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REVIEW

Homogeneous and heterogeneous catalysts for multicomponent reactions

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Organic synthesis performed through multicomponent reactions is an attractive area of research in organic chemistry. Multicomponent reactions involve more than two starting reagents that couple in an exclusive ordered mode under the same reaction conditions to form a single product which contains the essential parts of the starting materials. Multicomponent reactions are powerful tools in modern drug discovery processes, because they are an important source of molecular diversity, allowing rapid, automated and high throughput generation of organic compounds. This review aims to illustrate progress in a large variety of catalyzed multicomponent reactions performed with acid, base and metal heterogeneous and homogeneous catalysts. Within each type of multicomponent approach, relevant products that can be obtained and their interest for industrial applications are presented.

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1. Introduction

Organic-chemical synthesis performed through one-pot, tandem, domino or cascade reactions[1,2] have become a significant area of research in organic chemistry[3–10] since such processes improve atom economy. The one-pot transformations can be carried out through multi-step sequential processes where the consecutive steps take place under the same reaction conditions or, when this is not possible, they can be performed in two or more stages under different reaction conditions, with the correct addition sequence of reactants. There are cases however, in where the desired product can be prepared in a one-pot mode throughout a multicomponent reaction. Multicomponent reactions (MCRs) are defined as reactions that occur in one reaction vessel and involve more than two starting reagents that form a single product which contains the essential parts of the starting materials.[11,12] Thus, an ideal multicomponent reaction involves the simultaneous addition of reactants, reagents and catalyst at the beginning of the reaction and requires that all reactants couple in an exclusive ordered mode under the same reaction conditions. The success of multi-step sequential or multicomponent one-pot transformations, requires a balance of equilibria and a suitable sequence of reversible and irreversible steps. Thus, in the case of MCRs three types of reactions are known:[13] (a) Type I MCRs in which there is an equilibrium between reactants, intermediates and final products; (b) Type II MCRs in where an equilibrium exists between reactants and intermediates with the

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Avelino Corma

Avelino Corma was born in Moncófar, Spain in 1951. He studied Chemistry at the Universidad de Valencia (1967–1973), and received his Ph.D. at the Universidad Complutense de Madrid in 1976. He did his postdoctoral studies at the Department of Chemical Engineering at Queen's University (Canada, 1977–79). He is director of the Instituto de Tecnología Química (UPV-CSIC) at the Universidad Politécnica de Valencia since 1990. His current research field is catalysis, covering aspects of synthesis, characterization and reactivity in acid–base and redox catalysis. Avelino Corma is co-author of more than 700 articles and 100 patents on these subjects.

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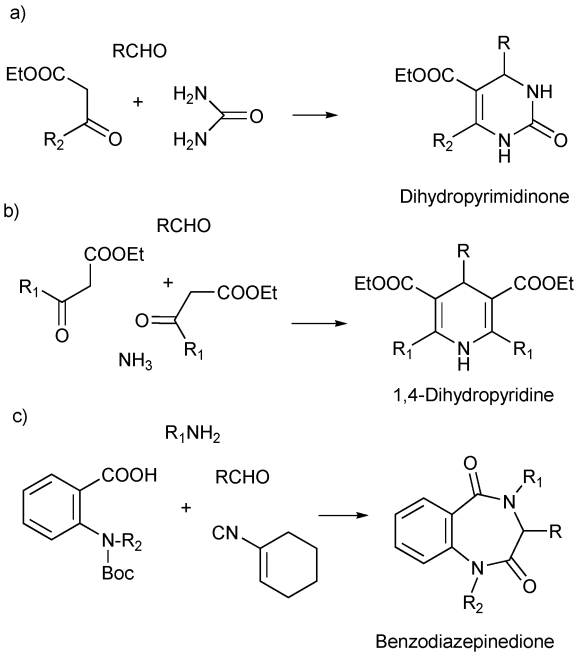
final product being irreversibly formed; (c) Type III MCRs which involve a sequence of practically irreversible steps that proceed from the reactants to the products. Type III MCRs are usual in biochemical transformations, but rarely occur in preparative chemistry.[13]

MCRs have been known for over 150 years and it is generally considered that this chemistry began in 1850 when Strecker[14] reported the general formation of α-aminocyanides from ammonia, carbonyl compounds and hydrogen cyanide. Since then, many multicomponent reactions have been developed, some of the first examples are the Hantzsch dihydropyridine synthesis (1882)[15] and the Biginelli[16] 3CR (1893) (Scheme 1). The first isocyanide-based 3CRs was introduced by Passerini in 1921, while in 1959 Ugi introduced the four component reaction of the isocyanides[17] which involves the one-pot reaction of amines, carbonyl compounds, acid and isocyanides. The Ugi reaction has been the most extensively studied and applied MCR in the drug discovery process.

One key aspect of multicomponent reactions is that they are an important source of molecular diversity.[18] For instance, a three component coupling reaction will provide 1000 compounds when 10 variants of each component are employed. This aspect together with its inherent simple experimental procedures and its one-pot character, make MCRs highly suitable for automated synthesis. They are powerful tools in modern drug discovery processes allowing rapid, automated and high throughput generation of organic compounds.[19–22] Additionally, the one-pot character delivers fewer by-products compared to classical stepwise synthetic routes, with lower costs, time and energy.

Although most of the established MCRs do not require a catalyst, the search for new MCR products has resulted in an intensified effort to find catalysts and new catalyzed MCRs. We will show that while a variety of homogeneous and heterogeneous catalysts have been reported to perform MCRs, the advantages inherent to the use of heterogeneous catalysts undoubtedly would reinforce the environmental benefits of these interesting reactions.

In this work we will review a large variety of MCRs, particularly three-component coupling reactions (A^3 coupling) performed with acid, base and metal heterogeneous catalysts as well as with bifunctional catalytic systems. We will present within each type of MCR, relevant products that can be obtained and their interest for industrial applications.



Scheme 1 Preparation of privileged scaffolds by (a) Biginelli reaction, (b) Hantzsch synthesis and (c) Ugi deBoc/cyclize methodology.

2. Solid catalysts of interest for MCR

The simplest approximation to heterogeneous catalysis starting from homogeneous mineral and organic acids has been to support them on porous solids. For instance, perchloric, sulphuric and phosphoric acids are normally supported on silica either by simple pore filling and/or by interacting with the surface of the solid. In the case of the sulfonic acids an heterogenization procedure involves the synthesis of organic polymers bearing sulphonic groups. In this case organic resins can be excellent catalysts, especially when their pore structure is adapted to the nature and dimensions of reactants.[23,24]

Inorganic solid acids can be prepared with acidity that ranges from weak to strong, going through solids with controlled intermediate acidities. One type of inorganic solid acid is the family of silicates. In high surface area silica, the silicon atoms are tetrahedrally coordinated and the system is charge neutral (Fig. 1a). However the silica nanoparticles terminate at the surface with silanol groups (Fig. 1b). In this silanol group the density of positive charge on the hydrogen of the hydroxyl group is very small and it can be considered as a very weak Brønsted acid site. Nevertheless they could be used for acid catalyzed reactions that require weak acidity, provided that the silica has a relatively high surface area. With this type of catalyst the reactants become activated by surface adsorption, being the heat of adsorption the additive effect of the small van der Waals and hydrogen bridging type of interactions.

Larger O–H polarizations are achieved when an isomorphic substitution of Al by Si occurs. In this case, the tetrahedrally coordinated Al generates a negative charge that is compensated

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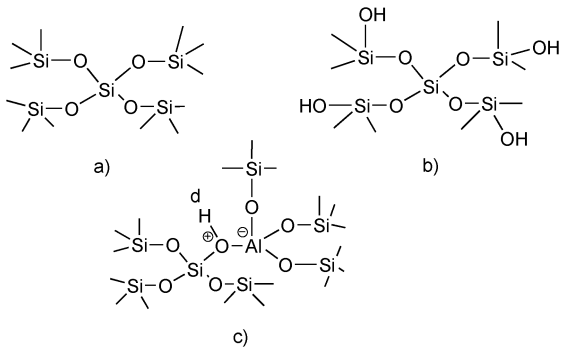


Fig. 1 Structure of silicates.

by the positive charge associated with the hydrogen of the bridging hydroxyl groups (Fig. 1c). These Brønsted acid sites are clearly stronger than the silanol groups and they exist in well prepared amorphous and long range structured silica aluminas and in crystalline aluminosilicates.[25–27] When the T–O–T' bond in aluminosilicates is not constrained, as it occurs in amorphous silica alumina, the tendency to release the proton and to relax the structure is lower and consequently the Brønsted acidity is mild. However, in the case of crystalline aluminosilicates such as zeolites the bridging T–O–T' bond is constrained and the Brønsted acidity of these materials is higher than in amorphous silica alumina. If one takes into account that it is possible to synthesize zeolites with different Al contents and with pores within a wide range of diameters,[28–30] it is not surprising that zeolites have found and still find a large number of applications as solid acid catalysts.[31] Their applications can be even enlarged through the synthesis of acid zeolites with pores of different dimensions within the same structure. Thus, structures with pores formed by 12 and 10 ring,[32] 18 × 10,[33] 14 × 12,[34] 17 × 12[30,35] and the recently discovered ITQ-43 with 24 × 12[36] rings, with pores in the mesoporous range have been presented.

If one takes into account that other metal atoms, such as Ti, Sn, Fe and Cr with catalytic activity for oxidations, can be incorporated in the structure of the crystalline microporous silicates or aluminosilicates[37–39] enlarging the reactivity of the zeolites and allowing the preparation of bifunctional acid-oxidations catalysts. When metal nanoparticles are formed on the internal and/or external surface of acid zeolites, bifunctional hydrogenation/dehydrogenation solid acid catalysts are obtained[40–43] allowing zeolites to catalyze multistep reactions.[44,45]

There are reactions that require sites with an acid strength stronger than that of zeolites. Then, solid catalysts containing sulfonic groups can be used. For instance, acidic resins with sulfonic acid groups are strong solid acid catalysts that can be useful for acid catalysis, provided that the reaction temperature does not surpass their thermal stability limit.[46] Along this line, Nafion is a strong solid acid catalyst but its surface area is too low. To avoid this limitation, Harmer *et al.* have shown that it is possible to partially depolymerize Nafion and to disperse it in silica.[47,48] The resultant high surface solid catalysts can be used in a relatively larger number of acid catalyzed reactions.[49–52] Nevertheless, the acidity of this hybrid material is somewhat lower than Nafion, owing to the interaction of sulfonic groups with the silanols of the silica.[53–54] In any case it should be considered that polymer derived catalysts may be difficult to regenerate if poisoned by deposition of organic compounds. Indeed, regeneration by calcination with air will be limited because of thermal stability, and washing out the adsorbed products with solvents can not always restore the initial activity.

Looking for strong acid catalysts, heteropolyacids such as $H_3PW_{12}O_{40}$ (H_3PW) are able to catalyze at low temperatures a wide range of homogeneous catalytic processes.[55] Heteropolyacids can be heterogeneized by either supporting them on a high surface area carrier such a silica[56] or by forming their cesium or potassium salts ($Cs_{2.5}H_{0.5}PW$ or $K_{2.5}H_{0.5}PW$) that are solids with micro and mesoporosity and are insoluble for organic reactions.[57]

Other solid acids such as metal organic frameworks bearing sulfonic groups or metal Lewis acids,[58] sulfonated zirconia[59,60] and metal phosphates have also been used as catalysts.[61,62]

With respect to solid bases, basic resins, amines and alkyl ammonium hydroxides grafted on silicas, or amines bearing part of MOF structures, KF on Al_2O_3, alkaline metal oxides on alumina and zeolites, zeolites exchanged with alkaline cations, alkaline earth oxides and anionic clays such as hydrotalcites and their corresponding mixed oxides are useful catalysts and their basic properties and catalytic activity have been very well described in a series of reviews.[31,63–68]

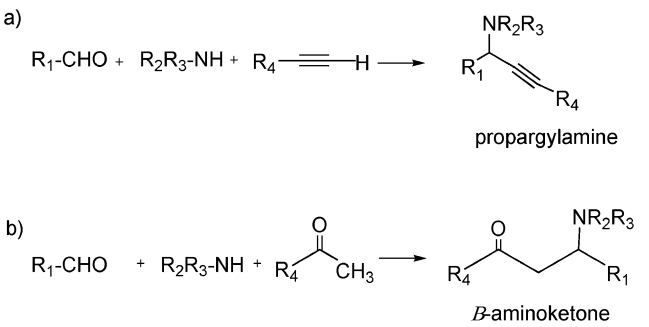
The solid acid and base catalysts named above account for the majority of the catalysts required for MCRs presented in this review. In those cases, in which significantly different catalyst will be required, we will briefly describe their nature.

3. Heterogeneous catalyzed multicomponent reactions

3.1 Synthesis of propargylamines

The Mannich reaction is a classic example of a three component condensation (A^3 coupling). In general, an aldehyde, an amine and an active hydrogen compound such as an enolyzable ketone or terminal alkyne, react affording the corresponding *β*-aminoketone or *β*-aminoalkyne (propargylamine) (Scheme 2).

Propargylamines are important synthetic intermediates for potential therapeutic agents and polyfunctional amino derivatives.[69–71] Traditionally these compounds have been synthesized by nucleophilic attack of lithium acetylides or Grignard reagents to imines or their derivatives. However these reagents must be used in stoichiometric amounts, are highly moisture sensitive, and sensitive functionalities such as esters are not tolerated. Therefore, the most convenient synthetic method for preparing propargylamines has been the Mannich one-pot three compo-



Scheme 2 Mannich type reactions.

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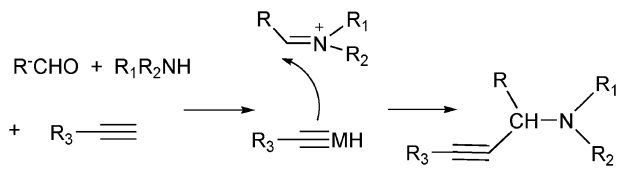
nent coupling reaction of an aldehyde, a secondary amine and a terminal alkyne. The reactions are usually performed in polar solvents (mostly dioxane) and in the presence of a catalytic amount of a copper salt (CuCl, $Cu(OAc)_2$)[72] which increases the nucleophilicity of the acetylenic substrate towards the Mannich reaction. Mechanistic studies indicate that the reaction involves the formation of an iminium intermediate from the starting aldehyde and amine. The C–H bond of the alkyne is activated by the metal to form a metal acetylide intermediate which subsequently reacts with the iminium ion leading to the corresponding propargylamine (Scheme 3).

A variety of transition metals such as Ag^{I} salts,[73] Au^{I}/Au^{III} salts,[74,75] Au^{III} salen complexes,[76] Cu^{1} salts,[77–78] Ir complexes,[79] $InCl_3$,[80] Hg_2Cl_2[81] and Cu/Ru^{II} bimetallic system[82] have been employed as catalysts under homogeneous conditions. In addition, alternative energy sources like microwave[83] and ultrasonic[84] radiations have been used in the presence of Cu^{I} salts. Considering that chiral propargylamines are widely present in many important bioactive compounds, enantioselective synthesis of propargylamines throughout this protocol have been recently developed using chiral Cu(I) complexes.[85,86]

However, operating under homogenous media two main drawbacks must be considered: the difficulty to recover and reuse the catalyst and the possible absorption of some of the metal catalyst on the final product (fine chemical). Currently the upper tolerance limit for the contamination of drugs or other compounds set aside for human consumption by transition metals is 5 ppm and future regulations are expected to lower this threshold to the ppb range.

In order to achieve the recyclability of transition metal catalysts, gold, silver and copper salts in ionic liquids, $[Bmim]PF_6$[87,72] as well as heterogeneous catalysts have been used to obtain propargylamines. Thus, different metal exchanged hydroxyapatites (metal–HAP) are able to catalyze the condensation of benzaldehyde, piperidine and phenylacetylene in acetonitrile under reflux temperature.[88] The results showed that the order of efficiency was Cu–HAP > $Cu(OAc)_2$ > Ru–HAP > Fe–HAP achieving yields of the corresponding propargylamine of 85%, 80%, 60%, and 25% respectively. A variety of structurally different aldehydes, amines and acetylenes in the presence of Cu–HAP were converted into the corresponding propargylamines with 55–92% yield. Cu–HAP was reused several times showing consistent activity even after the fourth cycle. Silica gel anchored copper chloride has been described by Sreedhar *et al.*[89] as an efficient catalyst for the synthesis of propargylamines *via* C–H activation. Both aromatic and aliphatic aldehydes and amines and phenylacetylene have been used to generate a diverse range of acetylenic amines in good to moderate yields (52–98%) using water as a solvent and without any organic solvent or co-catalyst. A stable and efficient catalyst for the three component coupling Mannich reaction of aldehydes, amines and alkynes was prepared by Li *et al.*[90] by immobilizing



Scheme 3 Proposed mechanism for the Mannich reaction.

Cu(I) on organic–inorganic hybrid materials. Thus, a silica-CHDA-CuI catalyst was prepared from benzylchloride functionalized silica gel which was subsequently reacted with 1, 2-diaminecyclohexane. This organic–inorganic hybrid material was reacted with couprous iodide to generate a silica-CHDA-CuI catalyst with 1.6 wt% of Cu. Reactions performed in the absence of solvent afforded the corresponding propargylamines in excellent yields (82–96%). No catalyst leaching was observed in the reaction media, and the catalyst remained active through at least 15 consecutive runs. Others immobilized metals such a Ag(I) and Au(I) exhibited lower activity than Cu catalysts while silica supported Pd(II) failed in this reaction.

Recently Wang *et al.*[91] have reported a novel silica-immobilized *N*-heterocyclic carbene metal complex (Si–NHC–Cu^{I}) as an efficient and reusable catalyst for the synthesis of propargylamines. Reacting different combinations of aldehydes, amines and alkynes at room temperature under solvent free conditions, produces the corresponding propargylamines in moderate to good yields (43–96%) after 24 h reaction time (see Table 1). Higher yields were obtained when the MCR was carried out at 70 °C in 4 h, while no metal leaching in the liquid media was observed.

Cu(0) nanoparticles have also been used by Kidway and co-workers[92] as active and recyclable catalysts in the synthesis of propargylamines following the Mannich protocol. The Cu nanoparticles prepared in a reverse micellar system (with size of 18 ± 2 nm) gave a diverse range of propargylamines in excellent yields (65–98%).

Different metal-supported zeolites such as Cu-modified zeolites (H–USY, HY, H–Beta, Mordenite and ZSM-5), have been successfully used for the synthesis of propargylamines.[93] The MCR between piperidine, benzaldehyde and phenylacetylene performed at 80 °C in the absence of solvent, showed that the order of activity was: Cu^{I}–USY > Cu^{I}–Y > Cu^{I}–Beta > Cu^{I}–ZSM–5 > Cu^{I}–Mordenite, indicating that the pore topology of the zeolites has a marked influence on the reaction efficiency (Table 2). The authors suggest that the formation of the iminium intermediate assisted by the zeolite is combined with the formation of the acetylide within the micropores leading to an efficient reaction. The scope of the Cu^{I}–USY catalyst was examined using different reagents, including bulky amines, and in all cases propargylamines were obtained in good to moderate yields (55–90%), though long reaction times (15 h) were required. Furthermore, Cu^{I}–USY could be recycled up to four times without loss of activity. Cu exchanged NaY zeolite has also been used as a catalyst in the synthesis of substituted propargylamines.[94] Different metal exchanged zeolites (Cu–NaY, Ag–NaY and Au–NaY) were prepared by conventional ion exchange method by treating NaY zeolite with an aqueous solution of different salts. When an equimolar mixture of benzaldehyde, piperidine and phenylacetylene were reacted at 100 °C for 5 h in the presence of Au–NaY zeolite the corresponding propargylamine was obtained in low yield (32%) whereas both Cu–NaY and Ag–NaY catalysts gave the propargylamine in moderate yields (43% and 52% respectively). Metal leaching of Cu–NaY and Au–NaY catalysts was observed in the reaction media, but Ag–NaY was stable and metal leaching was not detected. Several substituted propargylamines were prepared with Ag–NaY affording the corresponding propargylamines in moderate to

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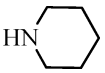
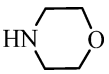
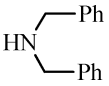
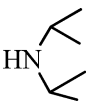
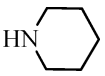
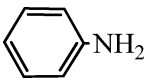
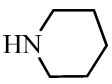
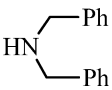
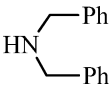
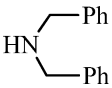
Table 1 Mannich reaction of different aldehydes amines and alkynes using Si–NHC–Cu^{I} catalyst[a]

Alkyne	Aldehyde	Amine	Yield (%)[b]
$C_6H_5C{\equiv}CH$	CH_2O		95
$C_6H_5C{\equiv}CH$	CH_2O		94
$C_6H_5C{\equiv}CH$	CH_2O		94
$C_6H_5C{\equiv}CH$	CH_2O		96
$C_6H_5C{\equiv}CH$	C_6H_5CHO		79 91[c]
$C_6H_5C{\equiv}CH$	C_6H_5CHO		71 88[c]
$C_6H_5C{\equiv}CH$	m–ClC_6H_4CHO		93[c]
p–$CH_3C_6H_5C{\equiv}CH$	CH_2O		96
n–$C_8H_{17}C{\equiv}CH$	CH_2O		78 92[c]
$EtOOCC{\equiv}CCH_3$	CH_2O		75[c]

[a] Reaction conditions: aldehyde (1.0 mmol), amine (1.1 mmol), alkyne (1.2 mmol), SiO_2–NHC–Cu^{I} (2 mol%), nitrogen, room temperature, 24 h. [b] Isolated yield. [c] 70 °C for 4 h.

Table 2 Results of the MCR between piperidine, benzaldehyde and phenylacetylene using different Cu^{I} catalysts[a]

Catalyst	Solvent	*T*/°C	Yield[b] (%)	Acid sites (mmol g^{-1})
Cu^{I}–USY	DMF	60	40	4.39
Cu^{I}–USY	Toluene	80	72	4.39
Cu^{I}–USY	THF	80	79	4.39
Cu^{I}–USY	MeCN	60	35	4.39
Cu^{I}–USY	none	80	95	4.39
Cu^{I}–Y	none	80	92	6.67
Cu^{I}–Beta	none	80	90	0.91–1.23
Cu^{I}–ZSM-5	none	80	80	1.04
Cu^{I}–Mor	none	80	71	1.48
H–USY	none	80	—[c]	6.67
CuCl	none	80	40–90[c]	—
none	none	80	—[d]	—

[a] Reaction conditions: 1 mmol of each component for 15 h with a zeolite loading of 20 mg. [b] Yields were evaluated by H–NMR analysis of the crude mixture. [c] Upon mixing without solvent, intense heat was evolved leading to decomposition, whereas in solvent good yields were obtained. [d] No transformation was observed.

good yields (42–97%) and high selectivities (90–99%) after 15 h. Very recently Namitharan *et al.*[95] have reported that Ni-exchanged Y zeolite (Ni–Y) exhibits excellent activity for the A^3 coupling of cyclohexanecarbaldehyde, morpholine and phenylacetylene giving the corresponding propargylamine in 97% yield under solvent free conditions at 80 °C. No leaching of metal ions provides strong support for the heterogeneous nature of the catalyst. In Table 3 the activity of Ni–Y zeolite is compared with other homogeneous and heterogeneous based catalysts. The Ni–Y zeolite could be recycled at least four times retaining yield and selectivity. A variety of aliphatic, aromatic, cyclic and heterocyclic alkynes were coupled using this catalyst, and yields between 84–97% were achieved. The authors claim that Ni^{II} is the catalytic site for the coupling reaction. In the mechanism proposed, the Ni^{II} species in Ni^{II}–Y zeolite react with the terminal alkyne and the subsequent cleavage of one of the oxo bridges in the zeolite generates the nickel(II) acetylide intermediate. Then, the acetylide reacts with the iminium ion generated *in situ* from aldehyde and amine to give the propargylamine while the Ni^{II}–Y zeolite is ready for a subsequent reaction cycle (Scheme 4).

A silver salt of 12-tungstophosphoric acid (AgTPA) has been reported by Reddy and coworkers[96] as a heterogeneous catalyst to prepare different propargylamines *via* a three component coupling reaction in very good yields (70–98%).

We have recently found that Cu–MOFs[97] were active and selective solid catalysts for the A^3 coupling of a large variety of aldehydes, amines and alkynes. The Cu–MOF catalyst deactivates because of a loss of crystallinity, but the original activity was fully restored by treating with DMF at reflux and regenerating the initial MOF structure.

While homogeneous gold complexes were reasonable active catalysts for the three component reaction, it has now been shown that gold supported catalysts can also catalyze the A^3 coupling for preparation of propargylamines with excellent success. For instance, Kantam *et al.*[98] reported the use of a gold support onto a layered double hydroxide (LDH–$AuCl_4$) for the Mannich reaction. A range of propargylamines was obtained in excellent yields (89–93%) at reflux of THF. However a significant deactivation of LDH–$AuCl_4$ after the second and third reuse was detected, which was attributed to the formation

Table 3 A^3 coupling of cyclohexanecarbaldehyde, morpholine and phenylacetylene using different Ni based catalysts[a]

Nickel source	Solvent	Yield(%)[b]
$Ni(OAc)_2{\cdot}4H_2O$	DMF	25[c]
$Ni(OAc)_2{\cdot}4H_2O$	toluene	21[c]
$Ni(OAc)_2{\cdot}4H_2O$	THF	20[c]
$Ni(OAc)_2{\cdot}4H_2O$	MeCN	26[c]
$Ni(OAc)_2{\cdot}4H_2O$	none	63
$NiCl_2{\cdot}6H_2O$	none	53
$Ni\ (SO_4)_2{\cdot}6H_2O$	none	55
$Ni(NO_3)_2{\cdot}6H_2O$	none	36
Ni/Al–HT	none	31
Ni–K10 clay	none	64
Ni–Al–MCM-41	none	73
Ni–Y zeolite	none	97
H–Y zeolite	none	0

[a] Cyclohexanecarbaldehyde (1.0 mmol), morpholine (1.2 mmol), phenylacetylene (1.2 mmol), Ni–Y (20 mg), 80 °C, 4 h. [b] Yield of isolated product. [c] 100 °C, for 15 h.

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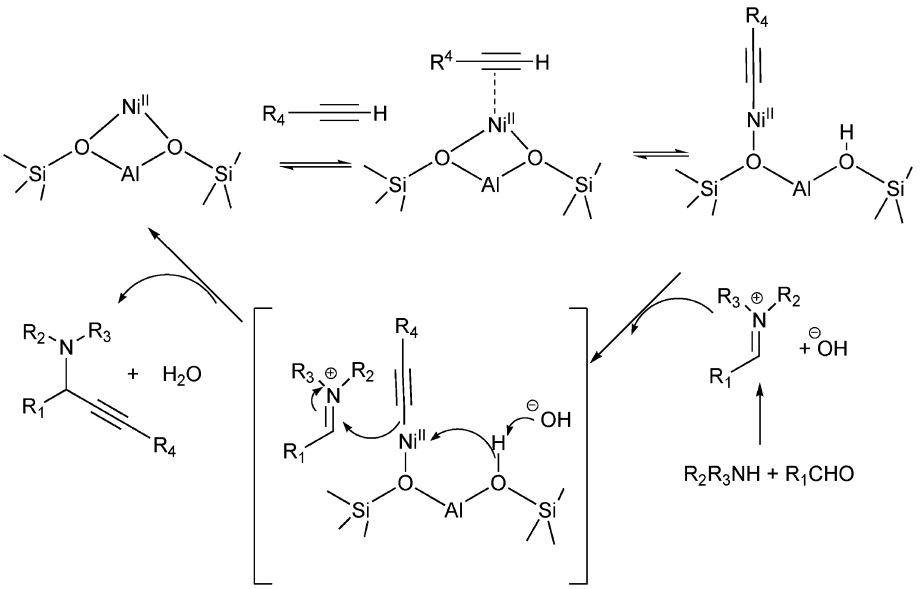


Scheme 4 Possible mechanism of Ni^{II}–Y-catalyzed three component coupling.

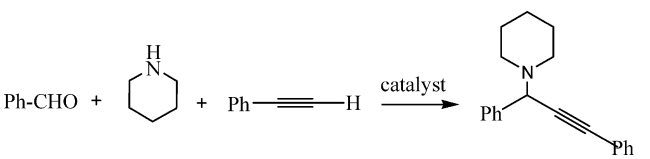
of Au(0) and Au(I) as revealed by XPS studies. Au nanoparticles (Au–np), prepared in a reverse micellar system, has also been used as a catalyst for the MCR of aldehydes, amines and alkynes.[99] It was found that the nature of reaction media has an important role in the MCR reaction. Among the different solvents investigated, the acetonitrile was the best for carrying out the coupling reaction. This was attributed to its high polarity that may result in the stabilization of the acetylide–Au intermediate which reacted with the iminium ion generated *in situ*, to give the corresponding propargylamine. A variety of structural aldehydes and amines with a wide range of functional groups were coupled affording the propargylamines in excellent yields (67–96%). The maximum reaction rate was observed for an average particle size of about 20 nm. In addition, the Au–np catalyst was reused without further purification for seven runs with only a slight drop in activity. Recently, Datta *et al.*[100] have reported that Au nanoparticles (7 nm) encapsulated with highly ordered mesoporous carbon nitride (Au/MCN) are an active and recyclable catalyst for coupling benzaldehyde, piperidine and phenylacetylene. However, better yields (>95%) were obtained by Corma *et al.* for the same reaction using Au nanoparticles supported on nanocrystalline ZrO_2 and CeO_2[101] (Table 4). Different studies and theoretical calculations have evidenced that cationic gold species can be stabilized on ZrO_2 and CeO_2 but not on other supports as shown in Table 4. The proposed mechanism involves the activation of the C_{sp}–H bond by Au(III) species stabilised by nanocrystalline ZrO_2 or CeO_2 to give a gold acetylide intermediate (A), which reacts with the immonium ion formed *in situ* (B) to give the corresponding propargylamine (Scheme 5). The catalytic activity TON (turn-over number) and TOF (turn-over frequency) is the highest reported up to now (see Table 4). The reaction was extended to different combinations of aldehydes, amines and alkynes giving excellent yields to the corresponding propargylamines. Besides, when a chiral amine was used in the presence of Au/ZrO_2 and Au/CeO_2 the corresponding chiral propargylamine was obtained with high yields (>97%) and excellent diasteroselectivities (99 : 1). Table 5 summarizes the results obtained in the MCR of benzaldehyde, piperidine, and phenylacetylene using different solid catalysts.

3.2 Synthesis of indole derivatives

Functionalized indoles are biologically active compounds[102] that can be obtained using a variety of approaches.[103] Recently, following the Mannich approach functionalized indols have been obtained by three component coupling and cyclization of *N*-tosyl protected ethynylaniline, paraformaldehyde and piperidine in the presence of Au/ZrO_2[101] (Scheme 6).

It was found that only a fraction of the total gold species *i.e.* only the Au(III) are active for this reaction. Thus, the MCR of paraformaldehyde, piperidine and *N*-protected ethynylaniline in the presence of Au/ZrO_2 in dioxane at 100 °C and after 5 h, yielded 95% of 2-(aminomethyl) indole. No propargylamines

Table 4 Three-component coupling of benzaldehyde, piperidine, and phenylacetylene with supported gold catalysts[a]



Catalyst[b]	Gold (mol%)	Conv. (%)[c]	Yield propargylamine (%)[d]	TON[e]
0.2% Au/SiO_2	0.013	< 5	—	—
3.0% Au/C	0.081	13	nd	161
1.5% Au/TiO_2	0.075	35	nd	464
4.5% Au/Fe_2O_3	0.247	40	nd	162
2.8% Au/ZrO_2	0.142	95	93	668
2.5% Au/CeO_2	0.127	100	>99	788

[a] Reaction conditions: benzaldehyde (1.0 mmol), piperidine (1.2 mmol), phenylacetilene (1.3 mmol), H_2O (MiliQ, 1.0 mL), 6 h, 100 °C. [b] The number (*e.g.* 0.2%) is the mass weight of gold loaded on the support (*e.g.* SiO_2). [c] Determined by GC analysis based on aldehyde. [d] Yields of isolated propargylamine based on benzaldehyde; n.d. not determined. [e] Calculated on the basis of total weight of gold.

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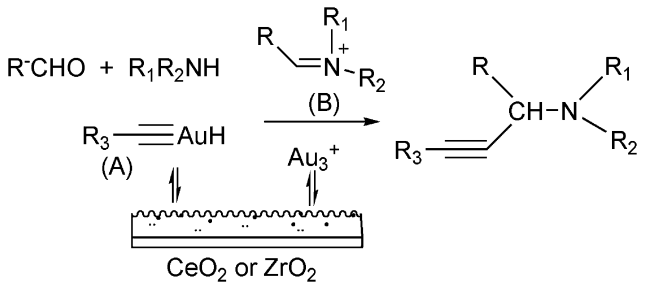

Scheme 5 Mechanism proposed in the presence of gold supported on CeO_2 or ZrO_2.

were detected in the reaction media. The reaction was also extended to different combinations of aldehydes and amines giving the corresponding indoles in good yields.

More recently the same authors[104] have prepared metal organic frameworks (IRMOF-3-Si–Au) containing a Au(III) Schiff base complex lining the pore walls. This material was obtained by reacting the $–NH_2$ groups of IRMOF-3 with salicylaldehyde to form the corresponding imine. The final step consists of reacting a gold precursor ($NaAuCl_4$) with the imine. A maximum functionalization of about 3% of the total amino groups was produced which allowed the introduction of up to 2 wt% of gold using this method. IRMOF-3-Si–Au catalyst was tested for the condensation reaction of N–tosyl protected ethynylaniline, piperidine and paraformaldehyde in dioxane at 40 °C (see Table 6). It was found that IRMOF-3-Si-Au gives much higher catalytic performance than other gold catalysts such as Au/ZrO_2 and homogeneous gold/salt complexes (Au(III) Schiff base complex) and $AuCl_3$. The results showed that the cationic gold Au(III) species are the active sites in this reaction which are more stable in heterogeneous media than in homogeneous media, while the higher activity of IRMOF-3-Si-Au catalyst should be attributed to the existence of well defined, stable and accessible isolated Au(III) active sites on this material. Good yields of indole derivatives (70–95%) were obtained from *N*-protected ethynylanilines, and different aldehydes and amines (Table 6). The IRMOF-3-Si-Au catalyst can be successfully reused and no gold leaching from the solid to the liquid media was detected. However, the reaction should be carried out with freshly prepared catalyst since catalyst amorphization occurs upon catalyst storage for long time.

3.3 Substituted benzo[*b*]furans

Benzo[*b*]furan derivatives are compounds of relevance because of their natural occurrence associated with their biological properties.[70,105] The most general methods to prepare benzo[*b*]-furans involve reductive cyclization of ketoesters by low valent titanium,[106] photochemical rearrangement of phosphate esters,[107] Suzuki coupling of boronic acids with organic halides or triflates catalyzed by palladium,[108] Sonogashira cross coupling reaction of *o*-halophenols with terminal alkynes in the presence of palladium and/or copper as catalysts.[109]

Recently, following the Mannich protocol, Kabalka *et al.*[110] have reported the synthesis of a variety of propargylamines in good yields from different alkynes, primary or secondary amines and paraformaldehyde using cuprous iodide doped alumina as the catalyst under microwave irradiation. The reaction was extended to the synthesis of 2-substituted benzo[*b*]furan derivatives when ethynylphenol was condensed with secondary amines (such as piperidine, morpholine, 1-phenylpiperazine *etc.*) and paraformaldehyde (see Table 7). In this case the Mannich adduct resulting from the A^3 coupling undergoes a subsequent cyclization into the benzofuran ring (Scheme 7). The reaction is highly efficient and moderated to good yields of 2-substituted benzo[*b*]furans (52–70%) were obtained in a short reaction time, but high amounts of catalyst were required.

3.4 Synthesis of *β*-aminocarbonyl compounds

N-Substituted aminocarbonyl compounds can be synthesised by the versatile Mannich type reaction (see Scheme 2). The MCR between an aldehyde, amine and ketones using Lewis[111]or Brønsted acids[112] and Lewis bases[113] as catalysts produces *β*-aminocarbonyl compounds (Scheme 8). *β*-Aminocarbonyl compounds are important building blocks for the synthesis of biologically active nitrogen-containing compounds such as *β*-amino alcohols, *β* amino acids and *β*-lactams and pharmaceuticals.[114,115]

Table 5 A^3 coupling of benzaldehyde, piperidine, and phenylacetylene using different solid catalysts

Catalyst	Yield (%)	Solvent	T °C	t(h)	Catalyst (mol%)	Molar ratio[a]	Ref.
CuI–[bmim]PF_6[b]	85	[bmim]PF_6	120	2	2	1 : 1.2 : 1.5	72
Cu-np[b]	94	CH_3CN	100	6	15	1 : 1 : 1.5[e]	92
Cu–HAP[b]	85	CH_3CN	reflux	6	0.10[d]	1 : 1.2 : 1.3	88
Silica gel CuCl[b]	86	H_2O	reflux	10	0.05	1 : 1.2 : 1.5	89
SiNHC–Cu[1b]	79–91[c]	—	rt	24	2	1 : 1.2 : 1.2	91
SiCHDA–Cu[1]	92	—	80	12	0.04[d]	1 : 1 : 1	102
USY–Cu[1]	95	—	80	15	0.02[d]	1 : 1 : 1.2	93
AgTPA[b]	92	CH_3CN	80	6	0.03[d]	1 : 1.2 : 1.3	96
Au–np[b]	94	CH_3CN	80	5	10	1 : 1 : 1.5	99
Ag–NaY[b]	81	—	100	15	5	5 : 5 : 5	94
Zn dust[b]	90	CH_3CN	reflux	9	15	1 : 1.1 : 1.2	103
Au/MCN[b]	61	Toluene	100	24	0.05	1 : 1.2 : 1.3	100
Au/CeO_2[b]	>99	H_2O	100	6	0.127	1 : 1.2 : 1.3	101
LDH–$AuCl_4$	92	THF	reflux	5	0.025[d]	1 : 1.2 : 1.5	98
Fe_3O_4 np[b]	45	THF	80	24	5	0.5 : 0.6 : 0.7	104
Ni–HY	85	—	80	10	0.02[d]	1 : 1.2 : 1.2[e]	95

[a] mmol of benzaldehyde : piperidine : phenylacetylene, under N_2. [b] Catalyst was recovered and reused. [c] At 70 °C for 4 h. [d] Grams of catalyst. [e] mmol of benzaldehyde : morpholine : phenylacetylene.

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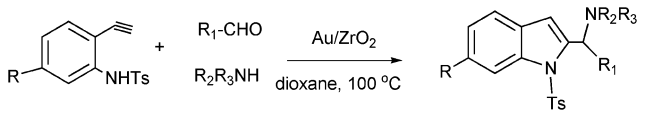


Scheme 6 Three component coupling and cyclization of an aldehyde, amine, and *N*-protected ethynylaniline.

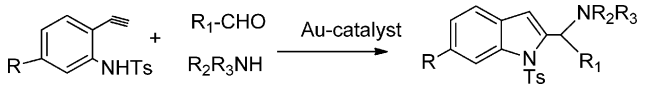
Mechanistically the reaction proceeds typically *via* imine formation through the condensation of aldehyde and amine followed by the attack of the enol form of ketone on imine to afford the desired product.

Recently, the synthesis of *β*-amino ketones by a three component Mannich reaction in liquid phase under solvent free and at room temperature, have been carried out using tungstated zirconia ($WOx\text{-}ZrO_2$).[116] WOx from ammonium metatungstate was incorporated into hydrous zirconia and calcined at 923 K to give a solid, which exhibits strong acidity. Different aromatic aldehydes, anilines and cyclohexanone give the corresponding *β*-amino ketones in good yields (66–90%) as a mixture of *syn* and *anti* stereoisomers. In most of the examples studied the *syn* selectivity was higher as compared to *anti* selectivity (Scheme 9).

Also, the sulfated ceria-zirconia ($SO_4^{2-}/Ce_xZr_{1-x}O_2$) reported by Reddy *et al.*[117] was an efficient catalyst for the synthesis of *β*-amino ketones *via* a Mannich reaction. The reaction between benzaldehyde, aniline and cyclohexanone proceeded smoothly to afford 82% of 2-[1-phenyl-1-*N*-phenylamino]methylcyclohexanone, with an *anti*/*syn* ratio of 18 : 82. The catalyst could be recycled and no appreciable change in activity was observed for 2–3 runs.

It is known that fluorine containing compounds produce an enhancement of biological activity as well as a decrease in toxicity.[118] Xia and co-workers[119] reported that fluorinated *β*-aminobutanones can be obtained through a one-pot three-component Mannich type reaction of unmodified acetone with aldehydes and fluorinated anilines in good to excellent yields (81–96%) catalysed by sulfamic acid (H_2NSO_3H, SA) at room temperature (Scheme 10). Due to its zwitter-ionic property this heterogeneous catalyst can be recycled and reused through simple filtration and washing.

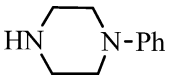
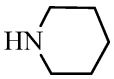
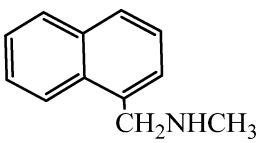
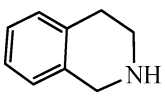
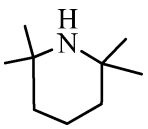
Table 6 Three component coupling and cyclization of an aldehyde, amine, and *N*-protected ethynylaniline using gold supported catalysts



Catalyst	R^1–CHO	R^2R^3NH	Yield (%)
Au/ZrO_2[a]	(HCOH)n R^1=H	piperidine	95
	Heptyl	piperidine	97
	Cyclohexyl	piperidine	75
	(HCOH)n R^1=H	pyrrolidine	87
	(HCOH)n R^1=H	morpholine	70
	(HCOH)n R^1=H	diethylamine	90
IRMOF–3–Si–Au[b]	(HCOH)n R^1=H	piperidine	90(16 h)
	Heptyl	piperidine	95(6 h)
	Cyclohexyl[c]	piperidine	80(4 h)
	(HCOH)n R^1=H	CA1[d]	83(12 h)
	(HCOH)n R^1=H	CA2[d]	91(6 h)

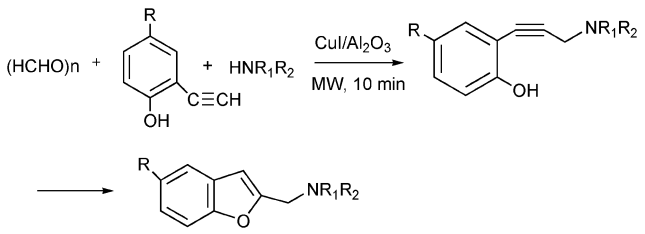
[a] Aldehyde (0.2 mmol), aniline (0.24 mmol) and *N*-protected ethynylaniline (0.26 mmol), gold (0.0007 mmol) dioxane (1.0 mL), h ; Ts: toluene-4-sulfonyl. [b] Aldehyde (0.40 mmol), aniline (0.24 mmol) and *N*-protected ethynylaniline (0.20 mmol), gold (14 mg, 0.001 mmol) dioxane (1.0 mL), 40 °C. [c] At 80 °C. [d] Chiral amines: CA1 (*S*)-(+)-2-(metoxymethyl)-pyrrolidine and CA2 (*S*)-(+)-2-methylpiperidine.

Table 7 A^3 coupling of *o*-ethynylphenol with secondary amines and paraformaldehyde using cuprous iodide doped alumina as the catalyst under microwave irradiation[a]

R	Amine	Yield (%)[b]
H		65
H	$n\text{-}(C_4H_9)_2NH$	68
H		65
H	$CH_3CH_2NHCH_3$	62
H		55
H		70
H		59
H		52

[a] Reaction conditions: paraformaldehyde (3 mmol), *o*-ethynylphenol (1 mmol), secondary amine (1 mmol), cuprous iodide (3 mmol) Al_2O_3 (1 g) irradiated at 300 W for 10 min. [b] Isolated yields.

SA is also an efficient and recyclable heterogeneous catalyst for the ultrasound assisted one-pot reaction of aldehydes with amines and ketones. Different aromatic aldehydes, anilines and acetophenone in ethanol at room temperature gave the corresponding *β*-amino ketone in 88–95% yield after 90–120 min. Also, *β*-aminocarbonyl compounds with *ortho* substituted aromatic amines are obtained in acceptable to good yields (53–95%) after 2–8 h in the presence of sulfamic acid catalyst under ultrasound irradiation (600 W).[120] The authors claimed that the accelerating effect of ultrasound can be an important tool for the



Scheme 7 Synthesis of substituted benzo[*b*]furans through a MC Mannich reaction followed by cyclization.

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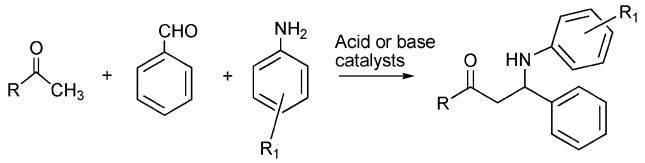


Scheme 8 Mannich reaction of aromatic aldehyde, ketones and amines.

one-pot Mannich reaction of sterically hindered arylamines. Recyclable Cu nanoparticles for the one-pot reaction to obtain *β*-amino ketones have been proposed by Kidwai and co-workers.[121] For comparative purposes various metal nanoparticles such as Au and Ni were selected for the Mannich reaction. The authors found that Cu-np (particle diameter of about 20 nm), was the most active catalyst. The catalyst was recovered and reused in four consecutive runs showing a gradual loss of activity. A variety of aromatic aldehydes, aromatic amines and acetophenone or cyclohexanone were coupled giving the corresponding *β*-amino ketones in good yields (Table 8). Optimum yields of *β*-amino ketones were achieved using a concentration of 10 mol% of Cu-np while increasing the Cu-np concentration, their oxidation to form CuO occurs, producing agglomeration and reducing the surface area of the nanoparticles and hence decreasing the catalytic activity.

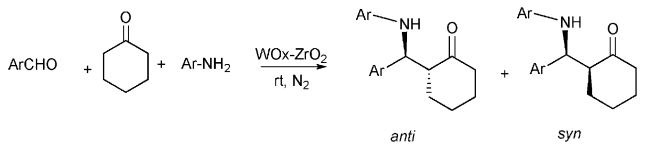
3.5 Synthesis of dihydropyrimidinones

The synthesis of functionalized dihydropyrimidinones (DHPM) represents an excellent example of the utility of one-pot multiple component condensation reactions.

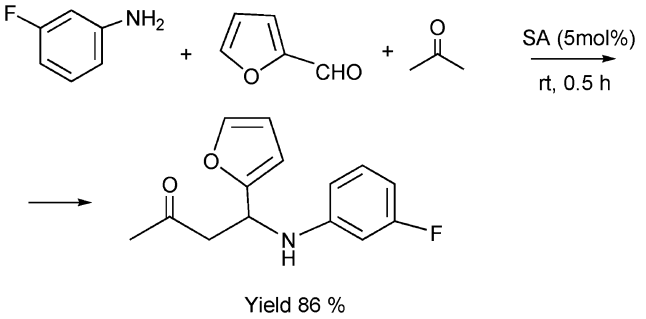
Aryl substituted 3,4-dihydropyrimidinones are important heterocyclic compounds in organic synthesis and medicinal chemistry due to their therapeutic and pharmacological properties. The DHPM and their derivatives exhibit a broad spectrum of biological effects such as antitumor, antiviral, antibacterial and antiinflammatory activities and antioxidative properties.[122] Furthermore, appropriately functionalized 3,4-dihydropyridimidones can act as calcium channel modulators, antihypertensive agents, α_{1a}-adrenergic antagonists and neuropeptide antagonists.[123]

Apart from non natural DHPM, several marine alkaloids isolated from the Sponge Batzella as batzelladine compounds are potential new leads for drug development for AIDS therapy.[124] More recently Monastrol, a 3,4-dihydropyrimidin-2(1*H*)-thione derivative has been identified and inhibits the mitotic kinesin Eg5 motor protein and can be considered as a new lead for the development of anticancer drugs.[125] Scheme 11 shows different 3,4-dihydropyrimidinones, (Monastrol, SQ 32926 and SQ 32547) reported to be effective as orally active antihypertensive agents.[126]

The simplest method for synthesising 3,4-dihydropyrimidin-2(1*H*)-one was reported first by Biginelli[16] and involves a three



Scheme 9 Three component reaction between aromatic aldehyde, aniline and cyclohexanone catalyzed by tungstated zirconia.



Scheme 10 Synthesis 4-(3-fluorophenylamino)-4-(furan-2yl)butan-2-one.

component one-pot cyclocondensation reaction of an aldehyde, an open chain *β*-ketoester and urea or thiourea in presence of acid catalysts such as hydrochloric acid in ethanol at reflux temperature[127,128] (Scheme 12).

The plausible mechanism (Scheme 13) of the acid catalyzed Biginelli condensation postulated by Kappe,[129] involves the formation of an *N*-acyliminium ion intermediate from the aldehyde and urea precursors. Interception of the iminium ion by ethyl acetoacetate, presumably trough its enol tautomer, produces an open chain ureide, which undergoes cyclization and subsequent dehydratation to yield the dihydropyrimidinones.

In recent years, many synthetic methods for preparing DHPM based on the Biginelli reaction have been reported which include classical conditions and microwave and ultrasound irradiation in the presence of Brønsted[130] and Lewis acids as catalysts. For instance, lanthanide triflates,[131] phase transfer catalysts (tetra-n-butyl ammonium bromide),[132] and NaCl in DMF.[133] However some of the reported methods suffer from drawbacks derived from the product isolation procedure and environmental pollution. Moreover, in the case of substituted aromatic and aliphatic aldehydes bearing sensitive functional groups the original Biginelli reaction is unsuitable and affords DHPM compounds in low yields (20–40%) due to the strongly acidic conditions and prolonged time of heating required.

Table 8 Mannich reaction of ketones, aromatic aldehydes and aromatic amines in the presence of Cu-np[a]

Ketone	R–CHO	R–NH_2	Time (h)	Yield (%)[b]
Acetophenone	Ph	Ph	4	93
Acetophenone	Ph	4–$CH_3C_6H_4$	9	97
Acetophenone	Ph	3,4–$(CH_3)_2C_6H_3$	10.5	92
Acetophenone	Ph	4–ClC_6H_4	9	95
Acetophenone	4–$CH_3C_6H_4$	Ph	8	97
Acetophenone	Ph	4–$OCH_3C_6H_4$	10	91
Acetophenone	Ph	4–$NO_2C_6H_4$	12	73
Acetophenone	4–$OCH_3C_6H_4$	Ph	9	91
Acetophenone	4–$NO_2C_6H_4$	Ph	12	74
p-methylacetophenone	Ph	Ph	10	85
p-nitroacetophenone	Ph	Ph	10	87
cyclohexanone	Ph	Ph	9	88
cyclohexanone	Ph	4–$CH_3C_6H_4$	11	90
cyclohexanone	Ph	4–ClC_6H_4	12	91
cyclohexanone	4–$OCH_3C_6H_4$	Ph	12	83

[a] Reaction conditions: acetophenone or cyclohexanone (1 mmol), aromatic aldehyde (1 mmol), aromatic amine (1 mmol), 10 mol% Cu-np(18± 2 nm) methanol as solvent, room temperature, nitrogen atmosphere. [b] Isolated yields.

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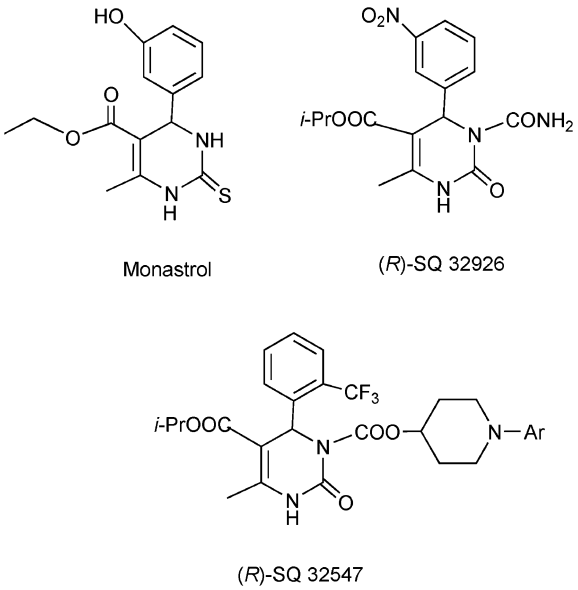
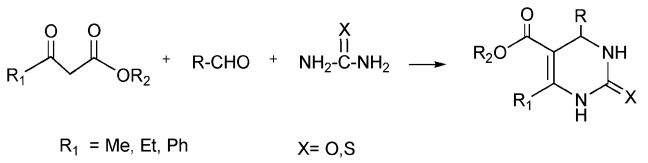


Scheme 11 Different 3,4-dihydropyrimidinones with pharmaceutical interest.

In the last years, replacement of conventional toxic and polluting Brønsted and Lewis acid catalysts by eco-friendly reusable solid acid heterogeneous catalysts, has achieved considerable importance in the synthesis of 3,4-dihydropyrimidinones. Thus, a wide variety of solid acid catalysts including supported Brønsted and Lewis acids, heteropolyacids, zeolites and metal complexes have been reported in the literature for performing the Biginelli reaction with variable success.[134–157] As an example, Table 9 summarizes results corresponding to the Biginelli reaction between benzaldehyde, ethyl acetoacetate and urea to synthesize 5-(ethoxycarbonyl)-6-methyl-4-phenyl-3,4-dihydropyridin-2(1*H*)-one over different heterogeneous catalysts using both conventional heating or microwaves. For instance, excellent yields of DHPM derivatives (85–98%) were reported using ZrO_2-pillared clay (Zr–Pilc) under microwave irradiation.[158] The efficacy of the procedure was exemplified by the synthesis of a biologically active racemic mixture of monastrol (a potent anticancer drug) and nitractin (an antibacterial and antiviral drug) which were obtained in high yields (90% and 87% respectively). The catalyst was recycled three times without any loss of activity. Also ion exchange resins such as the perfluorinated resin sulfonic acid Nafion NR-50, resulted in a very active and reusable catalyst[143] for the synthesis of DHPM derivatives with acceptable yields (74–96%). While the catalytic activity of metallophthalocyanine complexes[142] strongly depends on the metal, showing the order of activity: Co(II)-phthalocyanine > tetraphenoxyvanadyl(II)-phthalocyanine > Fe(II)phthalocyanine > Cu(II)-phthalocyanine > Ru(II)-phthalocyanine. Particularly, the Co(II) phthalocyanine complex was an efficient and recyclable heterogeneous catalyst giving good yields of different DHPM (82–98%).

Recently Shaabani *et al.*[152] have reported a Biginelli-like reaction which combines an aldehyde, a cyclic *β*-dicarbonyl compound (5,5-dimethyl-1,3-cyclohexanedione) and a urea derivative such as *N*-methylurea or thiourea, using silica supported sulfuric acid (SSA) as a solid acid catalyst and in



Scheme 12 Three component Biginelli reaction.

the presence of an ionic liquid (1-butyl-1,3-methylimidazonium bromide ([bmim]Br)). The reactions performed at 100 °C, yielded 4-aryl-7,7-dimethyl-1,7,7-trimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-dione derivatives (46–86% yield) (Scheme 14) in less than two hours. The authors found that the combination of the ionic liquid with SSA decreases the reaction time and produces an increase of the yield of the target compound with respect to the classical conditions using HCl and conventional solvents. The acceleration of the multicomponent reaction was associated with the existence of solvophobic interactions in the ionic liquid media that generate an internal pressure which promotes the association of the reactants in a solvent cavity during the activation process.

Finally, it is interesting to note that DHPMs obtained from the Biginelli type reaction are inherently asymmetric molecules and the influence of the absolute configuration at the sterogenic centre at C4 on biological activity is well documented.[159] Thus for instance, the 1,4-DHPM known as SQ32926 (see Scheme 11) is exclusively the (*R*)-enantiomer that carries the therapeutical desired antihypertensive effect. However no general asymmetric synthesis for this heterocyclic system has been reported up to now and resolution strategies have been so far the method of choice to obtain enantiomerically pure DHPM.

3.6 Synthesis of tetrahydroquinoline derivatives

Quinolines and their derivatives are achieving increasing importance due to their wide range of biological activity. Tetrahydroquinolines are an important class of natural product and exhibit diverse biological properties such as antiallergic, antiinflammatory, estrogenic and psychotropic activity.[160–161] The classical method for the synthesis of tetrahydroquinolines involves the aza Diels–Alder reaction between *N*-aryl-imines and nucleophilic olefins in the presence of Lewis acids, such as $FeCl_3$ in Et_2O/*t*-BuOH, $BF_3{\cdot}Et_2O$, $AlCl_3/Et_3N$[162] which are frequently used in stoichiometric amounts. Moreover, many imines are unstable, hygroscopic and difficult to purify, and so the one-pot approach that involves the condensation of aldehydes with anilines and alkenes in the presence of Lewis acid catalysts where the imine is *in situ* formed, is much more efficient and economic process to produce this type of compounds. We will describe here some examples of dihydroquinoline derivatives synthesis through MCR using heterogeneous catalysts.

3.6.1 Synthesis of aryl-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[c]-quinoline derivatives. Cyclopentatetrahydroquinoline derivatives can be obtained by a one-pot three component reaction from aromatic aldehydes, aromatic amines, and cyclopentadiene in the presence of acid catalysts. Sartori *et al.*[163] have reported the synthesis of cyclopentatetrahydroquinoline derivatives by one-pot three component reactions from aromatic aldehydes,

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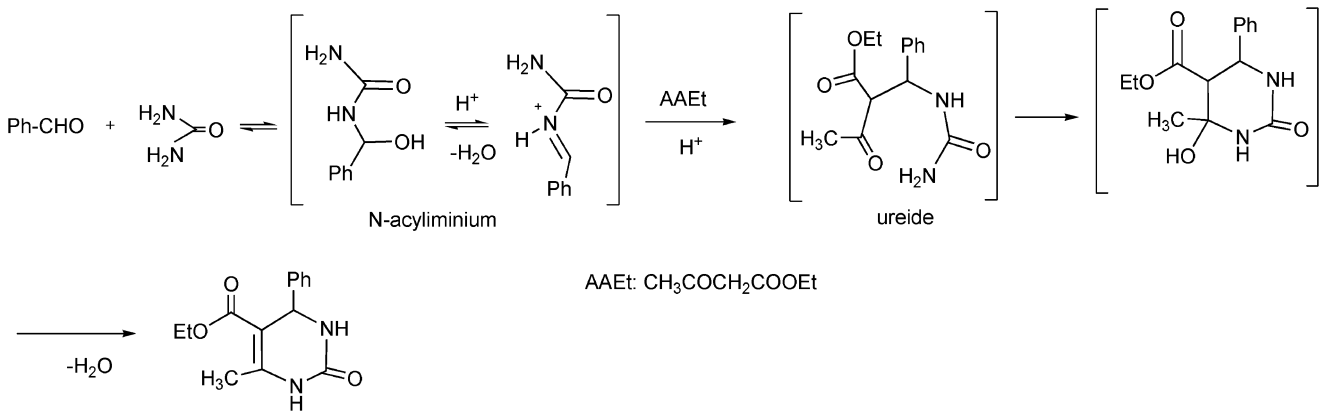

Scheme 13 Proposed mechanism of the acid catalyzed Biginelli reaction.

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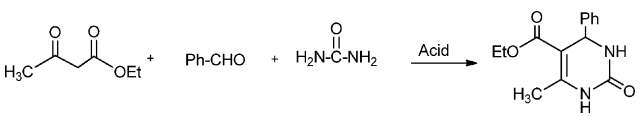
aromatic amines, and cyclopentadiene in the presence of acid clays as catalysts (Scheme 15). Montmorillonite KSF, acid Bentonite Bieliaca, and Hectorite are efficient catalysts to carry out this one-pot approach, Bentonite Bieliaca being the most efficient catalyst. Reactions performed in aqueous or polar solvents at 40 °C afforded the corresponding cyclopentatetrahydroquinoline derivatives in good yields (85–98%) and selectivities (97–99%) independently of the electronic effect of substituents. In all cases the reaction was regiospecific and stereospecific yielding exclusively the *endo* adduct (all *cis* product). The Bentonite catalyst could be reused five times without reducing its efficiency.

The authors propose that the aza-Diels–Alder cycloaddition may proceed through a concerted polar [$4\pi^+ + 2\pi$] cycloaddition with subsequent tautomerization (*via a*, Scheme 16) or by an intermolecular 1,2 C=N^+ addition-intramolecular cationic cyclisation sequence (*via b*, Scheme 16). The active species are produced by H-bond activation or by nitrogen protonation of the imine by the strong acid sites of the catalyst.

Kobayashi *et al.*[164] have prepared diverse tetrahydroquinoline derivatives (Scheme 17) using a polymer supported scandium ((polyallyl)scandium trifylamide ditriflate, (PA-Sc-TAD)) as a catalyst. Thus, diverse quinoline derivatives have been efficiently obtained (99–65%) from aldehydes (aromatic, aliphatic, hetero-

Table 9 Comparison of different catalysts used in the Biginelli reaction for the synthesis of 5-(ethoxycarbonyl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(*H*)-one



Catalysts	B:E:U[a]	Solvent	T (°C)	Catalyst (g)	t (h)	Yield DHPM	Ref.
I_2–Al_2O_3	2 : 2 : 2	—	MW	0.2[c]	0.02	90	145
SiO_2–$NaHSO_4$	1 : 1.2 : 1.2	CH_3CN	reflux	10[b]	1.5	93	135
Alum–SiO_2[g]	5 : 5 : 6	—	80	0.16	4	92	134
Ferrihydrite in a silica aerogel	50 : 62 : 75	EtOH	reflux	1.77(4 mmol of Fe)	84	65	138
Silica sulphuric acid	2 : 2 : 3	EtOH	reflux	0.23	6	91	144
$FeCl_3$–SiMCM-41	1 : 1 : 1.3	—	(MW)	10[d]	0.08	89	141
$FeCl_3$–Nanopore Silica	1 : 1 : 1.2	—	(MW)	10[d]	0.25	55	139
Montmorillonite	10 : 10 : 15	—	130	0.5	48	82	140
ZrO_2–pillared clay	2.5 : 2.5 : 3.7	—	(MW)	0.25	0.08	92	158
Nafion-NR-50	5 : 5 : 5	CH_3CN	reflux	0.25	3	96	143
Amberlyst-15	5 : 5 : 5	CH_3CN	reflux	0.25	5.5	85	143
Yb(III)-resin and Polymer-supported scavengers	0.5 : 0.5 : 1.5	—	120	0.17	48	80	147
$Ag_3PW_{12}O_{40}$	5 : 5 : 10	H_2O	80	10[d]	4	92	155
(PVP)-Cu complex[h]	1 : 1 : 1.3	MeOH	reflux	20[f]	24	70	156
Scolecite	5 : 5 : 6	CH_3CN	reflux	2[d]	0.5	83	153
ZrO_2/SO_4^{2-}	10 : 10 : 10	—	(MW)	0.1	0.5	98	148
Heulandite	6 : 6 : 7.2	Acetic acid	100	0.2	5	75	154
HY	10 : 8 : 10	Toluene	reflux	0.5	12	21	151
HZSM-5	10 : 8 : 10	Toluene	reflux	0.5	12	80	151
Ersorb-4	5 : 5 : 6	EtOH	80	1	8	93	137
Co(II)phthalocyanine	5 : 5 : 5	CH_3CN	reflux	2[b]	1	98	142
TS-1	4.7 : 4.7 : 7	—	50	0.01	0.16	98	150
HBF_4–SiO_2	1 : 1 : 1.5	Ethanol	r.t.	5[b]	2	94	157

[a] B:E:U mmol of benzaldehyde : ethyl acetoacetate : urea. [b] mol%. [c] 0.2 mmol of iodine adsorbed on 0.5 g of neutral alumina. [d] wt% based on total weight. [e] wt% based on β-ketoester. [f] wt% based on aldehyde. [g] Alum–SiO_2: $KAl(SO_4)_2 \cdot 12H_2O$ supported on silica gel. [h] PVP-Cu complex: Poly(4-vinylpyridine-divinylbenzene)–Cu(II) complex.

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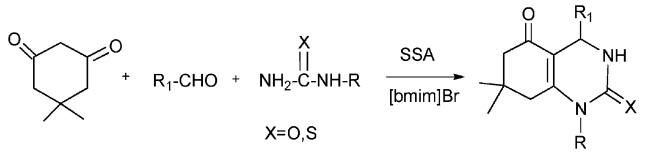
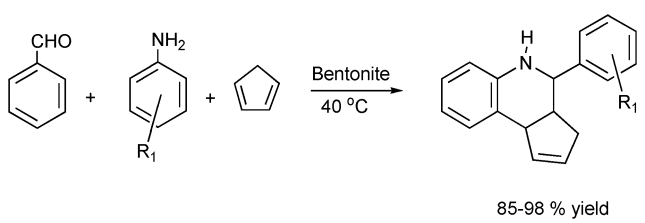


Scheme 14 Synthesis of 4-aryl-7,7-dimethyl-1,7,7-trimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-dione derivatives.

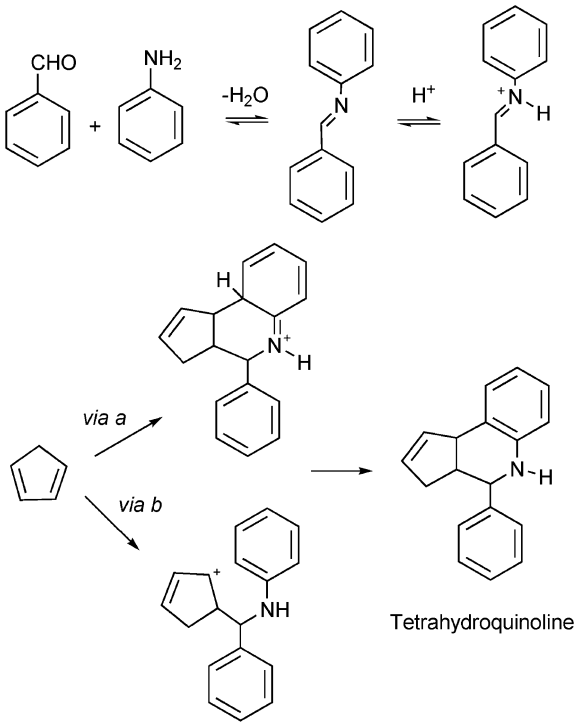
cyclic, and glyoxals and glyoxylates), aromatic amines and different olefins, at 40 °C in CH_2Cl_2:CH_3CN (2 : 1) as the solvent and 15 h reaction time. The method is especially useful for the construction of a quinoline library due to the efficiency and simplicity of the process.

3.6.2 Synthesis of aryl 1,2,3,4-tetrahydrospiro(3,1'-cyclopropyl)quinolines derivatives. Quinoline derivatives having a spyrocyclopropyl ring can be synthesised by a one-pot three component reaction using Montmorillonite KSF clay[165] under mild reaction conditions (Scheme 18). The aza-Diels–Alder reaction of methylenecyclopropanes, arenecarbaldehydes and arylamines were carried out in various solvents at room temperature under an ambient atmosphere. The results indicate that in acetonitrile and dichloromethane the corresponding adduct was obtained in good yields (100 and 90% respectively), whereas in acetone, ether or THF, a very low yield was achieved due to the coordination of the oxygen atom of the solvent to the active site. The recovered Montmorillonite catalyst was reused in several consecutive cycles giving similar results. Other solid catalysts such as silica gel, neutral alumina and zeolites showed no catalytic activity for this reaction.

3.6.3 Synthesis of aryl pyran[3,2-c] and furan[3,2-c]quinolines. Pyranoquinolines (pyran[3,2-c]quinolines) are present in several bioactive alkaloids and they are found to possess a wide spectrum of biological activities such as antiallergenic, psychotropic, *anti*-inflammatory, inmmunosupresssive and strogenic activity.[160] The most common method for preparing pyranoquinolines is by aza-Diels–Alder reaction of imines (derived from aromatic amines and aldehydes) with 3,4-dihydro-2*H*-pyran in the presence of Lewis acids such as $GdCl_3$,[166] $ZrCl_4$,[167] $KHSO_4$[168] *etc.* Recently, it has been reported that Brønsted and Lewis solid acids such as antimony chloride doped on hydroxyapatite ($SbCl_3$-HAP),[169] perchloric acid adsorbed on silica gel ($HClO_4$–SiO_2),[170] Fe^{3+}–K10 Montmorillonite clay and HY zeolite[171] are highly efficient and diastereoselective solid acid catalysts for the one-pot synthesis of pyrano and furoquinolines



Scheme 15 Synthesis of aryl-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[c]quinoline derivatives through a three component reaction.



Scheme 16 Proposed mechanism of formation of cyclopentatetrahydroquinolines.

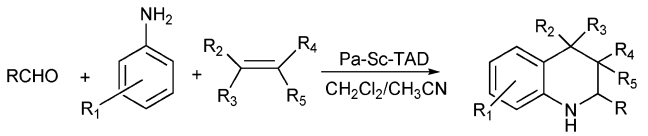
by coupling the three components, benzaldehydes, anilines and 3,4-dihydro-2*H*-pyran or 3,4-dihydro-2*H*-furan. (Scheme 19).

As in the case of spyrocyclopropyldihydroquinolines, the imines formed *in situ* by the condensation of benzaldehyde and aniline derivatives act as heterodienes which subsequently undergo the aza-Diels–Alder reaction with 3,4-dihydro-2*H*-pyran or 3,4-dihydro-2*H*-furan to form pyran and furanquinolines.

Different benzaldehyde derivatives and anilines were reacted with 3,4-dihydro-2*H*-pyran or 3,4-dihydro-2*H*-furan giving the corresponding pyran and furanquinolines in good yields. In all cases a mixture of *trans* and *cis* isomers were detected being the *trans* isomer the major product (Scheme 19). The Fe^{3+}–K10 Montmorillonite clay and HY catalysts were recovered and recycled in three consecutive reactions without lost of activity. In Table 10 the results obtained with different homogeneous and heterogeneous acid catalysts in the synthesis of 5-phenyl-3,4,4a,5,6,10b-hexahydro-2*H*-pyran-[3,2-*c*]quinoline are compared.

3.7 Synthesis of α-amino nitrile derivatives

α-Amino nitriles are a very useful intermediate compounds for the synthesis of versatile α-amino acids, various nitrogen-containing heterocyclic compounds (imidazoles, thiadiazoles



Scheme 17 MC synthesis of tetrahydroquinoline derivatives.

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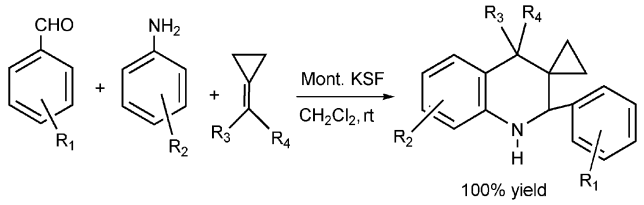


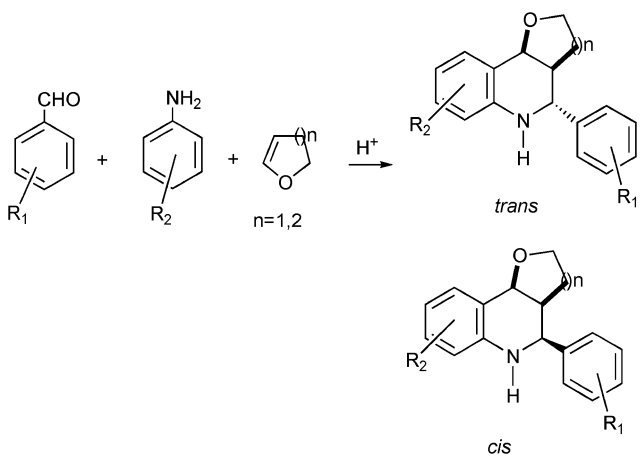
Scheme 18 Synthesis of aryl 1,2,3,4-tetrahydrospiro(3,1'-cyclopropyl)-quinolines derivatives through MCR.

etc.) and biologically useful molecules (such as for instance Saframycin A, a highly potent antitumor drug from Streptomyces lavendulae).[173,174]

The most important route for the synthesis of α-amino acids *via* the formation of α-amino nitriles is the well known Strecker reaction (1850).[14] The classical Strecker reaction involves a direct multi-component reaction of an aldehyde or a ketone, an ammonium salt and alkaline cyanides in aqueous solution to form α-amino nitriles, which can be subsequently converted to α-amino acids (Scheme 20).

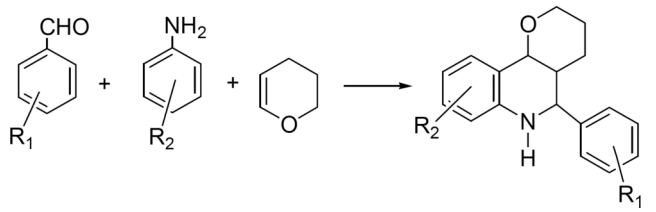
The reaction involving aldehydes is typically catalyzed by Lewis acids such as $BiCl_3$, $NiCl_2$, $InCl_3$, $LiClO_4$, $RuCl_3$.[175] However, in the case of ketones, the reaction is more difficult and other acid catalysts such as gallium triflate [$Ga(SO_3CF_3)$] or the related metal triflates, trimethylsilyltriflate and $Fe(Cp)_2PF_6$ are required.[176] Some of these Lewis acid catalysts are strong and expensive and their use involves harsh conditions, long reaction times and tedious aqueous work-up, leading to the generation of large amounts of toxic metal-containing waste.

Several modifications of the Strecker reaction have been reported using a variety of cyanating agents in the presence of solid or supported acids as heterogeneous catalysts. For instance, polyoxometalate salts ($K_5CoW_{12}O_{40}\cdot 3H_2O$) have been used as efficient and recyclable heterogeneous catalysts in the three-component condensation of aldehydes, amines, and KCN. The reaction is performed at ambient temperature in acetonitrile giving the corresponding α-amino nitriles in good to moderate yields (51-98%) and excellent selectivity.[177] Yadav and co-workers[178] prepared 2-anilino-2-phenylacetonitrile in 90% yield by treatment of benzaldehyde, aniline and trimethylsilyl cyanide



Scheme 19 Multicomponent synthesis of pyran- and furandihydroquinolines (n = 2 and 1 respectively).

Table 10 Results of the one pot reaction of benzaldehyde and aniline with 3,4-dihydro-2*H*-pyran in the presence of different acid catalysts.



Catalyst	Catalyst (mol%)	T (°C)	Solvent	Time (h)	Yield (%)	Ref.
$ZrCl_4$	10	rt	MeCN	0.60	88	170
$Bi(OTf)_3$	10	rt	IL[a]	2	90	175
$KHSO_4$	40	rt	MeCN	1	64	171
Fe^{+3}-K10	0.1[d]	rt	MeCN[c]	3.5	86	174
HY	0.1[d]	reflux	MeCN[c]	5	82	174
$SbCl_3$-HAP	1.6	reflux	MeCN[c]	2	85[b]	172
$HClO_4$-SiO_2	5	rt	MeCN	0.25	95	173

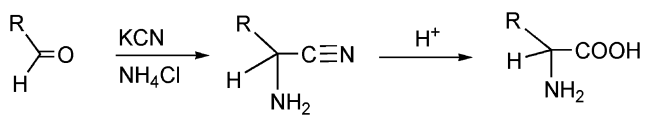
[a] IL= [Bmin]PF_6. [b] Only the *trans*-pyran[3,2-c]quinoline was obtained. [c] Under nitrogen atmosphere. [d] Grams.

(TMSCN) in dichloromethane at room temperature with Montmorillonite KSF clay as the catalyst (Scheme 21). No cyanohydrin trimethylsilyl ester (an adduct obtained from the aldehyde and TMSCN) was obtained under these reaction conditions. A variety of aldehydes were reacted with a range of amines and TMSCN in a one-pot procedure to produce aminonitriles in 85–94% yields.

The mechanism of the process involves the formation of imines or iminium ions and the subsequent nucleophilic attack of the cyanide ion of TMSCN to provide the final product.

Using the same approach, Heydari *et al.*[179] performed the synthesis of several α-amino nitriles using sulfamic acid (NH_2SO_3H, SA), a stable, non corrosive acid, as a heterogeneous catalyst. The three-component coupling reaction involving an aldehyde (aliphatic, aromatic, heterocyclic and conjugated aldehyde), an amine (aliphatic and aromatic) and TMSCN in the presence of 5 mol% of sulfamic acid at room temperature under solvent free conditions afforded the corresponding α-amino nitriles in excellent yields (82–98%) and selectivities in short reaction times (see Table 11). No undesired side products such as cyanohydrins were obtained under these conditions due to the rapid formation and activation of the imine intermediates catalyzed by sulfamic acid. The catalyst was recovered by simple filtration and recycled in subsequent three cycles giving similar yields.

A polymer, poly(4-vinylpyridine) (PVP)–SO_2 complex with mild acidity, has been prepared by Olah *et al.*[180] and used in the multicomponent synthesis of α-amino nitriles. The catalyst was prepared by passing SO_2 gas through 2% cross linked poly(4-vynilpyridine) at −78 °C. The Strecker reaction of aromatic and conjugated aldehydes, aliphatic, benzylic and aromatic amines and TMSCN was performed in dichloromethane at 50 °C giving



Scheme 20 3MC Strecker reaction.

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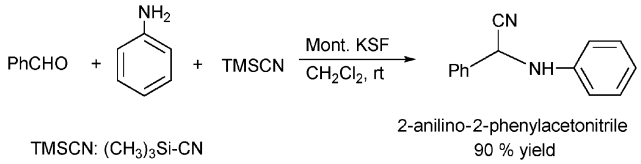


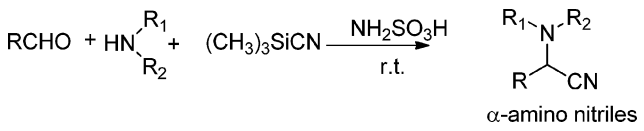
Scheme 21 Three component Strecker reaction of aldehyde, amine and TMSCN.

excellent yields (81–98%) of the corresponding α-aminonitriles. No differences in yield were found using aromatic aldehydes with electron donating or electron withdrawing groups, but attempts to perform the reaction with ketones failed. The PVP could be recycled to form the PVP–SO_2 complex.

A bio-supported catalyst, cellulose sulphuric acid,[181] (CSA) has been also used as a highly efficient, selective and recyclable catalyst for performing the MC condensation of aldehydes, amines and TMSCN. Reactions performed at room temperature in acetonitrile as a solvent, gave excellent yields (85–97%) in rather short reaction times (45–80 min). Lower yields were achieved with other solvents such as water, methanol, ethanol, dichloromethane, toluene or under solvent-free conditions. No undesired side products, such as cyanohydrin trimethylsilyl ether, were observed owing to the rapid formation of the imine intermediate.

Fluorinated amino acids are important building blocks in pharmaceuticals for anticancer drugs for the control of tumor growth, antihypertensive and anti allergic applications.[173] Following the Strecker route, efficient synthesis of α-amino nitriles using aldehydes, ketones and fluorinated ketones has been achieved with Nafion-H, Nafion SAC-13 (10-20% Nafion-H polymer on amorphous silica porous nanocomposite) silica gel and fumed silica.[182] When the reaction was carried out with aldehydes or ketones, primary amines and TMSCN at 60 °C in

Table 11 Synthesis of α-amino nitriles by the three component coupling reaction[a]



R	R_1	R_2	Yield (%)
Phenyl	H	Phenyl	98
n-Butyl	H	Phenyl	90
4-CH_3phenyl	H	Phenyl	97
2-Furyl	H	Phenyl	95
Cinnamyl	H	Phenyl	98
n-butyl	Ethyl	Ethyl	82
Phenyl	Ethyl	Ethyl	90
4-CH_3phenyl	Ethyl	Ethyl	85
2-Furyl	Ethyl	Ethyl	80
Cinnamyl	Ethyl	Ethyl	88
4-CH_3Ophenyl	Ethyl	Ethyl	91
Phenyl	Benzyl	Benzyl	94
i-Propyl	Benzyl	Benzyl	94
4-CH_3phenyl	*tert*-Butyl	H	84
Cinnamyl	*tert*-Butyl	H	88

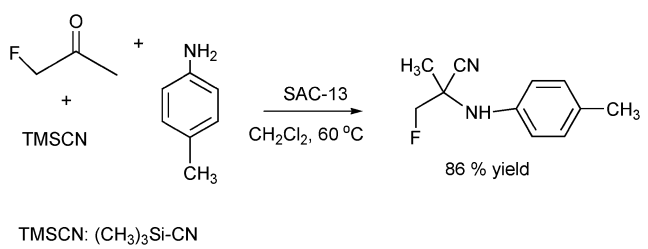
[a] Reaction conditions: aldehyde (3 mmol), amine (3.2 mmol), trimethylsilyl cyanide (3 mmol) and sulfamic acid (5 mol%) at room temperature.

dichloromethane as a solvent in the presence of Nafion, yields between 75–97% of the corresponding α-amino nitriles were obtained after 6 h reaction time. A similar result was obtained using Nafion SAC-13. When the Strecker reaction was performed with monofluoroacetone, *p*-toluidine and TMSCN, it was found that though silica and fumed silica showed catalytic activity, Nafion and Nafion SAC-13 gave the best yields (86%) (Scheme 22). It is worth mentioning that these catalysts gave comparable results to those obtained in the case of metal triflates ($Ga(OTf)_3$) and trimethylsilyl triflate (TMSOTf) with 96 and 74% yield respectively. The Nafion catalyst was reused for five consecutive runs and the catalytic activity remains practically unchanged. It is interesting to note that when ketones are involved in the reaction the nature of the solvent plays an important role. Acetonitrile, THF, and toluene are not suitable for the direct Strecker reaction of ketones, since they are more basic and interact with the acidic sites, thus reducing the catalytic activity.[183] However, dichloromethane minimizes such interactions enhancing the catalytic activity.

3.8 Synthesis of multi-substituted imidazole derivatives

Multi-substituted imidazole derivatives are an important class of compounds which exhibit a wide spectrum of biological activities as for instance antiinflammatory and antithrombotic activities.[184] The well known microtubule stabilizing agents such as Eleutherobin and Sarcodictyn, among other marine and plant derived products contain imidazole.[185] Also, Trifenagrel, a potent arachidonate cyclooxygenasa inhibitor that reduces platelet aggregation is structurally a 2,4,5-triarylimidazole[186] (Scheme 23). Furthermore 2,4,5-trisubstituted imidazole moieties are common structures in numerous synthetic compounds used in agriculture, for plant growth regulators, herbicides and fungicides.[187] In addition 2,4,5-triarylimidazole have received great attention for the development of fluorescence labelling agents for biological imaging applications[188] or chromophores for non linear optics systems.[189] Among them Lophine is one of the few long-lasting chemiluminescent molecules and its dimers have piezochromic and photochromic properties.[190]

Numerous classical methods for the synthesis of multisubstituted imidazoles have been developed. Among these methods a typical procedure is the multicomponent reaction approach involving the cyclocondensation of a 1,2-diketone (or α-hydroxy ketones), an aldehyde and ammonia or ammonium acetate in the presence of a homogeneous strong protic acid catalysts (such as phosphoric acid, sulphuric acid, acetic acid),[191] Lewis acids[192] or oxidant agents such as ceric ammonium nitrate.[193] The reactions are usually performed under reflux of a polar organic solvent



Scheme 22 Strecker reaction of monofluoroacetone, *p*-toluidine and TMSCN.

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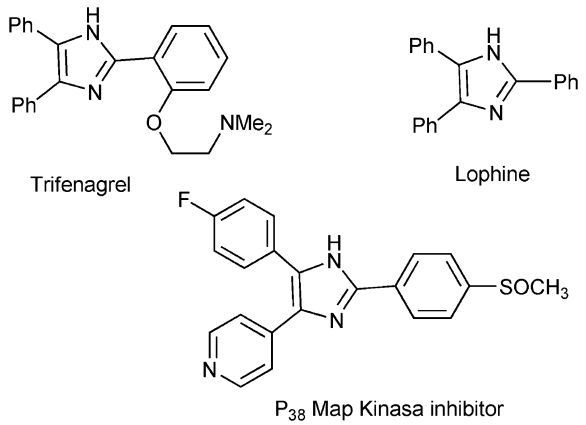

Scheme 23 Different 2,4,5-trisubstituted imidazole derivatives with pharmaceutical interest.

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(acetic acid, methanol, ethanol, DMF and DMSO) under inert atmosphere. More recently, microwave irradiation in the absence of any catalyst[194] has been used to produce multisubstituted imidazole derivatives with good success, however high reaction temperatures (180–210 °C) are required.

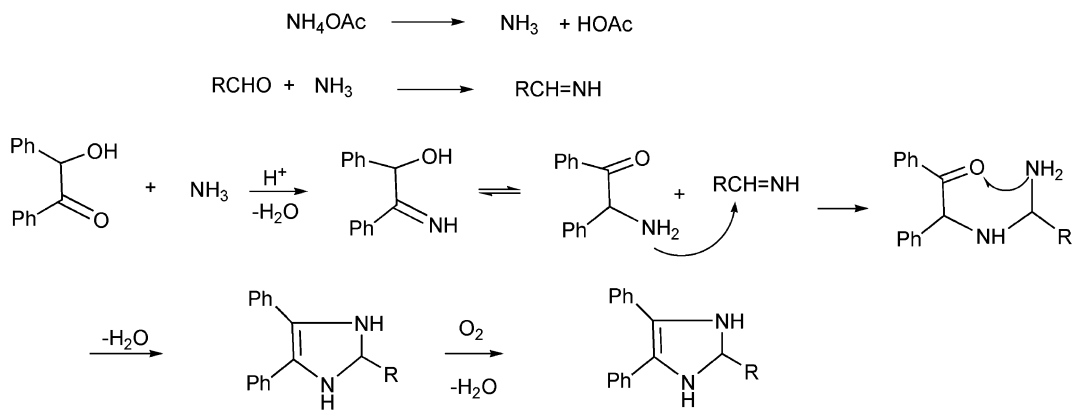
Some research groups have reported the one-pot condensation of 1,2-diketone, (or α-hydroxy ketone or α-keto-oxime), aldehydes and ammonium acetate under microwave irradiation using acetic acid as a solvent[195,196] or solid supports impregnated with ammonium acetate. Thus, Xu *et al.*[197] have reported the condensation of α-hydroxy ketone (benzoin) (instead of benzyl) with an aldehyde over silica gel or alumina impregnated with ammonium acetate. Reactions performed under solvent free conditions and microwave irradiation gave the corresponding trisubstituted imidazoles in good yields. Contrarily to conventional condensation of α-hydroxy ketones, no oxidizing reagents such as Cu(II) were required and an air oxidation mechanism of the hydroxyl to carbonyl group was proposed. In Scheme 24 the proposed mechanism starting from an aldehyde, an α-hydroxyketone, and ammonium acetate is displayed. The process involves the formation of an imine intermediate from the aldehyde and ammonia which undergoes the nucleophilic addition of the imine intermediate coming from a α-hydroxyketone and ammonia. Subsequent cyclocondensation and oxidation steps lead to the substituted pyrazole derivative.

Bentonite, Montmorillonite K-10 and KSF, and acid alumina impregnated with ammonium acetate have been used as solid acid catalysts to prepare 2,4,5-trisubtituted imidazole derivatives from 1,2-dicarbonyl compounds and aldehydes under microwave irradiation. Also 1,2,4,5-substituted imidazoles from 1,2-dicarbonyl compounds, aldehydes and primary amines were also obtained in good yields (Scheme 25). Comparison of the different supports show that acidic alumina was the most suitable support yielding imidazoles in 75–85% yield.[198]

HY zeolite and silica gel[199] have also been used as heterogeneous acid catalysts for the synthesis of triarylimidazoles by condensation of benzyl, benzaldehyde derivatives and ammonium acetate under solvent free conditions and microwave irradiation (Scheme 26). The corresponding triarylimidazoles were obtained in good yields (80–90%) after six minute reaction times.

Shaabani *et al.*[200] have reported that silica supported sulfuric acid (SSA) is an excellent and recyclable catalyst for the synthesis of trisubstituted imidazoles under reflux of water or solvent free conditions. When the reactions were performed with different aldehydes, 1,2-diketone, (or α-hydroxy ketone or α-keto oxime), ammonium acetate at reflux of water, the corresponding imidazoles were obtained in yields between 59–81% for 45–90 min. Under microwave irradiation similar yields were achieved after 10 min (Scheme 27). Sulfuric acid on silica catalyst could be reused for four consecutive runs maintaining its catalytic activity.

Recently Wang *et al.*[201] have prepared a polymer supported zinc chloride which was found to be extremely efficient as a Lewis acid catalyst for the preparation of 2,4,5-trisubstituted imidazoles. The polymer supported zinc was prepared from chloroacetylated polystyrene resin which reacted with diethanolamine and then zinc chloride was anchored to the polymer matrix (PSZC). The condensation of benzyl, benzaldehyde and ammonium acetate at reflux of ethanol in the presence of 15 mol% of catalyst give 96% yield of 2,4,5-triphenylimidazole after 1.5 h. For comparison purposes the reaction was carried out using different conventional Lewis acids such as $AlCl_3$, $FeCl_3{\cdot}6H_2O$, $NiCl_2{\cdot}6H_2O$, and $ZnCl_2$ in 20 mol% of catalyst which afforded lower yields of the 2,4,5-triphenylimidazole that the $ZnCl_2$ supported catalyst (52, 47, 71, and 83% respectively after 3 h). The condensation was extended to different substituted benzaldehydes achieving excellent yields of the



Scheme 24 Proposed mechanism for the formation of multi-substituted imidazole derivatives.

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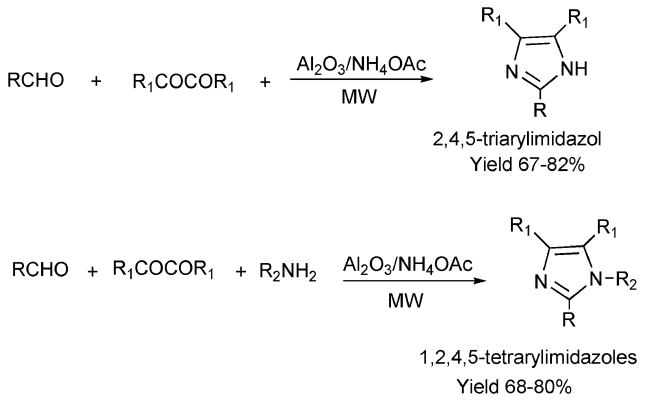


Scheme 25 MC synthesis of 2,4,5-trisubtituted and 1,2,4,5- tetrasubstituted imidazole derivatives.

corresponding imidazoles (85–95%). The immobilized catalyst was very stable and could be reused at least four times without further purification. Shelke *et al.*[202] have been prepared cellulose sulphuric acid (CSA) as a bio-supported and recyclable solid acid catalyst for the one-pot synthesis of 2,4,5-triarylimidazoles. The condensation reaction of benzil or benzoin, aldehydes and ammonium acetate under microwave irradiation gave excellent yields (90–95%) with rather short reaction times (1–3 min). In Table 12 comparative results obtained with different catalyst in the coupling of benzyl (or benzoin), benzaldehyde and ammonium acetate are summarized.

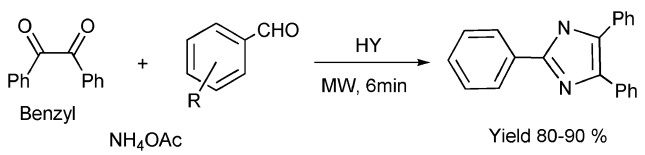
3.9 Synthesis of quinazolin-4-(3*H*)-one derivatives

4-(3*H*)-Quinazolinone derivatives were reported to possess analgesical, antibacterial, antifungical, antihelmentics, antiparkinson, anticancer, *anti*-HIV, MAO inhibitory, central nervous system and antiaggregating activity[203–205] (some examples are displayed in Scheme 28).

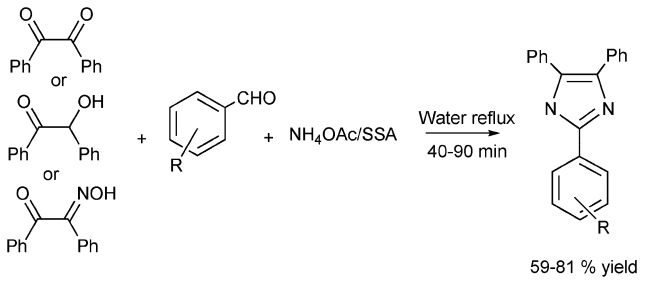
The most simple procedure for the synthesis of 4-(3*H*)-quinazolinones was reported by Niementowski in 1895[206] and involves the decondensation of 2-aminobenzoic acid (anthranilic acid) or aminobenzoic acid derivatives with amides (Scheme 29). Other methods include cycloaddition reactions of anthranilic acid derivatives with a diverse range of substrates including imidates and imino halides.

Recently, it has been reported that silica gel-supported ferric chloride[207] catalyzes efficiently the three component reaction of anthralinic acid, orthoesters and amines to afford 4-(3*H*)-quinazolinones in one-pot reaction (Scheme 30).

Total conversion and good yields (84–98%) in short reaction times (5–10 min) were obtained when the reaction was performed at reflux temperature under solvent free conditions. The silica gel-supported ferric chloride catalyst could be recovered and recycled without loss of activity. Nafion has also been used as an



Scheme 26 MC synthesis of 2,4,5-triarylimidazoles.



Scheme 27 Synthesis of 2,4,5-triarylimidazol from benzil or benzoin or benzylmonoxime, aldehyde and ammonium acetate in the presence of silica sulphuric acid (SSA) catalyst.

efficient catalyst in this multicomponent reaction to obtain 2,3-disubstituted 4-(3*H*)-quinazolinones under solvent free microwave irradiation.[208] An equimolar mixture of isatoic anhydride or anthranilic acid, triethyl orthoester, aromatic aniline and a catalytic amount of Nafion was subjected to microwave irradiation (2–6 min) affording the corresponding quinazolin-4-(3*H*)-ones in good yields (71–94%). Anilines having an electron donating group (methyl) gave higher yields (89%) than anilines with electron withdrawing groups (CF_3 and NO_2) (77%). Substituents on the orthoester did not result in much variation in yield. On the other hand, the recovered catalysts can be reused and did not show any reduced activity after six consecutive runs.

3.10 Synthesis of 4-arylaminoquinazoline derivatives

Natural and synthetic compounds possessing the quinazoline structural motif, particularly 4-arylaminoquinazoline derivatives, display a wide range of biological activities. For instance, 6,7-dimethoxy-4-(3-bromophenylamino) quinazoline (PD 153035) (Scheme 31) and its analogues exhibit high tyrosine kinase inhibitor activity.[209]

4-Arylaminoquinazolines can be obtained by reactions of 4-(3*H*)-quinazolones with aromatic amine hydrochlorides and dimethylcyclohexylamine in the presence of phosphorous pentoxide.[210] Other methods to obtain 4-arylaminoquinazolines involve the reaction of 2-aminobenzonitrile and different anilines in the presence of $AlCl_3$ and subsequent condensation of the products with formic acid.[211] A new multi-component synthesis of 4-arylaminoquinazolines has been reported by Heravi *et al.*[212] The protocol involves the reaction of 2-aminobenzamide, orthoesters, and substituted anilines in the presence of acid catalysts such as different Keggin-type heteropolyacids (Scheme 32).

Various anilines and orthoesters were reacted with 2-aminobenzamide in the presence of different heteropolyacids ($H_6[PMo_9V_3O_{40}]$, $H_5[PMo_{10}V_2O_{40}]$, $H_4[PMo_{11}VO_{40}]$, $H_3[PMo_{12}O_{40}]$) in acetonitrile under refluxing conditions. The order of activity of different heteropolyacids was $H_6[PMo_9V_3O_{40}] > H_5[PMo_{10}V_2O_{40}] > H_4[PMo_{11}VO_{40}] > H_3[PMo_{12}O_{40}]$. Using $H_6[PMo_9V_3O_{40}]$ as a catalyst, different 4-benzylaminoquinazolines were obtained in good yields (80–90%) within 2–3 h. In all cases, 3-quinazolin-4-one was also obtained as a by-product in low yield. Studies on the recyclability of the catalyst showed that when using the catalyst over three runs only a slight loss of activity was observed.

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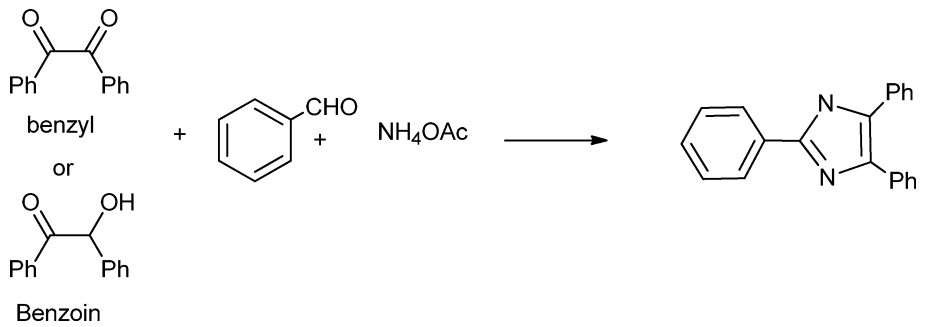
Table 12 MCR of benzyl (or benzoin), benzaldehyde and ammonium acetate using different solid acid catalysts



Catalyst	B:PhCHO:AA[a]	Solvent	Catal. (g)	*T*/°C	Time (min)	Yield (%)	Ref.
Al_2O_3	0.5 : 0.5 : 57	Et_2O	2.5[b]	MW(130W)	20	76	198
SiO_2[c]	5.0 : 5.0 : 100	CH_2Cl_2	15.4	MW(160W)	20	70	197
Al_2O_3[c]	5.0 : 5.0 : 100	CH_2Cl_2	17	MW(160W)	20	67	197
SSA	1.0 : 1.0 : 6.0	—	0.2	MW(160W)	10	85	200
SSA	1.0 : 1.0 : 6.0	—	0.2	130	50	83	200
HY	4.0 : 4.0 : 8.0	—	4	MW	6	81	199
PSZC	1.0 : 1.0 : 2.5	EtOH	15[d]	MW	90	96	201
CSA	1.0 : 1.0 : 2.5	—	0.1	MW(180)	1	98	202

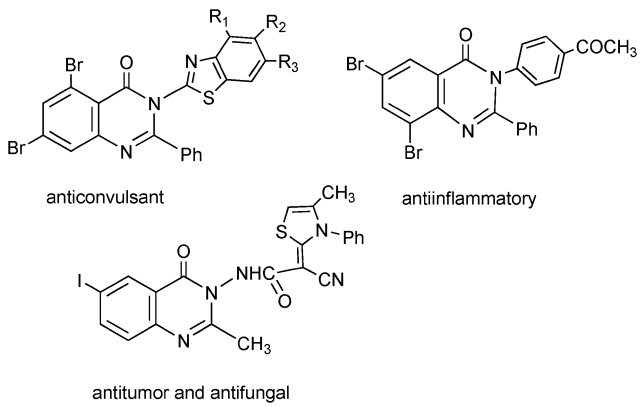
[a] mmol of benzyl : benzaldehyde : ammonium acetate. [b] 9.3 g of alumina impregnated with 4.4 g of ammonium acetate. [c] Benzoin was used instead of benzyl. [d] mol%.

3.11 Synthesis of Homoallylic amine derivatives

Homoallylic amines are excellent building blocks in the synthesis of β-amino acids, γ-amino alcohols, β-lactams antibiotics, aziridines, amino sugars HIV-protease inhibitors and other compounds (Scheme 33).[213]

The homoallylic amine moiety is not widely present in natural products, however compounds like Eponemycin,[214] which exhibits strong activity against B16 melanoma cells, or a depsipeptide Cryptophycin 337, which is analog of a potent antitumor compound Criptophycin,[215] contain this subunits (Scheme 34).

Generally, homoallylic amines are prepared either by addition of organometallic reagents to imines or by nucleophilic addition of allylstannane, allylsilane, allyltin, allylboron or allylgermanium reagents to imines in the presence of Lewis acid catalysts[216] such as BF_3–OEt_2, $TiCl_4$ and $PdCl_2(Ph_3P)_2$ or $PtCl_2(Ph_3P)_2$, lithium perchlorate.[217] The first addition of allylstannane with



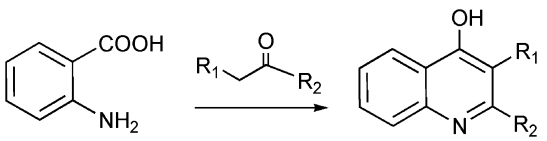
Scheme 28 4-(3*H*)-Quinazolinones with different pharmacological activities.

imine was catalyzed by $Ln(OTf)_3$ affording moderate yields in 24 h.[218] One of the main disadvantages of using Lewis acid catalysts is that the catalysts are deactivated or sometimes decomposed by the amine and water that is formed during the imine formation.

In order to circumvent some of the problems derived from the use of homogeneous catalysts, a one-pot A^3 protocol involving aldehydes, aromatic amines and allyltributylstannane has been developed recently (Scheme 35). The one-pot process involves the *in situ* formation of imine followed by the nucleophilic addition of the organometallic reagent.

Ionic liquids such as 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4), have been used as solvents and catalysts with success in this transformation.[219] However, similar yields were achieved with heterogeneous catalysts such as Montmorillonite KSF[220] clay. Using this catalyst, different aldehydes, anilines and allyltributylstannane were coupled at room temperature in acetonitrile producing the corresponding homoallylic amines in high yields (73–90%) and in short times (3–5.5 h) (see Table 13).[220] The Montmorillonite catalyst was reused showing a gradual decrease in activity. Thus when benzaldehyde, aniline and allyltributylstannane was reacted it afforded 90%, 85% and 80% yields over three cycles.

In all cases, the homoallylic alcohol coming from the reaction between aldehyde and allyltributylstannane as well as decomposition or polymerization of sensitive aldehydes was not



Scheme 29 Niementowski reaction.

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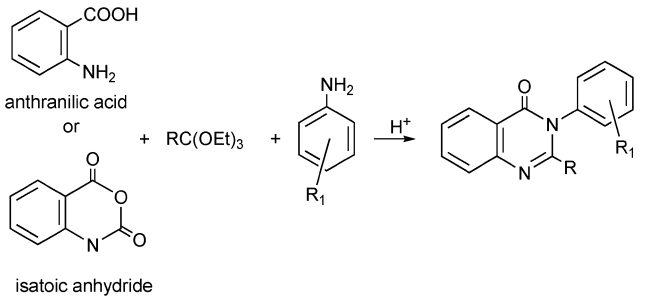
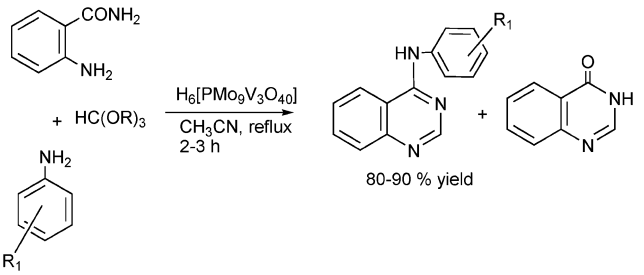


Scheme 30 MC synthesis of 2,3-disusbtituted-4-(3*H*)-quinazolinones from anthranilic acid or isatoic anhydride, orthoesters and amines.

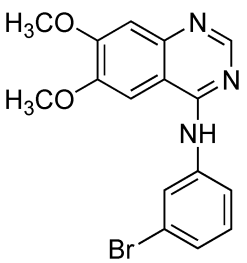


Scheme 32 Multicomponent synthesis of 4-arylaminoquinazolines from reaction of 2-aminobenzamide, aniline derivative and orthoesters.

observed. On the other hand, ketones did not react under similar reaction conditions.

Under the same reaction conditions, analogous selective preparation of homoallylic amines have also been performed using silica supported sodium hydrogen sulfate ($NaHSO_4$ SiO_2) as an acid catalyst.[221] The one-pot coupling between aldehydes (aromatic, heteroaromatic or aliphatic), aniline derivatives and allyltributylstannane in the presence of $NaHSO_4$–SiO_2 in acetonitrile at room temperature afforded the corresponding homoallylic amines in high yields (82–93%) within 1.5–3 h. Recently Yadav *et al.*[222] have introduced a common organic acid with mild acidity (sulfamic acid , NH_2SO_3H) (SA) as a recyclable solid catalyst for the three component synthesis of homoallylic amines. When the reaction was carried out with aldehydes and anilines with different substituents a room temperature and in absence of solvent, the corresponding homoallylic amines (82–90% yield) were obtained. $HClO_4$ supported on silica gel ($HClO_4$–SiO_2)[223] with low loading (0.01 mmol) is also an efficient catalyst for the synthesis of homoallylic amines through a 3CR of various aldehydes, aniline derivatives and allyltributylstannane in acetonitrile at room temperature (yields 82–90%).

Yin *et al.*[224] have synthesised polystyrene-bound super Brønsted acids and their ytterbium salts for the synthesis of homoallylic amines. The polystyrene-bound perfluoroalkyl sulfonic ytterbium (Yb–PS_2–RF_6) was the most efficient and recyclable catalyst in the coupling of aldehydes, anilines and allyltributylstannane achieving 86–95% yield of the corresponding homoallylic amines when benzoic acid is added as a promoter in the reaction media. It has been suggested[225] that the Brønsted acidity of benzoic acid acts not only regenerating the catalyst, but also that Brønsted and the Lewis acid sites are working as a combined catalyst to produce a double activation of the substrate. Using Yb–PS_2–RF_6 and benzoic acid as the co-catalyst, the authors designed a one-pot four-component coupling reaction involving benzaldehyde, aniline, allyltributylstannane and acrylic chloride in order to obtain homoallylic amides. A reaction performed at room temperature in acetonitrile give *N*-phenyl-*N*-(1-phenylbut-3-enyl) acryl amide in good yield (78%) (Scheme 36).



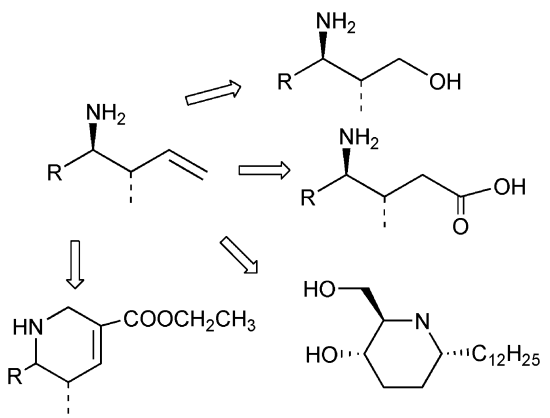
Scheme 31 PD 153035.

To examine the scope of the A^4 reaction a number of acid chlorides were reacted under the above conditons achieving different homoallylic amides (benzamides carboxamides, acryl amides, acetamides, and cinnamamides) in good to moderate yields (32–88%). Zhengfeng *et al.*[226] have proposed the synthesis of homoallylic amines from aromatic aldehydes, aromatic amines and allyltributylstannane in the presence of phosphomolybdic acid (PMA). A variety of different homoallylic amines were obtained in good to excellent yields (83–99%) at room temperature using 10 mol% of PMA and water as a solvent.

Table 14 summarizes the results and experimental conditions for the synthesis of *N*-(1-phenyl-3-butenyl)aniline from benzaldehyde, aniline and allyltributylstannane using different acid catalysts.

3.12 Synthesis of amidoalkyl naphthol derivatives

Compounds bearing 1,3-amino-oxygenated functional motifs are common in a variety of natural products and drugs including nucleoside, antibiotics and HIV protease inhibitors (such as ritonavir and lipinavir).[227] 1-Amidomethyl-2-naphthol is an important precursor of biological active 1-aminomethyl-2-naphthol derivatives. These compounds present hypotensive and bradycardiac effects.[227] Also it is noteworthy that aminote-



Scheme 33 Different transformations of homoallylic amines.

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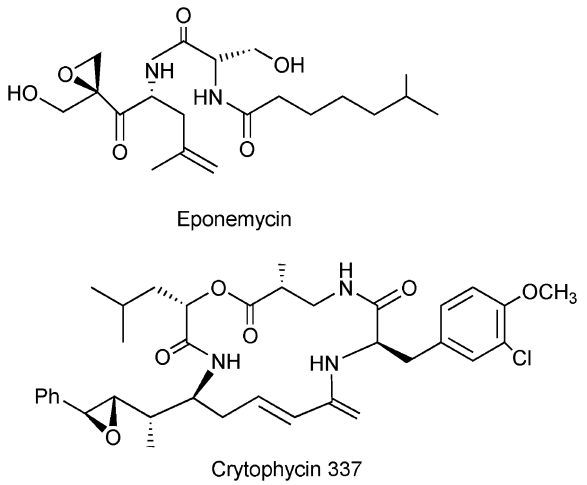


Scheme 34 Natural products containing homoallylic amines moiety.

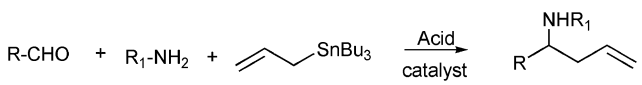
tralin derivatives presents several biological activities such as antidepressant, immunomodulator, and antitumor.[227]

Generally, 1-amidoalkyl-2-naphthol derivatives can be prepared through MCR (*via* a Ritter type reaction) of aryl aldehydes, 2-naphthol and acetonitrile or amides in the presence of Lewis or Brønsted acid catalysts (Scheme 37).

The main preparation methods involve the use of acetonitrile as a reactant and solvent (Method A), or acetamide under thermal (or microwave irradiation) and solvent free conditions (Method B). The reaction involves first the alkylation of 2-naphthol with benzaldehyde in the presence of an acid catalyst to give *ortho*-quinone methydes (*o*-QMs, I). Intermediate I reacts with acetonitrile (Method A) to obtain the intermediate II through a Ritter type reaction that after hydrolysis gives the desired product. Following method B the *o*-QMs generated *in situ* react with acetamide, which acts as a nucleophile, *via* conjugate addition to form 1-amidoalkyl-2-naphthol derivatives (Scheme 38).

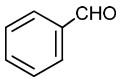
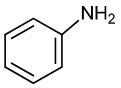
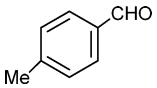
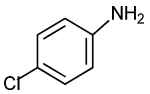
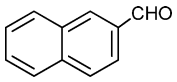
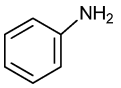
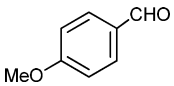
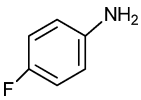
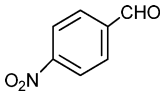
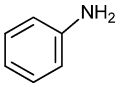
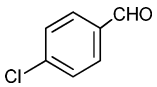
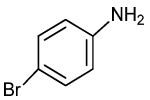
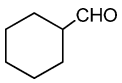
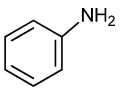
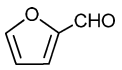
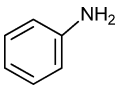
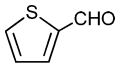
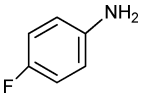
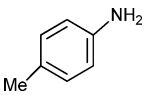
A variety of homogeneous (such as iodine,[228] $Ce(SO_4)_2$,[229] *p*-TSA[230]) and heterogeneous catalysts have been reported in the literature[231–237] to perform this MCR. Thus, Montmorillonite K-10 clay, Amberlyst-15, $K_5CoW_{12}O_{40}{\cdot}3H_2O$, $H_3PW_{12}O_{40}$, $FeCl_3$–SiO_2, Al_2O_3–SO_3H, $HClO_4$–SiO_2, Al_2O_3–$HClO_4$ catalysts have been used with different success for the preparation of 1-amidoalkyl-2-naphthol derivatives. It was found that aromatic aldehydes with electron-withdrawing groups reacted faster than those bearing electron donating groups. Table 15 summarizes the yields and experimental conditions for the formation of *N*-[phenyl-(2-hydroxynaphthalen-1-yl)-methyl]-acetamide using different acid catalysts reported in the literature.

Recently Shaterian *et al.*[239] have introduced the synthesis of 1-carbamate-alkyl-2-naphthol in the presence of silica-supported sodium hydrogen sulphate (SiO_2–$NaHSO_4$) as a catalyst. The benefit of using carbamates instead of amides is that the

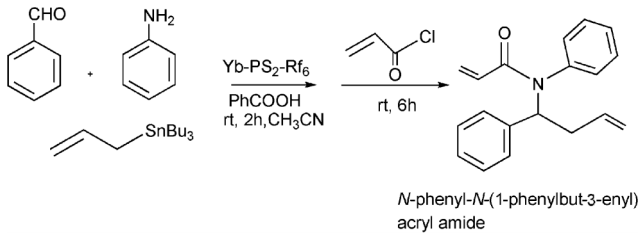


Scheme 35 Three component coupling condensation to obtain homoallylic amines.

Table 13 Montmorillonite clay as catalyst in the synthesis of homoallylic amines[a]

Aldehyde	Amine	Time (h)	Yield (%)
		4	90
		3.5	85
		5.5	82
		4	87
		3.5	80
		5.5	90
		4	73
		3	85
		3.5	88
$CH_3(CH_2)_8CHO$		5	82

[a] Reaction conditions: Aldehyde (5 mmol), amine (5 mmol), allyltributylstannane (5 mmol), Montmorillonite KSF (1 g), in CH_3CN (10 ml) at room temperature.



Scheme 36 Synthesis of homoallylic acrylic amide by a one-pot four component coupling reaction.

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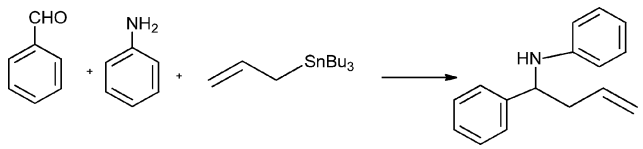
Table 14 Three component coupling reaction of benzaldehyde, aniline and allyltributylstannane using different acid catalysts at room temperature[a]



Catalyst	Yield (%)	t(h)	B:A:AS	Catalyst amount (g)	Solvent	Ref.
$[bmim]BF_4$	92	4.5	2 : 5 : 2	2[d]	—	
Mont KSF	90	4	5 : 5 : 5.1	1.00	CH_3CN	220
$NaHSO_4$ SiO_2	90	1.5	1 : 1 : 1.2	0.20	CH_3CN	221
NH_2SO_3H	90	1	5 : 5 : 5	5,00[b]	—	222
$HClO_4$–SiO_2	89	3	2 : 2 : 2.4	0.01[b]	CH_3CN	223
Yb-PS_2-Rf_6	95	5	10 : 10 : 3.3	0.1[c]	CH_3CN	224
PMA	97	24	0.2 : 0.2 : 0.2	0.04	H_2O	226

[a] B:A:AS mmol of benzaldehyde (B), aniline (A) and allyltributylstannane (AS). [b] mmol. [c] 10 mmol benzoic acid, 0.1 mol% of catalyst. [d] 2 mL.

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carbamates can be deprotected more easily than amides for the preparation of 1-aminomethyl-2-naphthol derivatives (Scheme 39). The three component condensation reaction between aldehydes, 2-naphthol and carbamates in the presence of SiO_2–$NaHSO_4$ was carried out under thermal and solvent free conditions (100 °C). A wide variety of substituted 1-carbamato-alkyl-2-naphthol using various aryl aldehydes, 2-naphthol, and methyl/benzyl carbamates were obtained in good to moderate yields (60–92%) within 20–30 min.

Das *et al.*[240] have found that perchloric acid supported on silica ($HClO_4$–SiO_2) is an efficient catalyst for the synthesis of *N*-[(2-hydroxynaphthalen-1-yl)methyl]amides through the condensation of 2-naphthol, aromatic aldehydes and urea (or an amide) (Scheme 40). The reaction was performed by heating the corresponding mixture at 125 °C during 3–7 h giving the corresponding target products in good yields (71–93%). The reaction proceeded similarly with amides such as acetamide, benzamide, and acrylamide. In this case, the corresponding *N*-[(2-hydroxynaphthalen-1-yl)methyl]amides were obtained in yields of 68–82% in 5.5–9 h. Interestingly, when the reaction was carried out using aliphatic aldehydes the selectivity of the target compound was very low.

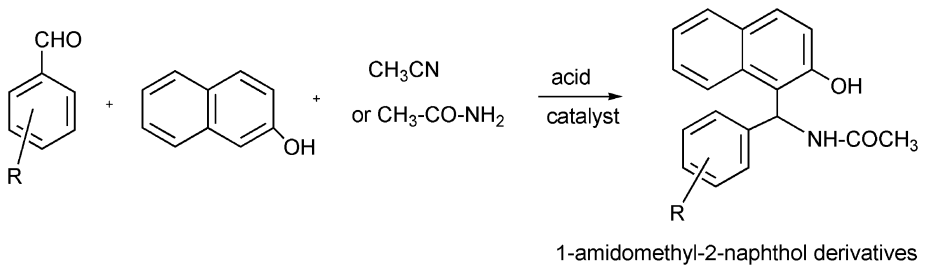
3.13 Synthesis of dihydropyridine derivatives

Dihydropyridines (DHPs) are an important class of compounds which cover a variety of pharmaceutical and agrochemical activities such as insecticidal, herbicidal and acaricidal.[241] Some of them have used as cardiovascular agents for the treatment of hypertension and angina pectoris[242] (nifedipine, nicardipine, and amlodipine) (Scheme 41), platelet antiaggregatory bactericidal agents, and bronchodilators.[243] In addition, they have been used as cerebral antischemic agents in the treatment of Alzeimer's disease[244] and also as a chemosensitizer in tumour therapy.[241] In addition, DHP presents applications in stereospecific hydrogen transfer reactions.[245]

The classical method to obtain DHPs is the MC Hantzsch reaction involving the condensation of and aldehyde, a *β*-ketoester and ammonia either in acetic acid or by refluxing in alcohol for long reaction times[15] (Scheme 42).

Numerous synthetic methods have been reported for the preparation of 1,4-dihydropyridine derivatives[246] under classical or modified conditions. For instance using microwave irradiation in the absence of a catalyst,[247,248] ionic liquids[249] or metal triflates as acid catalyst.[250] However, some of them suffer from drawbacks such as long reaction times, and low yields particularly when unsaturated and aliphatic aldehydes are involved.

Recently, heterogeneous acid and acid–base catalysts have been used for the preparation of DHPs. Thus, Gupta *et al.*[251] have reported that sulfonic acid covalently anchored onto the surface of silica gel (SiO_2–SO_3H) is an efficient and recyclable catalyst to synthesize 1,4-dihydropyridines (1,4-DHPs). Various aldehydes (aromatic, heterocyclic and unsaturated) and *β*-keto esters (ethyl and methyl acetoacetate) in the presence of ammonium acetate at 60 °C under solvent free conditions afforded the corresponding 1,4-DHPs in good yield (83–90%). For comparative purposes different supported sulfonic acid catalysts such as polystyrene and polyethylene glycol supported sulfonic acid, were also used in the coupling of 4-methoxybenzaldehyde, ethyl acetoacetate and ammonium acetate for the synthesis of diethyl 4-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (see Table 16). In Table 16 it is



Scheme 37 MC synthesis of 1-Amidomethyl-2-naphthol derivatives.

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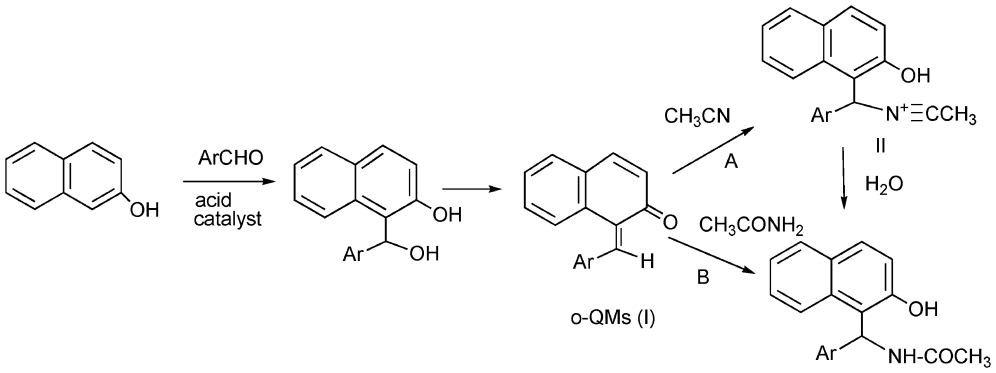

Scheme 38 Reaction phatways in the formation of 1-Amidomethyl-2-naphthol derivatives.

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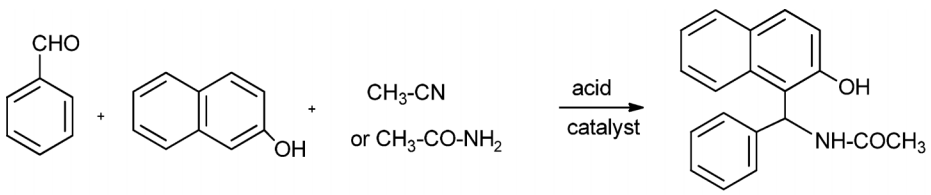
shown that SiO_2-SO_3H was the most active catalyst followed by polystyrene–SO_3H and PEG–SO_3H. In addition it was found that SiO_2–SO_3H is a stable catalyst, and no significant change in the activity was found after eight consecutive runs.

The mechanism proposed by the authors for the acid catalyzed synthesis of 1,4-DHPs is presented in Scheme 43. The first step is the formation of the Knoevenagel adduct from one equivalent of ethyl acetoacetate and benzaldehyde (intermediate A). On the other hand, a second equivalent of ethyl acetoacetate reacts with the ammonia generated by the ammonium acetate. The N-addition of ammonia to a protonated carbonyl group which suffers dehydration gives ethyl-3-aminobut-2-enoate (intermediate B). Subsequent cyclocondensation of both intermediates and dehydration give the DHP.

Recently Nikpassan *et al.*[252] have developed the synthesis of fused 1,4-DHPs starting from dimedone (5,5-dimethyl-1,3-cyclohexadienone), different aldehydes and ammonium acetate in the presence of HY zeolite. The reactions were carried out at reflux temperature of ethanol giving the corresponding 1,4-DHPs in good yields (70–90%) and in short reaction times (2.5–3.5 h) (Scheme 44). The catalyst was recovered and its activity was maintained after three consecutive runs.

N-Aryl-1,4-dihydropyridines and other related analogues are valuable compounds since they have applications as pharmaceuticals and agrochemicals. However, it is known that the classical Hantzsch reaction is not a suitable method for the preparation of *N*-aryl-1,4-dihydropyridines. For that reason, a complementary route to the Hantzsch synthesis has been developed to obtain *N*-aryl-1,4-DHP. This involves the coupling of aromatic amines, α,β-unsaturated aldehydes and ketoesters. Using sulfonic functionalized silica (SiO_2–SO_3H) [253] as a recyclable heterogeneous acid catalyst (Scheme 45) a series of

Table 15 MC synthesis of *N*-[phenyl-(2-hydroxynaphthalen-1-yl)-methyl]-acetamide using different acid catalysts[a]



N-[phenyl-(2-hydroxynaphthalen-1-yl)-methyl]-acetamide

Catalyst	Catalyst amount mol% or (g)	*T*/°C	Time (h)	Yield (%)	Ref.
Iodine	5	125, Meth B	5.5	86	228
$Ce(SO_4)_2$	100	Reflux	36	72	229
p-TSA	10	125, Meth B	0.6	89	230
Montm K-10	(0.1)	125, Meth B	1.5	89	233
Amberlyst-15	(0.25)	110, Meth B	0.2	86	235
$K_5CoW_{12}O_{40}\cdot 3H_2O$	1	125, Meth B	2	90	234
$H_3PW_{12}O_{40}$	2	100, Meth B[b]	1.4	90	232
$FeCl_3$. SiO_2	(0.025)	reflux, Meth A	20	80	236
$FeCl_3$. SiO_2	(0.025)	125, Meth B	0.18	86	236
Al_2O_3–SO_3H	20	reflux, Meth A	20	85	231
Al_2O_3–SO_3H	20	125, Meth B	0.06	83	231
Al_2O_3–SO_3H	20	MW, Meth C	0.06	87	231
$HClO_4$–SiO_2	0.6	reflux, Meth A	20	74	238
$HClO_4$–SiO_2	0.6	110, Meth B	0.66	89	238
$HClO_4$–SiO_2	0.6	MW, Meth C	0.25	86	238
Al_2O_3–$HClO_4$	5	125, Meth B	0.5	90	237

[a] Benzaldehyde: 2-Naphthol molar ratio= 1, Method A: acetonitrile (Ritter type reaction) Method B: acetamide (thermal and solvent free conditions). Method C: acetamide (microwave and solvent free conditions). [b] Tetraethyl ammonium chloride (1 mmol) was also added.

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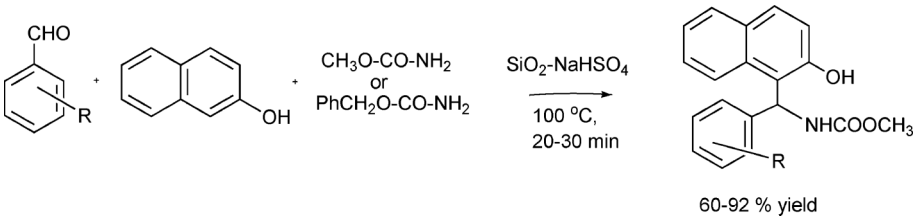
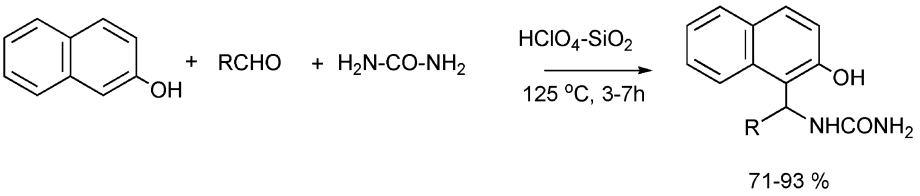
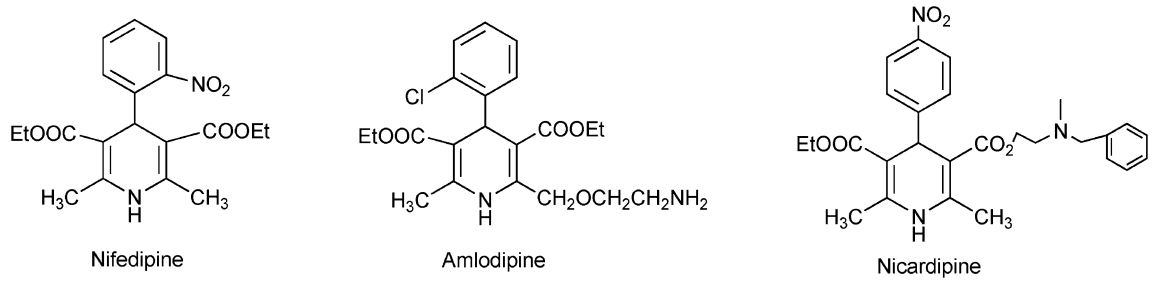


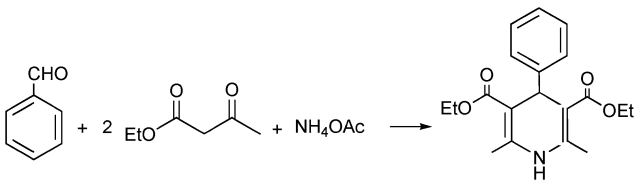
Scheme 39 Synthesis of 1-carbamato-alkyl-2-naphthol derivatives.



Scheme 40 Synthesis of *N*-[(2-hydroxynaphthalen-1- yl)methyl]amides derivatives.

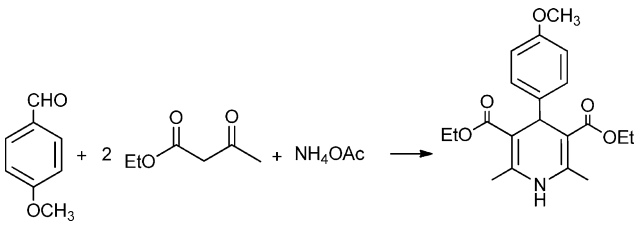


Scheme 41 1,4-Dihydropyridines of pharmaceutical interest.



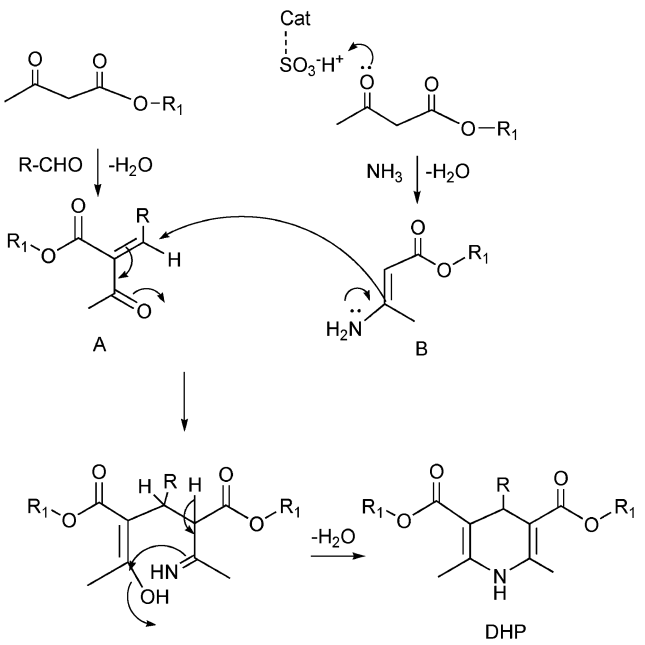
Scheme 42 Synthesis of DHPs through the MC Hantzsch reaction.

Table 16 Results of the synthesis of 1,4-DHP using different supported sulfonic acids as catalysts[a]



Catalyst	Time (h)	Yield (%)
SiO_2–SO_3H	5.00	95
Polystyrene–SO_3H	6.50	82
PEG-SO_3H	6.25	85

[a] Reaction conditions: 4-methoxybenzaldehyde (1 mmol), ethyl acetoacetate (2 mmol), ammonium acetate (1.5 mmol) catalyst (0.2 g), at 60 °C.



Scheme 43 Proposed mechanism for the formation of DHP in the presence of acid catalyst.

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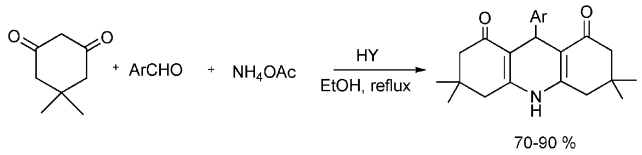
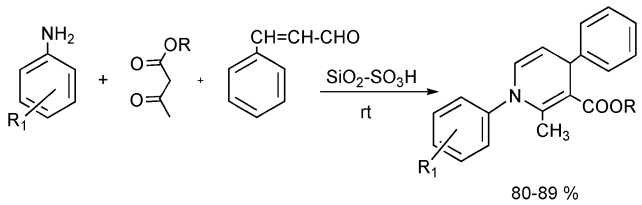


Scheme 44 Synthesis of fused 1,4-DHP.



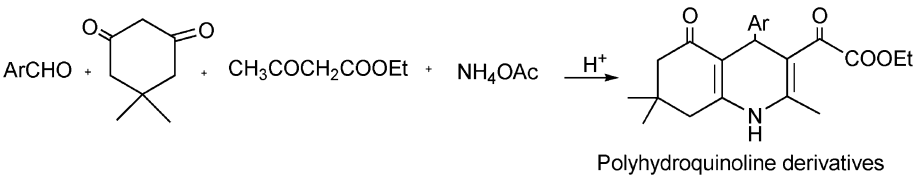
Scheme 45 Synthesis of *N*-aryl-1,4-dihydropyridines.

N-aryl-1,4-DHPs were successfully obtained (80–89% yields) starting from cinnamaldehyde, different aromatic amines and methyl or ethyl acetoacetate, at room temperature within a short time (5–30 min). However, low selectivity was obtained using aliphatic amines and cinnamaldehyde derivatives containing nitro groups in the aromatic ring.

Polyhydroquinoline derivatives, compounds containing a 1,4-DHP moiety, are a source of valuable drugs, which have been prepared efficiently through an A^4 Hantzsch type coupling condensation involving 1,3-cyclohexanediones (5,5-dimethyl-1,3-cyclohexadione or dimedone), ethyl acetoacetate, aldehydes and ammonium acetate in the presence of acid catalysts (Scheme 46).

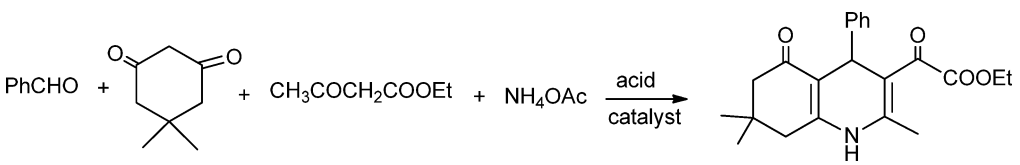
Various methods for the preparation have been reported using conventional heating, microwave and ultrasound irradiation in the presence of a wide variety of homogeneous and heterogeneous catalysts. They include trimethylsilyl chloride (TMSCl),[254] iron(III) trifluoroacetate,[255] metal triflates,[250] PTSA acid,[256] Brønsted ionic liquid,[249] glycine,[257] silica supported perchloric acid ($HClO_4$–SiO_2),[258] Montmorillonite K10,[259] heteropolyacid ($K_7[PW_{11}CoO_{40}]$),[260] HY zeolite[261] and nickel nanoparticles.[262] Using the Hantzsch protocol and catalysts referenced above, a series of polyhydroquinoline derivatives have been prepared in good yields. For comparison purposes Table 17 summarizes some results of the synthesis of ethyl 2,7,7-trimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-ethylcarboxylate from the 4CR of benzaldehyde, dimedone, ethyl acetoacetate and ammonium acetate using different heterogeneous catalysts reported in the literature.

Besides heterogeneous acid catalysts, solid base catalysts have also been used to perform the MC synthesis of 1,4-DHP. Thus, Antonyraj *et al.*[264] have reported the coupling of benzaldehyde, ethyl acetoacetate and ammonium acetate using hydrotalcites (HT) and hydrotalcite-like materials as solid base catalysts. Various Al/Mg hydrotalcites with different Mg/Al ratios were tested in the synthesis of 1,4-DHP (Table 18). The authors found that the activity decreased when increasing the Mg/Al atomic ratio, with $MgAl_2$-HT (with a Mg/Al = 2.1) being the most active catalyst. This catalyst possesses maximum aluminium content even though it possesses a lower Brønsted basicity than the other studied materials. In order to study the importance of the Brønsted basic OH groups present in HT-like lattice, the $MgAl_2$HT sample was subjected to calcination and the resulting Al/Mg mixed oxide ($MgAl_2$-CHT), which presents basic Lewis sites associated at O^{2-} centres, was tested in the synthesis of 1,4-DHP. A low yield of the 1,4-DHP was obtained in this case, which suggests that the presence OH groups in the hydrotalcite catalyst is required for the reaction. It is known that the original lamellar structure of hydrotalcites can be restored by hydration of the calcined mixed oxide (memory effect) while the carbonate anions are exchanged by hydroxyl anions resulting in a material with strong Brønsted basic character.[265,266] When the Hantzsch



Scheme 46 Synthesis of polyhydroquinoline derivatives through an A^4 coupling Hantzsch condensation.

Table 17 Results from the synthesis of ethyl 2,7,7-trimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-ethylcarboxylate using different catalysts



Catalyst	Catalyst amount mol% (g)	Solvent/*T*/°C	Time (min)	Yield (%)	B:D:E:A[a] (mmol)	Ref.
Montmorillonite	(0.2)	CH_3CH_2OH/80	50	98	2 : 2 : 2 : 3	259
HY	(0.1)	CH_3CN/rt	120	93	1 : 1 : 1 : 1.5	261
$K_7[PW_{11}CoO_{40}]$	1	CH_3CN/reflux	30	85	1 : 1 : 1 : 1	260
Glycine	10	MW	1	95	1 : 1 : 1 : 1.2	263
Ni np	10	MW	1	95	1 : 1 : 1 : 1.5	262

[a] B:D:E:A: Molar ratio Benzaldehyde:Dimedone:Ethyl acetoacetate:Ammonium acetate.

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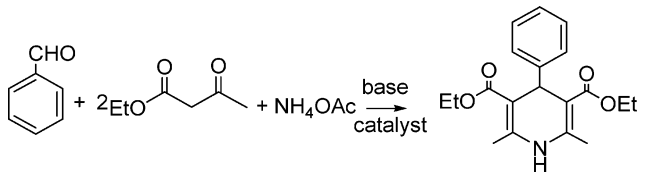
Table 18 Main characteristics and yields of DHP obtained for various hydrotalcites as catalysts[a]



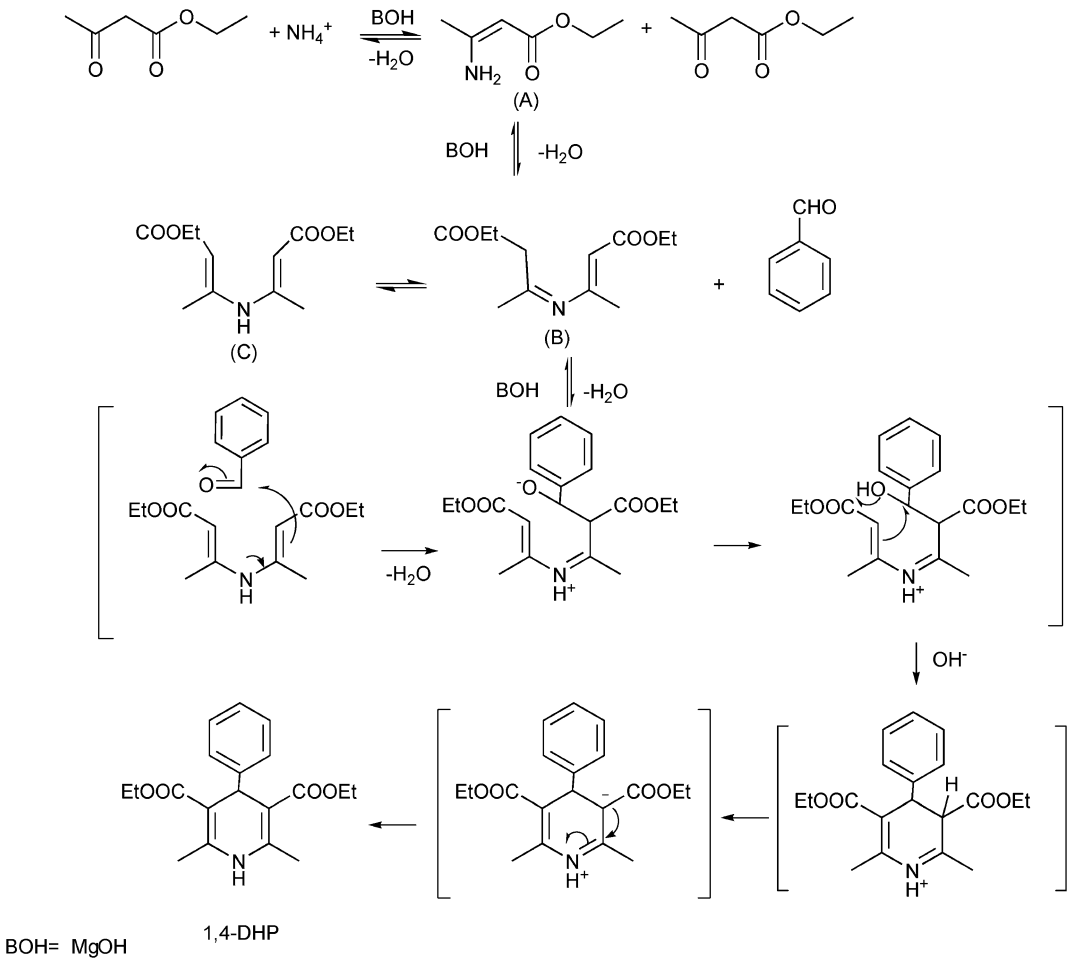
Catalyst	M(II)/Al	Surface area ($m^2\ g^{-1}$)	Yield (%)[b]	Yield (%)[c]
$MgAl_2$-HT	2.10	118	45	61
$MgAl_3$-HT	2.87	100	29	35
$MgAl_4$-HT	4.36	92	25	30
$NiAl_3$-HT	2.95	145	20	22
$CoAl_3$-HT	2.53	10	20	35
$MgAl_2$-CHT[d]	2.10	Nd[e]	—	15
$MgAl_4$-RHT	4.36	Nd	—	32
Blank	—	—	18	9

[a] Experimental conditions: benzaldehyde (0.0039 M), ethyl acetoacetate (0.0078 M) ammonium acetate (0.0039 M), room temperature. [b] 25 mg of catalyst, time 1 h, 10 mL EtOH. [c] 50 mg catalyst time 6.5 h, 10 mL MeCN. [d] Calcined at 450 °C for 5 h. [e] Nd: Not determined

reactions were carried out over a hydrated sample ($MgAl_4$-RHT) and $MgAl_4$-HT, similar results were obtained (Table 18). From these results, the authors conclude that the high activity of $MgAl_2$-HT is due to the appropriate cooperative behaviour of acid–base sites existing in this catalyst. With this optimized catalyst, different aliphatic, cyclic and aromatic aldehydes were reacted affording the corresponding 1,4-DHP in moderate to good yields (57–75%). When different nitrogen sources such as liquid ammonia, ammonium carbonate and ammonium acetate were used to synthesize 1,4-DHP, the maximum yield was obtained using ammonium acetate followed of ammonia and ammonium carbonate.

Finally, the synthesis of 1,4-DHP was also carried out using HT with different M(II) metals such as $NiAl_3$-HT and $CoAl_3$-HT, however the catalytic activity was considerably lower than those obtained with $MgAl_2$-HT catalyst.

The mechanism involving three reactants at different stoichiometry is complex. The first step is the proton abstraction from the active methylene group of ethyl acetoacetate by the base catalyst, followed by N-addition to a protonated carbonyl group which suffers a dehydration giving the ethyl-3-aminobut-2-enoate intermediate (A). Subsequent condensation with another molecule of ethyl acetoacetate results in the imine B (ethyl 3-(4-ethoxy-4-oxobutan-2-ylideneamino)but-2-enoate). A tautomerisation reaction of this imine in the presence of base catalyst will



Scheme 47 Reaction mechanism catalyzed by bases in the synthesis of 1,4-DHP.

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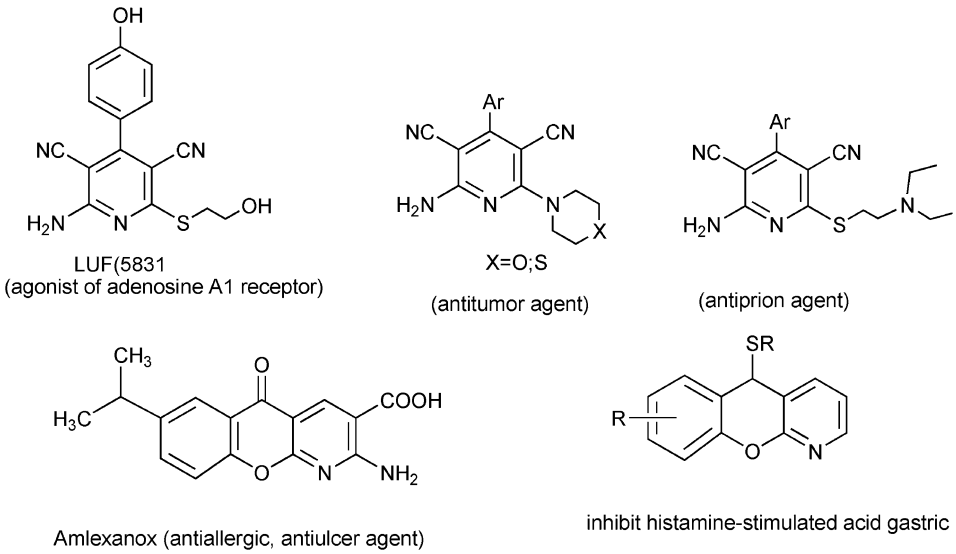
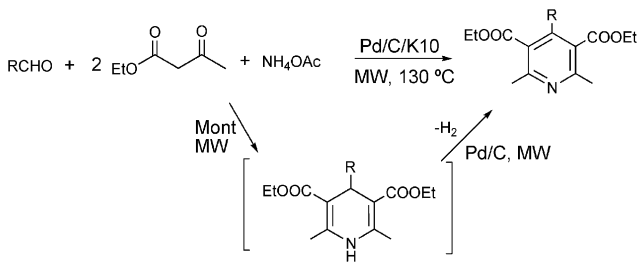
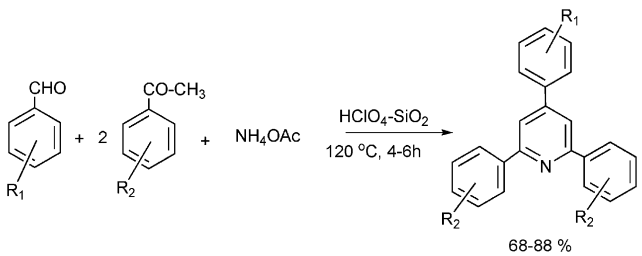


Scheme 48 Some examples of pyridine derivatives with pharmacological interest.

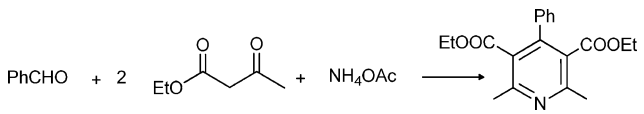


Scheme 49 Pyridine derivative synthesis.



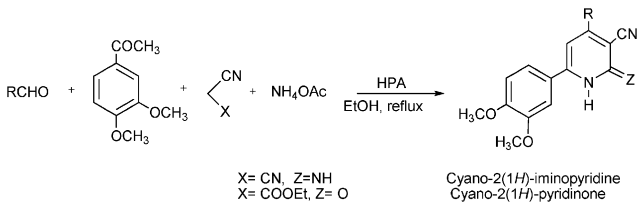
Scheme 50 MC synthesis of 2,4,6-triarylpyridine derivatives.

Table 19 MC Pyridine derivatives synthesis using bifunctional metal–acid heterogeneous catalysts[a]

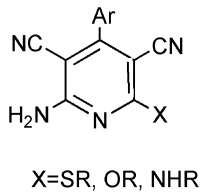


Catalysts	Method	*T*/°C	Time(h)	Yield (%)
$Pt/Al_2O_3/K10$	MW	130	1.5	15
$Pd/Al_2O_3/K10$	MW	130	1.5	20
Pd/C/K10	MW	130	1.5	78
Pd/C	MW	130	1.0	51
K10	MW	130	1.5	0
Pd/C/K10	CH	140	29	88
Pd/C/K10	CH	100	28	11
Pd/C/TfOH	CH	130	14	50
Pd/C/HOAc	CH	110	24	10

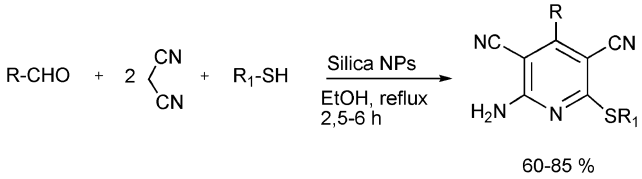
[a] Reaction conditions: benzaldehyde (1 mmol), methyl acetoacetate (2 mmol) and ammonium acetate (1 mmol). Toluene, pressure tube for conventional heating (CH).



Scheme 51 MC synthesis of 3-cyanopyridine derivatives.



Scheme 52 3,5-Dicyanopyridine derivatives.



Scheme 53 One-pot three components synthesis of substituted 2-amino-3, 5-dicyanopyridines.

form the enamine (C) which finally condensed with benzaldehyde to give the 1,4-DHP (Scheme 47).

3.14 Synthesis of pyridine derivatives

Pyridines are interesting compounds because their saturated and partially saturated derivatives are present in many biologically active and natural products such as for instance pyridoxol

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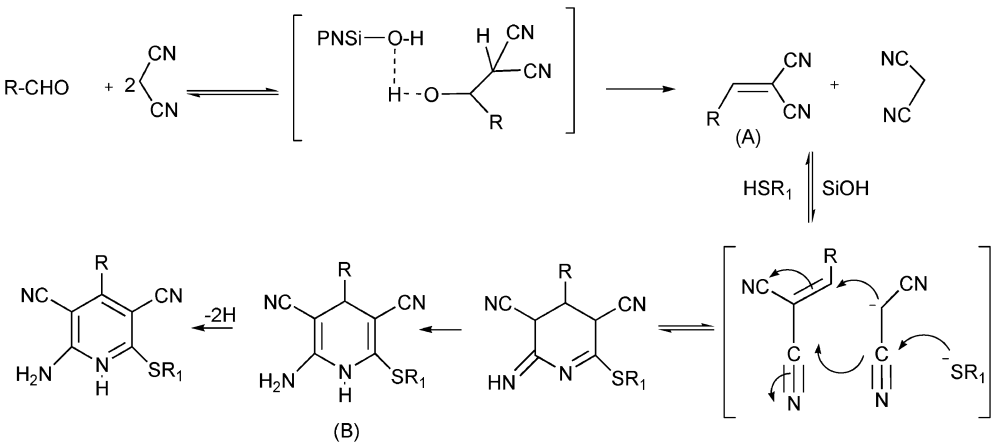
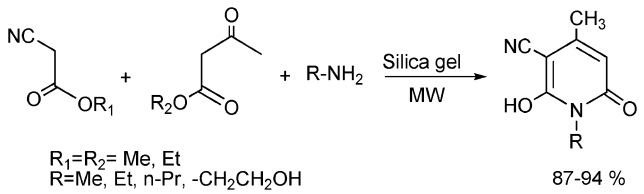
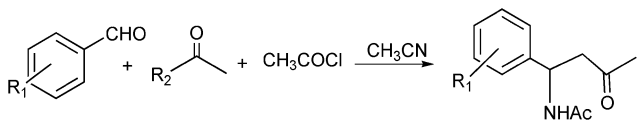


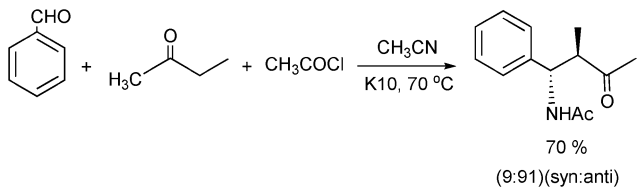
Scheme 54 Possible mechanism for the formation of substituted 3,5-dicyanopyridines.



Scheme 55 One-pot three component synthesis of 3-cyano-6-hydroxy-2(1*H*)-pyridinone derivatives.



Scheme 56 MC synthesis of *β*-acetamido ketone derivatives.



Scheme 57 MC synthesis of *β*-acetamido ketone using *α*-substituted ketones.

(vitamin B_6), NAD nucleotide (nicotin adenosin) and pyridine alkaloids.[267] The precursor compounds for the synthesis of pyridines are often 1,4-DHP, which can be prepared by the Hantzsch reaction mentioned above. Nowadays the synthesis of highly substituted pyridines by one-pot three component reactions has recently attracted much attention since this methodology allows one to obtain important medicinal pyridine derivatives that can act as ligands for a number of structurally diverse biological receptors. Some examples are presented in Scheme 48.

The traditional synthesis of pyridines involves the synthesis of 1,4-DHP followed by an additional step consisting in the oxidative aromatization to obtain the corresponding pyridine (Scheme 49). Some years ago Bocker *et al.*[268] demonstrated that the metabolism of 1,4-DHP drugs involves its catalyzed oxidation in the liver by cytochrome P-450. Due to the biological importance of the oxidation step of 1,4-DHPs, a large number of studies and reagents have been utilized to mimic the "*in vivo*" transformations. Many efficient oxidative aromatization processes using conventional oxidants, such as potassium permanganate,[269] ceric ammonic nitrate,[270] ruthenium trichloride,[271] as well as supported oxidants such as clayfen (iron(III) nitrate on clay),[272] or $Mn(pbdo)_2Cl_2$/MCM-41 in acetic acid[273] and a variety of other catalyst and reagents have been reported. However the use of liquid acids in the cyclization step along with the stoichometric amount of oxidant agent required for the oxidative aromatization produce significant drawbacks. In this section we will show different 3CRs (based mainly on Hantzsch type reaction) leading to a variety of pyridine derivatives.

3.14.1 Synthesis of 3,5-ethoxycarbonyl pyridine derivatives. As an alternative strategy to the homogeneous acid catalyzed Hantzsch reaction-oxidation, De Paolis *et al.*[274] developed a heterogeneous bifunctional noble metal–solid acid catalyst system (Pd/C/K10 Montmorillonite) for the one-pot three component reaction to obtain pyridines under microwave irradiation. The solid acid catalyzes the condensation of an aldehyde, a *β*-ketoester and ammonium acetate (Hantzsch reaction) to give 1,4-dihydropyridines which undergo dehydrogenation on the surface of the metal probably as a concerted reaction and results in pyridine derivative (Scheme 49).

The authors claimed that the presence of an acidic surface favors the dehydrogenation due to the anchoring of the intermediate (1,4-DHP) *via* its basic nitrogen. When the reaction was performed under conventional heating, a high yield was also achieved, however a longer reaction time was required (Table 19). Comparatively, triflic acid and acetic acid in the presence of Pd/C give lower yields than those obtained with Montmorillonite (Table 19). The scope of the reaction was shown by reacting a variety of aliphatic and aromatic aldehydes with ethyl acetoacetate and ammonium acetate affording the corresponding pyridines in good to moderate yields (45–95%) at 130 °C in short reaction time.

3.14.2 Synthesis of 2,4,6-triarylpyridine derivatives. Recently the synthesis of 2,4,6-triarylpyridines through one-pot condensation of aldehydes, ketones and ammonium acetate have been

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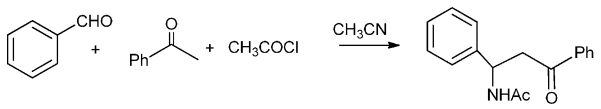
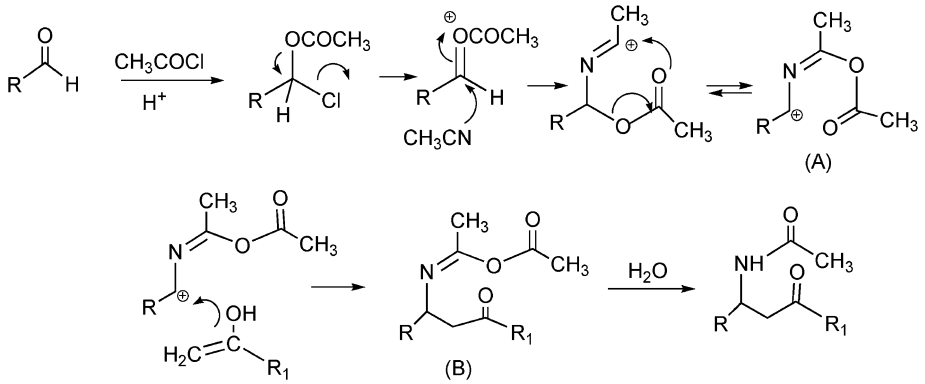
Table 20 Results obtained in the MCR of benzaldehyde, acetophenone, acetyl chloride and acetonitrile in presence of different solid acid catalyst



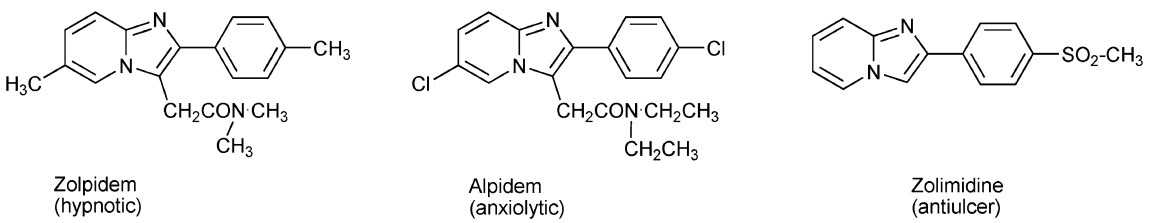
N-(3-oxo-1,3-diphenyl propyl) acetamide.

Catalyst (amount)	T (°C)	Time (h)	Yield (%)[a]	Ref.
$K_5CoW_{12}O_{40}\cdot 3H_2O$ (0.01% mol)	rt	1	86	304
$H_6P_2W_{18}O_{62}$ (0.7% mol)	80	0.4	86	303
$H_3PW_{12}O_{40}$ (0.05% mol)	rt	0.8	95	302
$H_3PMo_{12}O_{40}$ (0.08% mol)	rt	0.5	90	302
$H_3SiW_{12}O_{40}$ (0.08% mol)	rt	0.5	92	302
Amberlyst-15 (200 mg)	rt	6	89	306
HBeta	rt	8	89	301
Nafion (500 mg)	rt	4	96	305
Sulfated zirconia[b]	rt	1–3	95	307
Silica sulfuric acid (300 mg, 0.78 mmol H^+)	80	1–2	91	308
PMA/SiO_2(0.005 mol based on PMA)	rt	6	94	309

[a] Reactions are performed using 1 mmol benzaldehyde and 1 mmol acetophenone. [b] No data about the amount of catalyst are reported.



Scheme 58 Mechanism in the one-pot formation of *β*-acetamido ketones.

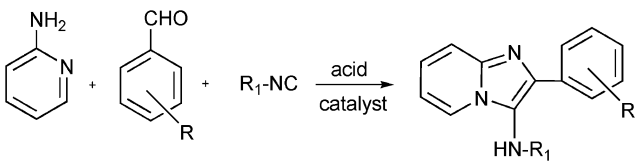


Scheme 59 Imidazopyridines of pharmacological activity.

carried out in the presence of perchloric acid supported on silica gel ($HClO_4$–SiO_2)[223] as heterogeneous catalyst (Scheme 50). It is known that the potential hazard to use perchlorates is connected with the explosive reactions when larger amounts are heated at high temperature. However recent methods indicate that the low acid loading on $HClO_4$–SiO_2 catalyst can be safely and effectively used for organic transformations.

Then, a variety of symmetric 2,4,6-triarylpyridines were synthesized in 68–88% yield, by heating a mixture of aromatic aldehydes, aromatic ketones and ammonium acetate in the presence of $HClO_4$–SiO_2 catalyst at 120 °C. In addition the catalyst could be recovered after reaction and reused seven times without significant decrease in activity.

3.14.3 Synthesis of 3-cyanopyridine derivatives. Substituted 3-cyanopyridines are increasingly useful compounds since they are important intermediates in pharmaceuticals, dyes and photo industries. Recently Heravi *et al.*[275] have prepared a series of 3-cyanopyridine derivatives through the MCR involving



Scheme 60 MC synthesis of imidazo[1,2-*a*]pyridines by Ugi reaction.

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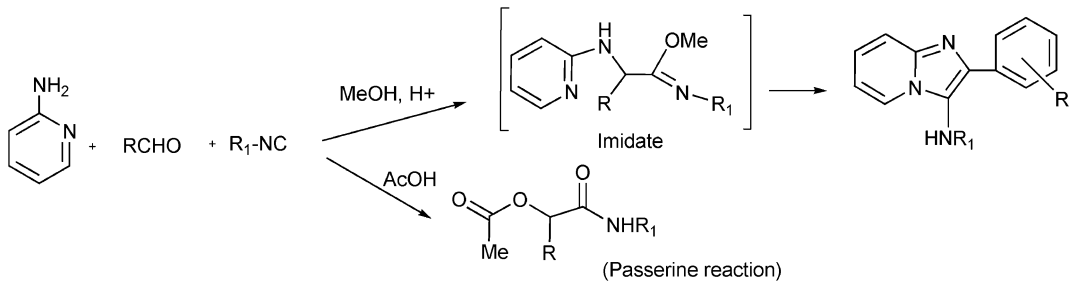
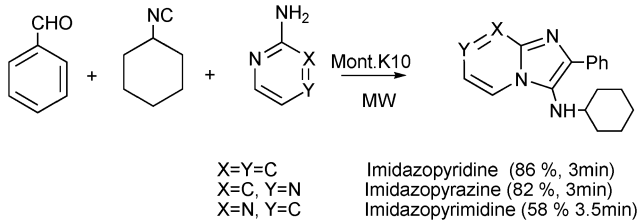
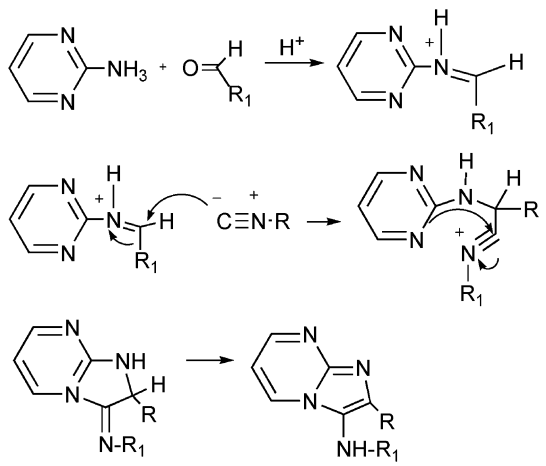


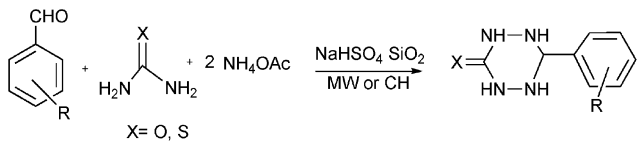
Scheme 61 Ugi and Passerine reactions.



Scheme 62 MC synthesis of imidazo-pyridine, -pyrazine and -pyrimidine using Montmorillonite K10 as the catalyst.

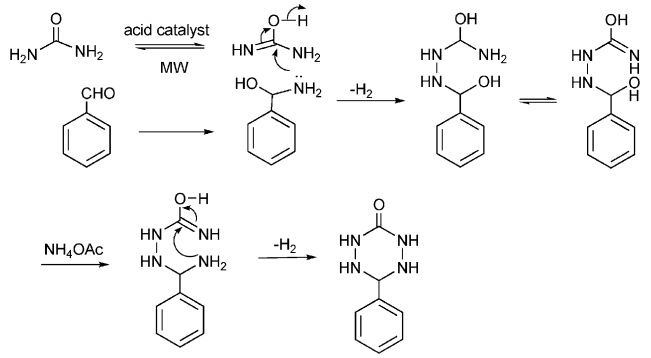


Scheme 63 Proposed mechanism for the MC synthesis of imidazo[1,2-*a*]pyrimidines.

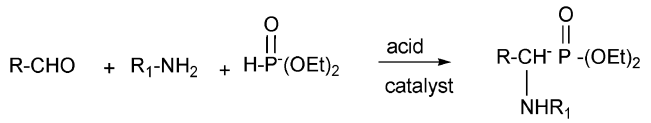


Scheme 64 MC synthesis of 6-aryl-1,2,4,5-tetrazinane-3-one (X=O) and 6-aryl-1,2,4,5-tetrazinane-3-thione (X=S) derivatives.

aldehydes, 3,4-dimethoxyacetophenone, malononitrile and ammonium acetate using different heteropolyacids as heterogeneous and recyclable acid catalysts (Scheme 51). The screening of different heteropolyacids ($H_{14}[NaP_5W_{30}O_{110}]$, $H_6[P_2W_{18}O_{62}]$, $H_4[PMo_{11}VO_{40}]$, $H_3[PMo_{12}O_{40}]$), showed that the highest activity was achieved with $H_{14}[NaP_5W_{30}O_{110}]$. It is known, that one of the factors that influence the oxidation capacity and activity of polyanions is the energy gap between the highest



Scheme 65 Proposed mechanism for the formation of 1,2,4,5-tetrazinane-3-ones.



Scheme 66 Synthesis of α-aminophosphonates.

occupied molecular orbital, HOMO, and the lowest unoccupied orbital (LUMO). It is suggested that the energy and composition of the LUMO have significant effects on the redox properties and activities of the different polyanions studied. The authors suggested that the highest activity exhibited by $H_{14}[NaP_5W_{30}O_{110}]$ should be attributed to the energy and composition of the LUMO and higher acidic protons.

Then, condensation of different aldehydes, 3,4-dimethoxyacetophenone, malononitrile and ammonium acetate in ethanol in the presence of $H_{14}[NaP_5W_{30}O_{110}]$ at 78 °C gave after 3 h the corresponding cyano-2-(1*H*)-iminopyridines in good yields (90–93%). When ethyl cyanoacetate was used instead of malononitrile the corresponding cyano-2(1*H*)-pyridinones were also obtained in excellent yields 91–94%.

3.14.4 Synthesis of 3,5-dicyanopyridine derivatives. 3,5-Dicyanopyridine is an important heterocyclic scaffold. Different substitutions at positions C2, C4 and C6 of the pyridine core have resulted in a large number of compounds with diverse biological activities. Among them, 2-amino-4-aryl-6-sulfanyl substituted compounds (Scheme 52) found different applications such as anticancer,[276] and antihepatitis B virus infection[277] among others. These compounds are considered as potential medicinal leads when developing therapeutic agents for

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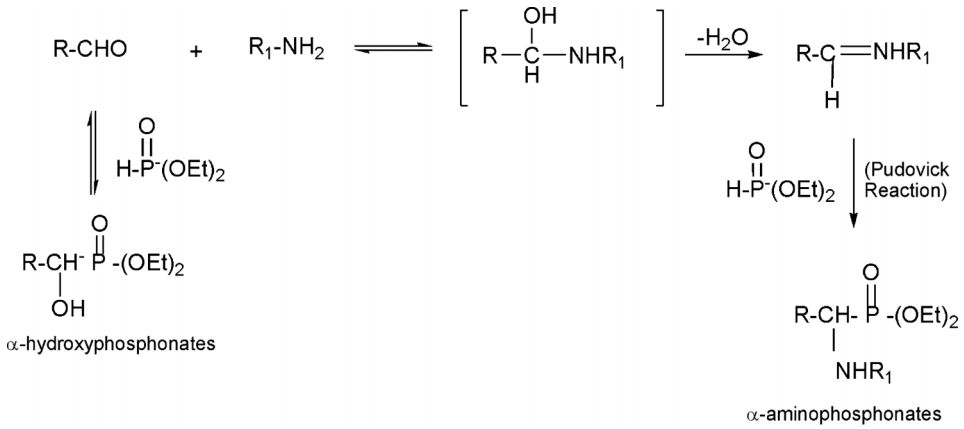

Scheme 67 Proposed mechanism for the preparation of aminophosphonates.

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the treatment of prion-induced fatal neurodegeneration diseases such as Creutzfeldt-Jacob disease in humans, bovine spongiform encephalopathy and scrapie in sheep. Recently, it has been found that 3,5-dicyanopyridine derivatives due to their capacity for recognition of adenosine receptors, are potential targets for developing new pharmaceutical agents for the treatment of Parkinson's disease, hypoxia-ischemia, epilepsy and asthma.[278]

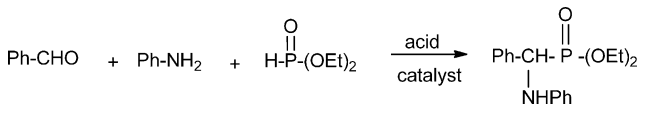
Due to their medicinal utility, various methods to prepare these compounds have been reported.[279] Some of them include Vilsmeier reactions of tertiary alcohols,[280] Diels–Alder reactions of 3-siloxy-1-aza-1,3-butadienes and 6-alkyl-3,5-dichloro-2*H*-1,4-oxazin-2-ones with different types of acetylenic compounds,[281] reaction of imines with enamines or carbonyl compounds[282] and [4 + 2] cycloadditions of oximinosulfonates.[283] However these methods involve multistep sequences, give low yields, use expensive and toxic catalysts and lack generality.

Recently, a new MCR strategy for the preparation of 3,5-dicyanopyridine pyridines has been reported by Evdokimov *et al.*[278,284] that involves the base catalyzed coupling of aldehydes, malononitrile and thiols. Homogeneous bases such as triethylamine or 1,4-diazabicyclo[2,2,2]octane (DABCO)[278,284] afford 3,5-dicyanopyridines in low yields (20–48%) due to the formation of appreciable enaminonitrile as a by-product. However, the use of other basic catalysts such as piperidine on microwave irradiation,[285] and Lewis acids such as ($ZnCl_2$) have considerably improved the yields of 3,5-dicyanopyridines.[286] Also, a basic ionic liquid such as 1-methyl-3-butylimidazolium hydroxide ([bmim]OH)[287] has been described as recyclable catalyst to produce highly substituted pyridines in high yields (65–95%) a room temperature. As an alternative to homogeneous base or acid catalysts, nanoparticles have attracted much attention in catalysis because their improved efficiency (high surface area) under mild an environmentally benign conditions. Recently, silica nanoparticles (silica NP) have been used as catalysts for the preparation of 2-amino-3,5-dicarbonitrile-6-sulfanylpyridines, *via* a single step multicomponent reaction of aldehydes, malononitrile and thiols[288] (Scheme 53).

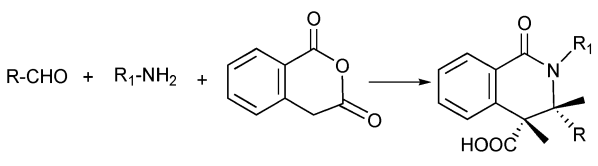
A series of 2-amino-3,5-dicarbonitrile-6-sulfanylpyridine derivatives was prepared in good yields (60–85%) starting from different aliphatic and aromatic aldehydes and thiophenol or alkyl thiols. The significant improvement in the yield of pyridines derivatives obtained using the silica NP compared to other catalysts such as $ZnCl_2$ (yield 45–67) Et_3N or DABCO (20–48%), or piperidine under microwave irradiation (60–81%) was attributed to the presence of hydroxyl groups on the surface of the catalyst. In accordance with the mechanism proposed by Evdokimov[278] the reaction starts by the formation of the Knoevenagel adduct (A) from the aldehyde and malononitrile. Subsequently a second molecule of malononitrile reacts with a Knoevenagel adduct through base catalyzed Michael addition followed by simultaneous thiolate addition to the nitrile group. Then, the cyclization process gives the dihydropyridine intermediate (B) after which posterior oxidation in the presence of air leads to the pyridine (Scheme 54).

The authors suggest that the polar amphoteric surface hydroxyl groups of the silica nanoparticles facilitate the interaction of adsorbed weak acidic and basic components due to stabilization of the corresponding transition states and intermediates by hydrogen boding. In addition, the participation

Table 21 Reaction conditions and yields of diethyl(phenyl)(*N*-phenylamino)methylphosphonate prepared by coupling benzaldehyde aniline and diethyl phosphonate using different catalysts



Catalyst (amount)	Solvent/T (°C)	Time (min)	Yield (%)	Ref.
Amberlyst-IR 120(0.10 g)	—/MW	2	90	345
Al_2O_3 acidic(5.75 g)	—/MW	6	87	348
$SbCl_3/Al_2O_3$(5 mol%)	CH_3CN/rt	180	90	350
ALkIT-5 (0.02 g)	CH_3CN/80	240	86	351
$H_3PW_{12}O_{40}$ (0.50 mol%)	CH_2Cl_2/rt	10	94	352
$Al(H_2PO_4)_3$(0.06 g)	—/100	90	93	353



Scheme 68 MC synthesis of tetrahydroisoquinolonic acid derivatives.

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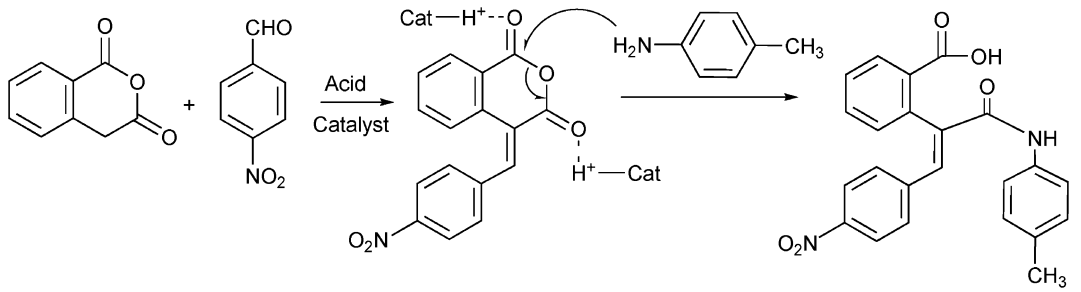


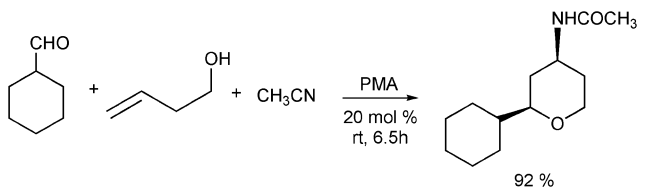
Scheme 69 Plausible reaction mechanism for the formation of *cis*-isoquinolonic acids.

of two proximate silanols groups (one acting as a hydrogen bond donor and another as an acceptor) in the reaction mechanism is also speculated.

Singh *et al.*[263] have recently reported the synthesis of 2-amino-3,5-dicarbonitrile-6-sulfanylpyridines (Scheme 53) using FK-alumina as the catalyst under microwave irradiation and conventional heating. Condensation of different aromatic aldehydes, malononitrile and thiophenols under microwave conditions give 62–93% yield of the corresponding pyridines in 5–10 min, whereas when refluxing in ethanol the reaction afforded the corresponding pyridines in 56–82% yield within 30–70 min.

Very recently Kantam *et al.*[289] have reported the one-pot three component synthesis of 2-amino-3,5-dicarbonitrile-6-sulfanyl-pyridines from diverse aldehydes with various thiols and malononitrile in the presence of nanocrystalline magnesium oxide (NAP-MgO, with a surface area of 590 $m^2\ g^{-1}$). Moderate to good yields (41–69%) of the pyridine derivative were obtained when the reaction was carried out under ethanol reflux. A possible rational clarification for the higher activity of NAP–MgO compared with other MgO samples [CM–MgO (30 $m^2\ g^{-1}$), NA–MgO (250 $m^2\ g^{-1}$)] is the presence of more surface Lewis acid sites (20%) along with the OH groups present on the edge and corner sites on the NAP–MgO. The authors suggest a dual activation of the substrate by the catalyst, thus Lewis base sites (O^{-2}/O^{-}) activate the malononitrile while Lewis acid sites (Mg^{+2}/Mg^{+}) activate the aldehyde and thiol. The catalyst can be recovered and reused at least up to four cycles without appreciable lost of activity.

3.14.5 Synthesis of 3-cyano-6-hydroxy-2(1*H*)-pyridinones. 3-Cyano-6-hydroxy-2(1*H*)-pyridinones and other 1-substituted derivatives are compounds widely used in the preparation of azo dyes, mainly as disperse dyes for polymeric materials.[290] Several methods have been described for the synthesis of 2(1*H*)-pyridinones. Among them, the most common method involves the condensation of *N*-alkylcyanoacetamides with *β*-ketoesters under pressure or in the presence of base.[291] Balalaie *et al.*[292] have performed the three component condensation of alkylacetoacetates, primary amines and alkyl cyanoacetates catalyzed by solid acids under microwave irradiation obtaining the corresponding 3-cyano-6-hydroxy-2(1*H*)-pyridinones in good yields (Scheme 55). Condensation of methyl acetoacetate, methyl cyanoacetate and methyl amine using different solid acids such as silica gel, Montmorillonite K-10, HY zeolite and acidic alumina give the corresponding pyridinones in moderate to good yields (93%, 65%, 60% and 55% respectively). The authors claimed that the reaction of *β*-ketoesters and primary amines afford the enamino-*β*-ketoester which react with alkylcyanoesters to give the final product. Using silica gel excellent yields of different 3-cyano-6-hydroxy-2(1*H*)-pyridinones (87–94%) were obtained after two minutes.

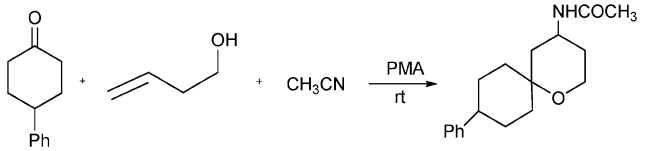


Scheme 70 Synthesis of *N*-(2-cyclohexyltetrahydro-2*H*-4-pyranyl)-acetamide.

3.15 Synthesis of *β*-acetamido ketone derivatives

β-Acetamido ketones are considered versatile intermediates since their basic skeleton exists in a number of pharmacologically or biologically active compounds.[293–294] Moreover they are important synthons for a variety of speciality chemicals[295] and pharmaceuticals such as nikkomycine and neopolyxine antibiotics.[296] The main route for the synthesis of these compounds is the Dakin–West reaction[297] which involves the condensation of an α-aminoacid with acetic anhydride in the presence of a base *via* an intermediate azalactone. Recently Bathia *et al.*[298] have proposed another general route for the synthesis of *β*-acetamido ketones that involves the condensation of an aryl aldehyde, an enolizable ketone or ketoester, acetyl chloride and acetonitrile in the presence of Lewis acid catalysts such as $CoCl_2$ (Scheme 56).The same author performed this MCR using Montmorillonite K10 as the acid catalyst.[299,300] The reactions were carried out at 70 °C using acetonitrile as reactant and as a solvent. Particularly for the coupling of substituted benzaldehydes, acetophenone, acetyl chloride and acetonitrile yields between 64–88% were achieved.

When α-substituted ketones were used, for instance, ethyl methyl ketone or propiophenone, a diastereomeric mixture of



Scheme 71 Spirocyclic-4-amidotetrahydropyrans.

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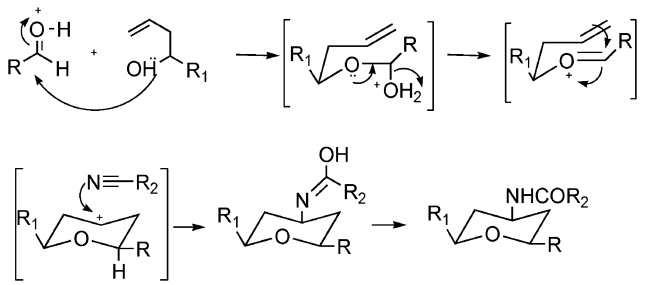


Scheme 72 Reaction mechanism for the formation of *cis*-amidotetrahydropyrans *via* Prins–Ritter reaction sequence.

the *β*-acetamido ketones were obtained, with the *anti* diasteroisomer being the most abundant (Scheme 57). In addition, the catalyst could be reused without considerable variation in yield and stereoselectivity.

Besides Montmorillonite K10, a variety of solid acid catalysts promoting this MCR have been reported. For instance, HBeta zeolite has been used as an active and reusable catalyst to perform this reaction at room temperature.[301] Using different substituted benzaldehydes and enolizable ketones 63–90% yields of the corresponding *β*-acetamido ketones can be achieved in 8–12 h. Also heteropolyacids,[302–304] acid resins,[305,306] sulfated zirconia,[307] sulfuric acid supported on silica[308] or phosphomolybdic acid supported on silica (PMA/SiO_2)[309] have been used to perform this MCR using a wide variety of aromatic aldehydes and ketones or ketoesters and giving in general excellent yields of the desired product. As an example, a summary of the different catalysts ad their activity performing the coupling of benzaldehyde, acetophenone, acetyl chloride and acetonitrile is presented in Table 20.

A plausible mechanism for this transformation is presented in Scheme 58. The acid catalyst activates the aldehyde which reacts with acetyl chloride and acetonitrile giving an intermediate (A) which subsequently reacts with the enolisable ketone giving the intermediate (B) which hydrolysis gives the *β*-acetamido ketone.

3.16 Synthesis of imidazo[1,2-*a*]pyridine derivatives

Imidazo[1,2-*a*]pyridines (Impy) is an important pharmacophore and is widely found in many natural and synthetic biologically active compounds[310] Moreover, they exhibit antiviral (antivaricella-zoster and anticytomegalo-zoster virus) *anti*-inflammatory, antipyretic, antifungal activities and calcium channel blockers.[311–313] They have also been found to be α-amyloid formation inhibitors, GABA and benzodiazepines receptor agonists.[314,315] Drug formulations containing imidazo[1,2-*a*]pyridines currently available on the market include Zolimidine (used for peptic ulcer and gastroesophageal disease), Zolpidem (hypnotic drug), and Alpidem (anxyolytic) (Scheme 59).[316]

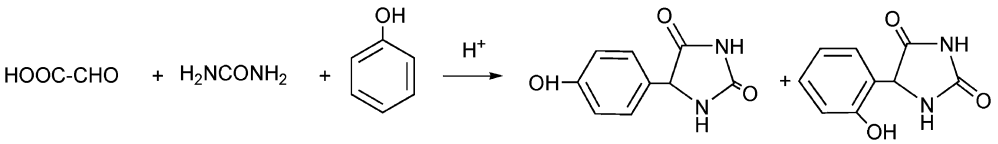
The classical route for the synthesis of Impy involves the coupling of 2-aminopyridines with lachrymatory α-haloketones.[317] However this approach does not readily lend itself to diversity oriented synthesis. In 1998 three research groups simultaneously published a new version of the Ugi reaction in which 2-aminopyridine, aldehydes and isocyanides react in the presence of an acid catalyst to give imidazo[1,2-*a*]pyridines in one step (Scheme 60).[318–320]

Reactions were performed at room temperature by combining all three reagents in methanolic solution in the presence of homogeneous acids such as $Sc(OTf)_3$,[319] perchloric acid[318] or glacial acetic acid.[320]

This robust approach allows for the preparation of a diverse range of substituted imidazo[1,2-a] annulated nitrogen heterocycles. However this synthesis suffers from several drawbacks such as the acid catalyzed polymerization of isocyanides and the competitive Passerine reaction, leading to moderate yields of the target compound, with relatively long reaction times (Scheme 61). In order to overcome those drawbacks, a variety of catalytic systems have been reported to perform this multicomponent reaction under classical conditions and under microwave irradiation. For instance, Lewis acids such as $ZnCl_2$,[321] ammonium chloride,[322,323] protic acids[324,325] or ionic liquids,[326] have been used as catalysts, however in most cases the catalyst is required in stoichiometric amounts in order to achieve a high yield of the target compound. Concerning to the use of heterogeneous catalysts, there are few studies. For instance, a variety of imidazo[1,2-*a*]pyridines were prepared starting from 2-aminopyridine, aldehydes and isocyanides using Montmorillonite K10 clay as the catalyst in a microwave reactor or by conventional heating at reflux of 1,4-dioxane,[321] although moderate yields (61–72%). Improved results were achieved with Montmorillonite K10 in the condensation of amino pyridines, pyrazines and pyrimidines with different aldehydes and isocyanides under microwave irradiation and in absence of any solvent (Scheme 62).[327] In this case the corresponding imidazo[1,2-*a*] annulated nitrogen heterocycles were obtained within 3–5 min in 56–88% yield.

The mechanism of formation of these heterocycles can be rationalized by the initial formation of iminium ion from the condensation of the amine with the aldehyde which is followed by the nucleophilic attack of isocyanide. Subsequently, internal nucleophilic attack of ring nitrogen leads to the bicycle adduct which upon aromatization and 1,3-shift of hydrogen atom results in the formation of the imidazole ring (Scheme 63).

Sulfuric acid supported on silica has also been used recently as a reusable acid catalyst[328] to perform the synthesis of 3-aminoimidazo[1,2-*a*]pyridines and -pyrazines by condensation of an aldehyde, 2-amino-5-substitutedpyridines or 2-aminopyrazine and alkyl or aryl isocyanides. Reactions performed at room



Scheme 73 Synthesis of DL-5-(4-hydroxyphenyl)hydantoin from amidoalkylation of phenol with urea and glyoxylic acid.

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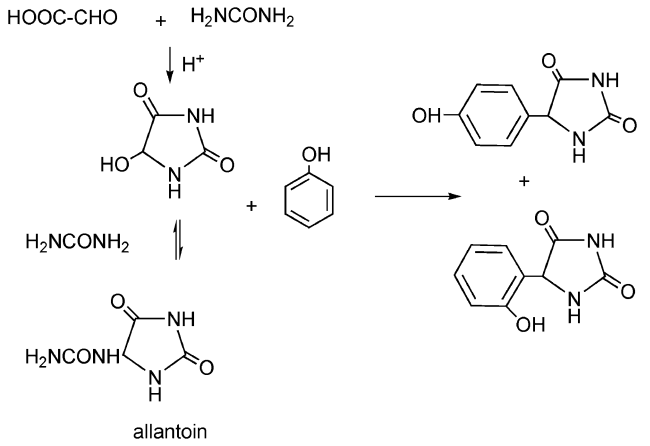


Scheme 74 Proposed mechanism in the formation of DL-5-(4-hydroxyphenyl)hydantoin.

temperature in methanol gave good yields (77–99%) of the corresponding 3-aminoimidazo[1,2-*a*]pyridines and -pyrazines.

3.17 Synthesis of 1,2,4,5-tetrazinan-3-one derivatives

1,2,4,5-Tetrazines are heterocyclic compounds with numerous biological activities such as bronchodilating, bactericidal, antiallergical, antiulcer, antinflammatory, pesticidal and antineoplasic activities.[329–331] Moreover, some tetrazoles have recently been introduced for the treatment of type 2 diabetes.[332]

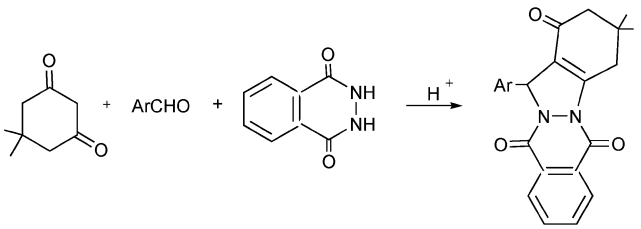
The formation of N–N bonds is not easy and 1,2,4,5-tetrazines have generally been prepared from hydrazine derivatives or from nitrilimines.[331] Recently Gopalakrishnan and co-workers[333] have reported the synthesis of 6-aryl-1,2,4,5-tetrazin-3-ones or thiones through a MC reaction involving urea, various substituted benzaldehydes, and ammonium acetate in the presence of $NaHSO_4$ supported on silica gel ($NaHSO_4$–SiO_2) as an acid catalyst (Scheme 64). Reactions performed under microwave irradiation afforded 6-aryl-1,2,4,5-tetrazin-3-ones in 68–75% yield within 2 or 3 min, while under thermal conditions (heating at 75 °C) lower yield was achieved (30–38%) in 35–43 min. The catalyst also resulted active when using thiourea, affording the corresponding 6-aryl-1,2,4,5-tetrazin-3-thiones in similar yields.

The proposed mechanism involves the nucleophilic addition of the aminoalcohol adduct (formed by reaction of benzaldehyde with ammonia) to the urea, followed by cyclization and dehydrogenation to the target compound (Scheme 65).

3.18 Synthesis of α-aminophosphonates

α-Aminophosphonates are an important class of biologically active compounds. Some of them act as peptide mimics,[334] antibiotics, enzyme inhibitors,[335] haptens of catalytic antibodies, pharmacological agents (antithrombotic, antibacterial, antiHIV, anticancer)[336] and plant-growth regulators.[337] Recently the syntheses of this type of organophosphorous compounds have attracted a lot of interest due to structural analogy to the corresponding α-amino acids and besides, they are key substrates in the synthesis of phosphonopeptides.

Several methods to obtain α-aminophosphonates have been developed in the last decades. One conventional method is the



Scheme 75 Synthesis of 3,4-dihydro-3,3-dimethyl-13-phenyl-2*H*-indazolo-[2,1-*b*]phthalazine-1,6,11(13*H*)-trione.

nucleophilic addition of dialkylphosphites to imines in the presence of base or Lewis acid catalysts[338] (Pudovik reaction).

However, recently the most common method to obtain α-aminophosphonates involves a three component coupling reaction of an aldehyde, an amine, and a di- or trialkyl phosphite in the presence of acid or base catalysts (Kabachnik–Fields reaction)[339] (Scheme 66). A variety of homogeneous Lewis acids catalysts such as metal triflates,[340] $ZrOCl_2 \cdot 8H_2O$,[341] $SbCl_3$/Al_2O_3,[342] indium in aqueous HCl,[343] Brønsted acids as such as *p*-toluenesulfonic acid, CF_3CO_2H, and ionic liquids,[344] as well as microwave irradiation itself[345] and ultrasonic irradiation itself or in the presence of $AlCl_3$[346] techniques have been used to promote this reaction.

Following this approach, recently, different heterogeneous catalysts have been used as a green alternative for the synthesis of α-aminophosphonates by coupling carbonyl compounds, amines and diethyl phosphate.

Thus, silica supported sulfuric acid (SSA), sodium hydrogen sulphate supported on silica gel and sulfamic acid (SA) have been selected to prepare α-aminophosphonates under solvent free conditions and at room temperature.[347] The results demonstrate the superiority of sulfamic acid compared with other catalysts. Complete conversions and good yields (76–94%) were obtained in the reaction between aldehydes (aromatic and heteroaromatic) and a range of amines (aliphatic, aromatic and cycloalkyl) and dimethyl phosphonate in a short reaction time (1–4 h). It is noteworthy to mention, that when the reaction was carried out using diethyl amine, different benzaldehydes (4-chlorobenzaldehyde, 4-methylbenzaldehyde and 4-isopropilbenzaldehyde) and diethyl phosphite the condensation failed to form the corresponding α-aminophosphonate. In these cases, only the α-hydroxyphosphonates were obtained in excellent yields after 15 min, as a result of the competing nucleophilic addition of diethyl phosphite to the carbonyl compound.

The mechanism proposed for the synthesis of α-aminophosphonate involves the formation of an imine promoted by the acid catalyst which is subsequently converted to an iminium ion, a more electrophilic intermediate, to facilitate the attack of dialkyl or diaryl phosphite nucleophile (Scheme 67). The authors explain that in the case of diethyl amine, the imine intermediate either being unstable or its formation being difficult, the base catalyzes the addition of diethyl phosphite to aldehyde that results in the formation of α-hydroxyphosphonate.

Acidic alumina has also been used as an acid catalyst in the synthesis of α-aminophosphonates under microwave irradiation.[348] Different aldehydes, amines and diethyl phosphite reacted on alumina under solvent free conditions using microwave irradiation producing high yields of the corresponding

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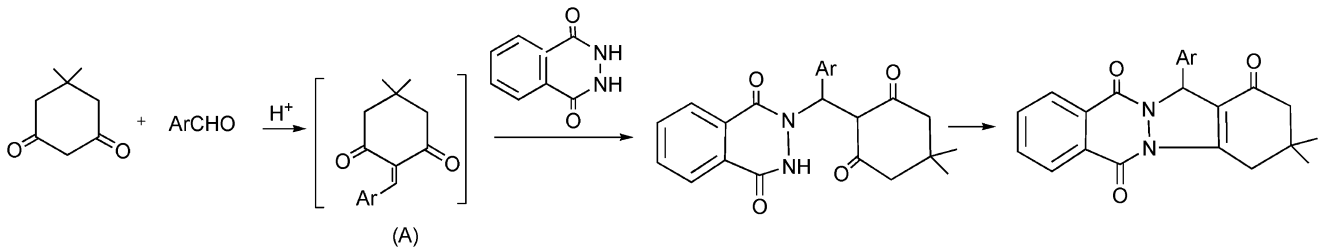
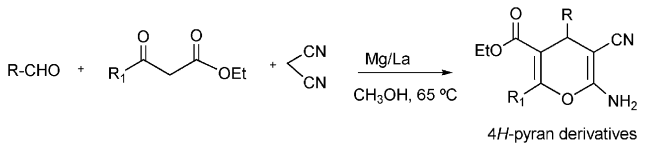


Scheme 76 Possible mechanism for the formation of 2*H*-indazolo[2,1-*b*]phthalazine-triones.

α-aminophosphonate (70–95%) in 6 min. No α-hydroxyphosphonate was detected in the reaction mixture. The MCR was also carried out in acidic alumina supported ammonium formate at room temperature yielding the desired compounds in good yields (59–76%) after 4–8 h. Neutral and basic alumina and magnesium oxide were not as effective as acidic alumina, giving α-hydroxyphosphonate as the major product. Montmorillonite KSF clay has also been used for the synthesis of α-aminophosphonate by three component condensation of aldehydes amines and diethylphosphite under microwave irradiation under solvent free conditions.[349] Various carbonyl compounds (aldehydes or ketones) and amines reacted with diethylphosphite to afford the corresponding α-aminophosphonate. In the case of aldehydes, the target compounds were obtained in excellent yields (80–92%) in short reaction times, whereas ketones gave phosphonates in lower yields (65–80%) after longer reaction times (6–8 min). When reactions were carried out by conventional heating in refluxing toluene, longer reaction times (5–10 h) were required to achieve good yields of the corresponding α-aminophosphonate (70–80%). Other solid acid catalysts such as Amberlyst-IR 120, $h_6p_2w_{18}o_{62}$, ALkIT-5 (a mesoporous metalosilicate) and $SbCl_3/Al_2O_3$ also promote this MCR. In Table 21 the results obtained in the coupling reaction of benzaldehyde aniline and diethyl phosphonate using different acid catalysts are compared.

3.19 Tetrahydroisoquinolonic acid derivatives

Tetrahydroisoquinolonic acid derivatives have attracted the attention of synthetic organic chemists due to their potential activity in the field of pharmaceuticals. This family of compounds exhibit a wide spectrum of biological activities including antiinflammatory, antiallergenic, *anti*-tumor activity, psychotropic and estrogenic behaviour.[354,355] Tetrahydroisoquinolonic acid derivatives have been reported as starting materials for the synthesis of natural phenanthridine alkaloids such as corolyne derivatives, decumbenine B.[356] and indenoisoquinolines[357] possessing significant antitumor activity. Tetrahydroisoquinolonic acid derivatives can be synthesised by cycloaddition reaction of homophthalic anhydrides with imines in the presence of conventional Brønsted and Lewis acids (such as acetic acid, HCl, $AlCl_3$, $FeCl_3$) and bases



Scheme 77 A^3 coupling process for the synthesis of 4*H*-pyran derivatives.

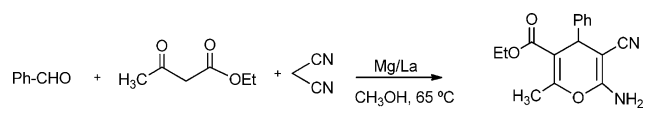
(Et_3N, Et_2NH).[358] When the reaction is performed under classical conditions, the reaction product resulting from this cycloaddition possesses two asymmetric centres and is therefore capable of existing as a mixture of *cis*- and *trans*-diastereoisomers, the *cis* compound being the main product. BF_3-Et_2O[359] and titanium(IV)chloride-*N*,N-diisopropylethylamine[360] have been used for the preparation of *trans*-isoquinolonic acid, meanwhile trimethyl orthoformate,[361] ionic liquids,[362] rare earth metal triflates (ytterbium(III) triflate),[363] and $KAl(SO_4)_2{\cdot}12.H_2O$[364] have been employed for the synthesis of *cis*-isomers.

Using this approach Azizian *et al.*[365] have reported the synthesis of *cis*-isoquinolonic acid derivatives by coupling homophthalic anhydride, aldehydes and amines in the presence of $KAl(SO_4)_2{\cdot}12H_2O$ (Alum) and silica sulphuric acid as heterogeneous catalysts (Scheme 68).

When a mixture of equimolar amounts of homophthalic anhydride, benzaldehyde and aniline in acetonitrile is allowed to react in the presence of Alum catalyst at room temperature, 1-oxo-2,3-diphenyl-1,2,3,4-tetrahydro-isoquinoline-4-carboxylic acid was obtained with yield of 88% after 7 h. The reaction was extended to a range of different aldehydes and amines giving the corresponding *cis*-isoquinolonic acid in good yields (81–91%). Similar results were obtained using silica sulphuric acid. It is noteworthy that in all cases the reaction is stereoselective in the preparation of *cis*-isoquinolonic acid derivatives.

Recently, Karimi *et al.*[366] have reported the use of sulfonic acid functionalized silica (SAFS) as a recyclable heterogeneous catalyst for the synthesis of isoquinolonic acids by a three component condensation of homophthalic anhydride, aldehydes and amines. When the reaction was carried out at room temperature in the presence of acetonitrile, good yields of the isoquinolonic acid derivatives were obtained (78–98%) in 1–5 h.

Table 22 Yield of 4*H*-pyran derivative using different solid base catalysts[a]



Catalyst	Time (h)	Yield (%)
MgO	5	67
KF–Alumina	5	74
Mg/Al hydrotalcite	3	82
Mg–Al–CO_3	4	64
Mg/La mixed oxide	1	92

[a] Reaction conditions: 4-chlorobenzaldehyde (1 mmol), malononitrile (1.1 mmol), ethyl acetoacetate (1.1 mmol) in MeOH at 65 °C.

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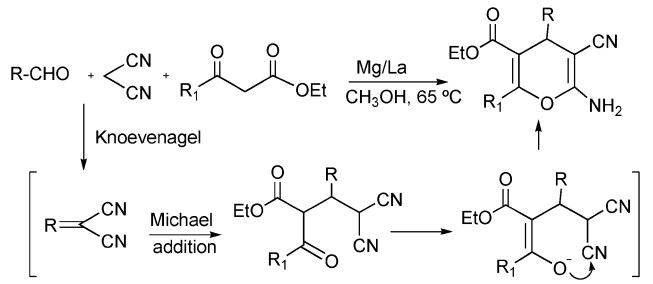
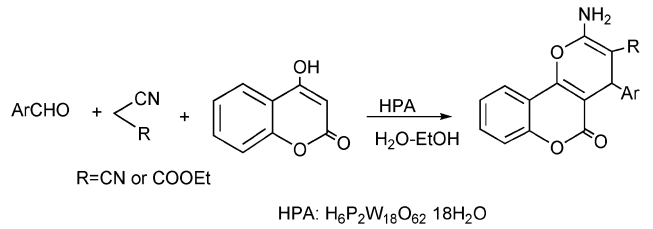


Scheme 78 Proposed mechanism for the A^3 coupling synthesis of 4*H*-pyran derivatives.



Scheme 79 MCR of 4-hydroxycoumarin, aldehydes and alkylnitriles.

The reaction was highly diastereoselective and only the *cis* diasteromer was obtained in all cases.

The mechanism proposed proceeded *via* the initial formation of an intermediate from homophthalic anhydride and an amine followed by (path i) initial methylene attack on to the aldehyde followed by Michael reaction or (path ii) nitrogen attack on to the aldehyde followed by methylene attack to give the final product (Scheme 69).

3.20 Synthesis of 4-amidotetrahydropyran derivatives

The 4-amidotetrahydropyran ring system is a core structure in a variety of natural products, among them ambrucitins VS, glycamino acid, and others.[367] The most general method to obtain tetrahydropyran derivatives is *via* Prins cyclization reaction using acid catalysts.[368] The Ritter amidation after Prins cyclisation (Prins–Ritter reaction) is a very useful methodology for natural product synthesis. Recently 4-amidotetrahydropyrans have been prepared by a three component coupling of carbonyl compounds, homoallylic alcohols and nitriles using phosphomolybdic acid ($H_3PMo_{12}O_{40}$, PMA) as catalyst *via* Prins–Ritter reaction (Scheme 70).[369] Various homoallylic alcohols and nitriles reacted at ambient temperature to produce the corresponding 4-acetoamidotetrahydropyrans in high yields (82–92%). In all cases the *cis* isomer was exclusively obtained.

For comparison purposes other solid acid catalysts such as Montmorillonite KSF and Amberlyst-15 were tested, however the PMA catalyst was more efficient in terms of conversion. Spirocyclic-4-amidotetrahydropyrans were also obtained in good yields (84–88%) from cycloketones, homoallylic alcohols and nitriles (Scheme 71).

The formation of 4-amidotetrahydropyran could be explained by hemiacetal formation followed by Prins cyclization and subsequent Ritter amidation (Scheme 72).

3.21 Synthesis of DL-5-(4-hydroxyphenyl)hydantoin

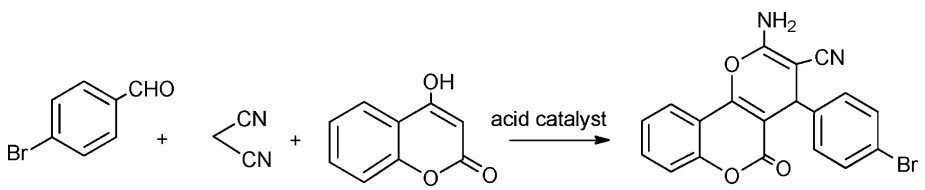
DL-5-(4-Hydroxyphenyl)hydantoin is an important intermediate for the enzymatic production of (*R*)-2-(4-hydroxyphenyl)glycine, a compound widely used in the preparation of semi-synthetic penicillins and cephalosporines.[370]

Various methods have been described for synthesising DL-5-(4-hydroxyphenyl)hydantoin in homogeneous media. However the most common method is by amidoalkylation of phenol with urea and glyoxylic acid in the presence of a larger excess of concentrated mineral acid (such as 35% hydrochloric acid)[371] (Scheme 73). In this reaction a mixture of the DL-5-(4-hydroxyphenyl)hydantoin (*para*-isomer) and DL-5-(2-hydroxyphenyl)hydantoin (*ortho*-isomer) is obtained the *para*-isomer being the major product.

The reaction proceeds possibly through the coupling of glyoxylic acid with urea leading allantoin which subsequently reacts with the phenol *via* a Friedel–Crafts alkylation in the presence of the acid catalyst giving the *ortho* and *para* isomers (Scheme 74).

Cativiela *et al.*[372] have reported the synthesis of DL-5-(4-hydroxyphenyl)hydantoin following this approach using solid acids catalysts such as clays (KSF and K10 Montmorillonite), beta zeolite, and sulfonic organic polymers. The condensation reaction of phenol, urea and glyoxylic acid performed in water at 70 °C in the presence of clay or beta zeolite afforded the target

Table 23 Synthesis of 2-amino-4-(4-bromophenyl)-3-cyano-4*H*,5*H*-pyrano[3,2-c]chromene-5-one from the condensation of 4-hydroxycoumarin, 4-bromobenzaldehyde and malononitrile



Catalyst (mmol%)	Solvent	Time (min)	Yield (%)
$H_6P_2W_{18}O_{62}\cdot 18H_2O$(1)	EtOH	120	72
$H_6P_2W_{18}O_{62}\cdot 18H_2O$(1)	H_2O	140	82
$H_6P_2W_{18}O_{62}\cdot 18H_2O$(1)	EtOH:H_2O[a]	60	87
NH_2SO_3(10)	EtOH:H_2O[a]	100	76
$H_{14}NaP_5W_{30}O_{110}$ (1)	EtOH:H_2O[a]	90	74

[a] EtOH : H_2O (50 : 50) under refluxing conditions.

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product in low yields (7.5% and 4.2% respectively, after 21 h) even when they were used as a co-catalyst with hydrochloric acid. The reaction was also tested with Dowex and Duolite, two sulfonic acid resins of different particle size. It was found that Dowex promotes the synthesis of the hydantoin more efficiently than Duolite due probably to the diffusion restrictions imposed by the larger particle size of the later. With Dowex, a yield of 74% of hydantoin was achieved, while with Duolite and Nafion resins the yield was somewhat lower (47%).

3.22 Synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-trione derivatives

Among the large variety of nitrogen-containing heterocyclic compounds, heterocycles containing the phthalazine moiety are of interest because they show important pharmaceutical and biological activities.[373] It has been reported that this type of compound possesses anticonvulsant,[374] cardiotonic[375] and vasorelaxant[376] activities. Various methods have been reported for the synthesis of phthalazine derivatives.[377] Recently, the multicomponent reaction of dimedone (5,5-dimethylcyclohexane-1,3-dione), phthalhydrazide (2,3-dihydro-1,4-phthalazinedione) and aromatic aldehydes in the presence of *p*-TSA to give 3,4-dihydro-3,3-dimethyl-13-aryl-2*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-trione derivatives has been reported[378] (Scheme 75). Good yields (83–93%) were obtained when the reaction was performed at 80 °C under solvent free conditions for several minutes.

Following this protocol, Shaterian *et al.*[379] have reported the use of silica supported sulfuric acid as an efficient heterogeneous catalyst for the preparation of 2*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-trione derivatives. Good yields of the corresponding products (84–93%) were obtained using different aromatic aldehydes, when the condensation reaction was carried out under solvent free conditions, at 100 °C within short reaction time (7–35 min). The catalyst could be successfully recovered and recycled at least for five runs without significant loss in activity.

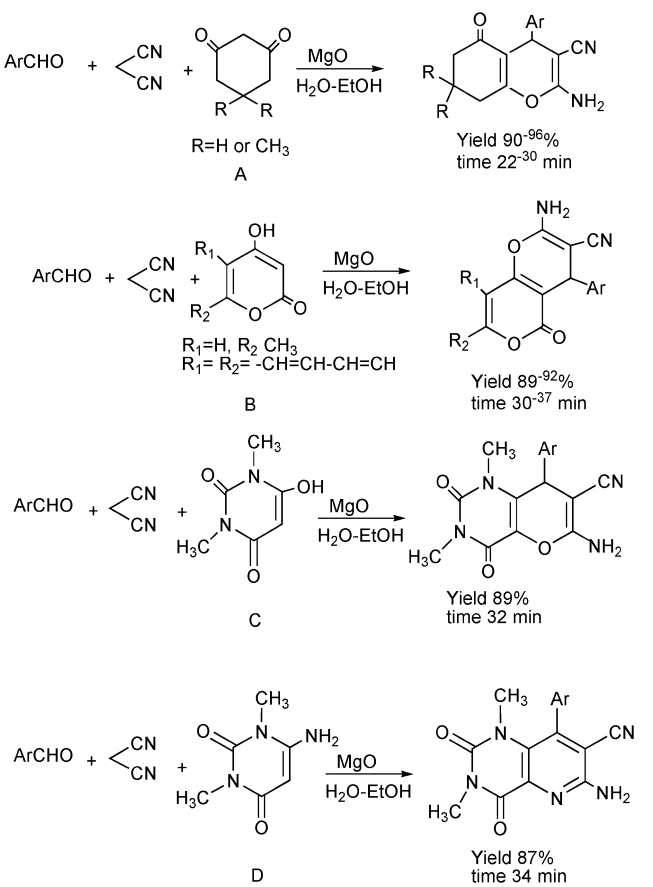
A possible mechanism for the formation of 2*H*-indazolo[2,1-*b*]phthalazine-triones is presented in Scheme 76 Initially a Knovenagel condensation between dimedone and benzaldehyde occurs to form a heterodyne intermediate (A). Then the subsequent Michael-type addition of the phthalhydrazide to the heterodyne (A) followed by cyclization affords the 2*H*-indazolo[2,1-*b*]phthalazine-trione product.

3.23 Synthesis of polyfunctionalized pyran, pyranodipirimidine and chromene derivatives

Compounds bearing 4*H*-pyran units present important biological and pharmacological activities. Its activity depends mainly on the presence of different heterocyclic ring systems. Among the different pharmacological activities exhibited by these compounds are anticancer, anticoagulants, antianaphylactics, and spasmolytics agents.[380,381] They are usually prepared by reaction between arylidenemalononitriles and activated methylene compounds in the presence of organic bases.[382] However, 4*H*-pyrans rings can be also obtained through a A^3 coupling reaction of an aldehyde, malononitrile and an active methylenic diketo compound. Initially the reaction proceeds by abstracting a proton from the malononitrile which subsequently reacts with the benzaldehyde forming an arylidenemalononitrile intermediate (Knoevenagel condensation). Subsequently, the arylidenemalononitrile intermediate reacts with methylenic diketo compound giving the 4*H*-pyran unit (Scheme 81). Depending on the structure of the diketocompound 4*H*-pyran rings bearing different heterocyclic ring systems can be obtained. In this section some examples involving this MCR performed under heterogeneous catalysis is presented.

3.23.1 Synthesis of polysubstituted 4*H*-pyran derivatives. 5-Substituted-2-amino-4-aryl-3-cyano-6-methyl-4*H*-pyrans (Scheme 77) are important drugs used in neurodegenerative diseases such as Alzheimer's disease and for the treatment of schizophrenia.[381] They can be obtained by the coupling of an aromatic aldehyde, malononitrile and an active methylenic diketocompound using radiative (microwave and ultrasonic irradiation) and non radiative techniques have been reported.[383] Thus, some ionic liquids under microwave irradiation,[384,385] as well as some organic bases such as tetrabutylammonium bromide,[386] and (*S*)-proline.[387] promote this transformation. Recently, Babu *et al.*[388] have synthesized this type of compound using a Mg/La mixed oxide as the heterogeneous basic catalysts.

Compared to other solid basic catalysts such as MgO, KF-Alumina, Mg/Al hydrotalcite, and Mg-Al-CO_3, the Mg/La mixed oxide catalyst was the most active promoting the coupling of benzaldehyde, ethyl acetoacetate and malononitrile in high yield (92%) (Table 22). This result was attributed to the presence



Scheme 80 Synthesis of pyran annulated heterocyclic systems *via* three component reaction.

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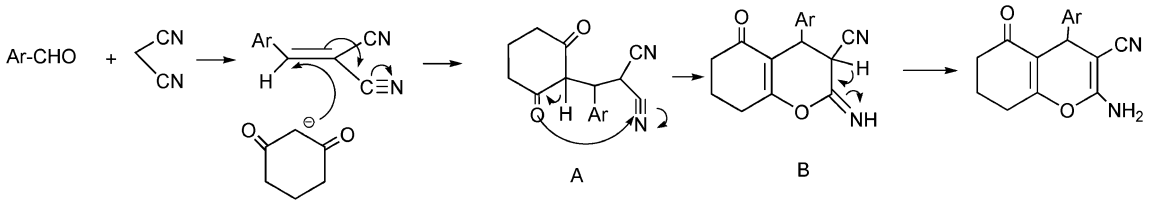


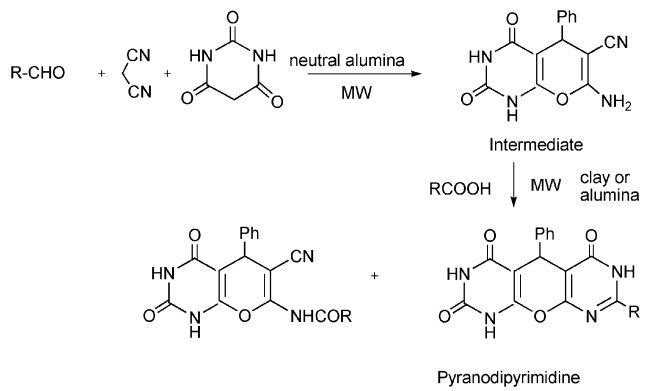
Scheme 81 Proposed mechanism for the one-pot synthesis of tetrahydrobenzopyran derivatives.

of La_2O_3 in proximity to MgO and leads to an increased basicity. The condensation of various aromatic and aliphatic aldehydes, malononitrile and several active methylene diketo-compounds afforded the corresponding 4*H* -pyran derivatives in variable yields (15–92%). The proposed mechanism is presented in Scheme 78. Recycling experiments showed that the Mg/La mixed oxide catalyzes the reaction with consistent activity even after four cycles.

3.23.2 Synthesis of dihydropyran [3,2-c]chromene derivatives. Dihydropyran[3,2-c]chromene derivatives are important heterocyclic compounds used in the treatment of neurodegenerative diseases including Alzheimer's disease, AIDS associated dementia, for the treatment of schizophrenia, Down's syndrome and Huntington's disease. In addition, 2-amino-chromene derivatives exhibit antihypertensive and antischemia activity.

Conventionally the synthesis of 2-amino-3-alkyl-4-aryl-5-oxo-4,5-dihydropyran[3,2-c]chromene involves the MC condensation of 4-hydroxycoumarin, aldehydes and alkylnitriles (Scheme 79) in the presence of organic bases (piperidine or pyridine in organic solvents). However, recently Heravi *et al.*[389] have reported this 3CR using heterogeneous acid catalysts such as $H_6P_2W_{18}O_{62}{\cdot}18H_2O$ as a Wells–Dawson type heteropolyacid catalyst.

A study of the synthesis of 2-amino-4-(4-bromophenyl)-3-cyano-4, 5-dihydropyran[3,2-c]chromene-5-one from the condensation of 4-hydroxycoumarin, 4-bromobenzaldehyde and malononitrile in the presence of a variety of solvents and catalysts was performed. As can be seen in Table 23, the best results were obtained with $H_6P_2W_{18}O_{62}{\cdot}18H_2O$ using a mixture of ethanol : water (50 : 50). The authors suggest that the reaction, which occurs in a pseudoliquid, is accelerated due to the participation of all bulk protons of the heteropolyanion.

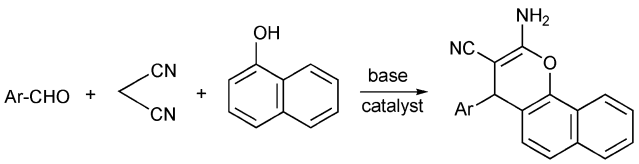


Scheme 82 One-pot synthesis of pyranodipyrimidine derivatives.

Coupling different aromatic aldehydes, 4-hydroxycoumarin and malononitrile in the presence of $H_6P_2W_{18}O_{62}{\cdot}18H_2O$, a wide variety of substituted 2-aminochromenes were obtained in high yields (80–90%) and selectivity (85–90%) in 35–80 min. When ethyl cyanoacetate was used as the reactant a longer reaction time (16 h) was required in order to obtain the corresponding 2-aminochromene in good yield (90%) and selectivity (90%). The catalyst was recyclable and could be reused without significant loss of activity during five consecutive runs.

Following the same protocol as above, tetrahydro-4*H*-benzo-[b]-pyran derivatives can be obtained by coupling aromatic aldehydes, malononitrile and cyclic *β*-diketones such as dimedone. Conventionally this A^3 coupling is performed under reflux in acetic acid,[390] although other homogeneous catalysts such as diammonium hydrogen phosphate,[391] and ionic liquids[392] (1,1,3,3-*N*,*N*,*N*′,*N*′-tetramethylguanidinium trifluoro acetate) have been reported to perform this MCR with variable success. Recently, Seifi *et al.*[393] presented a highly efficient method for the synthesis of a pyrano annulated heterocyclic system *via* a three component reaction of an aldehyde, malononitrile and a *α*-hydroxy or an *α*-amino activated C–H acid in the presence of MgO as the catalyst. The study of the effect of the solvent in the reaction between benzaldehyde, malononitrile and dimedone in the presence of MgO reveals that polar solvents such as ethanol and acetonitrile afford better yields (85% and 74% after 0.6 and 1.5 h respectively) than nonpolar solvents such as toluene (63% after 2.5 h), being the most effective solvent a mixture of water and ethanol (40 : 10) yielding 94% after 0.5 h. A variety of tetrahydrobenzo[b]pyran-, [2,3-d]pyrano- and pyrido[2,3-d]pyrimidine derivatives were synthesized with this protocol in excellent yields in the presence of MgO catalyst from aryl aldehyde, malononitrile and cyclic *β*-diketones (A: 1,3-cyclohexanedione or dimedone, B: 4-hydroxy-6-methylpyrone, 4-hydroxycoumarin, C: 1,3-dimethylbarbituric acid and D: 1,3-dimethyl-6-amino uracil) (Scheme 80).

The mechanism for the formation of these products involves the Knoevenagel condensation between the aromatic aldehyde and malononitrile as first step giving the *α*-cyanocinnamonitrile. Subsequently the methylene of the diketone is activated by MgO and reacts with the electrophilic carbon–carbon double bond (Michael addition) giving the intermediate (A) which cyclizes by



Scheme 83 3MC synthesis of 2-aminochromene derivatives.

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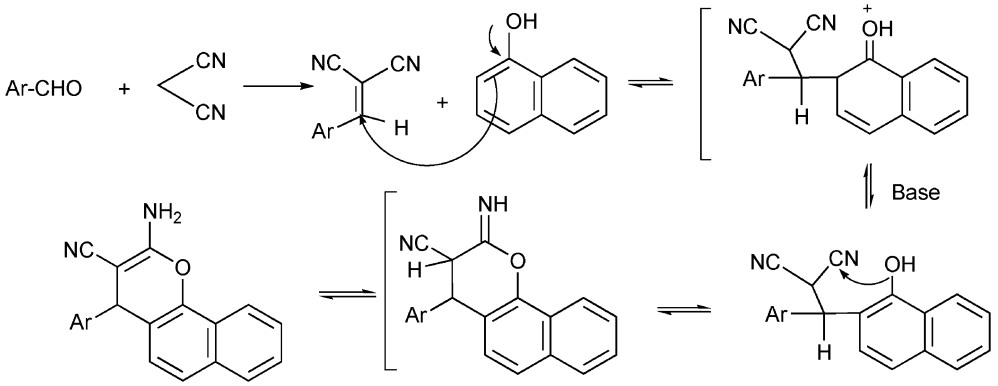

Scheme 84 Mechanism of the one-pot synthesis of 2-aminochromene derivatives.

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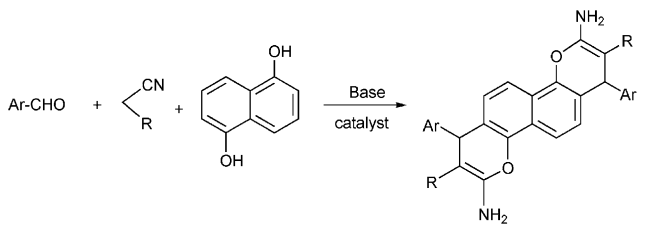
nucleophilic attack of the hydroxyl group on the cyano moiety, to form the intermediate B. Finally a tautomerization process affords the desired product (Scheme 81).

3.23.3 Synthesis of pyranodipyrimidine derivatives. Pyranodipyrimidines are an important class of tricyclic compounds which present a variety of biological activities such as antibacterial, HIV integrasa inhibitor, antitumor, and also are used as antiretroviral drugs.[394] In addition, N-alkylated pyranodipyrimidines show increased bioactivity due to their high lipophilicity which facilitates membrane transport and strengthens functional activity.[394]

The MCR involving benzaldehyde, malononitrile and barbituric acid or its thio analogue was performed using neutral alumina as the catalyst under microwave irradiation, and yields 7-amino-6-cyano-5-aryl-5*H*-pyrano[2,3-d]pyrimidine-2, 4(1*H*,3*H*)-diones, an intermediate in the synthesis of pyranodipyrimidines[395] (Scheme 82). This intermediate compound was allowed to react with different aromatic carboxylic acids adsorbed on Montmorillonite under microwave irradiation to give the desired product. Under these reaction conditions, a mixture of the target compound (yield 62–70%) along with the N-acylated pyranopyrimidines (yield 20–28%) was obtained. However, surprisingly, using acidic alumina, the pyranodipyrimidines were obtained in good yields (55–65%) and 100% selectivity in 4–5 min.

For comparison purposes the reaction was performed using a conventional procedure with hydrochloride acid at reflux temperature during 6.5–8 h. The yield of the pyranodipyrimidines was lower (35–48% yield) and the N-alcylated pyranopyrimidines were also obtained in a considerable amount. Although the N-acylated product is obtained in smaller quantities and is considered as a by-product this compound possesses various biological activities.[395]



Scheme 85 Synthesis of the naphthol[1,2-b;6,5-b']dipyrans derivatives from aryl aldehydes, malononitrile or ethyl cyanoacetate and 1, 5-naphthalenediol.

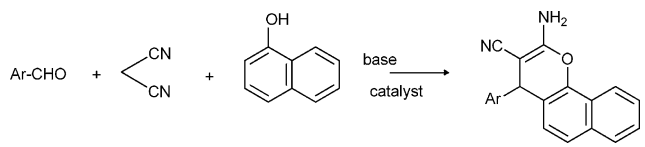
3.23.4 Synthesis of 2-amino-4*H*-benzo[h]chromene derivatives. Fused chromenes exhibit a wide spectrum of pharmacological applications such as antimicrobial,[396] antitumor,[397] cancer therapy,[398] sex pheromones[399] and central nervous system activity.[400] They are also widely employed as cosmetics, pigments, and potential biodegradable agrochemicals.[401]

The most straightforward synthesis for 2-aminobenzochromene derivatives involves a three-component coupling of aromatic aldehyde, malononitrile and an activated phenol in the presence of organic bases (such as piperidine), which is frequently used in stoichiometric amounts using ethanol or acetonitrile as solvents[402] (Scheme 83).

As in the previous reactions presented above, benzylidenemalononitrile is formed fast and in quantitative yield by the Knoevenagel condensation between benzaldehyde and malononitrile. Subsequent *ortho* C–alkylation of α-naphthol by reaction with the electrophilic C=C double bond and the nucleophilic addition of the hydroxyl moiety to the nitrile produces the final 2-aminochromenes (Scheme 84).

Nevertheless, diverse heterogeneous catalysts have been employed for this multicomponent reaction. Wang *et al.*[403] synthesized a series of 2-aminochromene derivatives from aryl aldehydes, malononitrile or ethyl cyanoacetate with 1-naphtol or

Table 24 Yields of 2-amino-chromene in the presence of different solid catalysts[a]



Catalyst	Yield (%) BM	Yield(%)chromene
γ-Alumina	13	84
Silica gel	35	61
Montmorillonite KSF	48	50
Hydrotalcite Pural MG30	72	24

[a] BM: benzylidenemalononitrile. Experimental conditions: benzaldehyde (10 mmol), malononitrile (10 mmol),1-naphthol (10 mmol), catalysts (0.50 g), 10 mL water at refluxing conditions after 2 h of reaction.

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1,5-naphthalenediol, in the presence of alumina coated with potassium fluoride (KF-Alumina). When aryl aldehydes, malononitrile or ethyl cyanoacetate and 1-naphthol react in the presence of FK-Alumina in refluxing ethanol for 5–6 h, the 2-amino-4-aryl-4*H*-benzo[*h*]chromene derivatives were obtained in slightly high yields (72–90%). When 1,5-naphthalenediol was used instead of 1-naphthol, naphthol[1,2-b;6,5-b']dipyrans derivatives were isolated in good yields (83–94%) (Scheme 85).

Basic alumina was proposed by Maggi *et al.*[404] as a catalyst in the synthesis of substituted 2-amino-2-chromenes by coupling benzaldehyde, malononitrile and α-naphthol using water as a solvent. Basic alumina exhibited better activity and selectivity to 2-amino-2-chromenes than Montmorillonite KSF, hydrotalcite and silica gel. In all cases mixtures of Knoevenagel adduct (KA) and the desired product were obtained (Table 24).

Excellent yields (83–98%) and selectivity to 2-aminochromene derivatives (85–99%) were obtained on basic γ-alumina when different aldehydes, malononitrile and α-naphthol, were reacted in water for 3 h. In addition, the reaction showed high regioselectivity affording only one of the two possible isomers that can be formed. The catalyst could be reused four times giving the same yield and excellent selectivity to chromene.

Nanosized magnesium oxide has been reported[405] as an efficient catalyst for the three component condensation of aldehyde, malononitrile and α-naphthol in methanol, water or PEG-water as the reaction medium. Thus, when a mixture of equimolar amounts of benzaldehyde, malononitrile and α-naphthol, in methanol or water was refluxed for 1 h in the presence of MgO, the corresponding 2-aminochromene was obtained with yields of 96% and 86% respectively. Meanwhile, using PEG–water (1 : 1) at room temperature, a 96% yield of aminochromene was obtained after 15 min reaction time. The catalytic activity of the nanosized MgO particles (100–200 nm) was superior to those exhibited by a commercially available MgO sample. The nanosized magnesium oxide was employed for the synthesis of a diverse set of 2-aminochromenes achieving yields of 70–98% within 15–90 min using PEG–water as a solvent. After the reaction the catalyst was reused in subsequent reactions with consistent activity.

More recently, Mg/Al hydrotalcite was found to be a highly effective catalyst for the synthesis of 2-aminochromenes *via* a multicomponent reaction in a dry state under single-mode microwave irradiation.[406] Thus, under optimal conditions (molar ratio aromatic aldehyde:malononitrile: α-naphthol 1 : 1 : 1 mmol, HT (Mg/Al = 3) at 140 °C), it is possible to obtain 2-aminochromenes in good yields (71–90%) in an interval of 5–34 min reaction time. When the reaction was carried out on calcined hydrotalcite the catalytic activity was lower than that the corresponding uncalcinated HT. On calcination at a high temperature the hydroxyl groups in the brucite layers are eliminated as water. Thus, the Brønsted basicity decreases, meanwhile the Lewis basicity increases, which indicates that Brønsted basicity is required for this reaction. The authors found that the catalyst was reusable however there was a reduction in the yield of the product after reuse (Table 25).

4. Conclusions and catalytic opportunities

A large number of MCRs have been presented all of which show quite good conversion and selectivity for preparing products of industrial interest. It was seen that most of the work has been performed using homogeneous catalysts ranging from Brønsted and Lewis acids to base catalyzed reactions. Mineral and organic Brønsted acids and basic amines were the most commonly used homogeneous catalysts together with organic and inorganic transition metal salts. The number of catalytic studies with solid catalysts is still limited and less sophisticated materials have been used. For instance, mineral acids impregnated on inorganic porous carriers were extensively used. With these catalysts one should expect acid leaching to occur. Then, while they can be useful for laboratory preparative uses they will be limited for industrial use. This is more so if sustainable processes are going to be implemented.

Supported heteropolyacids on silica and supported Lewis acids such as $AlCl_3$ and $SbCl_5$ on alumina give excellent results for various acid catalyzed MCRs. However, polar reactants and solvents will make these catalysts leach, while the presence of even small amounts of water could hydrolyze the supported Lewis acids. True heterogeneous catalysts such as silica and activated silica, activated alumina, montmorillonites, zeolites and organic resins with sulfonic groups have also been used successfully for Biginelli type reactions, and synthesis of imidazole and quinazoline derivatives. Even hybrid materials where organic molecules with sulfonic groups are grafted on inorganic solids (amorphous and ordered silicas) show reasonable to good activities for Hantzsch type reactions. However, it should be considered that if catalyst deactivation occurs it will be difficult in many cases to regenerate the hybrid organic–inorganic material. Metal substituted zeolites and zeolites with exchanged metal cations in where unusual metal valences are stabilized (for instance Cu(I)-zeolite) are also excellent catalysts for the A^3 coupling of aldehydes, amines and alkynes.

In the case of basic and bifunctional metal-base solid catalysts such as MgO and mixed oxides of Al, Mg and transition metals derived from hydrotalcites good results for the synthesis of pyran

Table 25 Yield of 2-aminochromenes from benzaldehyde, malononitrile and 1-naphthol in the presence of different catalysts[a]

Catalyst	B:M:N	Time (h)	Solvent/*T* (°C)	Yield (%)	Ref.
KF–Al_2O_3(0.5 g)	5 : 5 : 5	5	EtOH/80	83	403
Al_2O_3(0.5 g)	0.01 : 0.01 : 0.01	3	H_2O/reflux	96	404
MgO(0.05 g)	2 : 2 : 2	1	H_2O/reflux	86	405
MgO(0.05 g)	2 : 2 : 2	0.25	H_2O:PEG/rt	96	405
Mg/Al HT[b]	1 : 1 : 1	0.12	MW/140	84	406
[Bmim]BF_4[c]	5 : 5 : 5	1	H_2O/reflux	81	407
[Bmim]OH[c]	5 : 5 : 5	0.16	H_2O/reflux	91	407

[a] B:M:N: mmol of benzaldehyde:malononitrile:1-naphthol. [b] 50 wt% respect naphthol. [c] 0.5 mmol.

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and aminochromene derivatives have been obtained. These catalysts are stable and regenerable.

New possibilities are open for the preparation of catalysts containing acid and basic sites, if possible, with controlled distance and orientation[408] that can work in homogeneous phase but which can be recycled, or integrated in solid catalysts.

In conclusion MCRs present clear advantages for process intensification, avoiding costly and energy consuming intermediate separation and purification steps, and there are open possibilities for the use of mono and bifunctional catalysts for achieving fully green processes.

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