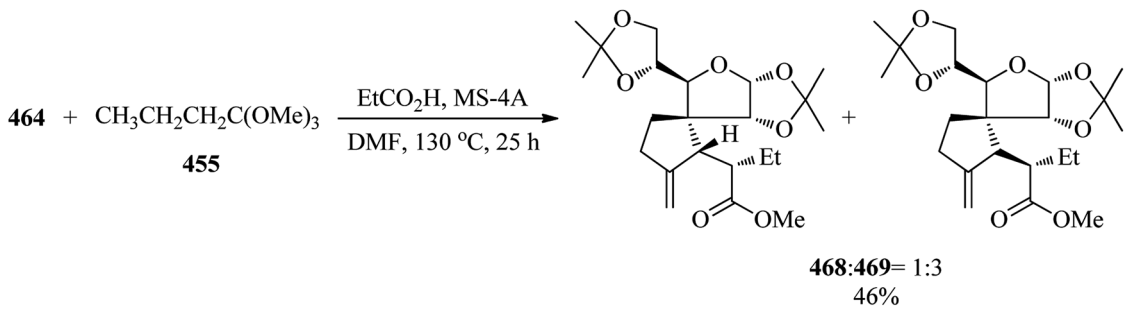


464

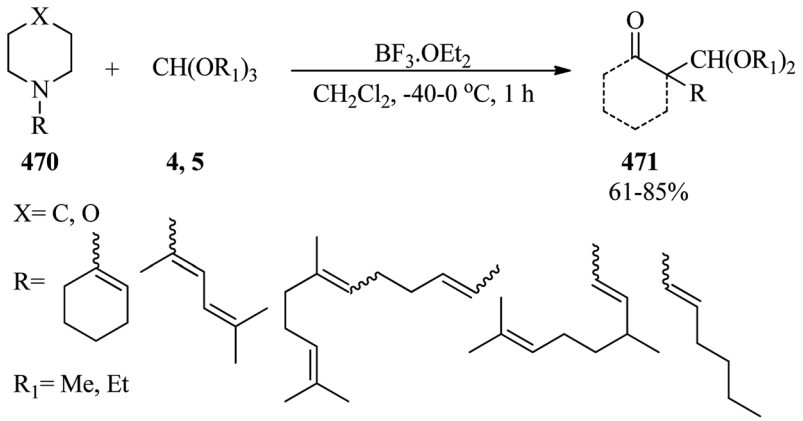


465:**466**:**467**= 1:2.5:10
87%

Scheme 136 The Claisen rearrangement of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose with triethyl orthopropionate.



Scheme 137 The Claisen rearrangement of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose with trimethyl orthobutyrate.

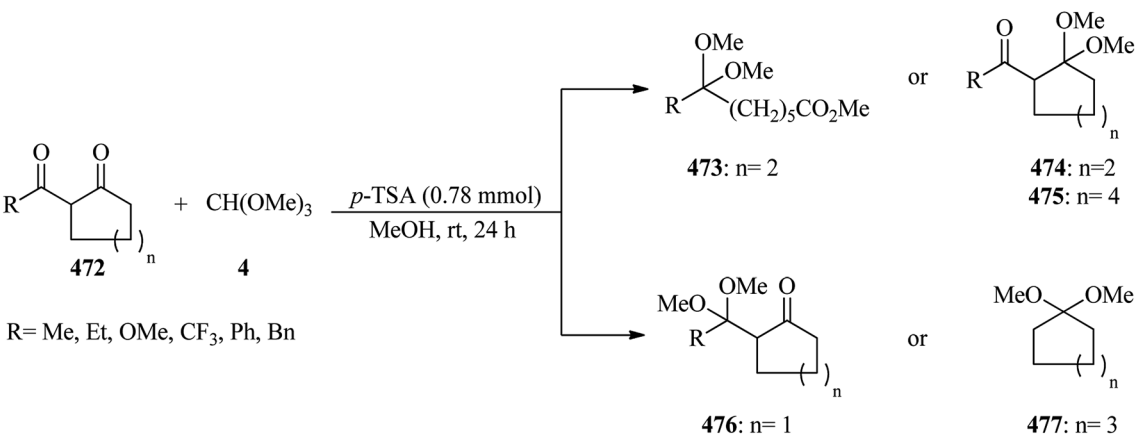


Scheme 138 The chemoselective preparation of diethyl acetals.

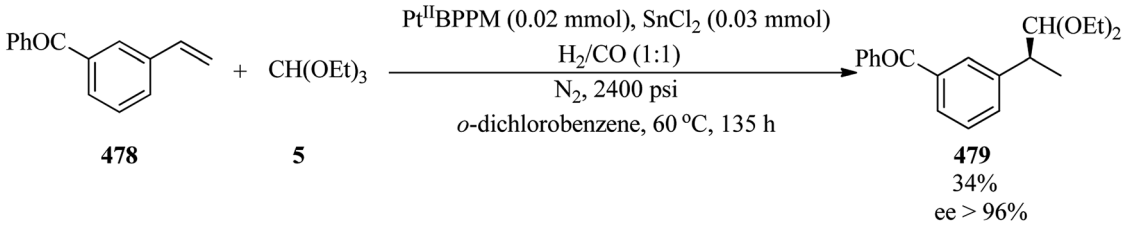
the reverse Claisen condensation of electron-donating substituted 2-acylcyclohexanones, where R was Me, Et or CH_2Ph with TMOF led to 7,7-dimethoxyalkanoate methyl esters (**473**) in 80–93% yields. On the other hand, 2-acyl cyclohexanone dimethyl acetal derivatives (**474**) in 80–85% yields were produced when R was Ph, CF_3 or OMe. Similar to the products (**474**), 2-acetylcyclooctanone derivative (R = Me) resulted in acetal (**475**) in 86% yield. Finally, 2-acetylcyclopentanone (R = Me) and 2-acetyl cycloheptanone (R = Me) gave rise to acetals (**476**) and (**477**) in 75 and 74% yields, respectively.[410]

In 1991, the highly enantioselective hydroformylation of vinyl aromatics (**478**) was reported by the Hegedus group in the presence of TEOF (**5**). They discovered that TEOF plays a special role in stereoselectivity. As can be seen in Scheme 140, the reaction proceeded with (Pt^{II}BPPM)/$SnCl_2$ (Pt^{II}BPPM: l-(*tert*-butoxycarbonyl)-(2*S*,4*S*)-4-(dibenzophospholyl)-2-[(dibenzophospholyl)methyl]pyrrolidine) in *o*-dichlorobenzene as solvent.[411]

In 2015, Pospech and co-workers introduced an intermolecular one-step methoxylation/acetalization reaction of donor–

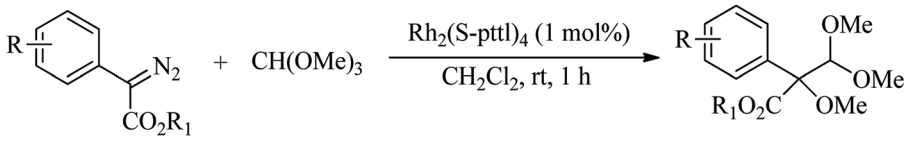


Scheme 139 The regioselective reaction of 2-acylcycloalkanones with TMOF.



478 **5** **479** 34% ee > 96%

Scheme 140 The enantioselective hydroformylation of vinyl aromatics.



480 **4** **481** 40-91%

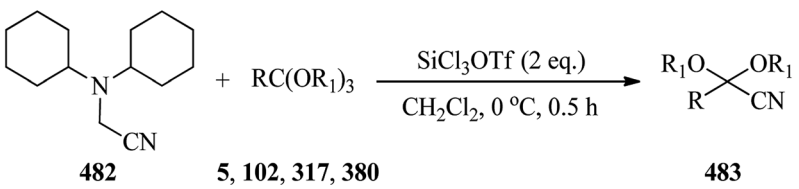
R= 4-F, 4-Cl, 4-Br, 2,5-F_2, 3,4-Cl_2, 3-OMe, 3-OEt-4-CO_2Et, 4-OTs, 4-OMs
R_1= Me, Et

Scheme 141 Methoxylation/acetalization of diazo compounds with TMOF.

acceptor substituted diazo compounds (**480**) with TMOF (**4**) utilizing Rh_2(*S*-pttl)$_4$ (1.0 mol%) in CH_2Cl_2 at room temperature to synthesize functionalized tertiary α-alkoxy-β-oxo-esters (**481**) in 1 h in 40–91% yields (Scheme 141). The concurrent C–O/C–C bond generation produces products with exclusive quaternary carbon centers containing substituent groups with various oxidation levels, such as esters, protected aldehydes and alkoxidse.[412]

In 2015, the cyanation of orthoesters (**5**, **102**, **317**, **380**),[413] with sterically congested α-cyanoamines, like dicyclohexylcyanoamine (**482**), as effective cyanating reagents, was described for the formation of cyanoacetals (**483**) by trichlorosilyl triflate ($SiCl_3OTf$) in CH_2Cl_2 at 0 °C within 0.5 h, in excellent yields (73–97%) (Scheme 142).[414]

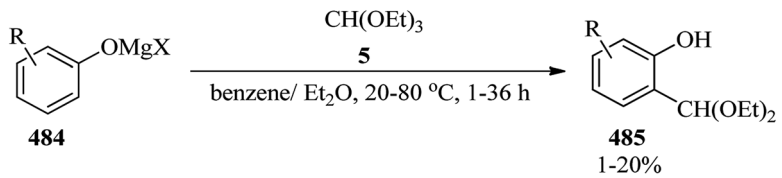
Casiraghi and co-workers prepared 2-hydroxyaryl-1-carboxyaldehyde diethylacetals (**485**) *via* the reaction of special phenol salts like magnesium halides (**484**) with TEOF (**5**) in benzene or diethylether at 20–80 °C (Scheme 143). This reaction was promoted by a C-regiospecific attack at the *ortho* positron of the phenoxy moiety.[415]



482 **5, 102, 317, 380** **483** 73-97%

R= H, *n*-Bu, Ph
R_1= Me, Et

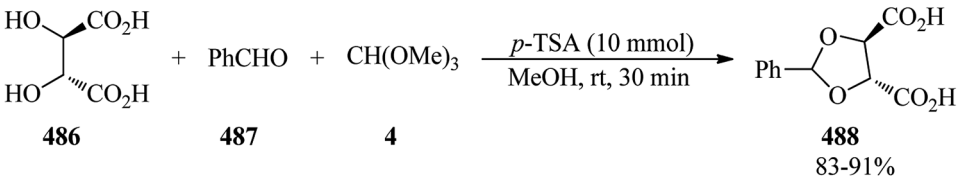
Scheme 142 The cyanation of orthoesters.



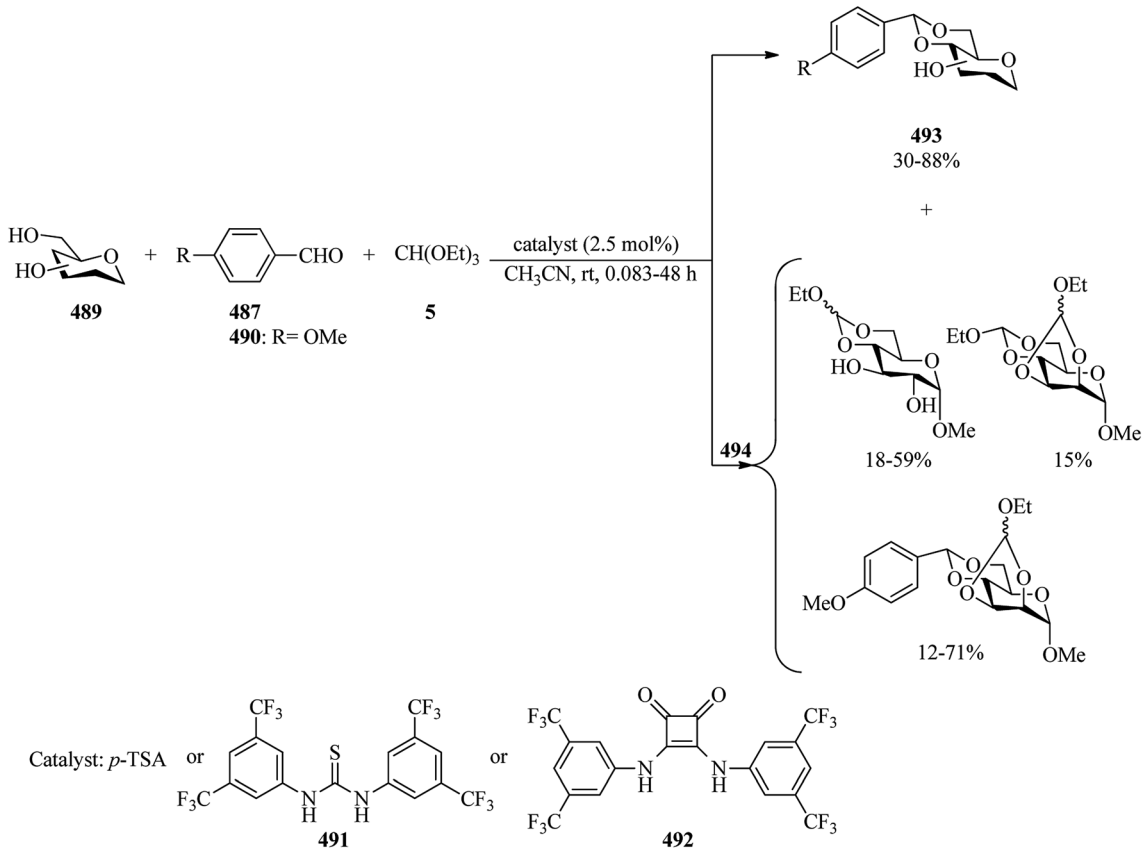
484 **485** 1-20%

R= H, 2-Me, 4-Me, 2-*i*-Pr, 2-*t*-Bu, 4-*i*-Pr, 4-*t*-Bu, 2,4-Me_2, 3,4-Me_2, 2,5-Me_2, 2-*i*-Pr-5-Me, 2-*t*-Bu-5-Me, 2-naphthyl

Scheme 143 The regioselective preparation of 2-hydroxyaryl-1-carboxyaldehyde diethylacetals.



Scheme 144 The formation of (−)-dimethyl 2,3-*O*-benzylidene-L-tartrate.



Scheme 145 The regioselective preparation of 4,6-*O*-arylidenated derivatives of sugars.

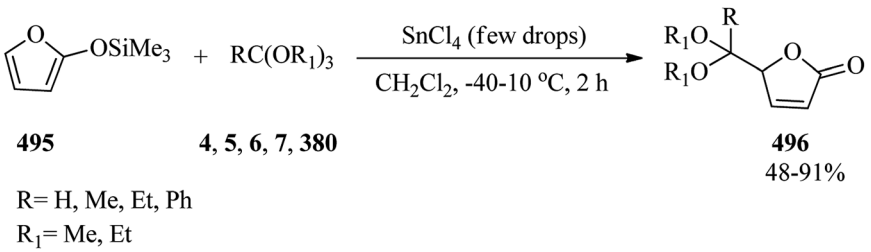
In 1993, Byun and Bittman synthesized (−)-dimethyl 2,3-*O*-benzylidene-L-tartrate and its enantiomer (**488**) in 83–91% yields *via* the reaction of L-tartaric acid (**486**), benzaldehyde (**487**), and TMOF (**4**) by *p*-TSA (10 mmol) in methanol at room temperature (Scheme 144).[416]

In 2013, Geng *et al.* prepared 4,6-*O*-arylidenated derivatives (**493**) and orthoesters (**494**), regioselectively *via* the protected/unprotected sugars (**489**), benzaldehydes (**487**, **490**), and TEOF (**5**) by organocatalysts such as thiourea (**491**)/squaramide derivatives (**492**) in anhydrous CH_3CN at room temperature (Scheme 145). In this procedure the influence of various parameters, such as the amount and type of aldehyde, catalyst and orthoester, was investigated on the time and yield of reaction. It was found that a strong acid-catalyst like *p*-TSA has a great effect in reducing the reaction time.[417]

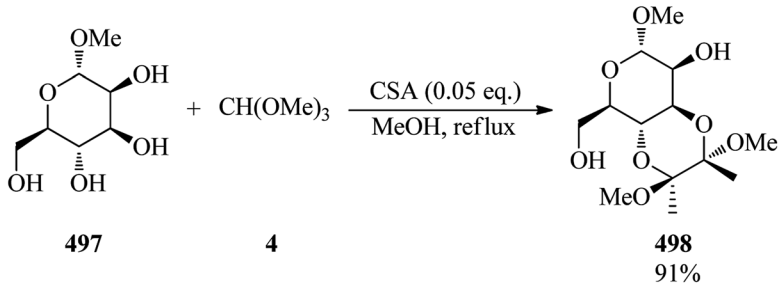
5-Substituted 5,5-dialkoxy-2-penten-4-olides (**496**) were made through the reaction of 2-(trimethylsiloxy)furan (**495**) with orthoesters (**4**, **5**, **6**, **7**, **380**) in the presence of a few drops of tin(IV)chloride ($SnCl_4$) in CH_2Cl_2 at −40 to 10 °C in 48–91% yields in a 2 h period (Scheme 146).[418]

The vicinal diequatorial diols reaction of 2,2,3,3-tetramethoxybutane (**497**) with TMOF (**4**) using camphorsulfonic acid in refluxing methanol for 12–18 h yielded butane 2,3-bisacetal (**498**) in moderate to excellent yields (54–91%) to protect *trans*-1,2-diols (Scheme 147).[419]

In 1991, Hoffman and Salvador described a one-pot conversion of cyclic ketones to *N*-methyl lactams. The reaction of ketones (**499**) with TEOF (**5**) by *p*-TSA in ethanol gave acetal (**500**) which was treated *in situ* with *N*-(((*p*-nitrobenzene)sulfonyl)oxy) methylamine (**501**) to furnish the *N*-methyl group of the imidate salt (**502**). Finally, dealkylation of the resulting *O*-ethyl imidate with sodium iodide in refluxing acetonitrile achieved lactams (**503**) in moderate to high yields (Scheme 148).[420]

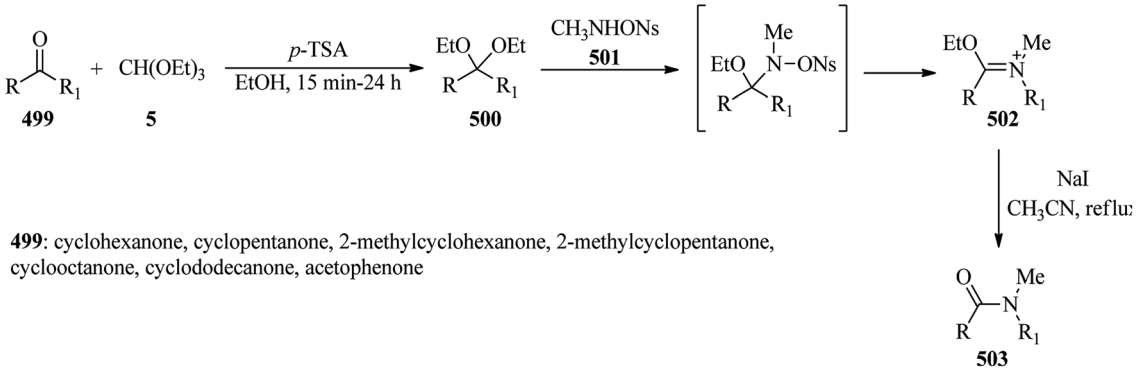


Scheme 146 The synthesis of 5-substituted 5,5-dialkoxy-2-penten-4-olides.

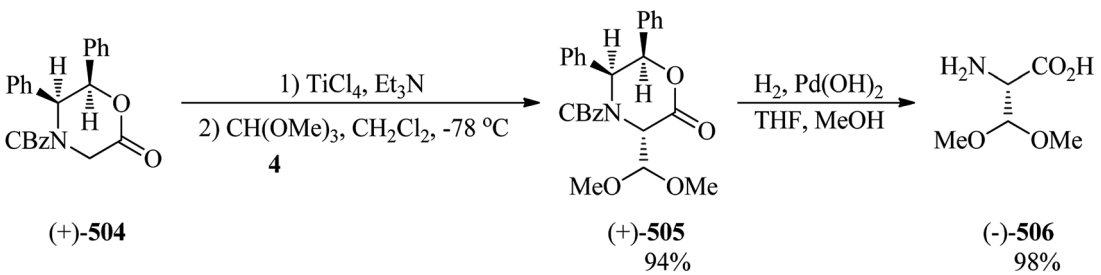


Scheme 147 The reaction of 2,2,3,3-tetramethoxybutane with TMOF.

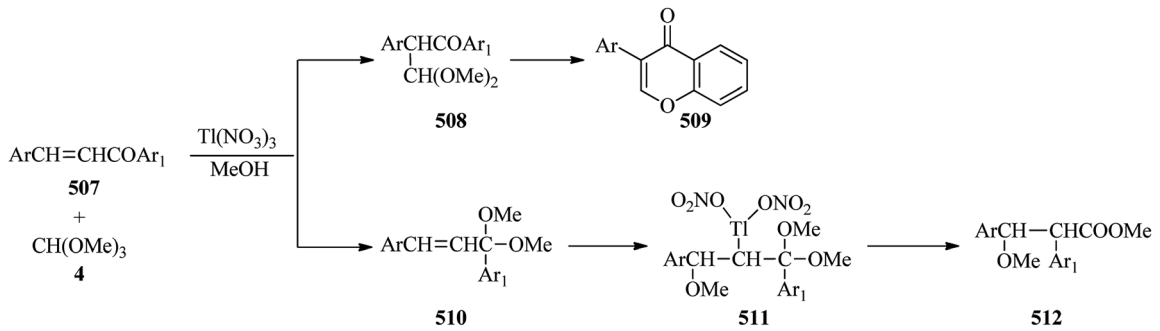
DeMong and Williams suggested an asymmetric synthesis of 2-amino-3,3-dimethoxypropanoic acid (−)-**506.** The key step is the quenching of a chiral glycine (**504**) titanium enolate with TMOF (**4**) in CH_2Cl_2 at −78 °C to form the appropriate α-dimethylacetal[421,422] (+)-**505** in 94% yield. The (−)-**506** was obtained in 98% yield through the hydrogenolysis of the lactone moiety by 20 mol% of $Pd(OH)_2$ in a combined THF/MeOH (3 : 1) medium; followed by utilizing trituration with ether to eliminate the dibenzyl by-product (Scheme 149).[422]



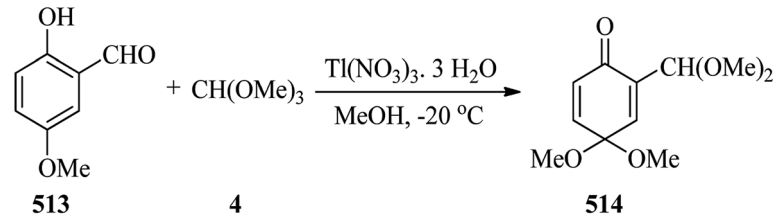
Scheme 148 The conversion of cyclic ketones to *N*-methyl lactams with TEOF.



Scheme 149 The asymmetric synthesis of 2-amino-3,3-dimethoxypropanoic acid.

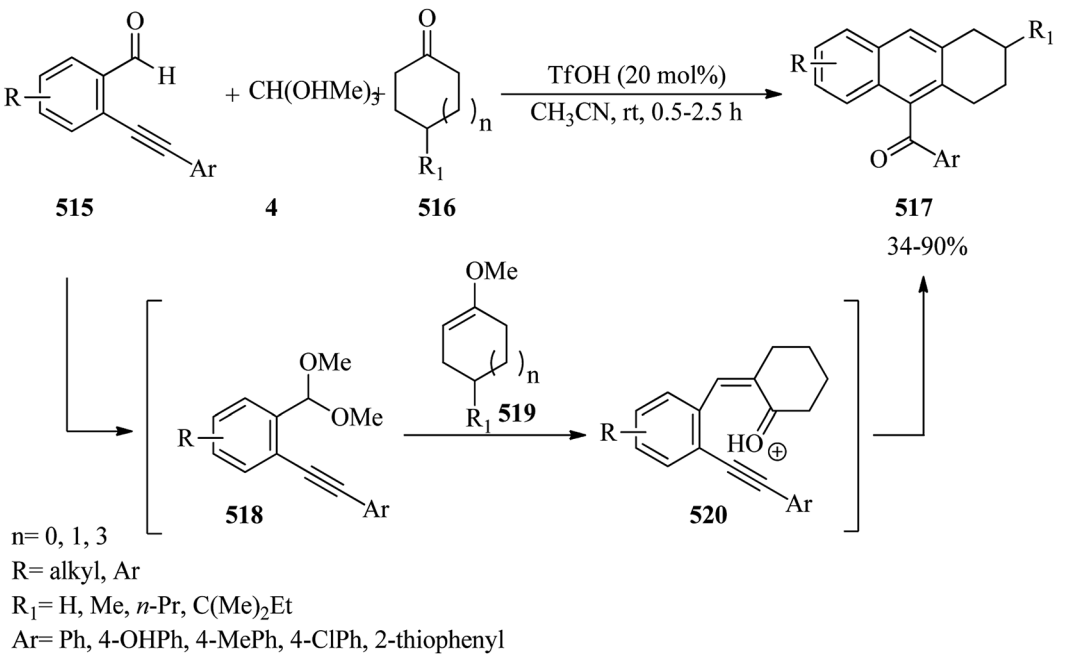


Scheme 150 The reaction of chalcones with TMOF.

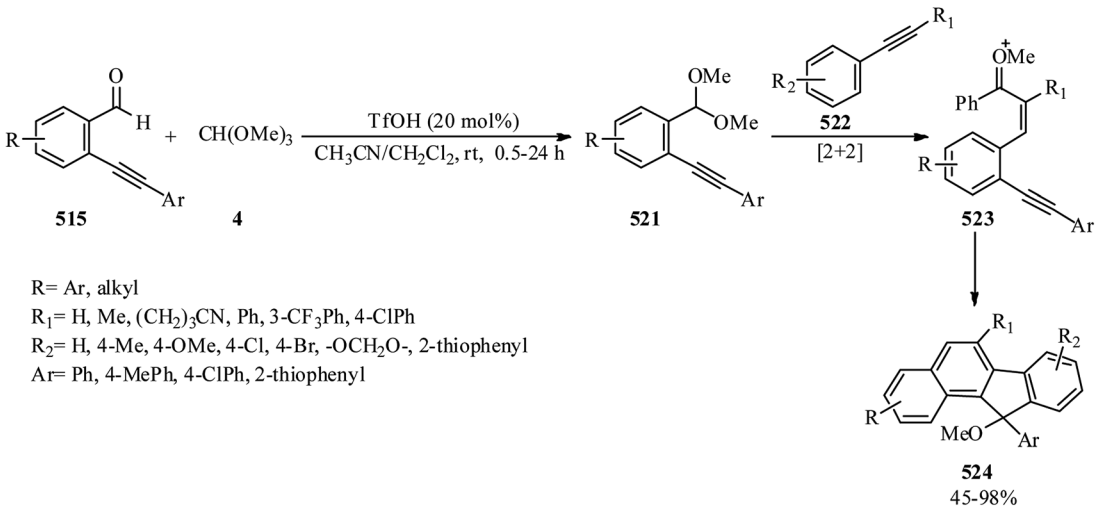


Scheme 151 The oxidation of 2-formyl-4-methoxyphenol with TMOF.

The reaction of chalcones (**507**) with TMOF (**4**) was accomplished using thallium(III) trinitrate (TTN) in acidic methanol to afford a 50 : 50 mixture of 3,3-dimethoxy-1,2-diphenylpropan-1-one (**508**, Ar = Ar_1 = C_6H_5) and methyl 2,3-diphenyl-3-methoxypropanoate (**512**, Ar = Ar_1 = C_6H_5). The keto acetal (**508**)[423] was obtained through normal Ar ring migration, while the ester (**512**) was obviously achieved by migration of the Ar_1 ring. As shown in Scheme 150, owing to the low rate of the treatment of chalcone with TTN and also the faster reaction of aldehydes and ketones with TMOF by TTN to form acetals and ketals,[424] the ketalization reaction of chalcone apparently competes with oxidative rearrangement. Hence, the oxidative rearrangement resulted in product (**508**) and the ketalization reaction formed intermediate (**510**) which upon treatment with TTN was converted into intermediate (**511**). Finally, the 1,2-migration of the Ar_1 group and the respective elimination of TTN furnished product (**512**) (Scheme 150).[425]



Scheme 152 The synthesis of naphthalenes *via* domino three-component condensation.

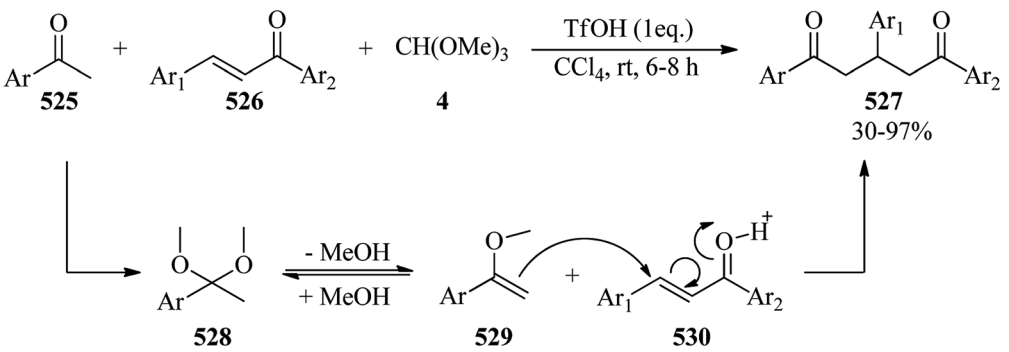


Scheme 153 The regioselective synthesis of substituted benzo[*a*]fluorenes.

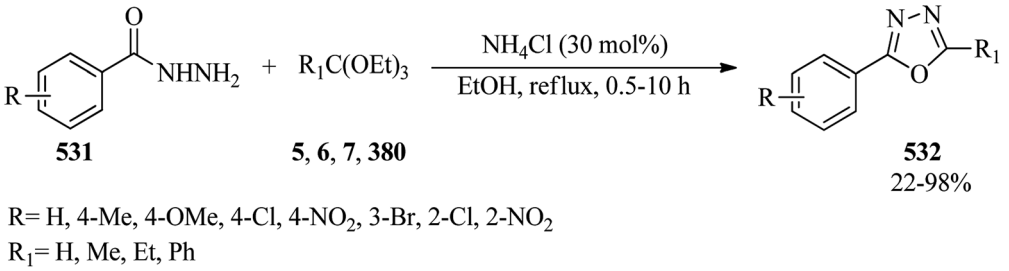
2-Dimethoxymethyl-4,4-dimethoxycyclohexa-2,5-dienone (**514**) could be prepared *via* oxidation of 2-formyl-4-methoxyphenol (**513**) with TMOF (**4**), utilizing thallium trinitrate[426,427] in methanol at −20 °C while the oxidation of 2-methoxycarbonyl-4-methoxyphenol furnished 2-methoxycarbonyl-3,4,4-trimethoxycyclohexa-2,5-dienone (Scheme 151).[427]

In 2007, Graham and Smith demonstrated that alcohols could be transformed directly into either acyclic or cyclic acetals in both tandem and sequential oxidation/acetalization processes using manganese dioxide, trialkyl orthoformates and an indium triflate catalyst in dichloromethane at ambient temperature.[428] In 2015, Manojveer and Balamurugan developed a convenient method for the synthesis of naphthalenes (**517**) *via* a domino three-component condensation reaction of *o*-alkynylbenzaldehydes (**515**), ketones (**516**), and TMOF (**4**) in the presence of TfOH (20 mol%) in acetonitrile at room temperature (Scheme 152). This transformation was initiated *via* the condensation of *o*-alkynylbenzaldehyde (**515**) with TMOF (**4**) by TfOH to obtain the *in situ* formed acetal (**518**), which was condensed with enol ether (**519**), arising from the reaction of ketones with TMOF, to form chalcone (**520**) which underwent intramolecular cyclization reaction to afford naphthyl ketones (**517**).[429]

Manojveer and Balamurugan presented a facile and efficient process to get substituted benzo[*a*]fluorenes (**524**), with regioselectivity *via* a domino three-component reaction of *o*-alkynylbenzaldehydes, alkynes, and TMOF by TfOH (20 mol%) in CH_3CN or CH_2Cl_2 at room temperature. This reaction proceeded through the reaction of aldehydes (**515**) with TMOF (**4**) by TfOH to obtain the *in situ* formed acetal (**521**). Subsequent [2 + 2] cycloaddition between acetal (**521**) and alkynes (**522**) generated the *cis*-isomer (**523**) which on intramolecular annulation reaction achieved substituted benzo[*a*]fluorenes (**524**) in 45–98% yields in 0.5–24 h (Scheme 153).[430]



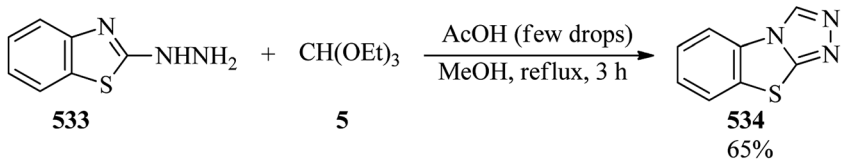
Scheme 154 The preparation of 1,5-diketones.



531 **5, 6, 7, 380** **532** 22-98%

R= H, 4-Me, 4-OMe, 4-Cl, 4-NO_2, 3-Br, 2-Cl, 2-NO_2
R_1= H, Me, Et, Ph

Scheme 155 Synthetic approach for substituted 1,3,4-oxadiazoles.



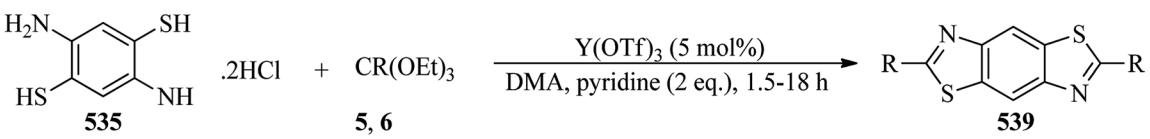
533 **5** **534** 65%

Scheme 156 The formation of 1,2,4-triazolo[3,4-*b*]benzothiazole.

TfOH catalyzed the one-pot three-component reaction of ketones, such as acetophenones and ethyl phenyl ketones (**525**), chalcones (**526**), and TMOF (**4**) in carbon tetrachloride (CCl_4) at room temperature to obtain a series of symmetrical and unsymmetrical 1,5-diketones (**527**) within 6–8 h. This reaction progressed through the *in situ* formation of acetals (**528**) from the reaction of ketones with TMOF which set up an equilibrium with the enol ether (**529**), as an Michael acceptor, which was followed by Michael addition with the activated chalcones by an acidic catalyst (**530**) to afford 1,5-diketones (**527**). Replacing acetophenones with ethyl phenyl ketones yielded a mixture of diastereomeric 1,5-diketones (where the *syn* diastereomers were the major product) in 55–95% yields (Scheme 154).[431]

4.23. Synthesis of benzoxazoles, benzothiazoles, benzimidazoles, oxazoles, oxadiazoles, and imidazoles

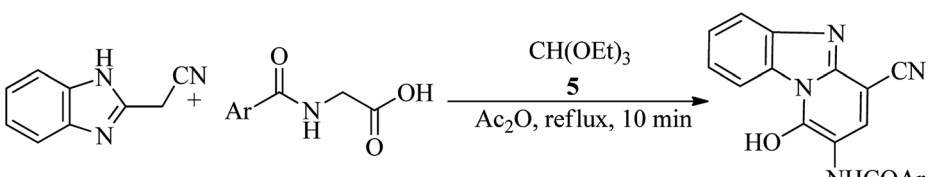
In 2009, Lee *et al.* reported a simple and effective procedure for the generation of benzoxazoles and oxazoles *via* the one-pot reduction-triggered heterocyclization reaction. Indium/acetic acid promoted the reaction of 2-nitrophenols with trimethyl orthoesters in refluxing benzene to produce benzoxazoles[432–434] in 50–98% yields in a 1 h period. In a similar manner, 1-aryl-2-nitroethanones upon treatment with trimethyl orthobenzoate using In/AcOH in refluxing acetonitrile afforded oxazoles in 1 h in 46–72% yields.[434] In 2014, Gnanasekaran and co-workers reported arylhydrazides (**531**) on reaction with orthoesters (**5**, **6**, **7**, **380**) by NH_4Cl (30 mol%) as catalyst in a polar solvent like



535 **5, 6** **539** 38-68%

536: R= CH_2Cl
537: R= $C_2Si(Me)_3$
538: R= CO_2Et

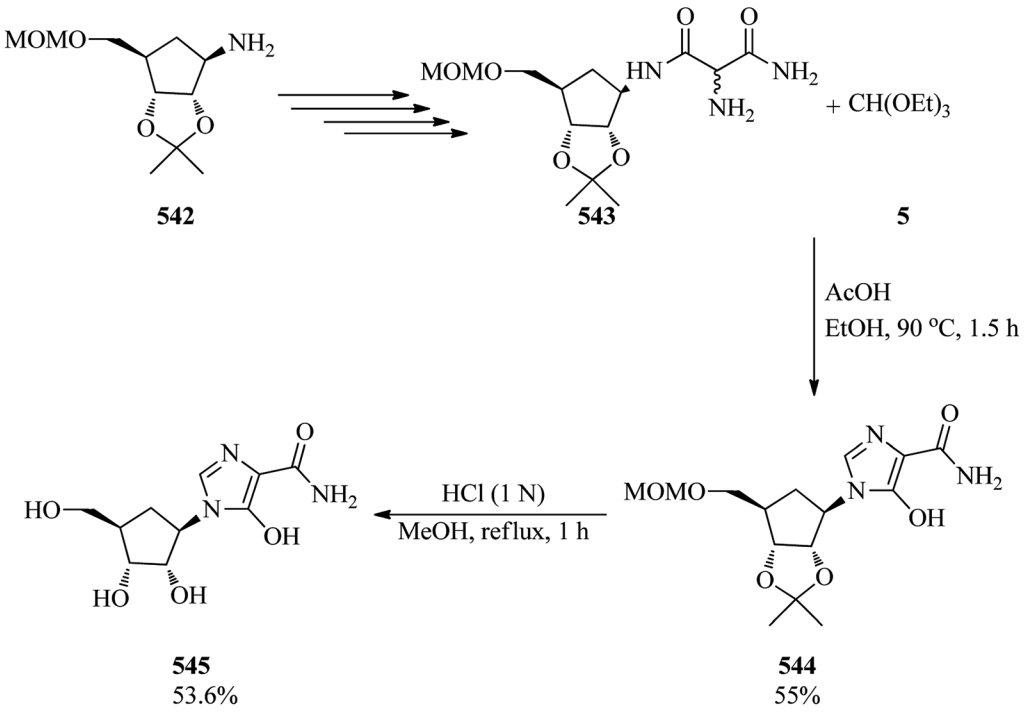
Scheme 157 The formation of disubstituted benzobisthiazoles.



540 **407** **541** 84-91%

Ar= Ph, 4-MePh, 4-OMePh, 4-ClPh

Scheme 158 The synthesis of pyrido[1,2-*a*]benzimidazole derivatives.

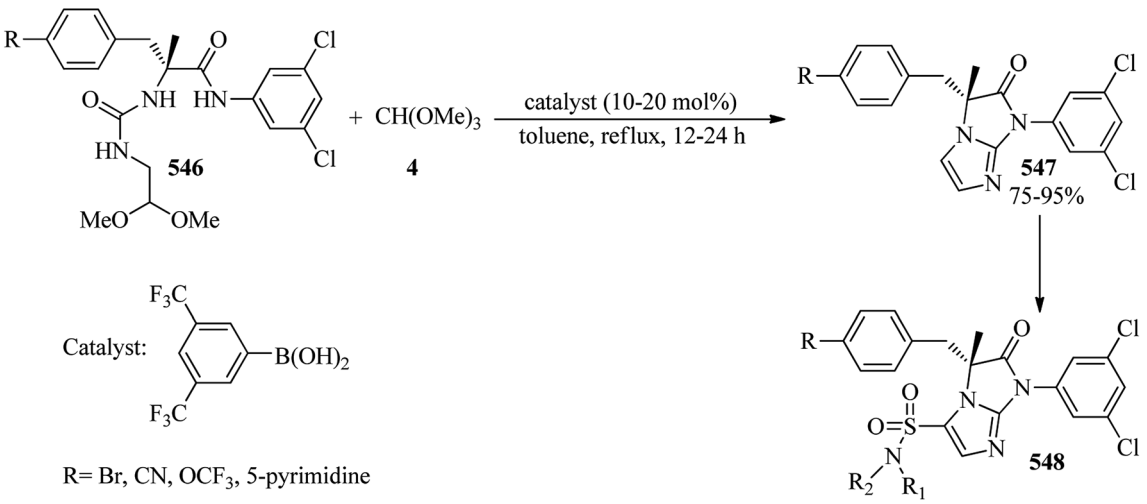


Scheme 159 Synthesizing a carbocyclic analog of bredinin.

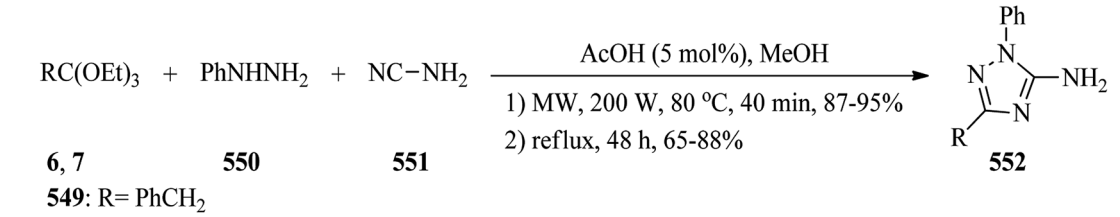
ethanol under reflux conditions yielding 2-substituted and 2,5-disubstituted 1,3,4-oxadiazoles (**532**)[435–437] within 0.5–10 h, in 22–98% yields (Scheme 155). The reaction was successful with electron-releasing and electron-withdrawing groups on the arylhydrazide precursor and progressed gently for both non-aromatic and aromatic orthoesters.[438]

In 2014, Al-Majidi obtained 1,2,4-triazolo[3,4-*b*]benzothiazole (**534**) as pale yellow crystals on treatment of 2-hydrazinobenzothiazole (**533**) with TEOF (**5**) in the presence of a few drops of acetic acid in refluxing methanol for 3 h in 65% yield (Scheme 156). The synthesized compound showed moderate antimicrobial activity against *Serratia* but was inactive against *Staphylococcus aureus*.[439]

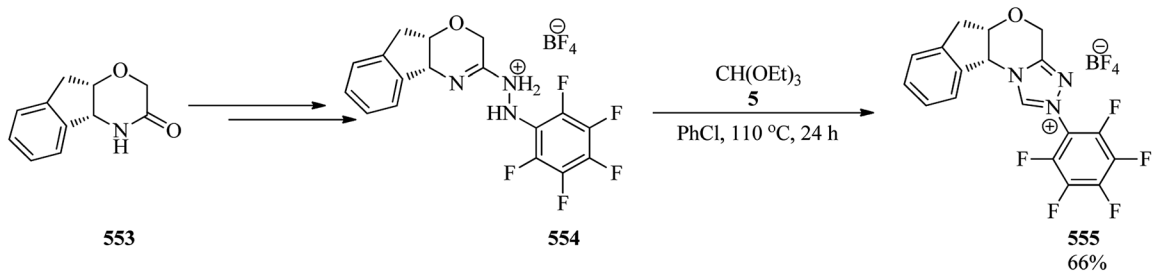
2-Oxo-2*H*-pyrimido[2,1-*b*]benzothiazole-3-carbonitriles were prepared through the cyclocondensation of cyanoacetamides with TEOF in nitrobenzene at 190–200 °C in 77–79% yields within 3 h.[440] In 2010, the Jeffries-EL group prepared some classes of synthetically useful 2,6-disubstituted benzobisthiazoles (**539**) based on the Lewis acid-catalyzed ring-closing reaction between diamino benzene dithiol (**535**) and substituted orthoesters (**5**, **6**, **536**, **537**, **538**) in dimethylacetamide (DMA) as organic solvent (Scheme 157). These products



Scheme 160 The cyclodehydration of ureas with TMOF.



Scheme 161 The synthesis of 5-amino-1-phenyl-1,2,4-triazoles.

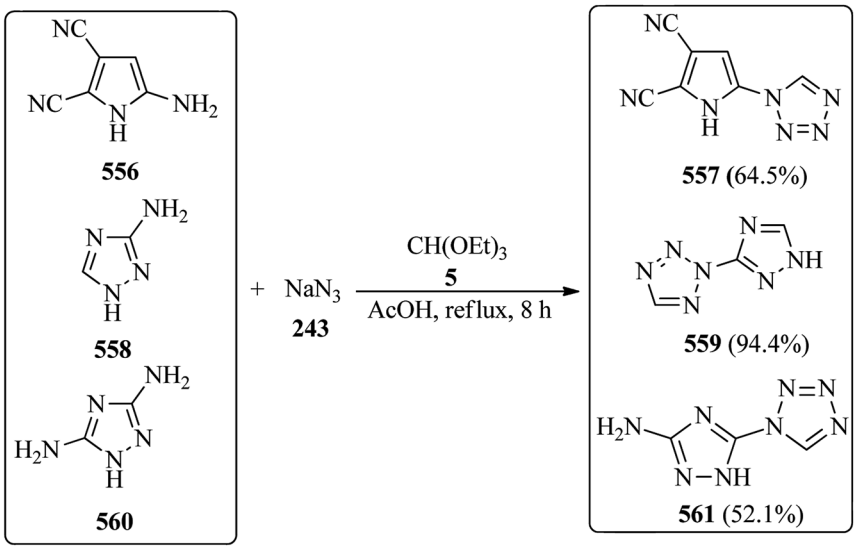


Scheme 162 The preparation of pentafluorophenyl triazolium salt.

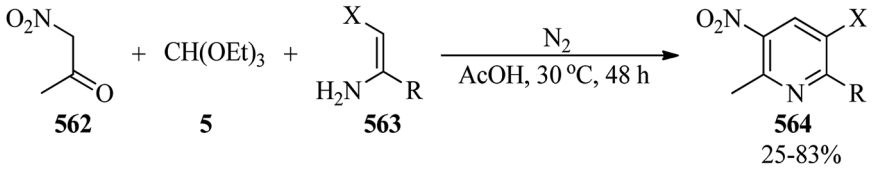
are of interest for the development of new organic semiconductors.[441]

Wang *et al.* developed a mild and facile two-step one-pot method for the synthesis of benzo and heteroaromatic fused imidazoles.[442–445] In first step, *ortho*-nitroanilines were converted into *ortho*-diamines by the reduction of the nitro group using iron powder. In the next step, cyclization occurred between *ortho*-diamines and TEOF by catalytic amounts of ytterbium triflate (0.005 equiv.) in acetic acid (1.0 M) at 75 °C to obtain the corresponding imidazoles within 3 h.[445] Benzimidazoles[308,446,447] were also prepared by Zhang *et al.* from *o*-phenylenediamines with orthoesters using sulfamic acid (0.05 mmol) in methanol at room temperature in 0.5–5 h in excellent yields (85–98%).[447] $ZrCl_4$ in ethanol at room temperature also accelerated this transformation within 0.8–6 h in excellent yields (81–95%).[448] In 2004, the one-pot three-component reaction of 2-cyanobenzimidazole (**540**), TEOF (**5**), and hippuric acid (**407**) was presented for the synthesis of pyrido[1,2-*a*]benzimidazole derivatives (**541**)[359,449] in refluxing acetic anhydride within 10 min, in excellent yields (84–91%) (Scheme 158).[359]

Due to the noteworthy biological activities of the natural nucleoside antibiotic, bredinin, such as antiviral and antihepatitis C effects, and its versatile biological activities, Nair and Zhang synthesized a new carbocyclic analog of bredinin (**545**) using (3*aS*,4*R*,6*R*,6*aR*)-6-((methoxymethoxy)methyl)-2,2-dimethyltetrahydro-3*aH*-cyclopenta[*d*][1,3]dioxol-4-amine (**542**)



Scheme 163 Synthesizing a library of nitrogen-rich heterocycles.



562 5 563 564

25-83%

X = CN, COPh, NO_2, COMe

R = Me, Ph

Scheme 164 The cyclocondensation of nitroacetone, TEOF, and enamines.

as a key precursor. In the first step, (**542**) was converted into the malondiamide intermediate (**543**) *via* side-chain functional group conversions. Subsequently, (**543**) on reaction with TEOF (**5**) by acetic acid as catalyst under heating in ethanol at 90 °C underwent cyclization to afford the appropriate 4-carbamoyl-imidazolium-5-olate ring (**544**) within 1.5 h in moderate yield (55%). In the final step, the deprotection reaction of the recent compound (**544**) resulted in (**545**) (Scheme 159). The resultant product displayed antiviral activity, although it was low, against a number of RNA viruses. More biological properties are under investigation.[450]

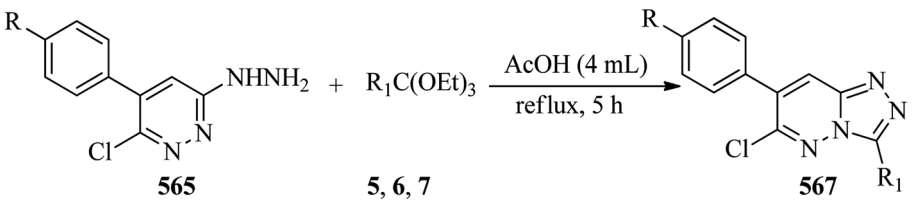
The cyclodehydration of urea derivatives (**546**) with TMOF (**4**) was accomplished in the presence of boronic acid (10–20 mol%) under refluxing toluene to attain compounds (**547**) in 75–95% yields in 12–24 h which as key intermediates were converted into a 1*H*-imidazo[1,2-*a*]imidazol-2-one LFA-1 antagonist (**548**) (Scheme 160).[451]

4.24. Synthesis of thiadiazoles, triazoles, and 1*H*-tetrazoles

2-Alkylamino-1,3,4-thiadiazoles have been synthesized *via* the ethanol-mediated reaction of 4-alkylthiosemicarbazide and TEOF, in a 1 : 2 molar ratio, through the accelerated role of concentrated hydrochloric acid by Tomalia and Pmge in 1973.[452] In 2015, Aouali *et al.* prepared 5-amino-1-phenyl-1,2,4-triazole derivatives (**552**) through the one-pot three-component reaction of orthoester (**6**, **7**, **549**), phenylhydrazine (**550**) and cyanamide (**551**) by acetic acid (5 mol%) in methanol through two different pathways: (a) utilizing microwave irradiation (200 W) at 80 °C, and (b) under classical heating conditions. The results indicated shorter reaction times and higher yields by the microwave method (87–95%, 40 min) (Scheme 161).[453]

Kerr and co-workers synthesized various chiral and achiral 1,2,4-triazolium salts as key precursors for the generation of N-heterocyclic carbine. In this paper, various 1,2,4-triazolium salts were obtained under different conditions, *e.g.* pentafluorophenyl triazolium salt (**555**) as a light tan solid was produced through the reaction of hydrazinium tetrafluoroborate (**554**), arising from morpholinone derivative (**553**), with TEOF (**5**) in chlorobenzene at 110 °C in 24 h in 66% yield (Scheme 162).[454]

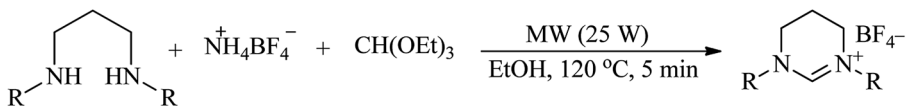
Chuprun *et al.* synthesized tetrazoles *via* the enantioselective reaction of α-amino acids with sodium azide and TEOF in the presence of glacial acetic acid both as catalyst and solvent at 55 °C within 4 h in weak to good yields (23–83%). The product structure was characterized by ^{1}H and ^{13}C NMR and mass spectra, and their stereoisomeric excess amounts were assigned by chiral HPLC (20–100%).[455] 1-(6,7,9,10,17,18,20,21-Octahydrodibenzo[*b*,*k*]-[1,4,7,10,13,16]hexaoxacyclooctadecen-2-yl)-



565 5, 6, 7 567

R, R_1 = H, Me, Et, OMe **566**: R_1 = OMe 20-60%

Scheme 165 The synthesis of some new [1,2,4]triazolo[4,3-*b*]pyridazines.

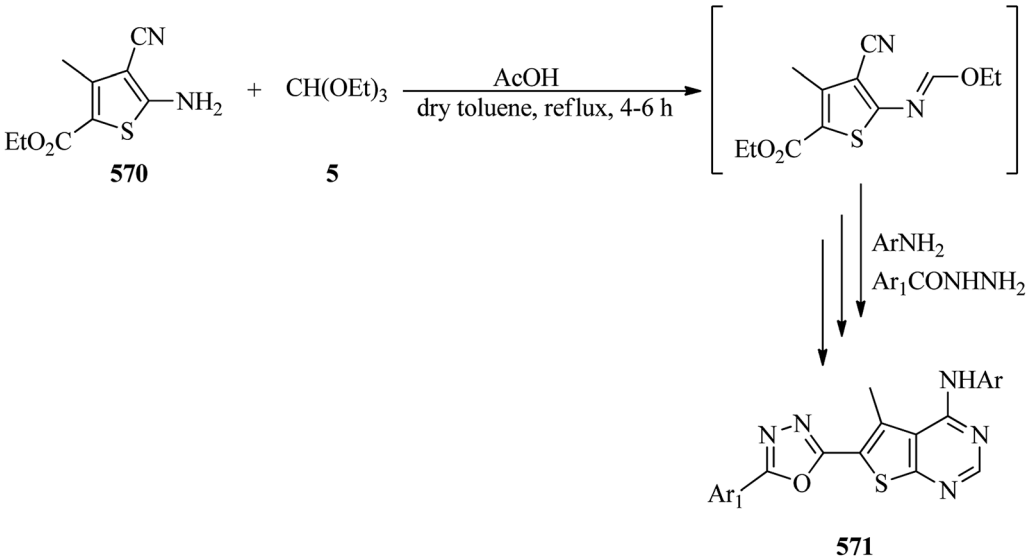


568 328 5 569

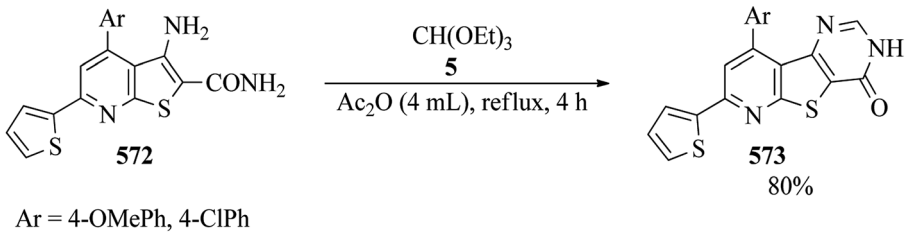
88-99%

R = Me, Et, $CH(Me)_2$, *t*-Bu, cyclohexyl

Scheme 166 The cyclization of *N*,*N*′-dialkyl ethane-1,2-diamines with ammonium salts and TEOF.

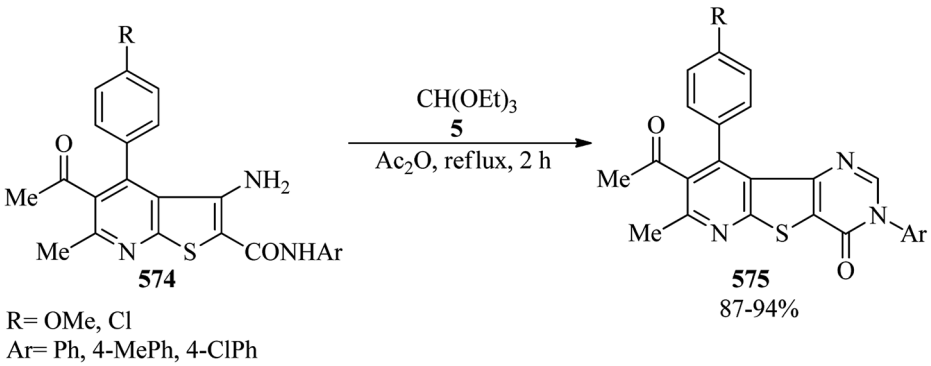


Scheme 167 Obtaining 1,3,4-oxadiazole tagged thieno[2,3-*d*]pyrimidine derivatives.

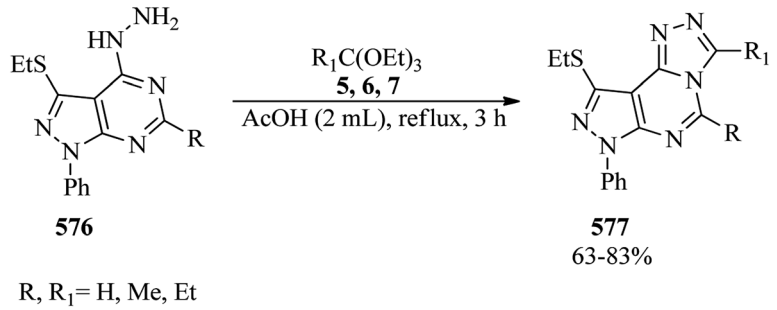


Scheme 168 The formation of 9-aryl-7-(2′-thienyl)-pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine-4(3*H*)-ones.

1*H*-tetrazole (**2**) could be synthesized *via* the domino three-component reaction of an arylamino derivative of dibenzo-18-crown-6 (**1**), TEOF, and sodium azide under heating in glacial acetic acid at 105 °C for 3 h in 73% yield.[456] $Yb(OTf)_3$ also promoted the reaction of amines, TEOF, and sodium azide in 2-methoxyethanol at 100 °C to prepare the 1-susbstituted 1*H*-1,2,3,4-tetrazoles[457–462] in 6–9 h in 71–91% yields. Some of the products revealed phytocidal activity.[462] Muralidharan *et al.* also synthesized a library of nitrogen-rich heterocycles, such as 2-(1*H*-tetrazol-1-yl)-1*H*-imidazole-4,5-dicarbonitrile (**557**), 1-(1*H*-1,2,4-triazol-3-yl)-1*H*-tetrazole (**559**), and 5-(1*H*-tetrazol-1-yl)-1*H*-1,2,4-triazol-3-amine (**561**) *via* the critical role of TEOF. As could be seen, the above-mentioned compounds were obtained *via* the reaction of TEOF and also NaN_3 (**243**) with 2-amino-1*H*-imidazole-4,5-dicarbonitrile (**556**), 1*H*-1,2,4-triazol-3-amine (**558**), and 1*H*-1,2,4-triazole-3,5-diamine (**560**), as starting materials, respectively (Scheme 163).[463]



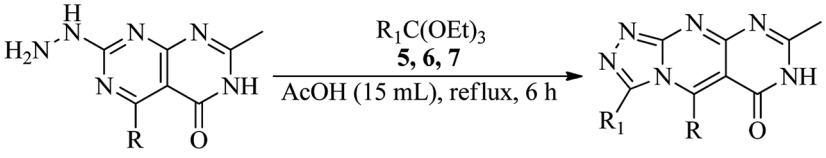
Scheme 169 The preparation of 8-acetyl-3,9-diaryl-7-methylpyrido[3′,2′:4,5]thieno[2,3-*d*]pyrimidine-4(3*H*)-ones.



576 577 63-83%

R, R_1= H, Me, Et

Scheme 170 Obtaining pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidines.



578 R= H, Me; R_1= H, Me, Et 579 40-90%

Scheme 171 The formation of pyrimido[4,5-*d*][1,2,4]triazolo[4,3-*a*]pyrimidin-6(7*H*)-ones.

4.25. Synthesis of pyridines

5-Nitropyridines (**564**) were obtained by Sagitullina *et al. via* the cyclocondensation of nitroacetone (**562**), TEOF (**5**) and enamines (**563**) in acetic acid media (Scheme 164).[464]

4.26. Synthesis of pyridazine derivatives

6-Methyl-3,4-diphenylpyrimido[4′,5′:4,5]selenolo[2,3-*c*]pyridazine-8(7*H*)-one was synthesized *via* the cyclocondensation reaction of 5-amino-3,4-diphenyl-6-substitutedselenolo[2,3-*c*]pyridazine with TEOF in acetic anhydride under reflux conditions within 8 h in 72% yield.[465] In 2015, Arghiani and coworkers reported a simple procedure for the synthesis of new [1,2,4]triazolo[4,3-*b*]pyridazines (**567**) on treatment of 6-choloro-5-(4-substituted phenyl)-3-pyridazinyl hydrazines (**565**) with orthoesters (**5, 6, 7, 566**) in refluxing acetic acid for 5 h (Scheme 165). The products were filtered off and crystallized from methanol.[466]

4.27. Synthesis of tetrahydropyrimidinium salts

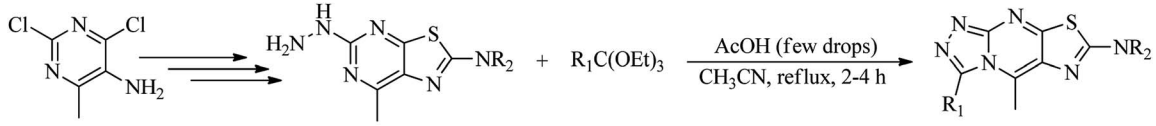
The cyclization of *N*,*N*′-dialkyl or diaryl ethane-1,2-diamines or propane-1,3-diamines (**568**) with inorganic ammonium salts (**328**) and TEOF (**5**) proceeds under microwave irradiation to afford the corresponding imidazolinium or tetrahydropyrimidinium salts (**569**). As can be seen in the Scheme 166, the microwave-assisted preparation of some 1,3-diaryl-3,4,5,6-tetrahydropyrimidium tetrafluoroborates was performed in ethanolic media. The TEOF is in 2–6 excess to the other substrates.[467]

4.28. Synthesis of pyrimidine derivatives

In the synthetic route to obtain 1,3,4-oxadiazole tagged thieno[2,3-*d*]pyrimidine derivatives (**571**), the first step was reported *via* the reaction of 5-amino-4-cyano-3-methylthiophene-2-carboxylate (**570**) with TEOF, in refluxing toluene through the catalytic activity of acetic acid (Scheme 167).[468]

In 2003, Abdel-Rahman and coworkers have reported that pyridine-2-carboxamide derivatives (**572**) were reacted with TEOF in refluxing acetic anhydride to furnish white crystals of 9-aryl-7-(2′-thienyl)-pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine-4(3*H*)-ones (**573**) (Scheme 168).[469–471]

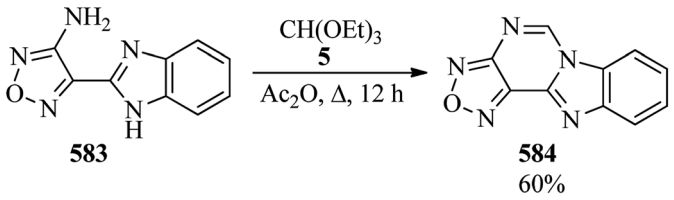
The cyclocondensation of 5-acetyl-3-amino-4-aryl-2-(*N*-aryl) carbamoyl-6-methyl-thieno[2,3-*b*]pyridines (**574**) with TEOF was



580 581 5, 6 582 62-89%

R= $-CH_2(CH_2)_2CH_2-$, $-CH_2(CH_2)_3CH_2-$, $-CH_2CH_2OCH_2CH_2-$, $-CH_2CH_2NMeCH_2CH_2-$
R_1= H, Me

Scheme 172 A novel thiazolo[5,4-*d*][1,2,4]triazolo[4,3-*a*]pyrimidine preparation approach.



Scheme 173 The synthesis of benzo[4,5]imidazo[1,2-*c*]-[1,2,5]oxadiazolo[3,4-*e*]pyrimidine.

accomplished in refluxing acetic anhydride, in a dual role of catalyst and solvent, to achieve 8-acetyl-3,9-diaryl-7-methylpyrido[3′,2′:4,5]thieno[2,3-*d*]pyrimidine-4(3*H*)-ones (**575**)[325,472] in excellent yields (87–94%) in 2 h (Scheme 169).[325]

Pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidines (**577**) were produced *via* the cyclocondensation reaction of pyrazolo[3,4-*d*] pyrimidine (**576**) with triethyl orthoesters (**5**, **6**, **7**) in a 1 : 2 molar ratio in acetic acid, in a dual role of solvent and catalyst, under reflux conditions within 3 h in 63–83% yields (Scheme 170).[473]

Pyrimido[4,5-*d*][1,2,4]triazolo[4,3-*a*]pyrimidin-6(7*H*)-ones (**579**) were made through cyclocondensation of 7-hydrazinyl-substituted pyrimido[4,5-*d*]pyrimidin-4(3*H*)-ones (**578**) with triethyl orthoesters (**5**, **6**, **7**) in equimolar amounts in refluxing AcOH in a 6 h period in 40–90% yields (Scheme 171). The products showed fluorescent and photophysical properties.[474]

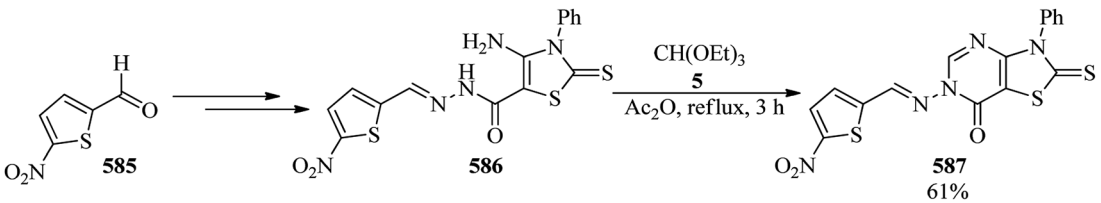
In 2016, 2,4-dichloro-5-amino-6-methylpyrimidine (**580**) was applied as a starting material for the synthesis of 5-hydrazinyl-7-methyl[1,3]thiazolo[5,4-*d*]pyrimidines (**581**) *via* a multi-step reaction which, on a cyclization reaction with orthoesters (**5**, **6**) in refluxing acetonitrile using catalytic amounts of acetic acid along with the elimination of 3 moles of ethanol, furnished novel thiazolo[5,4-*d*][1,2,4]triazolo[4,3-*a*]pyrimidines (**582**) for 2–4 h in high yields (62–89%) (Scheme 172).[475]

Benzo[4,5]imidazo[1,2-*c*]-[1,2,5]oxadiazolo[3,4-*e*]pyrimidine (**584**) was obtained *via* the cyclocondensation of 3-amino-4-(1*H*-benzo[*d*]imidazol-2-yl)-1,2,5-oxadiazole (**583**) with TEOF in boiling acetic anhydride for 12 h, in 60% yield (Scheme 173).[476]

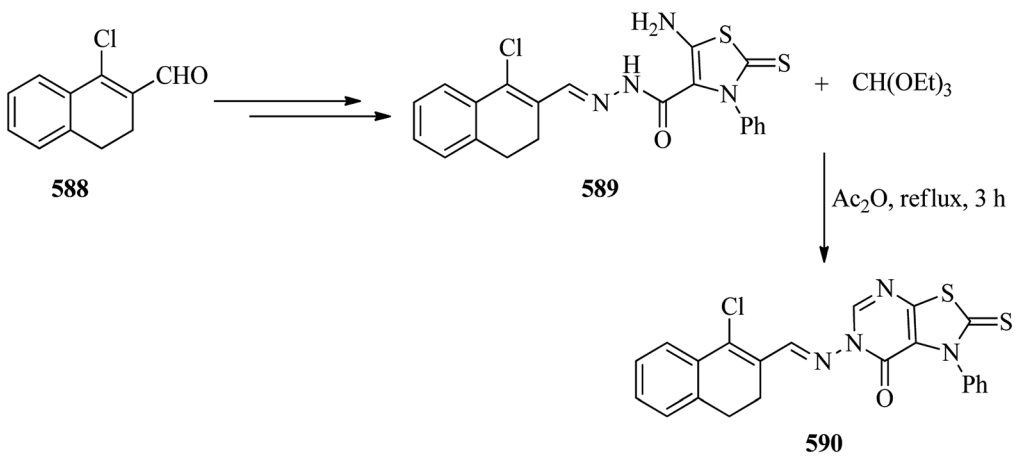
6-{[(5-Nitrothiophen-2-yl)methylene]amino}-3-phenyl-2-thioxo-2,3-dihydrothiazolo-[4,5-*d*]-pyrimidin-7(6*H*)-one (**587**)[477,478] as a brown compound was prepared *via* the cyclocondensation of thiazoline derivative (**586**), arising from 5-nitro-2-thiophenecarboxaldehyde (**585**), with TEOF in the presence of acetic anhydride under reflux conditions within 3 h in 61% yield (Scheme 174). The product (**587**) revealed good anti-inflammatory activity.[478]

Due to the growing biological importance of fused thiazoles, in 2007, Bondock *et al.* employed 1-chloro-3,4-dihydronaphthalene-2-carboxaldehyde (**588**) as a key precursor for the formation of thiazoline derivative (**589**) *via* a multi-step reaction. Subsequent cyclization with TEOF in acetic anhydride under reflux conditions yielded the thiazolo[5,4-*d*]pyrimidine derivative (**590**) in 60% yield in 3 h (Scheme 175). The compounds were screened and evaluated as antimicrobial agents.[479]

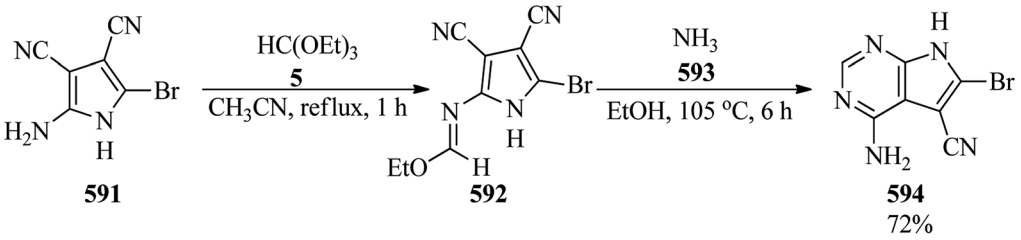
In 1998, Porcari and Townsend developed a fast and efficient method for the preparation of 4-amino-6-bromo-5-cyanopyrrolo



Scheme 174 The synthesis of 6-{[(5-nitrothiophen-2-yl)methylene]amino}-3-phenyl-2-thioxo-2,3-dihydrothiazolo-[4,5-*d*]-pyrimidin-7(6*H*)-one.



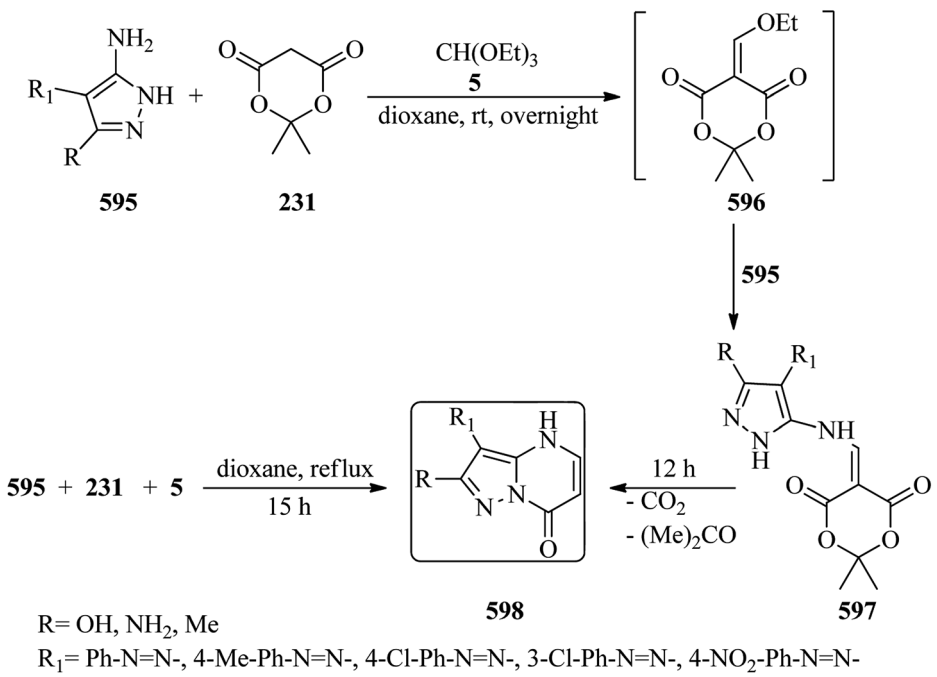
Scheme 175 Achieving thiazoline derivatives.



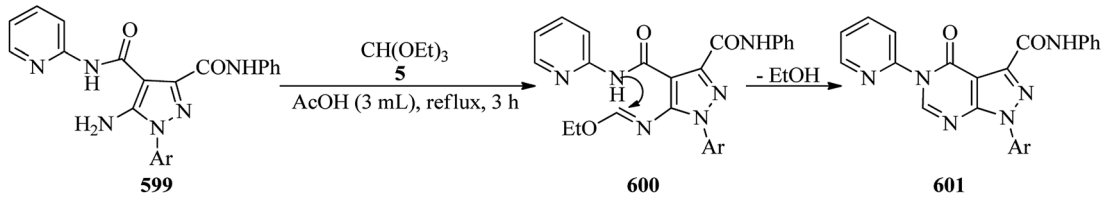
Scheme 176 The preparation of 4-amino-6-bromo-5-cyanopyrrolo[2,3-*d*]pyrimidine.

[2,3-*d*]pyrimidine (**594**) from 2-amino-5-bromo-3,4-dicyanopyrrole (**591**), TEOF (**5**), and ethanolic ammonia (**593**). In the first step the reaction of 2-amino-5-bromo-3,4-dicyanopyrrole (**591**) with triethylorthoformate (**5**) in dry acetonitrile at reflux temperature, for 1 h formed 2-bromo-5-(ethoxymethylene)iminopyrrole-3,4-dicarbonitrile (**592**) which was used without further purification. Ring annulation to obtain 4-amino-6-bromo-5-cyanopyrrolo[2,3-*d*]pyrimidine (**594**) was accomplished by dissolving the unpurified intermediate (**592**) in saturated ethanolic ammonia and heating this mixture at 105 °C in a sealed steel reaction vessel for 6 h (Scheme 176).[480]

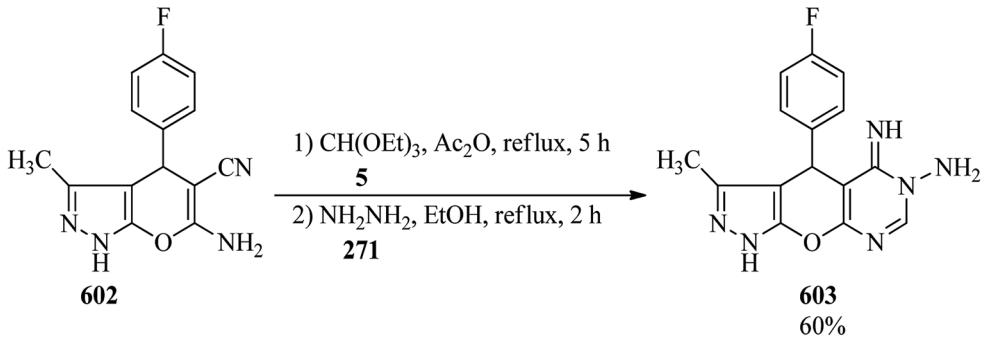
In 2015, Abdel Hameed *et al.* demonstrated a regioselective procedure for the synthesis of pyrazolo[1,5-*a*]pyrimdines-7(4*H*)-ones (**598**) *via* the reaction of 5-amino pyrazoles (**595**), Meldrum's acid (**231**), and TEOF (**5**) in dioxane at room temperature. This transformation took place *via* a Knoevenagel condensation of Meldrum's acid (**231**) with TEOF (**5**) to produce intermediate (**596**), as a Michael acceptor, followed by the regioselective Michael addition with the exocyclic amino moiety of 5-amino pyrazoles (**595**) to obtain the corresponding acyclic adducts (**597**) in dioxane at room temperature; which after isolation underwent an intramolecular cyclization and then the



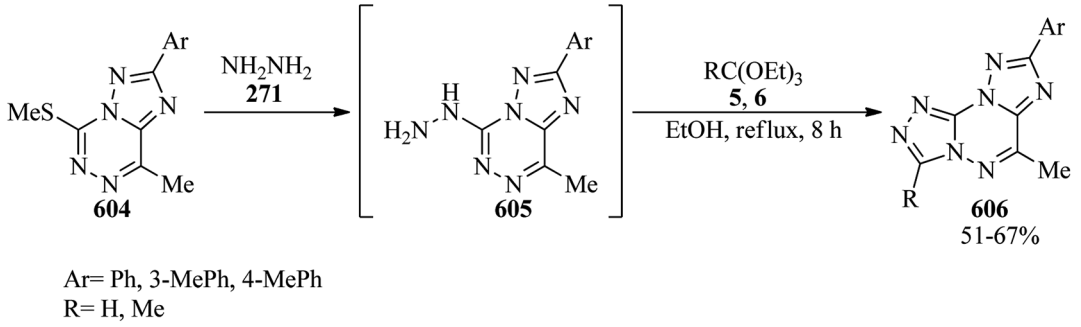
Scheme 177 The regioselective synthesis of pyrazolo[1,5-*a*]pyrimdines-7(4*H*)-ones.



Scheme 178 The synthesis of pyrazolo[3,4-*d*]pyrimidin-4-ones.



Scheme 179 The preparation of 4-(4-fluorophenyl)-5-imino-3-methyl-1,4-dihydropyrazolo[4′,3′:5,6]pyrano[2,3-*d*]pyrimidin-6(5*H*)-amine.

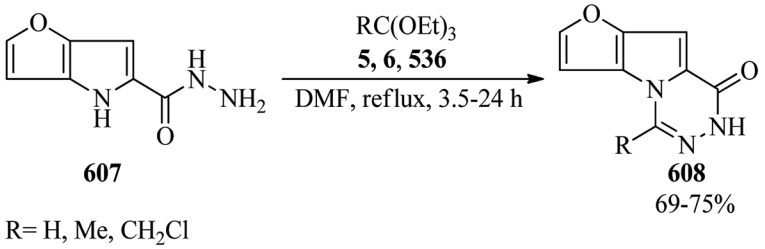


Scheme 180 The preparation of new bis[1,2,4]triazolo[4,3-*b*:1′,5′-*d*][1,2,4]triazines.

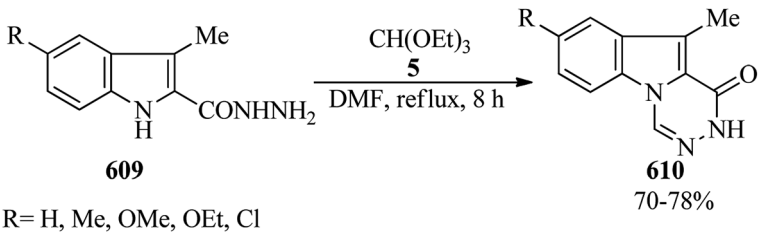
elimination of acetone and CO_2 to get pyrazolo[1,5-*a*]pyrimdines-7(4*H*)-ones (**598**) in refluxing dioxane for 12 h. The compound (**598**) could also be directly obtained at once *via* the one-step condensation reaction of substrates in refluxing dioxane for 15 h (Scheme 177).[481]

In 2008, a facile and high-yielding process was developed for the synthesis of pyrazolo[3,4-*d*]pyrimidin-4-ones (**601**) in excellent yields (82–92%). First, aminopyrazoles (**599**) were condensed with TEOF (**5**) in glacial acetic acid under reflux conditions for 3 h to form the intermediate (**600**) which was then followed by cyclization and removal of an equivalent ethanol to achieve (**601**) (Scheme 178).[482]

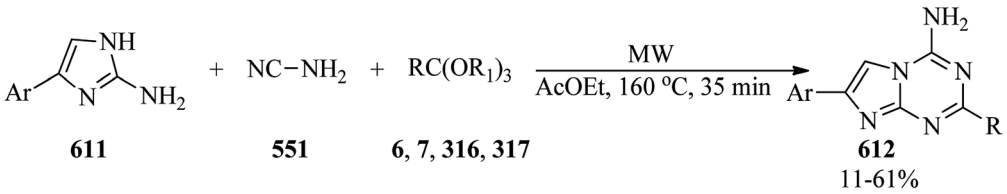
In 2015, 6-amino-3-methyl-4-fluorophenyl-1,4-dihydro-pyrano[2,3-*c*]pyrazole-5-carbonitrile (**602**) was employed as



Scheme 181 The synthesis of furo[2′,3′:4,5]pyrrolo[1,2-*d*][1,2,4]triazin-8(7*H*)-ones.



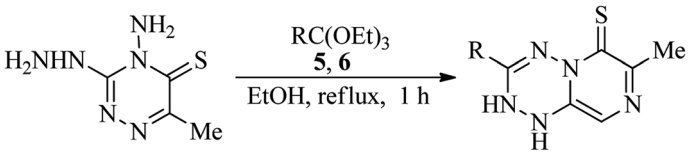
Scheme 182 The formation of new 8-substituted-10-methyl-l,2-dihydro-1-oxo-l,2,4-triazino[4,5-*a*]indoles.



611 **551** **6, 7, 316, 317** **612** 11-61%

Ar= Ph, 4-FPh, 4-ClPh, 4-MePh, 4-OMePh, biphenyl
R= Et, Pr, Bu
R_1= Et

Scheme 183 The synthesis of new 2-alkyl substituted 4-aminoimidazo[1,2-*a*][1,3,5]triazines.



613 **614** 58-78%

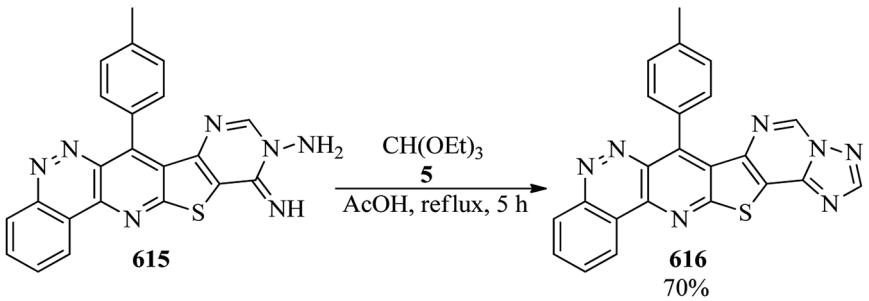
R= H, Me

Scheme 184 The preparation of [1,2,4]triazino[3,4-*b*][1,2,4,5]-tetrazine-6-thiones.

a starting material for the preparation of 4-(4-fluorophenyl)-5-imino-3-methyl-1,4-dihydropyrazolo[4′,3′:5,6]pyrano[2,3-*d*]pyrimidin-6(5*H*)-amine (**603**)[483,484] as yellow powder. Hence, in the first step, (**602**) was condensed with TEOF (**5**) in refluxing acetic anhydride for 5 h; which was followed by the reaction of the isolated solid with hydrazine hydrate (**271**) in ethanol under reflux conditions for 2 h to produce (**603**) in 60% yield (Scheme 179). The product was screened for antibacterial and antifungal activities compared with norfloxacin and fluconazole as standard drugs.[484]

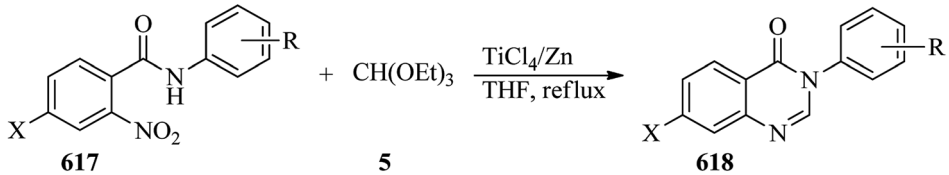
4.29. Synthesis of triazine derivatives

Montazeri *et al.* established a simple and catalyst-free method for the preparation of new bis[1,2,4]triazolo[4,3-*b*:1′,5′-*d*][1,2,4]triazines (**606**). This reaction progressed through the nucleophilic substitution reaction of 8-methyl-5-methylthio-2-aryl-6*H*-



615 **616** 70%

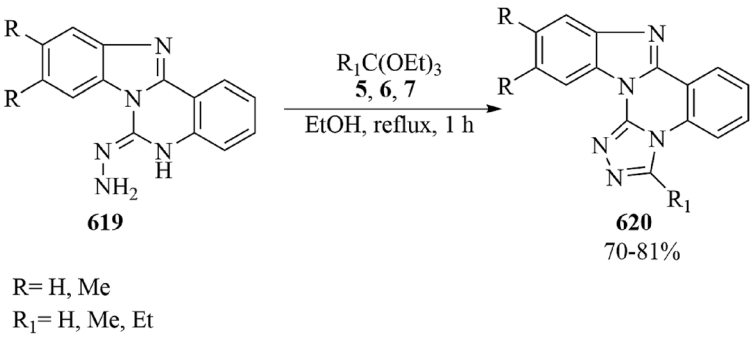
Scheme 185 The synthesis of 7-(*p*-tolyl)-1,2,4-triazolo[4‴,3‴:1″,6″]pyrimido[4″,5″:4′,5′]thieno[3′,2′:5,6]pyrido[3,2-*c*]cinnoline.



617 **5** **618** 79-93%

X = H, Cl
R = H, 4-Me, 4-Cl, 3-Cl-4-F, 4-Br

Scheme 186 The synthesis of quinazolin-4(3*H*)-ones.



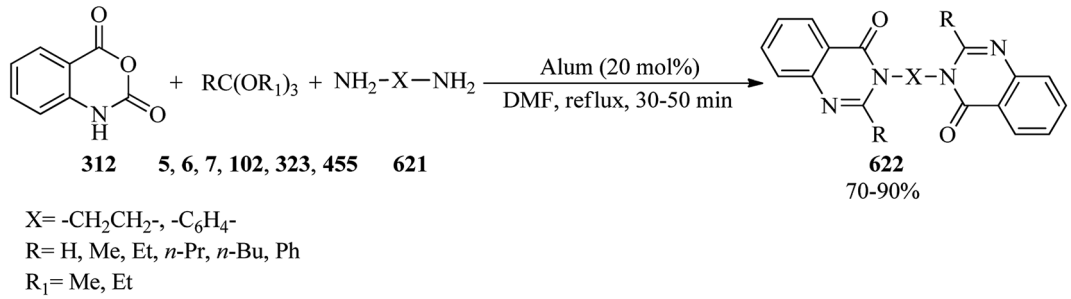
Scheme 187 Obtaining new benzimidazo[1,2-*c*][1,2,4]triazolo[4,3-*a*]quinazolines.

[1,2,4]triazolo[1,5-*d*][1,2,4]triazines (**604**) with hydrazine hydrate (**271**) in refluxing ethanol for 3 h to generate 5-hydrazino compounds (**605**); which was followed a cyclocondensation by triethyl orthoesters (**5**, **6**) under refluxing in ethanol for 8 h to produce products (**606**) in 51–67% yields (Scheme 180).[485]

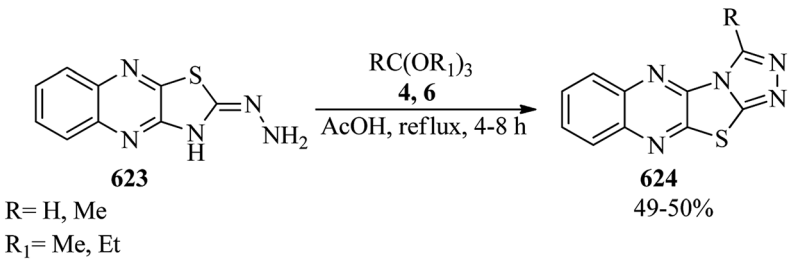
In 2017, the Zemanová group reported that 4*H*-furo[3,2-*b*] pyrrole-5-carbohydrazide (**607**) on reaction with orthoesters (**5**, **6**, **536**) in a polar solvent like DMF under reflux conditions yielded furo[2′,3′:4,5]pyrrolo[1,2-*d*][1,2,4]triazin-8(7*H*)-ones (**608**) within 3.5–24 h, in high yields (69–75%) (Scheme 181). The products were screened for their antibacterial activity on Gram-negative bacterial species *Escherichia coli* CCM 7929, *Pseudomonas syringae* CCM 2114 and Gram-positive bacterial species *Micrococcus luteus* CCM 732, *Bacillus pumilus* CCM 2218 and it was found to have good activity.[486]

In 1989, some new 8-substituted-10-methyl-l,2-dihydro-1-oxo-l,2,4-triazino[4,5-*a*]indoles (**610**) were prepared in 70–78% yields from the reaction of various 3-methylindole-2-carbohydrazides (**609**) with TEOF (**5**) in refluxing dimethylformamide within 8 h (Scheme 182). These derivatives were evaluated for their antimicrobial activity. Most of the compounds showed good activity against Gram-negative bacteria such as *Escherichia coli* and *Pseudomonas aeruginosa*. Chloro-substituted derivatives showed the highest activity against all of the organisms tested.[487]

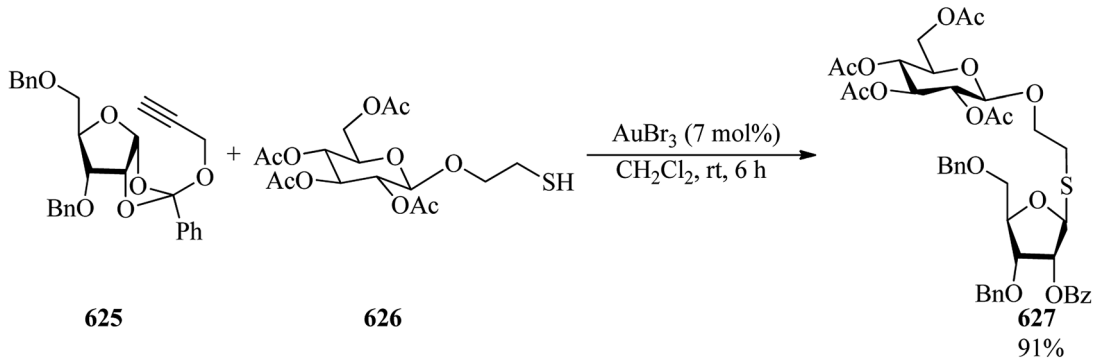
In 2018, Lim and *et al.* described a chemo- and regioselective procedure for the synthesis of new 2-alkyl substituted 4-aminoimidazo[1,2-*a*][1,3,5]triazines (**612**) in weak to good yields (11–61%) *via* the catalyst-free one-pot three-component reaction of 2-aminoimidazoles (**611**), trialkylorthoesters (**6**, **7**, **316**, **317**), and cyanamide (**551**) under microwave irradiation (Discover SP CEM) at 160 °C in ethyl acetate for 35 min (Scheme 183). It was found that a growth in length of the alkyl chain group on compound (**612**) resulted in a reduction in isolated yields. For example, the products originating from TEOAc (**6**) and triethyl orthopropionate, (**7**) obtained higher isolated yields than



Scheme 188 The formation of bis(quinazolinon-4(1*H*)-one) derivatives.



Scheme 189 The synthesis of novel 3-substitued [1,2,4]triazolo[3′,4′;2,3][1,3]triazolo[4,5-*b*]quinoxalines.



625 626 627 91%

Scheme 190 The synthesis of thiosaccharides and 1-thiotrehaloses.

triethyl orthobutyrate (**316**) or trimethyl orthovalerate (**317**), which could be ascribed to the proportionately lower reactivity of long-chain orthoesters for the preparation of compounds (**612**). Molecular and crystal building blocks of resultant molecules were examined using X-ray crystallography.[488]

4.30. Synthesis of tetrazine derivatives

Preyssler heteropolyacid ($H_{14}[NaP_5W_{30}O_{110}]$, 0.1 mmol) catalyzed the green one-pot reaction of 4-amino-3-hydrazino-6-methyl-1,2,4-triazin-5(2*H*)-one with orthoesters in acetic acid under reflux conditions to produce [1,2,4]triazino[4,3-*b*][1,2,4,5] tetrazines within 1–6 h in excellent yields (79–95%).[489] [1,2,4] Triazino[4,5-*b*][1,2,4,5]tetrazines were also prepared from the reaction of 6-methyl-4-amino-5-hydrazino-1,2,4-triazin-3-one with orthoesters.[490] [1,2,4]Triazino[3,4-*b*][1,2,4,5]-tetrazine-6-thiones (**614**) were synthesized in 58–78% yields upon treatment of 4-amino-6-methyl-3-hydrazino-4,5-dihydro-1,2,4-triazine-5-thione (**613**) with excess amounts of triethyl orthoesters (**5**, **6**) in refluxing ethanol for 1 h (Scheme 184).[491]

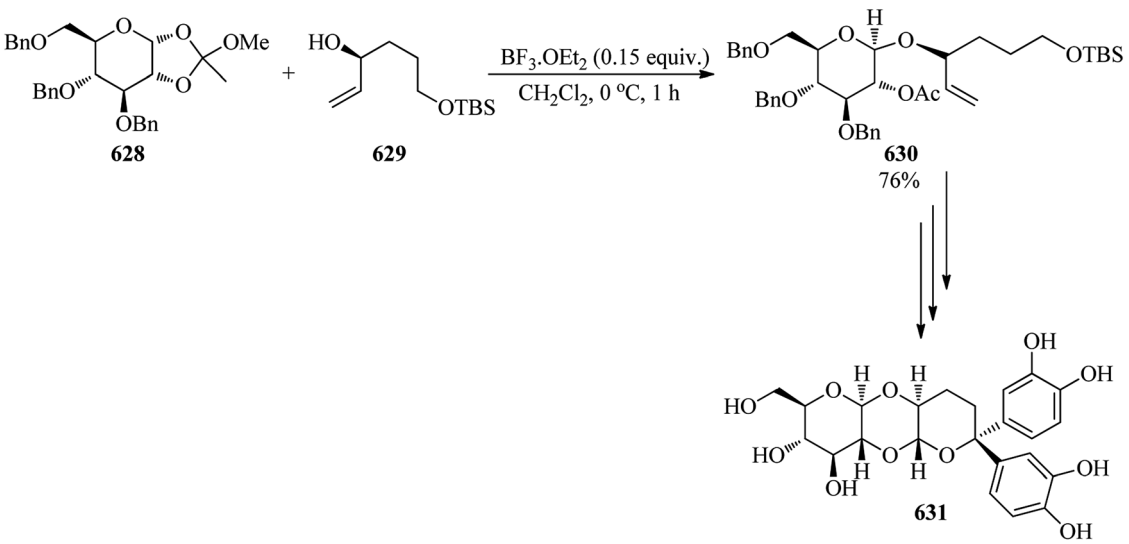
4.31. Synthesis of cinnoline derivative

The cyclocondensation of 10-amino-7-(*p*-tolyl)pyrimido [4″,5″:4′,5]thieno[3′,2′:5,6]pyrido[3,2-*c*]cinnoline-11-imine (**615**) with TEOF (**5**) was accomplished in refluxing acetic acid for 5 h to give 7-(*p*-tolyl)-1,2,4-triazolo[4‴,3‴:1″,6″]pyrimido[4″,5″:4′,5′] thieno[3′,2′:5,6]pyrido[3,2-*c*]cinnoline (**616**) in 70% yield (Scheme 185).[492]

4.32. Synthesis of quinazoline derivatives

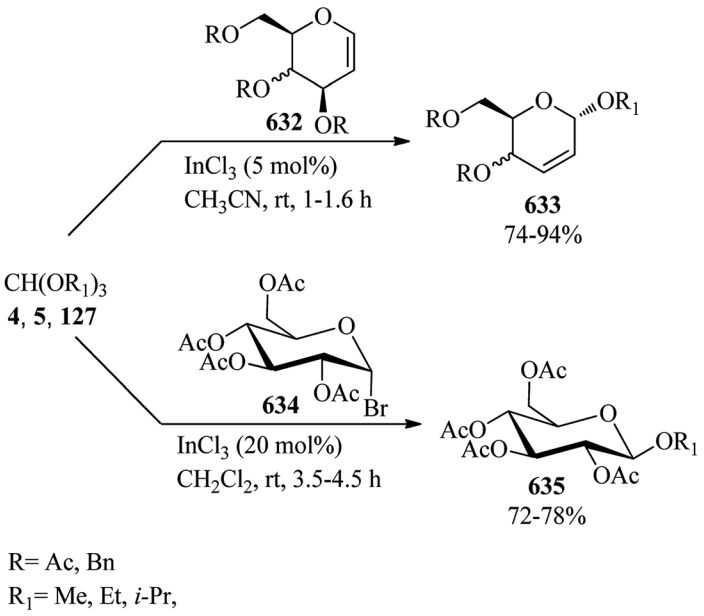
Cobalt(II) chloride ($CoCl_2$, 10 mol%) catalyzed the one-pot three-component reaction of anthranilic acid, TEOF, and anilines in CH_3CN at 70 °C to obtain 3-substituted-quinazolin-4(3*H*)-ones.[493–495] Both electron-donating and electron-withdrawing anilines provided the products in good yields (75–95%).[495] Quinazolin-4(3*H*)-ones (**618**) could also be obtained in good yields *via* the novel reductive cyclization of *o*-nitrobenzamides (**617**) and TEOF (**5**), promoted by $TiCl_4$/Zn in refluxing THF (Scheme 186).[496]

The cyclocondensation of 6-hydrazino-substituted benzimidazo[1,2-*c*]quinazolines (**619**) with orthoesters (**5**, **6**, **7**) was

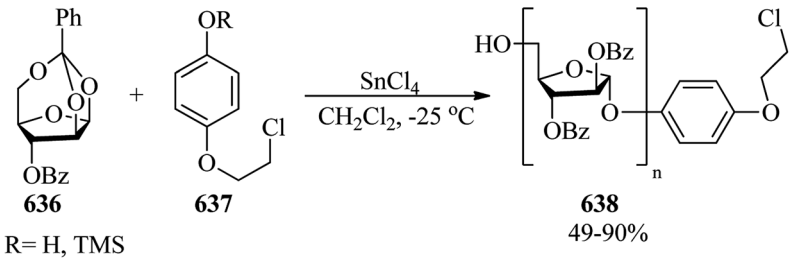


628 629 630 631

Scheme 191 The total synthesis of sinenside A.



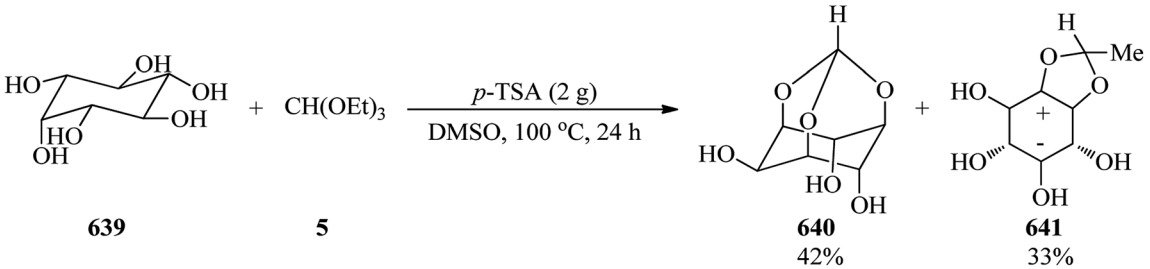
Scheme 192 The formation of *O*-glycopyranosides.



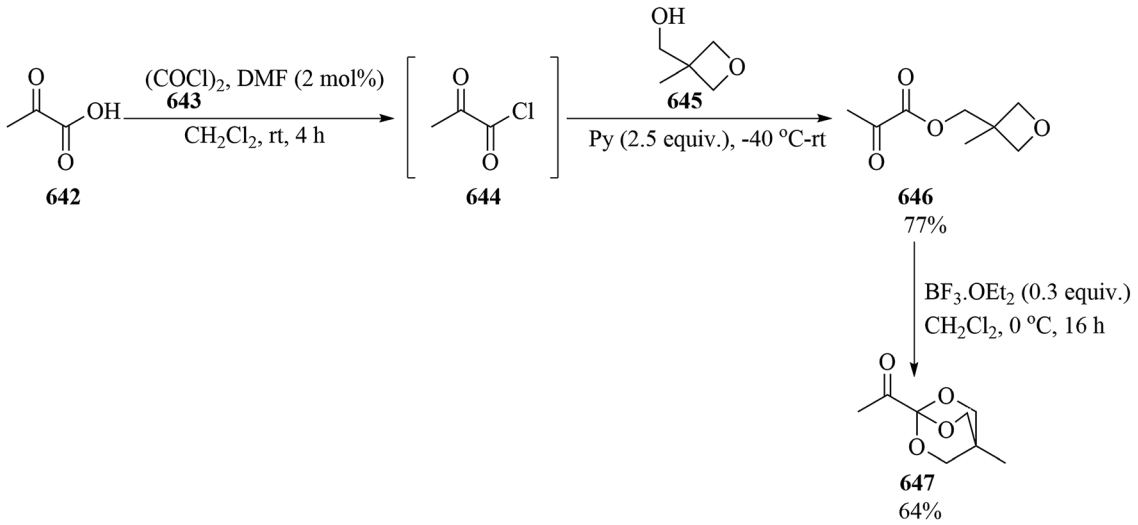
Scheme 193 Glycosyl acceptor synthetic procedure.

accomplished in refluxing ethanol to obtain new benzimidazo[1,2-*c*][1,2,4]triazolo[4,3-*a*]quinazolines (**620**) fin 1 h in high yields (70–81%) (Scheme 187).[497]

Bis(quinazolinon-4(1*H*)-one) derivatives (**622**) were also synthesized *via* the regioselective one-pot pseudo five-component cyclocondensation reaction of isatoic anhydride (**312**), orthoesters (**5**, **6**, **7**, **102**, **323**, **455**), and diamines (**621**) using $KAl(SO_4)_2 \cdot 12H_2O$ (alum, 20 mol%) as an inexpensive, eco-friendly, readily available, easily separable, and recyclable catalyst in refluxing DMF within 30–50 min in good to excellent yields (79–90%) (Scheme 188).[498] 4-Arylaminoquinazolines[499] were synthesized in excellent yields (84–96%) within 2 h *via* the one-pot three-component condensation reaction of 2-aminobenzamide, anilines, and orthoesters by a catalytic amount of Keggin-type heteropolyacid ($H_6[PMo_9V_3O_{40}]$, 0.03 mmol) in refluxing CH_3CN. Significantly, anilines containing electron-donating groups were obtained in slightly better yield. In this reaction, 3-quinazolin-4-one (**2**) was formed as a by-product in low yield.[500] Preyssler heteropolyacid H_{14} $[NaP_5W_{30}O_{110}]$ also progressed this transformation in refluxing CH_3CN within 2 h.[501]



Scheme 194 The synthesis of *myo*-inositol monoorthoformate and (±)-1,2-*O*-ethylidene-*myo*-inositol.



Scheme 195 The preparation of OBO orthoester.

4.33. Synthesis of quinoxalines

Novel 3-substitued [1,2,4]triazolo[3′,4′;2,3][1,3]triazolo[4,5-*b*] quinoxaline derivatives (**624**) were achieved through the cyclocondensation of [1,3]thiazolo[4,5-*b*]quinoxaline-2(3*H*)-one hydrazone (**623**) with orthoesters (**4**, **6**) in acetic acid under reflux conditions within 4–8 h (Scheme 189).[502]

4.34. Glycosidation, glycosylation, and oligomerization reactions

In 2015, Rao *et al.* employed propargyl 1,2-orthoesters (**625**) as key synthons and glycosyl donors for the synthesis of thiosaccharides and 1-thiotrehaloses (**627**) in a 1,2-*trans* diastereoselective form only *via* the glycosidation reaction[503–509] with glycosyl mercaptans (**626**), as glycosyl acceptor, using gold(III) bromide ($AuBr_3$, 7 mol%) as catalyst in CH_2Cl_2 at room temperature under argon atmosphere in excellent yields (83–94%) within 6 h (Scheme 190).[509]

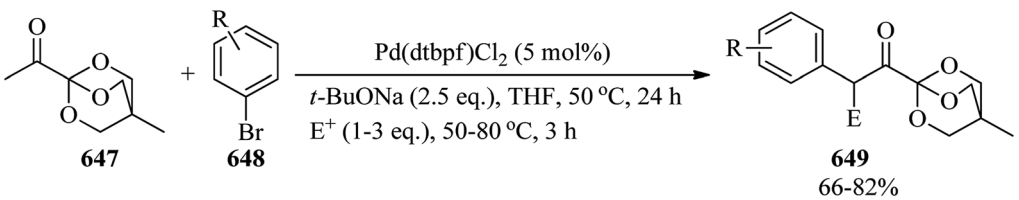
In 2015, Vadhadiya and Ramana reported the first total synthesis of sinenside A. In this survey, the glycosidation reaction of orthoester (**628**)[510] with allylic alcohol (**629**), as a glycosyl acceptor, by $BF_3 \cdot Et_2O$ (0.15 equiv.) as catalyst in dichloromethane at 0 °C in the presence of 4 Å molecular sieves obtained β-glucoside (**630**) in good yield (76%) in a 1 h period, which was employed as a key precursor for the synthesis of sinenside A (**631**) *via* a multi-step reaction (Scheme 191).[511]

The stereoselective *O*-glycosylation of glycals (**632**) and glycosylbromides (**634**) by orthoformates (**4**, **5**, **127**) in the presence of $InCl_3$ in corresponding solvents (CH_3CN and CH_2Cl_2) yielded *O*-glycopyranosides (**633**, **635**) at room temperature (Scheme 192). It must be mentioned that both perbenzyl and peracetyl glycals resulted in 2,3-unsaturated-*O*-glycosides with major α-selectivity while glycosylbromides furnished alkoxy glycosides with high β-selectivity in most cases.[512]

$SnCl_4$ catalyzed the oligomerization reaction of 3-*O*-benzoyl-β-D-arabinofuranose 1,2,5-orthobenzoate (**636**)[513,514] with 4-(2-chloroethoxy) phenol (**637a**) or (4-(2-chloroethoxy)phenoxy)trimethylsilane (CEP-OTMS, **637b**) as a terminating agent in CH_2Cl_2 at −25 °C to form selectively α(1 → 5) linked arabinofuranose oligomers, including 4-(2-chloroethoxy)phenyl (CEP) aglycon with a deprotected 5-OH group at the non-reducing end (**638**) (Scheme 193).[515] The resultant glycosyl acceptor (**638**) could be used in glycosylation reactions.[514,516]

4.35. Synthesis of (±)-1,2-*O*-ethylidene-*myo*-inositol

The reaction of *myo*-inositol (**639**) with TEOF (**5**) using *p*-TSA (2g) under heating in dimethyl sulfoxide at 100 °C has been used to obtain *myo*-inositol monoorthoformate (**640**) and



R= 4-N(Me)$_2$Ph, 4-MePh, 4-CF_3Ph
E= CH_2=C(Br)CH_2Br, BrCH_2CO_2Me, HCCCH_2Br, BnBr, BrCH_2C(O)Ph, EtI, CH_2CHCH_2Br

Scheme 196 The mono α-arylation of OBO orthoester.

(±)-1,2-*O*-ethylidene-*myo*-inositol (**641**) within a 24 h period in 42% and 33% yields, respectively (Scheme 194). It was found that the presence of the chiral carbon of ethylidene in the compound (**641**) formed a mixtures of the four diastereomers which were not isolated by silica gel column chromatography but were characterized by NMR spectra.[517]

4.36. α-Arylation and alkylation of protected pyruvate esters

In 2017, Esteves *et al.* interpreted a novel process for the enolate arylation and alkylation of protected pyruvate esters. Hence, in the first step, the orthoester-masked pyruvate equivalent (oxabicyclo[2.2.2]octyl orthoester, OBO)[518–521] was prepared through the reaction of pyruvic acid (**642**) with oxalyl chloride (**643**) to form pyruvoyl chloride (**644**) which underwent an esterification reaction with 3-methyl-3-oxetanemethanol (**645**) in the presence of pyridine to afford the ester (**646**) *via* a two-step reaction which on reaction with $BF_3 \cdot OEt_2$ in CH_2Cl_2 at 0 °C yielded the OBO orthoester (**647**) (Scheme 195). Then, the mono α-arylation (**649**) reaction was accomplished *via* the reaction of (**647**) with aryl bromide (**648**) by Pd(dtbpf)Cl_2 (5 mol%), utilizing at least two equivalents of base in THF at 50 °C for 24 h. Due to the greater acidity of the product than the starting material,[522] the resultant aryl ketone was deprotonated *in situ* by the extra base. Subsequent alkylation by different equivalents of electrophile at 50–80 °C obtained α-arylation and alkylation products (Scheme 196). In the final step, the OBO protective group was conveniently removed using acidic conditions such as *p*-TSA in ethanol at 90 °C for 3–8 h. The method also enabled mono- and diarylation reactions to happen on a readily available OBO-protected precursor.[521]

5. Conclusions

In this review, several types of orthoesters have been reported as applicable substrates in classified organic transformations. These treatments have been subdivided according to the reaction medium. This focus is because of the significance of economical and green reactions in organic syntheses. Based on the overall results, the reaction could happen in solvent-free media, in the presence of aqueous conditions, or in organic solvents. Detailed investigations in the form of a literature survey affirmed that the processes containing orthoesters progressed well in the absence of solvents. This important attainment has let researchers design new procedures to achieve compounds with multi-functionalized motifs in the absence of hazardous solvents, utilizing the greater activity potential of substrates and reagents, as they could come into contact effectively within short periods. The aqua-mediated reactions were not extensive, which may be due to the hydrolysis affinity of orthoesters in water. Traditional organic solvents were also mentioned a great deal in reports. The greatest usage involved alcohols, dichloromethane, acetic anhydride, acetonitrile, acetic acid, benzene and its derivatives, and THF. Other common solvents used in lower abundance were DMF, ether, DMSO, dioxane, and CCl_4. Some transformations were done under heating conditions and some others required microwave or ultrasound assistance for promotion. Based on the many mentions, TEOF was the most commonly used alkyl orthoester in a vast range of reactions. The authors hope that this article will guide general readers to gain an intense interest in using orthoesters, as versatile and easily-handled synthons, in a great range of reactions with a focus on the environment.

Conflicts of interest

There are no conflicts to declare.

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