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Recent advances in the application of indoles in multicomponent reactions

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Indoles are some of the most versatile and common nitrogen-based heterocyclic scaffolds and are frequently used in the synthesis of various organic compounds. Indole based compounds are very important among heterocyclic structures due to their biological and pharmaceutical activities. The last decade, in particular, has witnessed considerable activity towards the synthesis of indole derivatives due to the possibilities for the design of polycyclic structures by the incorporation of multiple fused heterocyclic scaffolds in an attempt to achieve promising new heterocycles with chemical and biomedical relevance. In this study, we provide an overview on recent applications of indole in the multicomponent reactions for the synthesis of various heterocyclic compounds during the period of 2012 to 2017.

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1. Introduction

Heterocyclic compounds are important tools in our daily life having an extensive variety of applications such as sanitizers, pharmaceuticals^{2,3} and antioxidant compounds, ^{4,5} corrosion inhibitors, ^{6,7} dye stuff, ⁸ copolymers, ^{9,10} and as building blocks in

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the synthesis of organic compounds and natural products. Multicomponent reactions (MCRs) have been extensively used for the synthesis of heterocyclic compounds. 11-13 MCRs represent a great tool in organic synthesis for the construction of variety-oriented series of building blocks with potentially interesting biological activities. 14-17 The attractiveness of the MCR approach is its easy operation, high selectivity and yield by using minimum synthetic requirements. Indole scaffolds have been known for their value in the development of new compounds of pharmaceutical interest. 18-20 Up to date, several



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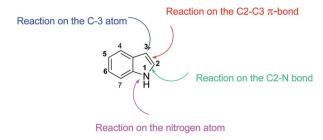
review articles have been published based on the reactions of indole. 21,22 Herein, in continuation of our studies towards the synthesis of heterocyclic compounds and multicomponent reactions, $^{23-32}$ and since there is a wide range of reactions that include indole in the preparation of heterocyclic compounds, this review presents the recent applications of indole in the synthesis of diverse heterocyclic compounds during the period from 2012 to 2017. This review first discusses indoles' C-3 carbon atom reactivity applicable to electrophilic reactions, followed by MCRs in which the N position of indole is reacted as a nucleophile to afford N-substituted indole products. In Section 2.3, indole cycloaddition reactions have been discussed including cycloaddition reactions of the C2–C3 π -bond (Section 2.3.1) and the C-N sigma bond (Section 2.3.2). Finally, in Section 2.4, miscellaneous reactions of indole will be reviewed.

Multicomponent reactions of indoles

The indole structure is a heterocyclic compound which easily participates in chemical reactions. Its bonding sites are analogous to pyrrole. As shown in Scheme 1, indole is reactive at four different positions including the carbon atom 3, nitrogen atom 1, the C2–C3 π -bond and the C2–N sigma bond. Indole can be protonated with strong acids such as hydrochloric acid, which protonates the C3 position, more easily than the N atom. The cycloaddition reaction is another reaction of indole compounds. The C2–C3 π -bond of indole has a propensity towards cycloaddition reactions but cycloaddition reactions of the C2–N sigma bond are also observed.

2.1. The C-3 position reactions of indoles

Gámez-Montaño's group reported the one-pot Ugi-azide 33 multicomponent reaction of indole 1, isocyanides 2, aldehydes 3 and TMSN $_3$ 4 (Scheme 2). In the first step, intermediate A was obtained, and then *N*-acylation was performed between A and



Scheme 1

chloroacetyl chloride to give the intermediate B, which underwent an $S_N 2$ reaction with the potassium ethyl xanthogenate salt to give the final xanthates 5 (Scheme 2).³⁴

The one-pot multicomponent reaction of 3-acetylindole 1, aromatic aldehydes 3, ethyl cyanoacetate 6, and ammonium acetate 7 in the presence of piperidine as catalyst was established to access several 6-indolylpyridine-3-carbonitrile derivatives 8 (Scheme 3).³⁵ The anti-proliferative activities of products were evaluated and showed good results.

Indole 1, carbon disulfide 9 and substituted α -bromo propiophenones 10 were reacted νia a three component domino [3+2] heterocyclization reaction for the preparation of two-carbon-tethered 1,3-oxathiole–indole pair compounds 11 (Scheme 4). The results showed that functional groups such as bromide and chloride provide ample opportunity for further functional group manipulations, for example, by modern cross-coupling reactions.

A regioselective Sonogashira³⁷ cyclization reaction was carried out in the presence of CuI as catalyst and 2,2'-(1*E*,1'*E*)-(1*R*,2*R*)cyclohexane-1,2-diylbis(azan-1-yl-1-ylidene)bis(methan-1-yl-1-ylidene)diphenol as ligand to obtain benzyl-3-(indol-3-yl)-2-phenyl-2,3-dihydroisoindolinones 14. The reaction involved the one-pot multicomponent reaction of indoles 1, 2-iodo-*N*-phenylbenzamides 12 and terminal alkyne 13 under



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Scheme 2

Scheme 3

aerobic conditions followed by a nucleophilic addition (Scheme 5).38

Ar= 4-MeOC₆H₄, 4-FC₆H₄, 4-ClC₆H₄, 4-BrC₆H₄, 2-Thiophenyl

Magnetic nanoparticles (Fe₃O₄-NPs) catalyzed the synthesis of pyrano[2,3-d]pyrimidines 17 and pyrido[2,3-d]pyrimidines 18. The reactions were performed *via* the one-pot three component reaction of indole 1, malononitrile 15 and barbituric acids 16a or 6-amino uracil derivatives 16b in EtOH (Scheme 6).39

Baruah et al. presented the synthesis of 3-alkylated indole derivatives 20 and 21 under a microwave-assisted threecomponent reaction of indole-3-aldehydes 1, alkyl nitriles 15

or barbituric acids 16 with 1,4-dihydropyridine (DHP) derivative 19 (Scheme 7).40 In each case, DHPs are converted to pyridines. In fact, 1,4-dihydropyridine is the reducing agent.

Preparation of a wide variety of new 6-(1H-indol-3-yl)-2-oxo-4aryl-1,2,3,4 tetrahydropyrimidine-5-carbonitriles 23 was accessed by combining 3-(cyanoacetyl)-indoles 1 with an arylaldehyde 3 and urea 22 in the presence of PEG-400 and a catalytic amount of thiazolium anions (NHCs) (Scheme 8).41

A three-component reaction for the synthesis of functionalized 3-{1-[2-(1*H*-indol-3-yl)ethyl]-4,5,6,7-tetrahydro-1*H*-indol-3-

$$R = 5$$
-Br, 5-OMe, 2-Me Ar= Ph, 4-BrC₆H₄, 4-Tolyl

Scheme 4

 R^1 = H, 1-Me, 2-Me R^2 = H, 5-OMe, 5-Me, 5-NO₂ R^3 = (CH₂)₃OMe, Ph, 4-FC₆H₄, 4-MeOC₆H₄ PTS= Polyoxyethanyl- α -tocopheryl sebacate OH HO—
Ligand

Scheme 5

yl}indolin-2-ones **26** has been described by Jiang and Yan. The reaction involves a one-pot condensation of indole **1** with dimedone **24** and 3-phenacylideneoxindoles **25** in refluxing acetonitrile with *p*-toluenesulfonic acid as catalyst (Scheme 9). 42

Modha and co-workers provided a novel procedure for the synthesis of diversely substituted spiroindolines 30 *via* the post-Ugi gold-catalyzed diastereoselective domino cyclization. In this methodology, the Ugi reaction of indole-3-aldehydes 1, propargylamine 27, acids 28 and isocyanides 2 gave the products 29 in good yields which reacted with Au(PPh₃)SbF₆ in chloroform to produce spiroindolines 30 in moderate yields (Scheme 10).⁴³ In another study, the same group used other amines instead of propargylamine for the synthesis of analogues of these products.⁴⁴

The indolylmalonamides **33** have been prepared *via* the three-component reaction of indole derivatives **1**, chromene-3-carboxylates **31** and amines **32** in the presence of La(OTf)₃ as

a Lewis acid catalyst (Scheme 11).⁴⁵ Indolylmalonamide products 33 showed notable fluorescence activities when they are exposed to long wave UV light (366 nm).

Polyfunctionalized indole derivatives 35 and 36 were generated from the Yonemitsu-type⁴⁶ trimolecular condensation of indoles 1 with aldehydes 3 and 1,3-dicarbonyl compounds 34, such as malonates and acetoacetates using Lewis acid catalysts under microwave irradiation. The formation of bis-indolic derivative 36 can be easily rationalized in the one pot reaction, where a double addition of indole to the aldehyde is assumed. As already suggested by Gao and Wu,⁴⁷ the adduct 35 is probably converted into a reactive indolenine derivative A⁴⁸ by the loss of an active methylene fragment, which reacts with another molecule of indole (Schemes 12 and 13).⁴⁹ Macroporous copper oxide (mpCuO) was also used as catalyst in this reaction and the same products were isolated in good yields.⁵⁰ Docking studies against enoyl acyl carrier protein reductase predicted

 $\rm R^1=H,\,6\text{-}CH_3$ $\rm R^2=H,\,4\text{-}Me,\,4\text{-}OH,\,4\text{-}OMe,\,3,4\text{-}(OMe)_2,\,3\text{-}OH\text{-}4\text{-}OMe,\,4\text{-}OH\text{-}3\text{-}OMe,\,4\text{-}NO_2,\,3\text{-}NO_2,\,4\text{-}CI}$ NHC= Thiazolium ion PEG= Polyethylene glycol

Scheme 8

Scheme 9

that the compounds bind at the active site with high binding affinity values. In another study, Li *et al.* used L-proline as catalyst in this reaction.⁵¹ The results are summarized in Table 1.

Khalafi-Nezhad *et al.* developed the use of trimethylsilyl iodide (TMSI) as a multifunctional agent in the one-pot

synthesis of 9-(1*H*-indol-3-yl)xanthen-4-(9*H*)-ones 37 from the reaction of indoles 1, 2-methoxybenzaldehydes 3 (as *O*-methyl protected salicylaldehydes) and β -dicarbonyl compounds 24 (Scheme 14).⁵²

The functionalized indole-3-yl pyridines **40** were prepared *via* an efficient one-pot condensation of cyanoacetylindoles **1**, 3-

Au(PPh₃)SbF₆
CDCl₃
r.t., 2 h

$$R^2$$
 R^3
 $R^4 = H, Me$
 $R^2 = H, 6-Me$
 $R^3 = t-Bu, -(CH2)2C6H5, Benzyl, 4-Methoxybenzyl
 $R^4 = n-Bu, t-Bu, Cyclohexyl$

30
40-84%$

Scheme 10

$$R^{3} + R^{2} + R^{4} + R^{4} + R^{5} \cdot NH_{2}$$

$$R^{1} + R^{2} + R^{4} + R^{5} \cdot NH_{2}$$

$$R^{1} + R^{2} + R^{4} + R^{5} \cdot NH_{2}$$

$$R^{1} + R^{2} + R^{4} + R^{5} \cdot NH_{2}$$

$$R^{2} + R^{5} \cdot NH_{2}$$

$$R^{3} + R^{2} \cdot R^{5} \cdot NH_{2}$$

$$R^{3} + R^{5} \cdot NH_{2}$$

$$R^{5} + R^{5}$$

Scheme 11

formylchromones 38 and ammonium acetate 7 under stannous chloride 39 mediation in DMF (Scheme 15).⁵³

Wan and co-workers used polyethylene glycol (PEG-200) in a three-component reaction of indoles **1**, aldehydes **3**, and malononitrile **15** to afford 3-indole derivatives **41** in good to excellent yields (Scheme **16**). ⁵⁴ L-Proline, ⁵⁵ tetrabutylammonium fluoride (TBAF), ⁵⁶ Zn-salphen, ⁵⁷ Cu(OAc)₂ (ref. 58) and Cu(III) ⁵⁹ were also used as catalysts in this reaction and the results are shown in Table 2.

Singh's group described a highly efficient methodology for the synthesis of 3-amino-alkylated indoles 44 *via* the one-pot three-component Mannich⁶⁰ type reaction of amines 42, alcohols 43 and indoles 1. Treatment of amines 42 and alcohols 43 with KOH in toluene in the presence of (Fe(NO₃)₃·9H₂O/TEMPO)⁶¹ as catalyst, yielded iminium ion **A**. Then, the iminium ion **A** was reacted with indoles 1 to obtain novel 3-substituted indoles 44 (Scheme 17).⁶² In another study, ferric hydrogen sulfate (FHS)⁶³ was applied as catalyst and the same

Scheme 12

Review

Scheme 13

 $\begin{tabular}{lll} \textbf{Table 1} & \textbf{Comparison of different conditions for the synthesis of products 35 and 36} \end{tabular}$

Entry	Solvent	Catalyst	Temperature	Time	Yield (%)
1 2 3	CH ₃ CN H ₂ O EtOH	Sc(OTf) ₃ mpCuO L-Proline	r.t.		58-79 (ref. 49) 78-95 (ref. 50) 70-99 (ref. 51)

products were prepared in 87–98%. It was observed that electron-withdrawing groups on the aldehyde reacted rapidly and were better reagents in this reaction. Furthermore, *N*-methylaniline showed better reactivity in comparison with *N*-ethylaniline due to the low steric effects. *N*-Alkylanilines were used in excess to avoid the formation of bis(indolyl)alkanes. The reaction was also catalyzed by L-proline, haberlite, IRA-400 Cl resin and polyaniline-fluoroboric acid-dodecyl hydrogen sulfate salt (PANI-HBF₄). Catalyst-free conditions in MeOH have also been reported in 72 h by 28–99% yields. A comparison of different catalysts and experimental setups is given in Table 3.

Mahmoodi and co-workers developed the one-pot cyclo-condensation of mono- or bis(indole-3-carbaldehyde) 1 or 45,^{69,70} thiosemicarbazide 46, and phenacyl bromides 47 in the presence of a catalytic amount of AcOH for the preparation of the novel mono- and bis(indol-3-yl)hydrazineyl thiazole derivatives 48 and 49 (Scheme 18).⁷¹ The products were evaluated for *in vitro* antibacterial activity against Gram-positive and Gram-

negative bacteria. Some of the products have good antibacterial activity. The product **48** with OCH₃ as a donating group exhibited high activity against Gram-positive bacteria.

Shinde and Jeong developed the reaction between indole 1 and formaldehyde 3 with tertiary aromatic amines 42 in the presence of silica-supported tungstic acid (STA) as a heterogeneous acid catalyst under solvent-free conditions. The protocol was performed *via* the three component Mannich type Friedel–Crafts addition for the preparation of *N*,*N*-dialkyl amino arylated indole derivatives 50 (Scheme 19).⁷² Application of sodium dodecyl sulfate (SDS) as surfactant in this reaction was also reported by Kumar *et al.* resulting in 78–94% yields of products.⁷³

Mild aminoacylation of indoles 1 through a multicomponent process with ynol ethers 51 and sulfonyl azides 52 was established by Alford and Davies for the synthesis of oxo-tryptamines 53 (Scheme 20).⁷⁴ First, 4-alkoxy *N*-sulfonyltriazoles A^{75} were generated from ynol ethers 51 and sulfonyl azides 52, and treated with indoles 1. Then, the obtained enol ethers **B** were converted to the amino ketones 53 for the α -aminoacylation of enols.⁷⁶

N-Methyl indole **1** was reacted with diazooxindole **54** and nitrostyrene **55** in the presence of [Ru] and squaramide as catalysts *via* an asymmetric Michael addition⁷⁷ for the synthesis of 3,3'-bis(indole) derivatives **56** (Scheme 21).⁷⁸

Novel spirooxindole-pyrrolidine compounds **61** and **62** were obtained through 1,3-dipolar cycloaddition of azomethine ylides generated from isatin **57** and sarcosine **59** or thioproline

Scheme 14

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Scheme 15

R= H, t-Bu, 4-OMeC₆H₄, 3-MeOC₆H₄, 2-MeOC₆H₄, 4-MeC₆H₄
3-MeC₆H₄, 2-MeC₆H₄, 4-i-PrC₆H₄, 4-COMeC₆H₄, 4-COMeC₆H₄
4-NO₂C₆H₄, 3-NO₂C₆H₄, 2-NO₂C₆H₄, 4-BrC₆H₄, 4-ClC₆H₄
3-ClC₆H₄, 2-ClC₆H₄, 2,4-Cl₂C₆H₃, 4-FC₆H₄, 4-CF₃C₆H₄

Scheme 16

60 with the dipolarophile 3-(1*H*-imidazol-2-yl)-2-(1*H*-indole-3-carbonyl)acrylonitrile **58** (Scheme 22). Anticancer activity studies were carried out for the synthesized compounds against A549 lung adenocarcinoma cancer cell line. Several of the products showed very high activity against the cancer cell line. Reddy and co-workers also studied this reaction in

MeOH as solvent under reflux conditions in 2–3 h giving 80–93% yields. The antimicrobial activity of all products were evaluated against several bacteria and fungi, and showed good activity.⁸¹

A one-pot four-component condensation strategy was employed by Naureen's group for the discovery of indole-based tetra-arylimidazoles **64**. This method involves the reaction of 2-arylindole-3-carbaldehydes **1**, substituted anilines **42**, benzil **63** and ammonium acetate 7 in acetic acid (Scheme 23).⁸² The anti-urease activity of the synthesized compounds was evaluated and showed good results.

The same authors synthesized several new trisubstituted imidazoles, 3-(4,5-diaryl-1H-imidazol-2-yl)-2-phenyl-1H-indoles **65**, *via* the condensation of substituted indole aldehydes **1**, benzil **63** and ammonium acetate **7** in refluxing acetic acid (Scheme 24). ⁸³ The products were evaluated for their α -glucosidase inhibition and showed significant α -glucosidase inhibitory activity.

Table 2 Comparison of different conditions for the synthesis of products 41

Entry	Solvent	Catalyst	Temperature (°C)	Time (h)	Yield (%)
1	${ m H_2O}$	PEG-200	r.t.	3	55-98 (ref. 54)
2	EtOH	L-Proline	r.t.	30-72	58-98 (ref. 55)
3	_	$TBAF \cdot 3H_2O$	60	2	55-97 (ref. 56)
4	DCM	Zn-salphen, DIPEA	r.t.	6	13-60 (ref. 57)
5	PEG-400	$Cu(OAc)_2$	70	15-40	48-98 (ref. 58)
6	H_2O	Cu(III)	30	12-24	70–96 (ref. 59)

$$\begin{split} R^{1} &= \text{Ph, Morpholyl, Pyrrolidyl} \\ R^{2} &= 4\text{-Cl, 4-NO}_{2}, \text{Ph, 4-MeC}_{6}\text{H}_{4}, \text{4-MeOC}_{6}\text{H}_{4}, \text{3-MeOC}_{6}\text{H}_{4} \\ &3,4,5\text{-(MeO)}_{3}\text{C}_{6}\text{H}_{2}, \text{4-}\textit{t-}\text{Bu-C}_{6}\text{H}_{4}, \text{Cyclohexyl, Naphthalyl} \\ R^{3} &= \text{H, Me} \end{split}$$

R⁴= H, 5-OMe, 5-Br

Table 3 Comparison of different conditions for the synthesis of product 44

Entry	Solvent	Catalyst	Temperature (°C)	Time (h)	Yield (%)
1	Toluene	(Fe(NO ₃) ₃ ·9H ₂ O/TEMPO)	r.t.	32-39	79–87 (ref. 62)
2	_	FHS	45	1-4	87-98 (ref. 63)
3	_	L-Proline	r.t.	5-18	68-89 (ref. 65)
4	MeOH	IRA-400 Cl resin	r.t.	1.5-3	70-85 (ref. 66)
5	H_2O	PANI-HBF₄	r.t.	30-50 min	88–97 (ref. 67)
6	МеОН		30	72	28–99 (ref. 68)

Andreana and his group utilized the one-pot reaction of 4-nitroindolylacetaldehyde 1, methylamine 32, methyl isocyanide 66 and 3-hydroxyphenylpyruvic acid 67 for the synthesis of (\pm) -thaxtomin A (TA) 68 as a herbicidal natural product. First, the prerequisite dipeptide A was isolated which

through a base-mediated keto-amide cyclization reaction afforded two diastereomeric compounds **B**. Then, compound **B** was treated with KOH under microwave irradiation to provide the intended product **68** (Scheme 25).⁸⁴ This natural product was synthesized previously by Zhang *et al.* and has

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R¹= Et, Ph, Cyclohexyl, 2-Naphthyl R²= Ms, Ts, (CH)₂TMS R³= H, Me, Benzyl R⁴= Me, Ph R⁵= H, 5-Me, 5-OMe, 5-Br CuTC = (copper(I) thiophene-2-carboxylate)

Scheme 20

been demonstrated to possess activity against the tobacco mosaic virus.⁸⁵

A one-pot three-component reaction of indole-3-aldehyde derivatives **1**, ethyl cyanoacetate **6**, and guanidine hydrochloride **69** under three different conditions, including microwave irradiation, grindstone technology and reflux, was developed to afford 2-amino-5-cyano-4-[(2-aryl)-1*H*-indol-3-yl]-6-hydroxypyrimidines **70** (Scheme 26)⁸⁶ The products **70** were evaluated for their antimicrobial activity against nine pathogenic bacteria and showed mild to moderate activity.

Bhattacharjee *et al.* employed ammonium chloride (NH₄Cl) as catalyst for the preparation of 9-(1*H*-indol-3-yl)-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one 71 *via* the one-pot three-component reaction of indole 1 with salicylaldehyde 3 and dimedone 24 (Scheme 27).⁸⁷ In another study, Ganguly *et al.* developed this reaction in the presence of L-proline as catalyst in $\rm H_2O$ for 2 h in 86–96% yield.⁸⁸

So and Mattson reported on the synthesis of glycine products 73 in the presence of chiral BINOL-based phosphoric-acid as catalyst. The process involves the multicomponent coupling reactions of indole derivatives 1, nitrodiazoester 72 and anilines 42 in methyl *t*-butyl ether (MTBE) as solvent (Scheme 28).89

The three-component reaction of indoles 1, α -oxoketene dithioacetals 74, and aldehyde 3 or 75 was investigated for the synthesis of dihydrocoumarins 76 and quinolines 77 (Scheme 29). The reaction mechanism was presented in Scheme 30. The electrophilic reaction of aldehyde 3 with two nucleophiles 1 and 74 resulted in the formation of intermediate A which was converted into a chromene-type intermediate B through an intramolecular substitution. Finally, hydrolysis of intermediate B formed 77. The reaction mechanism of aldehyde 75 is shown in Scheme 31. First, the condensation of 75 and indoles 1 produced the intermediate D. The NH₂ group of 75 attacked the C2 position of the indole ring, and formed the intermediate E.

Scheme 21

Scheme 22

Scheme 23

Cleavage of an endocyclic C-N bond allowed the formation of a quinoline derivative F.⁹¹ Then, compound 74 reacted with NH₂ group of quinoline F and final product 76 was obtained.

Borah *et al.* investigated the one-pot multicomponent reaction of 3-(cyanoacetyl)-indoles $\bf 1$, aromatic aldehydes $\bf 3$ and ethyl acetoacetate $\bf 34$ in the presence of $InCl_3$ under microwave irradiation to produce the functionalized 3-(pyranyl)-indole derivatives $\bf 78$. When ammonium acetate $\bf 7$ was used as the source of ammonia in this reaction, the one-pot four-component reaction was carried out and 3-(dihydropyridinyl)-indole derivatives $\bf 79$

were obtained (Scheme 32).⁹² The results show that electron donating groups (EDG) in the aldehyde increase the product yield, whereas electron withdrawing groups (EWG) decrease the yield of products.

A sulfone-containing Brønsted acid ionic liquid was used in a one-pot reaction of indole 1, salicylaldehydes 3 and 1,1-diphenylethylene 80 for the synthesis of substituted chromane derivatives 81 (Scheme 33).⁹³

A series of indole incorporated thiazolylcoumarins ${\bf 83}$ were synthesized from the reaction of indole derivatives ${\bf 1}$,

Scheme 24

Scheme 25

$$\begin{array}{c} \text{CHO} \\ \text{CHO} \\ \text{NC} \\ \text{NC} \\ \text{NC} \\ \text{NR} \\ \text{NC} \\ \text{NR} \\ \text{NR$$

Scheme 26

thiosemicarbazide **46** and 3-(2-bromoacetyl)-2*H*-chromen-2-ones⁹⁴ **82** using a catalytic amount of acetic acid (Scheme 34).⁹⁵ The antibacterial, anticancer and DNA cleavage activities of products were evaluated. The results showed that all products have a good activity towards the screened bacterial strains.

Song *et al.* established the [3 + 3] cyclization of 3-(cyanoacetyl)-indoles **1** with dialkyl acetylenedicarboxylates (DMAD) **84** and isocyanides **2** for the preparation of 4-*H*-pyran derivatives **85** containing an indole scaffold (Scheme 35).⁹⁶

Efficient synthesis of indol-3-yl substituted pyran derivatives **86** was investigated by Ji and co-workers via the one-pot multicomponent reaction of 3-cyanoacetyl indoles **1**, aldehydes **3** and malononitrile **15** in the present of piperidine as catalyst under ultrasonic irradiation (Scheme 36).⁹⁷ Thiamine hydrochloride (vitamin B₁) and cetyltrimethylammonium bromide (CTAB) were also utilized as catalysts in this reaction for 25 min giving 92–94% vield.⁹⁸

A Knoevenagel⁹⁹ coupling of salicylaldehyde 3 and Meldrum's acid 87 followed by a Michael type reaction with indole 1

Scheme 27

Scheme 28

in the presence of a (saccharin)-based functional ionic liquid (imidazolium saccharinate) was reported by Kumar *et al.* This multicomponent reaction was performed *via* lactonization decarboxylative elimination to functionalize the C-3 of indoles with dihydrocoumarin to yield indole-3-dihydro-coumarins 88 (Scheme 37).¹⁰⁰

Biheterocycles containing indole and azole skeletons **90** and **91** were prepared from the multicomponent reaction of indoles **1**, 1,2-diaza-1,3-dienes **89** and aldehydes **3** or alkynes **13** (Scheme 38). ¹⁰¹ The synthesized compounds were screened for

their *in vitro* biological studies. The results showed that some of them have anticancer activity against MCF7 and Caco-2 human tumor cell lines.

Stefani and co-workers utilized a mild approach for the synthesis of indole-3-glyoxyl derivatives **94** and indole-3-glyoxyl-1,2,3-triazoles **96**. For this purpose, the reaction of indole **1**, oxalyl chloride **92** and various nucleophiles **93** was carried out in *N*,*N*-diisopropylethylamine (DIPEA) to afford indole-3-glyoxyl derivatives **94** (Scheme 39). On the other hand, indole-3-glyoxyl-1,2,3-triazoles **96** were obtained from the one-pot

Scheme 29

Scheme 30

multicomponent reaction of these reactants and organic azides 95 via click¹⁰² chemistry (Scheme 40).¹⁰³

Indole 1 was reacted with anilines 42 and aldehydes 3 via an anhydrous $\rm ZnCl_2$ catalyzed one-pot three-component reaction to afford diarylmethyl indoles 97 in toluene and 3-arylmethyl indoles 98 in MeOH. The reaction of indole 1 with benzaldehyde 3 in the presence of catalyst formed the azafulven A which reacted with another indole 1 to generate the kinetically stable bis(indolyl)methane B. In the presence of anilines, bis(indolyl) methane converted to the target products 97 (Schemes 41 and 42). 104

A series of biologically important 3-(1-arylsulfonylalkyl) indoles **100** were prepared by Huang *et al.* This process was carried out using a catalyst-free three-component reaction of indoles **1**, carbonyl compounds **3**, and arenesulfinic acids **99** at room temperature (Scheme 43).¹⁰⁵ Bis(indolyl) methanes **A** were found as the key intermediates in this reaction.

The synthesis of bis(indolyl)methanes 101 was reported by Dhumaskar and Tilve via the reaction of two molecules of indole 1 with aldehydes 3 under solvent-free conditions without any catalyst (Scheme 44).106 Two different methods were employed for this reaction. In method A, the mixture of aldehyde and indole was kept at ambient temperature in a test tube while in method B, the mixture was ground using a mortar and pestle. Method B resulted in the formation of products in shorter reaction times than method A. According to the results, anisaldehyde with an electron donating group at the para position and heptaldehyde failed to react completely. Mohammadi Ziarani and co-workers developed this reaction using the sulfonic acid functionalized silica (SiO₂-Pr-SO₃H) as catalyst and obtained the same products in short reaction times and good yields (5-20 min and 87-96% vields).107

Mohammadi Ziarani and coworkers synthesized a novel class of symmetrical 3,3-di(indolyl)indolin-2-ones 102 from the

Scheme 32

$$R^3$$
 R^2 R^2 R^4 R^2 R^4 R^4

reaction of indoles **1** with isatins **57** in the presence of SBA-Pr-SO₃H as a solid acid catalyst under mild reaction conditions (Scheme 45). The antimicrobial activities of the products were

tested and the results demonstrated that the MIC value of one of the products ($R^1 = R^3 = H$, $R^2 = Bn$) against *B. subtilis* was equal to that of chloramphenicol.

Scheme 34

 R^{2} + $R^{3}O_{2}C$ - $CO_{2}R^{3}$ + $R^{4}NC$ - $CH_{2}CI_{2}$ + $R^{2}O_{2}C$ - $CO_{2}R^{3}$ + $R^{4}NC$ - $CH_{2}CI_{2}$ + $R^{2}O_{2}C$ - $CO_{2}R^{3}$ + $R^{4}NC$ - $R^{2}O_{2}C$ - $R^{3}O_{2}C$ - $R^{3}O_{2}C$

R¹= Me, *n*-Hexyl, 4-MeOC₆H₄, Benzyl, 4-Methoxybenzyl 4-Threefluorobenzyl, 3-Bromobenzyl

R²= H, 5-OMe, 5-Br

R3= Me, Et

R⁴= t-Bu, Cyclohexyl

Scheme 35

Scheme 36

Geng's group developed the one-pot four component reaction of 3-(cyanoacetyl)indoles 1, aromatic aldehydes 3, 1-(9-butylcarbazol-3-yl)ethanone 103 and ammonium acetate 7 for the preparation of several 3-cyano-2-(1*H*-indol-3-yl)-6-(9-butylcarbazol-3-yl)pyridine derivatives 104. The reaction was performed using AcOH and

ethane-1,2-diol (glycol) under microwave irradiation (Scheme 46).¹⁰⁹

Zn²⁺ supported on montmorillonite KSF (Zn²⁺@KSF) as an efficient heterogeneous catalyst promoted the preparation of mono and bis-indolylimidazole derivatives **106** and **107**. This reaction was carried out from the condensation of indole-3-

Scheme 38

Scheme 39

carbaldehyde derivatives **1** or bis-aldehydes **105**,¹¹⁰ aniline derivatives **42** and benzil **63** (Scheme 47).¹¹¹ The antibacterial activity of the synthesized compounds was examined and some of them exhibited promising activities.

Naidu *et al.* explored the one-pot three-component reaction of 2-cyano-3-(1*H*-indol-3-yl)-pent-2-enedinitrile or ethyl-2,4-dicyano-3-(1*H*-indol-3-yl)but-2-enoate derivative **108**, aryl aldehydes **3** and 6-aminouracil derivatives **16** (obtained from the reaction of 3-(cyanoacetyl)-indoles **1** and nitrile **14**) for the synthesis of some hexahydropyrimido[4,5-*b*]-1,8-naphthyridine

derivatives **109** and **110**. It was found that when the indole derivative **108** ($R^1 = H$; $R^2 = CO_2Et$) was treated with benzaldehyde (**4a**) and uracil **16** ($R^4 = Me$) the ester group participated in the cyclization process instead of the nitrile group, and the trioxo-nitrile compound **110** was obtained (Scheme 48).¹¹²

The three-component coupling reaction of indoles 1, β -ketoesters 34 and arylboronicacids 111 *via* the regioselective palladium-catalyzed oxidative reaction was studied for the preparation of indole-based heterocycles 112 (Scheme 49).¹¹³

Aldehyde= Formaldehyde

Scheme 41

Indole coupled more rapidly than β -ketoester with the arylboronic acid, and this rate variation was important under the three-component reaction conditions, possibly because the coupling with β -ketoester involves an unstable enone intermediate.

Siddalingamurthy *et al.* described the synthesis of indole-3-propanamide derivatives **113** and **114** *via* the three-component reaction of *N*-methyl indole **1**, aromatic aldehydes **3** and Meldrum's acid **87** in the presence of choline chloride/urea ionic liquid as catalyst. At first, Meldrum's adduct **A** was generated,

$$R^{2} + R^{3}COR^{4} + ArSO_{2}H \xrightarrow{CH_{2}Cl_{2}} R^{2} + R^{3}COR^{4} + ArSO_{2}H \xrightarrow{R^{1}} R^{2} + R^{3}COR^{4} + R^{3}COR^{4} + R^{3}COR^{4} + R^{3}COR^{4} + R^{3}COR^{4} + R^{3}COR^{4} + R^{3}CO$$

$$\begin{split} R^1 &= \text{H, Me, SO}_2C_6H_4 \\ R^2 &= \text{H, 7-Me, 5-OMe, 7-CO}_2\text{Et, 6-Cl, 5-Br, 5-NO}_2, \text{ 2-Ph} \\ R^3, R^4 &= (\text{H, H}) \text{ (H, Ph), (H, 4-MeC}_6H_4), (\text{H, 4-MeOC}_6H_4), (\text{H, 3,4-(MeO)}_2C_6H_3)} \\ &\qquad \qquad \text{(H, 2-ClC}_6H_4), (\text{H, 4-ClC}_6H_4), (\text{H, 4-BrC}_6H_4), (\text{H, 4-NO}_2C_6H_4), (\text{H, 2-ThienyI}), \text{ CyclohexyI} \\ Ar &= \text{Ph, 4-MeC}_6H_4, \text{ 4-ClC}_6H_4 \end{split}$$

Method A: r.t., 3 min to 6 days, 51-96% Method B: Grounding, r.t., 2 min to 2 days, 60-98%

R¹= H, Me R^2 = Ph, 3-MeOC₆H₄, 4-MeOC₆H₄, 2-CIC₆H₄ 4-CIC₆H₄, 2-NO₂C₆H₄, 4-NO₂C₆H₄, 2-Furyl, 2-Pyridyl

Scheme 44

which then reacted with various amines, and the indole-3propanamide derivatives 113 were formed. On the other hand, when Meldrum's adduct was treated with H₂O, corresponding acid products 114 were obtained (Scheme 50).114

A one-pot four-component reaction of 3-(cyanoacetyl)indole 1, benzaldehyde derivatives 3, 3-acetylpyridine 114, and NH₄OAc 7 was explored for the preparation of 2-(indol-3-yl) pyridine derivatives 115 (Scheme 51). In the same paper, 4aryl-2-(1H-indol-3-yl)-6-arylnicotinonitriles 117 were also obtained based on this process, from the reaction of 3-(cyanoacetyl)indole 1, aromatic aldehydes 3, aromatic ketones 116, and NH₄OAc 7 under two different conditions (Scheme 52).¹¹⁵

Deb et al. reported a base-promoted three-component onepot approach for the synthesis of 3- $(\alpha,\alpha$ -diarylmethyl) indoles 119 via arylation of in situ generated 3-indolylalcohols A in an EtOH-H₂O solvent system. Substituted indoles

benzaldehydes 3 and electron-rich aromatics 118 were used as starting materials in this reaction (Scheme 53).116

The N position reactions of indoles

Martinez-Ariza et al. reported a two-step one-pot procedure for the synthesis of N-1-quinoxaline-indoles 123 from the reaction of indoles 1, amines 120 and glyoxaldehydes 121. In the first step, α-iminoketones A were formed from the reaction of amines 120 and glyoxaldehydes 121, which were then treated with indole 1 for the preparation of compounds 122. The deprotection-cyclization of 122 was performed for the synthesis of target products 123 (Scheme 54).117

Hulme and co-workers reported a one-pot two-step multicomponent reaction of indole 1, arylglyoxaldehyes 121 and amines 42 for the synthesis of α-oxo-acetamidines 125 under microwave conditions. The main reaction step was the N-1 addition of indole to α-iminoketones A (obtained from the reaction of arylglyoxaldehyes 121 and amines 42), followed by an air- or oxygen-mediated oxidation (Scheme 55).118

2.3. The cycloaddition reactions of indoles

2.3.1. The cycloaddition reactions of indoles at the C2-C3 π -bond. The tetracyclic tetrazole scaffold compounds 128 were constructed via a one-pot four-component Ugi-Pictet-Spengler reaction¹¹⁹ of indole 1, carbonyl compounds 3, isocyanoacetaldehyde (dimethylacetal) 126 and trimethylsilyl azide (TMSN₃) 2. The reaction was carried out using methanesulfonic acid without any solvent at room temperature. First, the Ugi reaction was performed to obtain compounds 127, which was

Scheme 45

 $\begin{array}{l} \text{Ar= Ph, 4-MeC}_6\text{H}_4, \, 3\text{-MeOC}_6\text{H}_4, \, 4\text{-MeOC}_6\text{H}_4, \, 4\text{-i-PrC}_6\text{H}_4, \, 4\text{-}i\text{-BuC}_6\text{H}_4\\ \, 4\text{-(CH}_3)_2\text{NC}_6\text{H}_4, \, 4\text{-OHC}_6\text{H}_4, \, 4\text{-CIC}_6\text{H}_4, \, 4\text{-BrC}_6\text{H}_4, \, \text{Naphthyl} \end{array}$

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then followed immediately by the Pictet-Spengler reaction for the preparation of final products 128 (Scheme 56).¹²⁰

Jiang *et al.* described an aerobic dehydrogenative coupling interaction between indole derivatives **1**, diazoacetates **129** and conjugated α -keto esters **130** in the presence of sequential

 $Rh_2(OAc)_4$ and $CuCl_2$ as catalysts for the synthesis of polyfunctional cyclopenta[b]indoles **131** (Scheme 57).¹²¹

A acid-catalyzed multicomponent tandem cyclization protocol was applied by Cai *et al.* for the preparation of polyfunctional dihydroindolizino[8,7-*b*]indoles **134** and **135**. The

Scheme 48

$$R^2$$
 + β-ketoester + R^3 R^4 R^4

process involves the reaction of indole derivatives ${\bf 1}$, arylglyoxal monohydrates ${\bf 132}$ and ${\it trans}$ - β -nitrostyrenes ${\bf 133}$ or malononitrile ${\bf 15}$ under mild, metal-free conditions (Scheme ${\bf 58}$). 122

The silica supported ionic liquid of [pmim] HSO_4SiO_2 (silica supported 1-methyl-3-(triethoxysilylpropyl)imidazolium hydrogen sulfate) was used as an efficient catalyst for the

Scheme 51

Method A: solvent free: 120 °C, 1-11 h, 53-85% Method B: reflux: AcOH, 1.5-10 h, 43-87%

R¹= H, 4-OMe, 4-N(Me)₂, 2-Cl, 4-Cl, 4-Br R²= H, 4-OMe, 4-Cl

Scheme 52

$$R^{2}$$
 $R^{1} + R^{3}CHO$
 R^{2}
 R^{3}
 $R^{1} + R^{3}CHO$
 R^{2}
 R^{3}
 R^{1}
 R^{2}
 R^{1}
 R^{2}
 R^{1}
 R^{2}
 R^{1}
 R^{2}
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 R^{3}
 R^{4}
 R^{1}
 R^{2}
 R^{3}
 R^{3}
 R^{4}
 R^{5}
 R^{5}

 R^1 = H, Me R^2 = H. Br

 R^3 = Ph, 4-MeC₆H₄, 4-OMeC₆H₄, 2-ClC₆H₄, 3-ClC₆H₄, 4-ClC₆H₄, 4-NO₂C₆H₄, 2-Thiophenyl, 2-Pyridyl Ar= 4-Methylphenol, 4-Methoxyphenol,4-(*t*-Butyl)phenol, 2-Naphthyl, 6-OMe-2-Naphthyl, 6-Br-2-Naphthyl

Scheme 53

synthesis of 2-amino-4,5-dihydro-4-arylpyrano[3,2-*b*]indole-3-carbonitrile derivatives **136**. The reaction was carried out *via* the three-component condensation of indoles **1**, aromatic aldehydes **3** and malononitrile **15** (Scheme 59). Other catalysts such as KHPO₄ under ultrasonic irradiation and triphenylphosphine (PPh₃)¹²⁵ were also used in this reaction as demonstrated in Table 4.

Galvan *et al.* accomplished the reaction of indole-2-aldehydes **1**, imines **137** and alkenes **138** *via* stereoselective [3+2] carbocyclization to achieve cyclopenta[b]indoles **139** or tetrahydroquinolines **140**. It was found that the model coupling reaction could be changed to give related products **139** or **140** in the presence of different acid catalysts (Schemes 60 and 61). ¹²⁶

$$H_2N$$
 NHBoc H $C_2H_4Cl_2$ MW , 100 °C, 10 min H $C_2H_4Cl_2$ R^3 R^4 $R^$

 R^1 = H, Me, Methylendioxy (R^1 & R^2) R^2 = H, Me, OMe, F R^3 = H, OMe, OCF₃ R^4 = 4-Br, 6-Br

Scheme 54

Scheme 55

 $\begin{array}{l} R^1,\,R^2 \!\!=\! (H,\,Et),\,(H,\,\emph{i-}Pr),\,(Me,\,Et),\,(H,\,4 \!\!-\! ElC_6H_4),\,(H,\,4 \!\!-\! NO_2C_6H_4),\,(H,\,3,4,5 \!\!-\! MeOC_6H_2)\\ \qquad \qquad (H,\,(CH_2)_2C_6H_5),\,(H,\,Ph),\,(H,\,4 \!\!-\! FC_6H_4),\,(H,\,(CH_2)_2SMe),\,Cyclohexyl,\,1 \!\!-\! Benzylpyridinyl\,X \!\!=\! H,\,CO_2Me \end{array}$

Scheme 56

Kundu and co-workers established a new synthetic protocol for the preparation of pyrido- and pyrimido-indoles **141** and **142** employing ethyl 2-amino-1*H*-indole-3-carboxylates **1**, aromatic aldehydes **3**, and terminal alkynes **13** in the presence of a Brønsted acid such as trifluoroacetic acid (TFA) (Scheme 62). When the reaction catalyzed by Yb(OTf)₃ as a Lewis acid, pyrimidoindoles **142** were prepared as the single products in 58–75% yield.

Tron's group have prepared heteroarylogous 1*H*-indole-3-carboxamidines **143** utilizing a three-component interrupted Ugi reaction of *N*-alkyl-*N*-(1*H*-indol-2-ylmethyl)amines **1**,¹²⁸ isocyanides **2** and carbonyl compounds **3** (Scheme 63).¹²⁹

Silvani *et al.* reported an impressive method to prepare dihydroimidazo[1',5':1,2]pyrido[3,4-*b*]indol-2-ium salts **145**

utilizing a Ugi/Bischler-Napieralski/heterocyclization MCR. The Ugi reaction was carried out following a general procedure, consisting of the sequential addition of aldehydes 3, amines 42, acids 28 and, finally, indole 1 for the synthesis of compounds 144. Treatment of intermediate compounds 144 in MeOH under the Bischler–Napieralski and heterocyclization gave the intended products 145 (Scheme 64).¹³⁰

A gold-catalyzed multicomponent reaction of vinyl indoles 1 with two *N*-allenamides **146** and **147** was investigated by Pirovano *et al.* to prepare tetrahydrocarbazole **148** in 78% yield (Scheme 65).¹³¹

Chiral phosphoric acid was used as the catalyst in the asymmetric aza-Diels-Alder reaction¹³² of indole derivatives **1** with 2-azadiene generated *in situ* from oxetane **149**¹³³ and 3,5-

 $R^{1}=H, 4-CI, 4-F, 4-MeO, 5-Me, 6-Me \\ R^{2}=Ph, 4-OMeC_{6}H_{4}, 4-MeC_{6}H_{4}, 4-BrC_{6}H_{4}, 4-FC_{6}H_{4}, 3-OMeC_{6}H_{4} \\ R^{3}=Ph, 4-OMeC_{6}H_{4}, 4-MeC_{6}H_{4}, 3-MeC_{6}H_{4}, 4-BrC_{6}H_{4}, 3-BrC_{6}H_{4}, 4-FC_{6}H_{4}, 4-FC_{$

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 $\begin{array}{l} {\sf R=H,\,7\text{-}Me,\,5\text{-}OMe} \\ {\sf Ar^1=Ph,\,4\text{-}MeC_6H_4,\,4\text{-}MeOC_6H_4,\,3\text{-}MeOC_6H_4,\,benzo[1,3]dioxyl} \\ {\sf 4\text{-}NO_2C_6H_4,\,4\text{-}ClC_6H_4,\,4\text{-}BrC_6H_4,\,2\text{-}BrC_6H_4,\,1\text{-}Naphthyl,\,3\text{-}Thienyl,\,2\text{-}Benzofuryl}} \\ {\sf Ar^2=Ph,\,4\text{-}MeC_6H_4,\,4\text{-}MeOC_6H_4,\,4\text{-}OHC_6H_4,\,4\text{-}ClC_6H_4,\,2\text{-}ClC_6H_4,\,2\text{-}BrC_6H_4}} \\ {\sf 1\text{-}Naphthyl,\,2\text{-}Thienyl} \end{array}$

Scheme 58

Scheme 59

dimethoxyaniline 42 to obtain a series of indole-alkaloid-type polycycles 150 (Scheme 66).¹³⁴ The authors hypothesized that the introduction of a hydrogen-bond acceptor on the aldehyde moiety may help to orient the transition state and lower the activation barrier for the desired process. Thus, they employed substrates with a simple ether group in proximity to the aldehyde moiety, and encouragingly, the desired aza-

Diels–Alder reaction proceeded cleanly to form the desired products with good yields and diastereoselectivities. The biological activity evaluation of the products showed that the cytotoxicities of products in human lung carcinoma and human cervical carcinoma cells exhibited inhibitory effects against cell proliferation with IC_{50} values in the range of 15.0–27.5 μ M.

Table 4 Comparison of different conditions for the synthesis of product 136

Entry	Solvent	Catalyst	Temperature (°C)	Time (min)	Yield (%)
1	$\mathrm{CH_{3}CN}$	[pmim]HSO ₄ SiO ₂	80	6-8 h	84-90 (ref. 123)
2	EtOH	KHPO_4	60	30	85-92 (ref. 124)
3	H ₂ O-EtOH	PPh_3	60	30-50	85-92 (ref. 125)

Scheme 60

$$R^{2} \xrightarrow{\text{II}} \begin{array}{c} \text{NH}_{2} \\ \text{I} \end{array} \begin{array}{c} \text{NH}_{2} \\ \text{II} \end{array} \begin{array}{c} \text{N$$

Scheme 61

The annulation of indoles 1, 2-amino benzyl alcohols 42 and benzaldehydes 3 in a two step three-component tandem reaction was used to form benzazepinoindoles 151. In the first step, indoles were C-3 alkylated and the intermediates A were obtained. Then in the second step, intermediates A underwent a 7-endo-trig cyclization (the modified Pictet–Spengler cyclization reaction) to obtain the intended products 151 (Scheme 67).¹³⁵

A stereoselective Povarov reaction 136,137 catalyzed by iodine was developed by Wang and co-workers for the preparation of *exo*-tetrahydroindolo[3,2-c]quinoline derivatives **153**. The procedure involved a reaction between indoles **1**, aldehydes **3**

and amines **152** in toluene (Scheme 68). The results showed that only reactive amines could be included in this reaction to give the desired products **153** with high stereoselectivity.

Gallium(III) (GaBr₃) catalyzed a three component [4 + 3] cycloaddition reaction of indoles **1**, aldehyde/ketone/ketal derivatives **3** and dienes **154** to furnish cyclohepta[b]indoles **155**. The authors have proposed the mechanism of formation of the product via nucleophilic addition of the C3 of indole to electrophile **3** to give the alcohol **A**, which in the presence of a Lewis acid generated the indolyl cation **B**. The treatment of **B** with diene component **154** afforded the corresponding products (Scheme 69).¹³⁹

R¹= H, 5-Me, 6-F R²= Ph, 4-MeC₆H₄, 4-*t*-BuC₆H₄, C₆H₉ Ar= 4-MeC₆H₄, 4-ClC₆H₄, 4-FC₆H₄

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 R^1 = H, 5-Cl, 5,6-(OMe)₂ R^2 = Me, n-Bu, Benzyl, EtC₆H₄ R^3 = Benzyl, Naphthyl, Cyclohexyl, n-Penthyl, MeOAc R^4 = H, i-Pr, Ph, 4-ClC₆H₄, n-Hexyl, Cyclohexyl

Scheme 63

NC + R¹CHO + R²NH₂ + R³CO₂H
$$\frac{\text{MeOH}}{40 \, ^{\circ}\text{C}}$$
 NH $\frac{144}{64-84\%}$ R¹ R² $\frac{144}{64-84\%}$ R³ $\frac{144}{64-84$

Scheme 64

Damavandi and Sandaroos have synthesized 2,9-dihydro-2-oxo-4-aryl-1H-pyrido[2,3-b]indole-3-carbonitriles **158** by the one-pot multicomponent cyclocondensation reaction of 1-methyl-1H-indol-2-ol **1**, substituted (triethoxymethyl) arenes **156** and cyanoacetamide **157** in the presence of silica supported ionic liquid [pmim]HSO₄SiO₂ as a catalyst (Scheme 70).¹⁴⁰

A new series of diketopiperazine-fused tetrahydro-β-carboline ring systems **160** were obtained *via* the Pictet–Spengler/Ugi-4CR/deprotection-cyclization reactions. According to the proposed mechanism, the Pictet–Spengler cyclization of indole **1** and ethyl glyoxalate **159** followed by a deesterification reaction produced 2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-1-carboxylic acid **B**. The reaction of acid **B**, amines **42**, isocyanides **2** and aldehyde **3** *via* the Ugi reaction gave the intermediate products **C**. The deprotection cyclization reaction of this intermediate generated the target products **160** (Scheme 71).¹⁴¹

A stereoselective catalyst-free three-component reaction of 2-isocyanoethylindole 1, malononitrile 15 and aldehyde 3 was developed for the construction of polycyclic spiroindolines 161 in high yields (up to 90%) with excellent levels of diastereoselectivity (Scheme 72). The presence of an electron-withdrawing group on the aldehyde led to a decrease in yields of the products.

John and co-workers developed a multicomponent reaction involving *N*-protected 3-nitroindole **1** a primary amine **162** and an enolizable ketone **163** for the preparation of a series of functionalized pyrrolo[3,2-*b*]indoles **164** (Scheme 73).¹⁴³ It was found that the yield of product **164** decreased to 45% with 1-phenylethylamine. With cyclohexylamine, the product **164** was obtained in moderate yield (53%) and with adamantylamine the MCR failed, proving that the reactivity decreases with an increase in the steric bulk of the amine component.

Scheme 65

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R= H, 5-Me, 6-Me, 7-Me, 5-Br, 6-Br, 6-F 5-OMe, 5-OH, 6-OBn, 6-CO $_2$ Me

Scheme 66

Scheme 67

The Lewis acid catalyzed three-component [3 + 2] cycloaddition reaction of pentafulvene **165** with *in situ* generated indolylmethanol **A** has been developed for the construction of pentaleno[1,2-b]indoles **166** (Scheme 74).¹⁴⁴ It was found that aromatic aldehydes bearing electron-withdrawing groups ($R^3 = Cl$, Br, F) were tolerated well under the reaction conditions and

Ar = $2,4,6-(i-Pr)_3C_6H_2$ (R)-**B**

 $\label{eq:R=H, 7-Me, 5-Br} R= H, 7-Me, 5-Br \\ Ar= Ph, 4-MeC_6H_4, 4-MeOC_6H_4, 3,5-(MeO)_2C_6H_3, 4-Me_2NC_6H_4, 2-ClC_6H_4, 4-ClC_6H_4\\ 3,4-Cl_2C_6H_3, 3-BrC_6H_4, 4-BrC_6H_4, 4-FC_6H_4, 3-NO_2C_6H_4, 4-NO_2C_6H_4, Piperonyl, 3-Thienyl (A-Particle Property of A-Particle P$

$$R^{2}$$
 R^{3} R^{4} R^{4} R^{2} R^{3} R^{4} R^{4} R^{5} R^{5} R^{4} R^{5} R^{5

R1= H, Me, Benzyl

R²= 5-Me, 5-OMe, 5-MeO₂C, 5-Cl, 5-Br, 5-I

 R^3 , R^4 = (H, Et), (H, Ph), (H, 4-OMeC₆H₄), (H, 4-CF₃C₆H₄), (H, 2-Furyl)

(H, 2-Thienyl), Cyclohexyl, dimethoxybis(methylsulfonyl)methyl

154

Diene=

Ga^{III}= GaBr₃ or Ga(OTf)₃ Tf =trifluoromethanesufony

Scheme 69

Scheme 70

afforded the cycloaddition products in moderate to good yields. However, aldehydes with electron-rich substituents ($R^3 = 2,4$ -OMe, Me) were unable to take part in the cycloaddition reaction.

Alpers et al. developed a photoinduced three-component radical [4 + 2]-cyclization-allylation reaction between 3-(2iodoethyl)indoles 1, acceptor-substituted alkenes 167, and allyl zirconocenes of the structure Cp $ZrCl(\sigma-allyl)$ 168 for the synthesis of hexahydrocarbazoles 169 (Scheme 75).145

A copper(1)-catalyzed cascade multicomponent reaction strategy was performed for the construction of 5-hydroxy-1Hpyrrol-2(5H)-ones 171 bearing an indole moiety. The reaction was carried out using substituted indole 1, (Z)-3-iodoacrylic acids 170 and terminal alkynes 13 (Scheme 76).146

2.3.2. The cycloaddition reactions of indoles at the C-N sigma bond. An enantioselective multicomponent coupling reaction for the synthesis of pyrrolo[1,2-a]indoles 173 was reported using a chiral disulfonimide as catalyst. The [3 + 2] cyclization reaction between the imine A (generated in situ from indole-2-aldehyde derivatives 1 and anilines 42) and 2,3dihydrofuran 172 led to products 173 (Scheme 77).147 It was observed that the yields of products synthesized from substituted anilines at the 3- and 5-positions with halogen atoms groups were lower than those synthesized from 3,5-bis(trifluoromethyl)aniline.

The Ugi four-component condensation of indole-2-aldehyde derivatives 1, acids 28, anilines 42 and isocyanides 2 in the presence of orthogonal copper and palladium catalysts under microwave heating was accomplished for the synthesis of two important indole-fused heterocycles 174 and 175. First, the Ugi adduct A was obtained via the intramolecular cyclization conditions and served as a precursor in subsequent selective post-transformations. 5,6-Dihydroindolo[1,2-a]quinoxalines 174 were prepared by a copper catalyzed N-H arylation pathway, while 6,7-dihydroindolo[2,3-c]quinolones 175 were formed by palladium catalyzed C-H arylations without the protection of the indole N1 moiety (Scheme 78).148 In another approach to synthesize these compounds, no catalyst has been employed in this reaction and the products were obtained in good yields. 149

 $R^1=t$ -Bu, Cyclopropyl, 4-Methylbenzyl, 4-Methoxybenzyl, 2-Chlorobenzyl, 4-Fluorobenzyl $R^2=H$, Ph, 3,5-(MeO) $_2$ C $_6$ H $_3$, 4-ClC $_6$ H $_4$, 3-Methylbuthanal $R^3=t$ -Bu, n-Bu

Scheme 71

 $\begin{array}{l} \text{Ar= Ph, 3-MeC}_6 \text{H}_4, \, 4\text{-MeC}_6 \text{H}_4, \, 4\text{-FC}_6 \text{H}_4, \, 3\text{-CIC}_6 \text{H}_4, \, 4\text{-CIC}_6 \text{H}_4, \, 3\text{-CI}_2 \text{C}_6 \text{H}_3, \, 3\text{-BrC}_6 \text{H}_4 \\ \, 4\text{-BrC}_6 \text{H}_4, \, 2\text{-NO}_2 \text{C}_6 \text{H}_4, \, 3\text{-NO}_2 \text{C}_6 \text{H}_4, \, 4\text{-NO}_2 \text{C}_6 \text{H}_4, \, 4\text{-SO}_2 \text{MeC}_6 \text{H}_4, \, 2\text{-Naphthyl} \\ \end{array}$

Scheme 72

 R^1 = Ts, Boc, CO_2Et R^2 = H. Cl. Br

 R^3 = n-Pentyl, n-Hexyl, Ph, 4-MeC₆H₄, 4-OMeC₆H₄, 4-ClC₆H₄, Benzyl

Scheme 73

Scheme 74

$$R^{1} = H, 5-Me$$

$$R^{2} = CO_{2}Me, CONMe_{2}$$

$$R^{3} = H, Me$$

$$R^{1} = H, Me$$

$$R^{2} = CO_{2}Ne, CONMe_{2}$$

$$R^{3} = H, Me$$

$$R^{3} = H, Me$$

$$R^{4} = CO_{2}Ne, CONMe_{2}$$

$$R^{4} = CO_{2}Ne$$

Scheme 75

Scheme 76

R¹= 4-Me, 5-Me, 5-Cl, 6-Cl, 6-Br, 4-F, 5-F, 6-F, 5-CF₃ R², R³= 3,5-(CF₃)₂, 3,5-(Cl)₂, (3F, 5-CF₃), (3-Cl, 5-F)

 R^1 = H, 5-OMe, 5-Cl R^2 = *i*-Bu, CH₂NHBoc, Ph, 3-MeOC₆H₄, 4-NO₂C₆H₄, 3,4-Cl₂C₆H₃ R^3 = H, 5-Cl R^4 = Cyclohexyl, *n*-Bu, *t*-Bu

Scheme 78

2.4. Miscellaneous reactions of indoles

Pandey *et al.* have published their results on the synthesis of diverse indole-2-carboxamides $177 \text{ } \nu ia$ a two-step

multicomponent reactions. Initially, Et₃N was added to amino ester hydrochloride **176** and after 10 minutes, 1*H*-indole-2-carboxylic acid **1**, aldehyde **3**, and isocyanide **2** were

 $R^1 = 3,4,5-(MeO)_3C_6H_2$, $4-MeOC_6H_4$, $4-ClC_6H_4$, $4-BrC_6H_4$

 $R^2 = t$ -Bu, 2,4,4-trimethylpentanyl

R³= EtOH, Benzyl, 4-Methoxybenzyl, 4-Chlorobenzyl, 3,4-Dichlorobenzyl 3-Methoxybenzyl, 3-Propyl morpholine, 4-Methyl pyridine

Scheme 80

DMF

successively added to the mixture to produce corresponding indole-fused diketopiperazines A.¹⁵⁰ Then, compound A in the presence of amines formed the functionalized carboxamides 177 (Scheme 79).¹⁵¹ The biological activities of products were evaluated and showed that most products have anti-leishmanial activity against intracellular amastigotes form of *Leishmania donovani*.

Fu and co-workers designed a strategy for the preparation of 3,2'- 179 and 3,3'-bis-indoles 180 through the microwave-assisted regioselective reaction of indoles 1, arylglyoxal monohydrate 133 and diverse *N*-aryl enaminones 178 in HOAc (Scheme 80). The 2-unsubstituted indoles resulted in 3,2'-bis-indole frameworks 179, while indoles bearing a methyl or phenyl group at C2 led to the 3,3'-bis-indoles 180 with simultaneous formation of three sigma-bonds.

3. Conclusion and outlook

This review summarizes recent studies on the application of indoles in multicomponent reactions for the synthesis of a variety of heterocyclic compounds during the period of 2012 to 2017. Indole is a significant nitrogen-based heterocycle with particular importance in the synthesis of complex heterocyclic scaffolds. Indole fragments have been recently attracting much attention due to their biological and pharmaceutical activities. Diversely multisubstituted indole substances are useful building blocks in pharmaceutical and organic syntheses. Consequently, the novel methodologies for the synthesis of complex heterocyclic frameworks involving indole are expected to receive further increasing attention in the future.

Conflicts of interest

There are no conflicts to declare.

5. Abbreviations

CTAB	Cetyltrimethylammonium bromide
DCE	1,2-Dichloroethylene
DIPEA	N,N-Diisopropylethylamine
DMAD	Dialkyl acetylenedicarboxylate

DPP Diketopyrrolopyrrole EA Ethyl acetate FHS Ferric hydrogen sulfate **MTBE** Methyl tert-butyl ether mpCuO Macroporous copper oxide MW Microwave NHC N-Heterocyclic carbene **Nanoparticles** NPs PEG Polyethylene glycol

Dimethylformamide

PMDETA Pentamethyldiethylenetriamine PTS Polyoxyethanyl-α-tocopheryl sebacate

SDS Sodium dodecyl sulfate
STA Silica-supported tungstic acid
TBAF Tetra-n-butylammonium fluoride
TFA Trifluoroacetic acid

THF Tetrahydrofuran

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References

- 1 A. Sniady, M. S. Morreale, K. A. Wheeler and R. Dembinski, *Eur. J. Org. Chem.*, 2008, **2008**, 3449.
- 2 A. J. Cocuzza, D. R. Chidester, S. Culp, L. Fitzgerald and P. Gilligan, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 1063.
- 3 E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, 57, 10257.
- 4 P. Vitaglione and V. Fogliano, *J. Chromatogr. B*, 2004, **802**, 189.
- 5 B. F. Abdel-Wahab, G. E. Awad and F. A. Badria, *Eur. J. Med. Chem.*, 2011, 46, 1505.
- 6 J. Talati and D. Gandhi, Corros. Sci., 1983, 23, 1315.
- 7 P. B. Raja and M. G. Sethuraman, Mater. Lett., 2008, 62, 113.
- 8 C. Stead, Dyes Pigments, 1982, 3, 161.
- 9 L. Guo and D. Zhang, J. Am. Chem. Soc., 2009, 131, 18072.
- 10 E. Butuc and G. M. Gherasim, J. Polym. Sci., 1984, 22, 503.

- 11 J. D. Sunderhaus and S. F. Martin, *Chem.-Eur. J.*, 2009, **15**, 1300.
- 12 J. Zhu, Eur. J. Org. Chem., 2003, 2003, 1133.
- 13 B. Jiang, T. Rajale, W. Wever, S. J. Tu and G. Li, *Chem.-Asian L.*, 2010, 5, 2318.
- 14 I. Ugi, A. Dömling and B. J. Werner, *Heterocycl. Chem.*, 2000, 37, 647.
- 15 C. O. Kappe, Acc. Chem. Res., 2000, 33, 879.
- 16 R. V. A. Orru and M. de Greef, *Synthesis*, 2003, 1471.
- 17 T. Ngouansavanh and J. Zhu, Angew. Chem., 2006, 118, 3575.
- 18 M. Somei and F. Yamada, Nat. Prod. Rep., 2005, 22, 73.
- 19 A. C. Kinsman and M. A. Kerr, *J. Am. Chem. Soc.*, 2003, **125**, 14120.
- 20 F. J. Chang, J. B. Rangisetty, M. Dukat, V. Setola, T. Raffay, B. Roth and R. A. Glennon, *Bioorg. Med. Chem. Lett.*, 2004, 14, 1961.
- 21 M. Shiri, M. A. Zolfigol, H. G. Kruger and Z. Tanbakouchian, Chem. Rev., 2009, 110, 2250.
- 22 M. Shiri, Chem. Rev., 2012, 112, 3508.
- 23 G. Mohammadi Ziarani and P. Hajiabbasi, *Heterocycles*, 2013, 87, 1415.
- 24 G. Mohammadi Ziarani, R. Moradi and N. Lashgari, *ARKIVOC*, 2016, 1, 1.
- 25 G. Mohammadi Ziarani, R. Moradi and N. Lashgari, *Tetrahedron: Asymmetry*, 2015, **26**, 517.
- 26 G. Mohammadi Ziarani, N. Hosseini Nasab and N. Lashgari, *RSC Adv.*, 2016, **6**, 38827.
- 27 G. Mohammadi Ziarani, F. Aleali and N. Lashgari, RSC Adv., 2016, 6, 50895.
- 28 G. Mohammadi Ziarani, P. Gholamzadeh, N. Lashgari and P. Hajiabbasi, *ARKIVOC*, 2013, (i), 470.
- 29 G. Mohammadi Ziarani, N. Lashgari, F. Azimian, H. G. Kruger and P. Gholamzadeh, *ARKIVOC*, 2015, (vi), 1.
- 30 T. Ahmadi, G. Mohammadi Ziarani, P. Gholamzadeh and H. Mollabagher, *Tetrahedron: Asymmetry*, 2017, 28, 708.
- 31 R. Moradi, G. Mohammadi Ziarani and N. Lashgari, *ARKIVOC*, 2017, (i), 148.
- 32 M. Rahimifard, G. Mohammadi Ziarani and B. M. Lashkariani, *Turk. J. Chem.*, 2014, **38**, 345.
- 33 I. Ugi, R. Meyr, U. Fetzer and C. Steinbrückner, *Angew. Chem.*, 1959, **71**, 386.
- 34 R. E. Gordillo-Cruz, A. Rentería-Gómez, A. Islas-Jácome, C. J. Cortes-García, E. Díaz-Cervantes, J. Robles and R. Gámez-Montaño, Org. Biomol. Chem., 2013, 11, 6470.
- 35 N. S. El-Sayed, A. N. Shirazi, M. G. El-Meligy, A. K. El-Ziaty, D. Rowley, J. Sun, Z. A. Nagib and K. Parang, *Tetrahedron Lett.*, 2014, 55, 1154.
- 36 J. Y. Liu, H. Zhang, B. M. Feng, B. Jiang, S. L. Wang and S. J. Tu, Org. Biomol. Chem., 2012, 10, 5036.
- 37 K. Sonogashira, J. Organomet. Chem., 2002, 653, 46.
- 38 S. Sarkar, R. Pal and A. K. Sen, *Tetrahedron Lett.*, 2013, **54**, 4273.
- 39 M. Kidwai, A. Jain and S. Bhardwaj, Mol. Diversity, 2012, 16,
- 40 B. Baruah, P. S. Naidu, P. Borah and P. J. Bhuyan, *Mol. Diversity*, 2012, **16**, 291.

- 41 S. Fatma, D. Singh, P. Mishra, P. K. Singh, P. Ankit, M. Singh and J. Singh, RSC Adv., 2013, 3, 22527.
- 42 Y. H. Jiang and C. G. Yan, Synthesis, 2016, 48, 3057.
- 43 A. Kumar, D. D. Vachhani, S. G. Modha, S. K. Sharma, V. S. Parmar and E. V. Van Der Eycken, *Beilstein J. Org. Chem.*, 2013, 9, 2097.
- 44 S. G. Modha, A. Kumar, D. D. Vachhani, J. Jacobs, S. K. Sharma, V. S. Parmar, L. Van Meervelt and E. V. Van der Eycken, *Angew. Chem., Int. Ed.*, 2012, 51, 9572.
- 45 J. J. Jennings, C. P. Bhatt and A. K. Franz, *J. Org. Chem.*, 2016, **81**, 6211.
- 46 J. Inanaga, K. Hirata, H. Saeki, T. Katsuki and M. Yamaguchi, *Bull. Chem. Soc. Jpn.*, 1979, **52**, 1989.
- 47 K. Gao and J. Wu, Org. Lett., 2008, 10, 2251.
- 48 J.-i. Matsuo, Y. Tanaki and H. Ishibashi, *Tetrahedron*, 2008, **64**, 5262.
- 49 A. Viola, L. Ferrazzano, G. Martelli, S. Ancona, L. Gentilucci and A. Tolomelli, *Tetrahedron*, 2014, 6781.
- 50 G. A. Khan, J. A. War, G. A. Naikoo, U. J. Pandit and R. Das, *J. Saudi Chem. Soc.*, 2016, **22**, 6.
- 51 M. Li, A. Taheri, M. Liu, S. Sun and Y. Gu, *Adv. Synth. Catal.*, 2014, **356**, 537.
- 52 A. Khalafi-Nezhad, M. Nourisefat and F. Panahi, *Synthesis*, 2014, **46**, 2071.
- 53 N. Poomathi, D. Muralidharan and P. T. Perumal, *Tetrahedron Lett.*, 2013, **54**, 7091.
- 54 L. Wang, M. Huang, X. Zhu and Y. Wan, *Appl. Catal.*, *A*, 2013, 454, 160.
- 55 Y. H. He, J. F. Cao, R. Li, Y. Xiang, D. C. Yang and Z. Guan, *Tetrahedron*, 2015, 71, 9299.
- 56 N. Singh, B. K. Allam, D. S. Raghuvanshi and K. N. Singh, *Adv. Synth. Catal.*, 2013, 355, 1840.
- 57 D. Anselmo, E. C. Escudero-Adán, M. Martínez Belmonte and A. W. Kleij, *Eur. J. Inorg. Chem.*, 2012, 4694.
- 58 S. Chandrasekhar, V. Patro, G. P. K. Reddy and R. Grée, *Tetrahedron Lett.*, 2012, 53, 6223.
- 59 H. Jiang, L. Wang and J. Xie, J. Chem. Res., 2016, 40, 338.
- 60 C. Mannich and W. Krösche, Arch. Pharm., 1912, 250, 647.
- 61 E. Zhang, H. Tian, S. Xu, X. Yu and Q. Xu, *Org. Lett.*, 2013, **15**, 2704.
- 62 V. K. Singh, L. K. Sharma and R. K. P. Singh, *Tetrahedron Lett.*, 2016, 57, 407.
- 63 H. Eshghi, M. Rahimizadeh, Z. Bakhtiarpoor and M. Pordel, *Chin. Chem. Lett.*, 2012, 23, 673.
- 64 M. Rahimizadeh, H. Eshghi, M. Mokaber-Esfahani and M. Gholizadeh, *J. Chin. Chem. Soc.*, 2014, **61**, 1265.
- 65 A. Kumar, M. K. Gupta and M. Kumar, *Green Chem.*, 2012, 14, 290.
- 66 G. Harichandran, S. David Amalraj and P. Shanmugam, J. Saudi Chem. Soc., 2018, 22, 208.
- 67 C. L. Devi, V. J. Rao and S. Palaniappan, *Synth. Commun.*, 2012, 42, 1593.
- 68 J. F. Cao, Y. L. Chen, Z. Guan and Y. H. He, *Z. Naturforsch.*, 2014, **69**, 721.
- 69 N. Mahmoodi and A. Ghavidast, *Chem. Heterocycl. Compd.*, 2014, 49, 1451.

- 70 R. Gali, J. Banothu, M. Porika, R. Velpula, R. Bavantula and S. Abbagani, *RSC Adv.*, 2014, 4, 53812.
- 71 N. O. Mahmoodi, B. Khalili, O. Rezaeianzade and A. Ghavidast, *Res. Chem. Intermed.*, 2016, 42, 6531.
- 72 V. V. Shinde and Y. T. Jeong, C. R. Chim., 2015, 18, 449.
- 73 A. Kumar, M. K. Gupta, M. Kumar and D. Saxena, *RSC Adv.*, 2013, 3, 1673.
- 74 J. S. Alford and H. M. L. Davies, J. Am. Chem. Soc., 2014, 136, 10266.
- 75 T. Miura, T. Tanaka, T. Biyajima, A. Yada and M. Murakami, *Angew. Chem.*, 2013, **125**, 3975.
- 76 H. M. Davies and S. J. Hedley, Chem. Soc. Rev., 2007, 36, 1109.
- 77 A. Michael, J. Prakt. Chem., 1887, 35, 349.
- 78 D. F. Chen, F. Zhao, Y. Hu and L. Z. Gong, *Angew. Chem., Int. Ed.*, 2014, **53**, 10763.
- 79 Y. Arun, K. Saranraj, C. Balachandran and P. T. Perumal, Eur. J. Med. Chem., 2014, 74, 50.
- 80 Y. Arun, G. Bhaskar, C. Balachandran, S. Ignacimuthu and P. Perumal, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 1839.
- 81 D. Kathirvelan, J. Haribabu, B. S. R. Reddy, C. Balachandran and V. Duraipandiyan, *Bioorg. Med. Chem. Lett.*, 2015, 25, 389.
- 82 S. Naureen, F. Chaudhry, N. Asif, M. A. Munawar, M. Ashraf, F. H. Nasim, H. Arshad and M. A. Khan, *Eur. J. Med. Chem.*, 2015, **102**, 464.
- 83 S. Naureen, S. Noreen, A. Nazeer, M. Ashraf, U. Alam, M. A. Munawar and M. A. Khan, *Med. Chem. Res.*, 2015, 24, 1586.
- 84 J. P. Bourgault, A. R. Maddirala and P. R. Andreana, *Org. Biomol. Chem.*, 2014, **12**, 8125.
- 85 H. Zhang, X. Ning, H. Hang, X. Ru, H. Li, Y. Li, L. Wang, X. Zhang, S. Yu and Y. Qiao, *Org. Lett.*, 2013, **15**, 5670.
- 86 R. Gupta, A. Jain, Y. Madan and E. Menghani, *J. Heterocycl. Chem.*, 2015, **51**, 1395.
- 87 S. Bhattacharjee, D. K. Das and A. T. Khan, *Synthesis*, 2014, **46**, 73.
- 88 N. C. Ganguly, S. Roy, P. Mondal and R. Saha, *Tetrahedron Lett.*, 2012, **53**, 7067.
- 89 S. S. So and A. E. Mattson, Asian J. Org. Chem., 2014, 3, 425.
- 90 C. Liu, L. Zhou, D. Jiang and Y. Gu, *Asian J. Org. Chem.*, 2016, 5, 367.
- 91 H. S. P. Rao and S. Sivakumar, J. Org. Chem., 2006, 71, 8715.
- 92 P. Borah, P. S. Naidu, S. Majumder and P. J. Bhuyan, *Mol. Diversity*, 2014, **18**, 759.
- 93 A. Taheri, B. Lai, J. Yang, J. Zhang and Y. Gu, *Tetrahedron*, 2016, 72, 479.
- 94 S. K. Sahu, A. Mishra and R. K. Behera, *Indian J. Heterocycl. Chem.*, 1996, 91.
- 95 R. Gali, J. Banothu, R. Gondru, R. Bavantula, Y. Velivela and P. A. Crooks, *Bioorg. Med. Chem. Lett.*, 2015, **25**, 106.
- 96 P. Song, L. Zhao and S. Ji, Chin. J. Chem., 2014, 32, 381.
- 97 T. Chen, X. P. Xu and S. J. Ji, *J. Heterocycl. Chem.*, 2013, **50**, 244.
- 98 S. Fatma, D. Singh, P. Ankit, P. Mishra, M. Singh and J. Singh, *Tetrahedron Lett.*, 2014, 55, 2201.
- 99 E. Knoevenagel, Ber. Dtsch. Chem. Ges., 1898, 31, 2596.

- 100 A. Kumar, P. Kumar, V. D. Tripathi and S. Srivastava, *RSC Adv.*, 2012, 2, 11641.
- 101 S. Mantenuto, S. Lucarini, M. de Santi, G. Piersanti, G. Brandi, G. Favi and F. Mantellini, *Eur. J. Org. Chem.*, 2016, **2016**, 3193.
- 102 H. C. Kolb, M. Finn and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2001, **40**, 2004.
- 103 H. A. Stefani, S. N. S. Vasconcelos, F. B. Souza, F. Manarin and J. Zukerman-Schpector, *Tetrahedron Lett.*, 2013, 54, 5821.
- 104 S. G. Subramaniapillai and A. Ganesan, *Tetrahedron Lett.*, 2014, 55, 694.
- 105 W. Huang, J. Yang, X. Li, L. Yuan, Y. Ma, Q. Zhou and D. Liang, Phosphorus, Sulfur Silicon Relat. Elem., 2016, 191, 772.
- 106 K. L. Dhumaskar and S. G. Tilve, Green Chem. Lett. Rev., 2012, 5, 353.
- 107 G. Mohammadi Ziarani, Z. Aslani and S. Asadi, *Iran. J. Catal.*, 2015, 5, 143.
- 108 G. Mohammadi Ziarani, R. Moradi, A. Badiei, N. Lashgari, B. Moradi and A. A. Soorki, *J. Taibah Univ. Sci.*, 2015, **9**, 555.
- 109 L. J. Geng, G. L. Feng, H. L. Zhang and Y. M. Zhang, J. Chem. Res., 2013, 37, 503.
- 110 S. Bartlett and A. Nelson, Org. Biomol. Chem., 2004, 2, 2874.
- 111 N. O. Mahmoodi, I. Nikokar, M. Farhadi and A. Ghavidast, *Z. Naturforsch.*, 2014, **69**, 715.
- 112 P. S. Naidu, S. Kolita, S. Majumder and P. J. Bhuyan, *Synthesis*, 2015, 47, 701.
- 113 R. Y. Nimje, M. V. Leskinen and P. M. Pihko, *Angew. Chem.*, *Int. Ed.*, 2013, **52**, 4818.
- 114 E. Siddalingamurthy, K. M. Mahadevan and T. O. S. Kumar, *Synth. Commun.*, 2013, **43**, 3153.
- 115 L. Y. Zeng and C. Cai, Synth. Commun., 2013, 43, 705.
- 116 M. L. Deb, P. J. Borpatra, P. J. Saikia and P. K. Baruah, *Synthesis*, 2017, **49**, 1401.
- 117 G. Martinez-Ariza, M. Ayaz and C. Hulme, *Tetrahedron Lett.*, 2013, **54**, 6719.
- 118 G. Martinez-Ariza, N. McConnell and C. Hulme, *Org. Lett.*, 2016, **18**, 1864.
- 119 A. Pictet and T. Spengler, *Ber. Dtsch. Chem. Ges.*, 1911, 44, 2030.
- 120 P. Patil, K. Khoury, E. Herdtweck and A. Dömling, *Bioorg. Med. Chem.*, 2015, 23, 2699.
- 121 L. Jiang, W. Jin and W. Hu, ACS Catal., 2016, 6, 6146.
- 122 Q. Cai, D. K. Li, R. R. Zhou, W. M. Shu, Y. D. Wu and A. X. Wu, *Org. Lett.*, 2016, **18**, 1342.
- 123 S. Damavandi, Eur. J. Chem., 2012, 9, 1490.
- 124 S. Damavandi and R. Sandaroos, *Res. Chem. Intermed.*, 2013, **39**, 1251.
- 125 M. Ghashang, S. S. Mansoor and K. Aswin, *Res. Chem. Intermed.*, 2014, **41**, 6665.
- 126 A. Galván, J. Calleja, A. B. González-Pérez, R. Álvarez, A. R. De Lera, F. J. Fañanás and F. Rodríguez, *Chem.-Eur. J.*, 2015, **21**, 16769.
- 127 R. K. Arigela, R. Kumar, S. Samala, S. Gupta and B. Kundu, *Eur. J. Org. Chem.*, 2014, **2014**, 6057.
- 128 X. Wang, S.-Y. Wang and S.-J. Ji, Org. Lett., 2013, 15, 1954.

- 129 F. La Spisa, F. Meneghetti, B. Pozzi and G. C. Tron, Synthesis, 2015, 47, 489.
- 130 A. Silvani, G. Lesma, S. Crippa and V. Vece, Tetrahedron, 2014, 70, 3994.
- 131 V. Pirovano, L. Decataldo, E. Rossi and R. Vicente, Chem. Commun., 2013, 49, 3594.
- 132 P. A. Grieco, D. T. Parker, M. Cornwell and R. Ruckle, J. Am. Chem. Soc., 1987, 109, 5859.
- 133 J. A. Burkhard, G. Wuitschik, M. Rogers-Evans, K. Müller and E. M. Carreira, Angew. Chem., 2010, 122, 9236.
- 134 Z. Chen, B. Wang, Z. Wang, G. Zhu and J. Sun, Angew. Chem., Int. Ed., 2013, 52, 2027.
- 135 S. Samala, M. Saifuddin, A. K. Mandadapu and B. Kundu, Eur. J. Org. Chem., 2013, 3797.
- 136 L. S. Povarov and B. M. Mikhailov, Izv. Akad. Nauk SSSR, Ser. Khim., 1963, 953.
- 137 L. S. Povarov, V. I. Grigos and B. M. Mikhailov, Izv. Akad. Nauk SSSR, Ser. Khim., 1963, 2039.
- 138 X. S. Wang, M. Y. Yin, W. Wang and S. J. Tu, Eur. J. Org. Chem., 2012, 4811.
- 139 X. Han, H. Li, R. P. Hughes and J. Wu, Angew. Chem., Int. Ed., 2012, 51, 10390.
- 140 S. Damavandi and R. Sandaroos, J. Chem. Sci., 2013, 125, 95.
- 141 I. Khan, S. Khan, V. Tyagi, P. S. Chouhan and P. M. S. Chauhan, RSC Adv., 2015, 5, 102713.

- 142 X. Wang, S. Y. Wang and S. J. Ji, Org. Lett., 2013, 15, 1954.
- 143 P. V. Santhini, S. A. Babu, A. Krishnan, R. E. Suresh and J. John, Org. Lett., 2017, 19, 2458.
- 144 P. Santhini, S. S. Chand, J. John, R. L. Varma, F. Jaroschik and K. Radhakrishnan, Synlett, 2017, 28, 951.
- 145 D. Alpers, F. Hoffmann and M. Brasholz, Synlett, 2017, 28, 919.
- 146 M. I. D. Mardjan, S. Perie, J. L. Parrain and L. Commeiras, Org. Biomol. Chem., 2017, 15, 3304.
- 147 A. Galván, A. B. González-Pérez, R. Álvarez, A. R. De Lera, F. J. Fañanás and F. Rodríguez, Angew. Chem., Int. Ed., 2016, 55, 3428.
- 148 L. Zhang, F. Zhao, M. Zheng, Y. Zhai, J. Wang and H. Liu, Eur. J. Org. Chem., 2013, 5710.
- 149 P. Purohit, A. K. Pandey, B. Kumar and P. M. S. Chauhan, RSC Adv., 2016, 6, 21165.
- 150 S. Pandey, S. Khan, A. Singh, H. M. Gauniyal, B. Kumar and P. M. S. Chauhan, J. Org. Chem., 2012, 77, 10211.
- 151 S. Pandey, S. S. Chauhan, R. Shivahare, A. Sharma, S. Jaiswal, S. Gupta, J. Lal and P. M. S. Chauhan, Eur. J. Med. Chem., 2016, 110, 237.
- 152 L. P. Fu, Q. Q. Shi, Y. Shi, B. Jiang and S. J. Tu, ACS Comb. Sci., 2013, 15, 135.