catalysts

MDPI

Review

Recent Advances in Multicomponent Reactions Catalysed under Operationally Heterogeneous Conditions

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Abstract: Multicomponent reactions (MCRs) have been gaining significance and attention over the past decade because of their ability to furnish complex products by using readily available and simple starting materials while simultaneously eliminating the need to separate and purify any intermediates. More so, most of these products have been found to exhibit diverse biological activities. Another paradigm shift which has occurred contemporarily is the switch to heterogeneous catalysis, which results in additional benefits such as the reduction of waste and an increase in the safety of the process. More importantly, it allows the user to recover and reuse the catalyst for multiple runs. In summary, both methodologies adhere to the principles of green chemistry, a philosophy which needs to become overarchingly enshrined. The plethora of reactions and catalysts which have been developed gives hope that chemists are slowly changing their ideology. As a result, this review attempts to discuss multicomponent reactions catalysed by operationally heterogeneous catalysts in the past 10 years. In this review, a further distinction is made between the MCRs which lead to the formation of heterocycles and those which do not.

Keywords: multicomponent; operationally heterogeneous; reusable catalysts; environmentally benign; green chemistry; heterocyclic; acyclic

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1. Introduction

An obvious question which may immediately spring to mind when considering the vitality of catalysing multicomponent reactions under heterogeneous catalysis in synthetic organic chemistry is, "Why should one attempt multicomponent reactions? And why should the latter be performed under heterogeneous conditions instead of the classic homogeneous single-step reactions?". The answer to this is two-fold. First and foremost, heterogeneous reactions are environmentally benign. Nowadays, our planet is continuously giving red alerts to humanity due to the environmental negligence and harm exerted in the previous 100 years, hence it is high time that waste production in the chemical industry be controlled via the use of recyclable catalysts, amongst other methods. Secondly, the use of more than two reagents simultaneously in multicomponent reactions allows for the formation of products which can never be produced by the single-stage stepwise reactions carried out in the past. In view of the outlined points, this review aims to underline the importance of various multicomponent reactions that have been studied under operationally heterogeneous conditions and reported in the past 10 years.

Yet, before embarking on such a review, it is critical to outline that nowadays, the use of the terms homogeneous and heterogeneous is becoming problematic. One of the founding pillars of green chemistry centres on the use of catalytic instead of stoichiometric amounts of reagents, which speeds up chemical reactions, hence resulting in shorter reaction times and possibly also renders the reactions viable at lower temperatures [1]. From an environmental perspective, if the catalyst is recoverable and reusable it would be even

more benign and sustainable. In scientific diction, heterogeneous catalysts are those which can be recovered by filtration at the end of the reaction, whilst those which remain dissolved in the reaction mixture and cannot be filtered off nor reused are homogeneous [2].

The classical Ostwald definition of homogeneous and heterogeneous catalysts distinguishes between the two by stating that the former are those which are in the same phase as the reactants and the latter are those which are not [3]. Recent advances in catalytic systems and the development of metal clusters and nonclusters, nanoparticles, and nanocomposites, have evidenced that Ostwald's definition is imprecise, if not completely irrelevant. A nanoparticle is a particle which is in the nanometre size range of 1–100 nm. Although these particles exist in a different phase, they normally remain suspended in solutions and are usually stabilized by the addition of appropriate surfactants [4]. During the course of a reaction, nanoparticles may aggregate with time to form nanoclusters and herein lies the fulcrum of the problem. When, and until what size, is a nanoparticle considered to be in the same phase as the reactants?

At this juncture, it is therefore crucial to distinguish whether a catalyst may be operationally or mechanistically homogeneous or heterogeneous. A catalyst may be described as operationally heterogeneous or homogeneous depending on whether the catalytic activity gets retained on a filter during a hot filtration test or ends up in the filtrate. An operationally heterogeneous catalyst is therefore one which should be able to be retrieved at the end of the reaction, rendering it environmentally friendly. However, in a supposedly homogeneously catalysed reaction by, for example, a metal complex, the actual active catalyst could be a nanoparticle metal cluster which forms by the transformation of the dissolved catalyst. In such a scenario, the reaction would be mechanistically heterogeneous but operationally homogeneous. Alternatively, in a heterogeneously catalysed reaction by a metal, a small fraction of the metal could be, in truth, dissolving in the reaction mixture, catalysing the reaction and then precipitating out once more onto the solid catalyst.

Keeping in mind all of the above, it is second-to-none to come up with another definition that it is clear and unambiguous. For greater clarity, Crabtree came up with two better terms that can be used to diversify catalysts, which are: homotopic and heterotopic [4]. The former term describes catalysts which have only one type of active site to catalyse a reaction (such as a metal–ligand complex), whilst a heterotopic one would be that which has several identical sites (Figure 1). A prime example would be palladium–charcoal, which is used to catalyse the hydrogenation of alkenes.

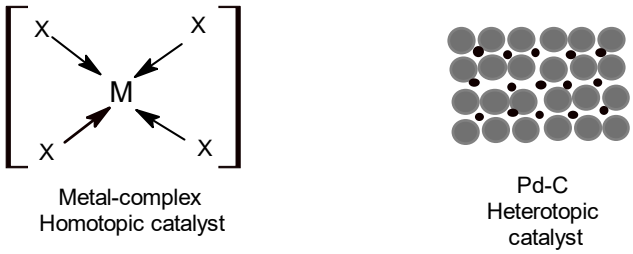


Figure 1. Homotopic catalysts have one active site, whilst heterotopic catalysts have several identical sites.

Keeping this definition in mind, the following discussion will revolve around the use of both types of catalysts which can still be ultimately recovered at the end of the reaction and reused, irrespective of the intrinsic mechanistic pathways. That is to say that, whenever the term heterogeneous is used, it could be that the catalyst is operationally heterogeneous but mechanistically either homo- or heterotopic.

This review will focus on environmentally benign catalysis in multicomponent reactions which have become crucial tools in synthetic chemistry, and which have generated interest due to their economic and ecological advantages [5]. Multicomponent reactions

are one-pot processes in which three or more diverse reactants combine together simultaneously or in a stepwise domino fashion [6]. Not all multicomponent reactions proceed in the same fashion: the pathways can be either divergent or convergent (Figure 2). During convergent synthesis, separate reactants combine together in independent reactions to form intermediates, which subsequently react and combine together to form the final product. Conversely, in divergent pathways, reactants add on one after the other.

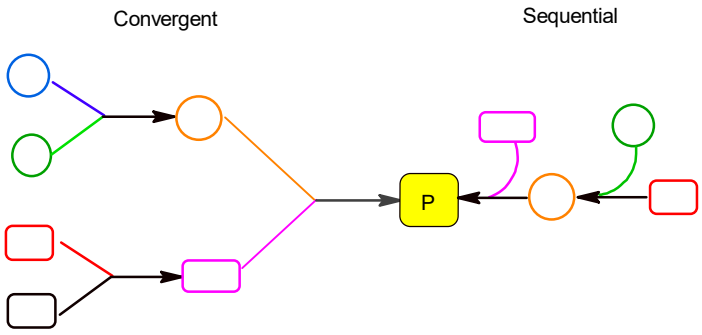


Figure 2. Convergent vs. divergent synthesis.

Multicomponent reactions (MCRs) exhibit a wide range of benefits over their classic sequential counterparts which involved reacting and purifying products individually in a sequential manner. First and foremost, in MCRs, purification is shortened and, hence, less solvent is required for purification purposes. In addition, multicomponent reactions are usually rapid and may be regio- and stereospecific [6]. Most often, the reactants of MCRs are simple, cheap, and readily available (in some cases they are even naturally sourced), making the process overall cheaper and more sustainable. Because most of the reactants will be incorporated into the final product, less waste is generated, resulting in what is known as an atom-economic reaction with a small *E* factor (E factor is a term introduced by Sheldon and is defined as the ratio of the mass of waste to the mass of product) [7].

$$EF = \frac{[\sum m\,(raw\ materials) + \sum m\,(reagents) - m\,(product)]}{m\,(product)}$$

In truth, the above is the simple *E factor* because it does not take water or solvents into account. The complete *E factor* considers the solvents and water that are used but not recovered at the end of the entire process, including in purification. From a biological perspective, the products of MCRs have a diverse and broad applicability. Amongst the plethora of reported uses, there are MCRs for which the products demonstrate antileishmanial [8], anti-inflammatory [9], anticancer [10], or antifibrotic activity, amongst others [11]. Moreover, MCR products also find uses as cloth pigments, food additives, flavourings, colourants [12], etc. This review aims to outline the importance of various multicomponent reactions studied under operationally heterogeneous conditions in the past 10 years. The following discussion will attempt to classify MCRs into two main categories: those leading to acyclic product formation and those which result in heterocyclic products. In relation to this, the review is further subdivided on the basis of the type of heterocycles and the state-of-the-art in their synthesis. Although a similar review for multicomponent reactions does exist, it is more focused on the mechanistic aspects and not so much on whether or not they are heterogeneously catalysed, and refer to a shorter timeframe [13].

2. Heterocyclic Compound Synthesis

Heterocycles are crucial in everyday life due to their diversity and uses. In biological reactions, such as those taking place in human cells, molecules are usually required to attach to chemoreceptors in cell membranes in order to elicit harmful/beneficial responses

or trigger a sequence of reactions. These chemoreceptors have specific shapes and polarities that only allow for pairings with specific compounds, such as heterocycles, which, owing to their cyclic nature and lack of rotational activity, have fixed shapes and can bind effectively.

2.1. Heterocycles Containing 1-Heteroatom

2.1.1. Pyrroles

The pyrrole moiety is the main component of heme and chlorophyll, which are essential in two interlinked living organisms: heme is the oxygen-absorbing pigment in red blood cells in humans and chlorophyll is the green pigment in plants that allows for photosynthesis to take place. Undoubtedly, pyrrole derivatives constitute an important class of compounds which have other uses and have been synthesized in a multitude of ways, one of which involves the four-component reaction of an amine, an aldehyde, nitromethane, and a β-dicarbonyl compound. Li et al. catalysed this reaction efficiently using a molybdenum complex supported on magnetic nanoparticles of cobalt ferrite ($CoFe_2O_4$) in the presence of excess nitromethane at 90 °C (Figure 3) [14]. Various aromatic and some aliphatic amines were used, with yields mainly ranging 70–90% in 4–8 h (with two exceptions in a broad substrate range of 43 products). Positively, the catalyst could be easily recovered and reused for up to five consecutive runs with no loss of activity.

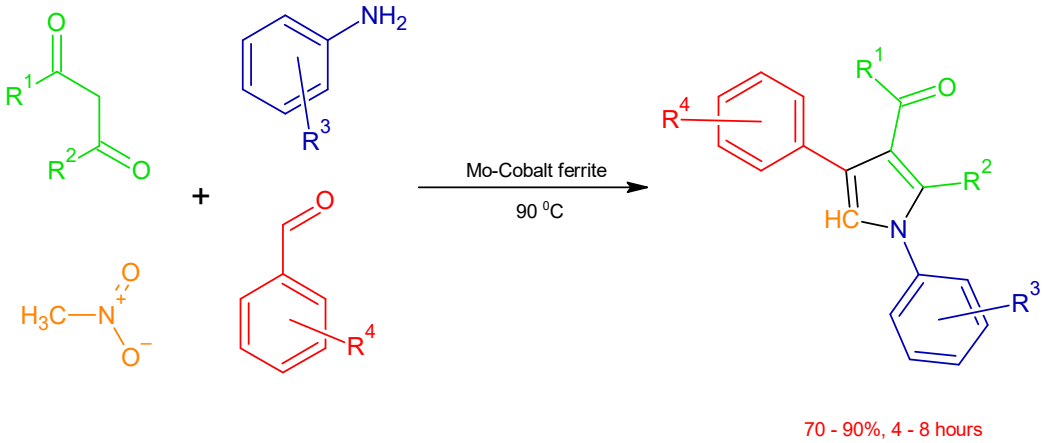


Figure 3. Pyrrole synthesis—four-component synthesis involving nitroalkanes, aldehydes, 1,3-dicarbonyl compounds, and primary amines.

The reaction was also mediated by graphite in a study by Nandeesh et al., which had a smaller substrate scope (16 products) in reactions taking 4–6 h to complete, with yields of 60–88% [15]. Nitromethane was once more used in excess to serve simultaneously as both a reactant and a solvent.

2.1.2. Furans

The furan ring is quintessential in nature and is a structural motif in terpenes and alkaloids that elicits medicinal and agricultural activities [16]. Furan derivatives have been synthesized in various ways, such as by the 3-component reaction (3CR) of an aldehyde, an amine, and a dialkyl acetylene dicarboxylate using tin(II) oxide nanoparticles in ethanol solvent at room temperature (Figure 4) [17].

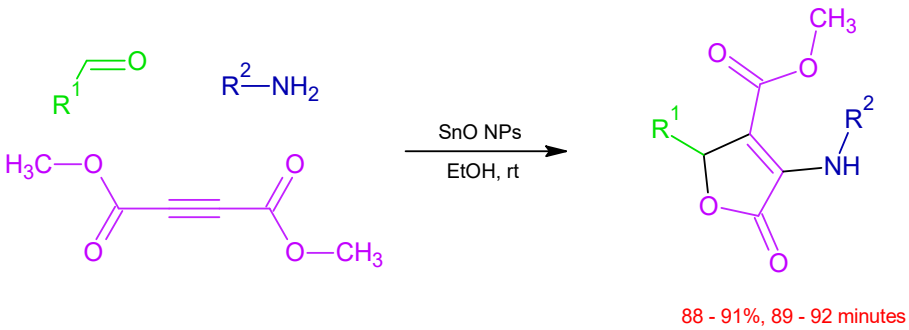


Figure 4. Furan synthesis using an aldehyde, an amine, and a dialkyl acetylene dicarboxylate.

2.1.3. Pyridines

Even if the Hantzsch synthesis was developed over 100 years ago by Arthur Hantzsch, nowadays, the reaction is still being developed as it leads to the formation of 1,4-dihydropyridines (1,4-DHPs), which may exhibit antihypertensive and antianginal activity by blocking heart calcium channels [18,19].

One of the latest studies of this reaction was carried out by Rahman et al., who utilized an iron–silica nanocomplex to catalyse the combination of ethyl acetoacetate, various aldehydes, and ammonium acetate in ethanol under reflux conditions (Figure 5) [20].

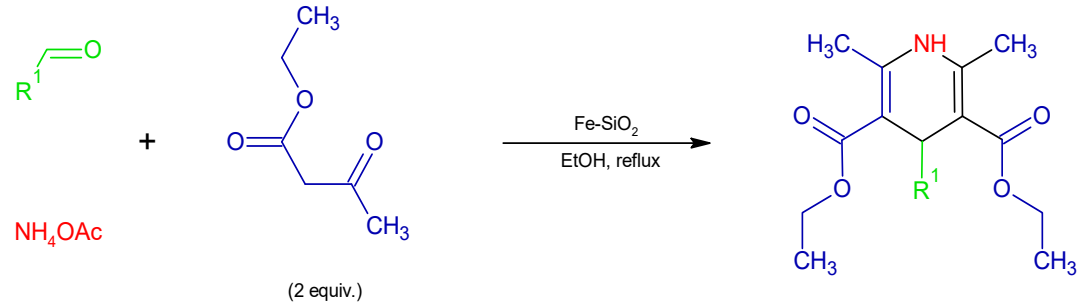


Figure 5. Hantzsch synthesis between aldehydes, ammonium acetate, and ethyl acetoacetate to yield 1,4-DHPs.

Sulphated tin oxide (STO) was established as an alternative catalyst for the Hantzsch reaction, involving acetoacetanilide as the β-dicarbonyl compound (Figure 6). Yields ranged 90–94% when the reactions were performed at 80 °C in acetonitrile solvent for 2.5 h. Positively, the catalyst could be reused for up to five cycles with a three percent reduction in yield between the first and fifth trial [21].

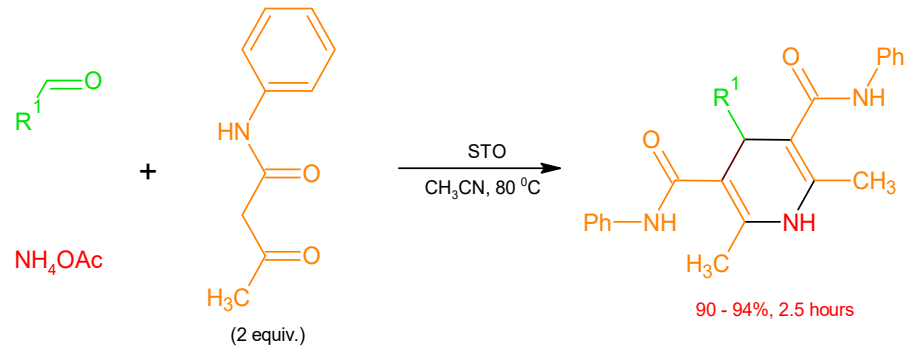


Figure 6. 1,4-DHPs obtained by the reaction of aldehydes, ammonium acetate, and acetoacetanilide using sulphated tin(IV) oxide (STO).

Although 1,4-DHPs are the usually reported products of the Hantzsch synthesis, the 1,2-isomers can also be synthesized, as was successfully communicated by Bosica et al. In this synthetic study (Figure 7) [22], phosphotungstic acid (PW) was heterogenized on alumina before utilising it at room temperature to result in 1,2-DHPs yields ranging between 62 and 94%, obtained in 3.5–6 h. The catalyst could be reused for up to eight consecutive cycles with very minor loss of activity.

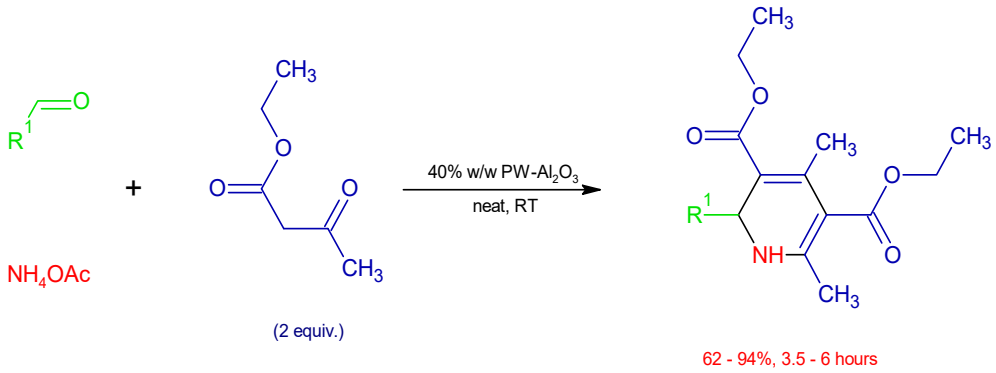


Figure 7. 1,2-DHP synthesis using phosphotungstic acid (PW) supported on alumina at room temperature in neat conditions.

Instead of DHPs, there are also various studies which have managed to synthesize aromatized pyridines. A case in point, Khalifeh et al. developed recyclable copper nanoparticles supported on activated charcoal in order to form 2-amino-3-cyanopyridine derivatives under reflux conditions in the presence of air in acetonitrile solvent (Figure 8) [23]. Yields varied between 71 and 94% after stirring for 6–8 h. Impressively, the catalyst could be recycled for up to eight consecutive runs (six percent overall drop in yield).

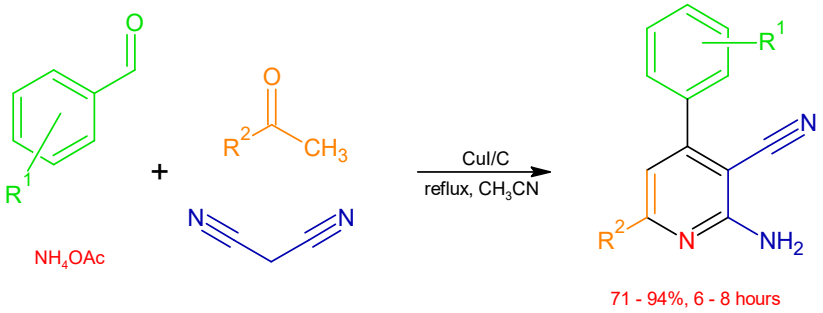


Figure 8. 2-Amino-3-cyanopyridine derivatives via the reaction of aldehydes, ketones, ammonium acetate, and malononitrile using CuI/C as catalyst.

In truth, the above reaction has been studied to great lengths, and amongst the catalysts that have been tried, there are also those listed in Table 1. In some instances, cyclic aliphatic ketones such as cyclohexanone have been also employed.

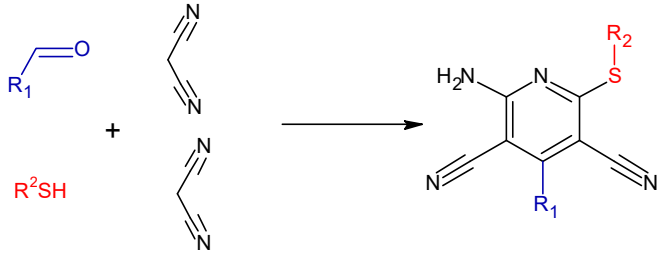
Table 1. Synthesis of 2-amino-3-cyanopyridines.

Author (Date) Reference	Catalyst and Conditions	Yields, Recycling Runs
Heravi et al. (2015) [24]	Magnetite nanoparticles (1 mg) 80 °C Neat conditions 2–3 h	Yields: 82–90%, 7 examples Recycling runs: 4 (8% decrease in yield)
Yahyazadeh et al. (2018) [25]	Aminopropylated-salicylaldehyde-copper(II)-zirconia-coated magnetite 80 °C Neat conditions	Yields: 85–96%, 17 examples Recycling runs: 5 (5% decrease in yield)

Afradi et al. (2017) [26]	Niacin–magnetite MW 7–10 min	Yields: 73–95%, 15 examples Recycling runs: 6 (7% decrease in yield)
Challa et al. (2021) [27]	Amberlyst 15 Ultrasound RT Acetonitrile solvent 10 min	Yields: 75–92%, 17 examples Recycling runs: N/A
Achagar et al. (2022) [28]	$Na_2CaP_2O_7$ nanoparticles Neat 30 min	Yields: 84–95%, 13 examples Recycling runs: 3 (3% decrease in yield)

Similar in structure to the just-mentioned pyridines, 2-amino-3,5-dicarbonitrile-6-sulfanylpyridines have also been explored in terms of their synthesis and biological applications. As summarized in Table 2, nano-tin(IV) oxide, nano-titania, natural dolomitic limestone, borax, and a magnetite-supported Schiff base have all been used.

Table 2. Catalysts employed in the synthesis of 2-amino-3,5-dicarbonitrile-6-sulfanylpyridines.



Synthesis of 2-amino-3,5-dicarbonitrile-6-sulfanylpyridines

Author (Date) Reference	Catalyst and Conditions	Reaction times, Yields, Recycling Runs
Safaei et al. (2014) [29]	6 mol% tin(IV) oxide nanoparticles Ethanol solvent 60 °C	54–142 min, 79–92% Catalyst recycling: 5 runs (7% drop in yield)
Molla et al. (2014) [30]	10 mol% Borax Ethanol solvent Reflux	30–120 min, 75–92%, 19 examples Catalyst recycling: 5 runs (no specific data given)
Kumari et al. (2016) [31]	5 mol% graphene oxide/titania Water solvent RT	60–120 min, 79–89%, 9 examples Catalyst recycling: 7 runs (22% drop in yield)
Godugu et al. (2020) [32]	Dolomitic limestone (5.0 wt.%) 50% Ethanol/water 45–50 °C Ultrasound radiation	30–45 min, 90–98%, 18 examples No recycling data specified
Ebrahimiasl et al. (2019) [33]	Magnetite@Cobalt(II) Schiff base 100 °C Neat conditions	11–20 min, 90–98%, 8 examples Recycling runs: 5 (3% drop in yield)

2.1.4. Pyridinones

Quite similar in structure are the class of compounds, pyridinones, which have been synthesized via an MCR employing Meldrum's acid, during which decarboxylation and acetone loss take place (Figure 9). Interestingly, these compounds have been found to have antiurease activity (ureases are enzymes found ubiquitously in nature and are implicated in conditions such as peptic ulceration, stomach cancer, formation of urinary stones, etc.) [34]. The recoverable catalyst, silica-propylsulfonic acid, was used in neat conditions at 140 °C to obtain the products in 25–60 min in excellent yields (78–90%) [35].

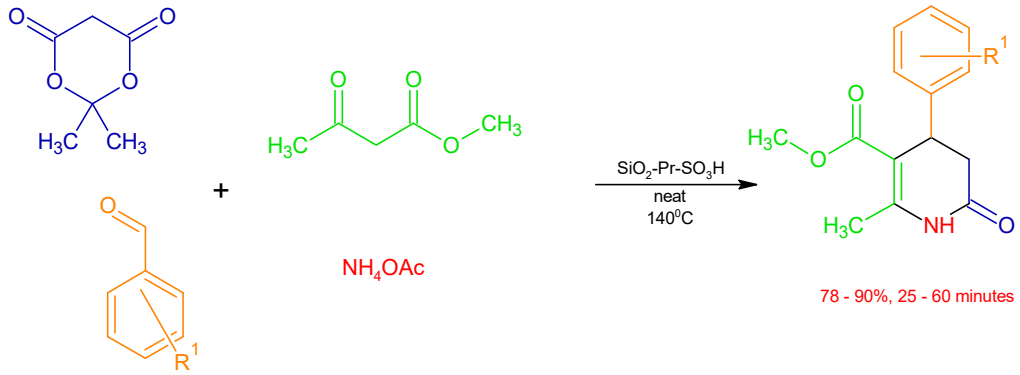


Figure 9. Pyridinone synthesis via the combination of Meldrum's acid, aryl aldehydes, and methyl acetoacetate.

2.1.5. Coumarins

The spectrum of applications of coumarins in everyday life is exceptionally broad and their uses vary from anticlotting agents to dyes in laser technology, anti-HIV compounds, and fluorescent indicators [36]. A common approach to their synthesis involves the combination of 4-hydroxycoumarin, carbonyl compounds, and active methylenes. Khodabakhsi et al. synthesized titanium dioxide nanowires to produce novel pyranocoumarins, also known as pyrano [2,3-*c*] chromenes, in ethanol/water solvent under reflux conditions (Figure 10) [37]. Yields were excellent and reaction times were relatively short.

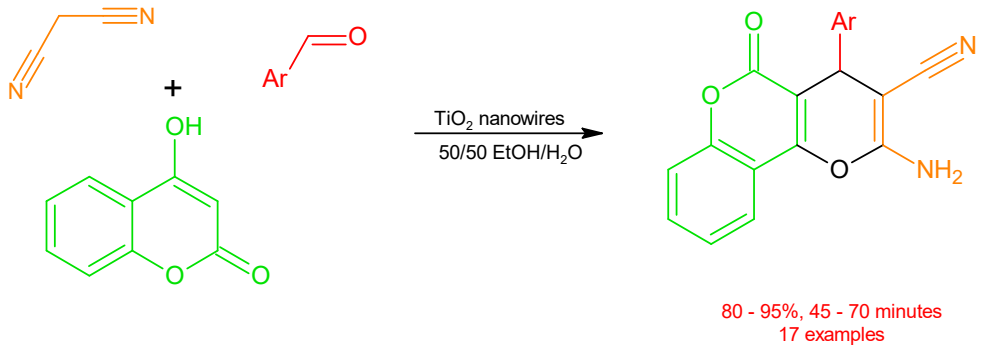


Figure 10. Pyrano [2,3-*c*] coumarin derivative synthesis using titania nanowires in ethanol/water solvent under reflux conditions.

A similar approach was taken by Kerru et al., whose zinc oxide catalyst, supported on fluorapatite, yielded furan-coumarin derivatives (Figure 11) at room temperature in ethanol solvent in less than 20 min [38].

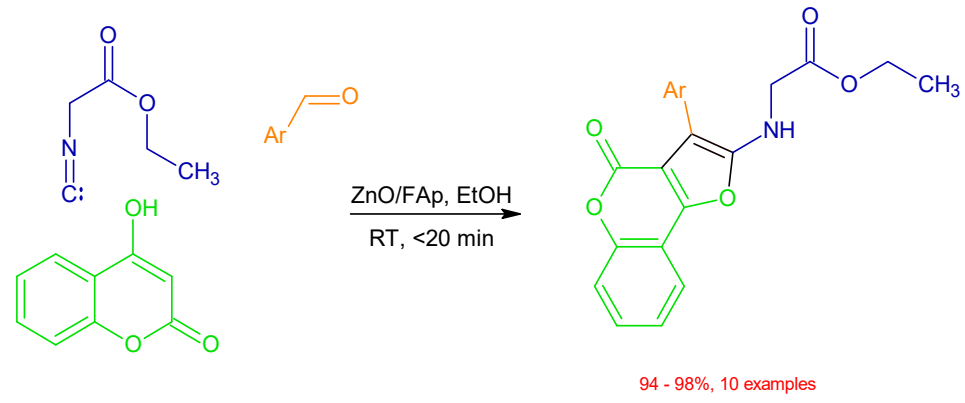


Figure 11. Furo [3,2-*c*]coumarin derivatives synthesized using zinc oxide supported on fluorapatite.

2.1.6. Chromenes

2-Amino-4*H*-chromenes, i.e., derivatives of benzopyran, possess a wide range of biological properties, chief amongst them being their diuretic and anticoagulant activities, as well as being cognitive enhancers for the treatment of neurodegenerative diseases such as Parkinson's and Alzheimer's [39]. Amongst the several methods developed for their synthesis, various research papers have investigated the reaction between aldehydes, an activated methylene compound, and a nucleophile such as a naphthol or a phenol (Figure 12). One such study employed a piperazine-functionalized nickel–ferrite nanocatalyst in a neat reaction at 110 °C to obtain yields ranging between 81 and 95% in 40–60 min. In addition to 2-naphthol, other nucleophiles were tried, including 1-naphthol and 3,5-dihydroxytoluene, with yields for the former being in the range of 78–87% and for the latter in the range of 80–85% [40].

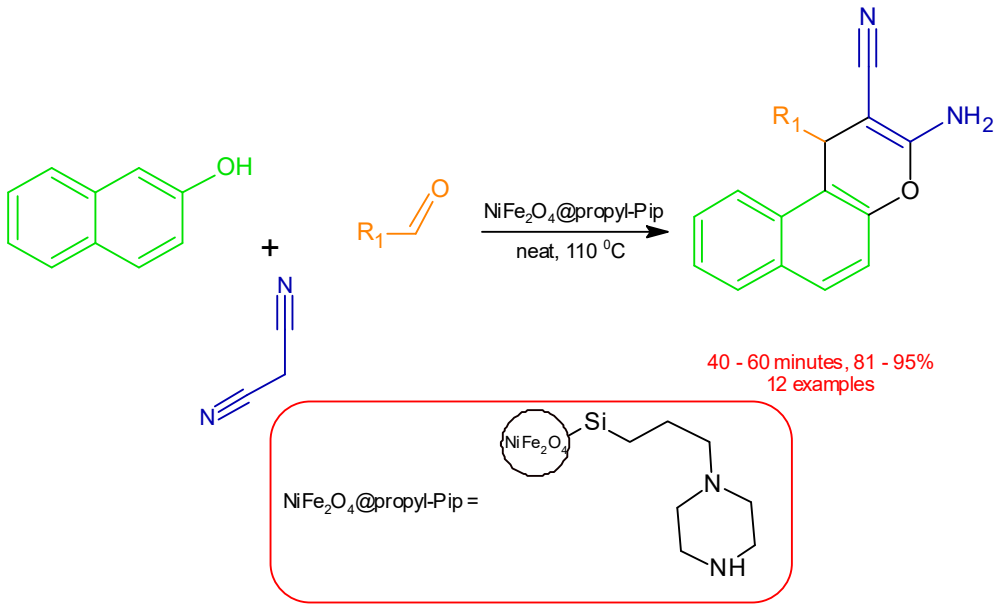


Figure 12. Chromene synthesis via the combination of 2-naphthol, an aldehyde, and malononitrile.

A noteworthy catalyst that was developed for the same reaction was prolinamide-functionalized polyacrylonitrile. The reactions involving 2-naphthol gave excellent yields (91–98%) at a lower temperature (80 °C, 1 h) and in water as solvent [41].

Other recent advances in this synthetic reaction are summarized in Table 3.

Table 3. Recent heterogeneous catalysts employed in the synthesis of chromenes.

Author (Date) Reference	Catalyst and Conditions	Product yields, Catalyst Recycling Runs
Banerjee et al. (2015) [42]	10 mol% tetragonal zirconium(IV) oxide nanoparticles Water solvent 80 °C 40–55 min	88–94%, 9 examples Catalyst reused for 10 runs (92 → 80%)
Rama et al. (2019) [43]	20 mol% nickel(II) oxide Water solvent 50 °C Ball-milled for 30–60 min	76–99%, 10 examples Catalyst reused for 3 runs (98 → 93%)
Sobhani et al. (2020) [44]	1 mol% piperazine–graphene oxide 50% aqueous ethanol solvent 50 °C 5–150 min	70–98%, 33 examples Catalyst reused for 6 runs (90 → 85%)
Chahkamali et al. (2022) [45]	5 mol% (Γ-Fe_2O_3-Im-Py)$_2WO_4$ 90 °C Neat 5.5–19 h	45–91% (17 examples) Catalyst reused for 5 runs (91 → 85%)

2.1.7. Xanthenes

Produced via a similar mechanism to chromenes, symmetrical xanthene derivatives are synthesized by the reaction of 2-naphthol or a β-dicarbonyl compound with aldehydes (Figure 13). Bansal et al. studied this reaction using copper sulphide quantum dots to obtain the products in excellent yields (88–95%) in a maximum of 15 min at 80 °C in neat conditions. Positively, the catalyst could be reused for up to five cycles [46].

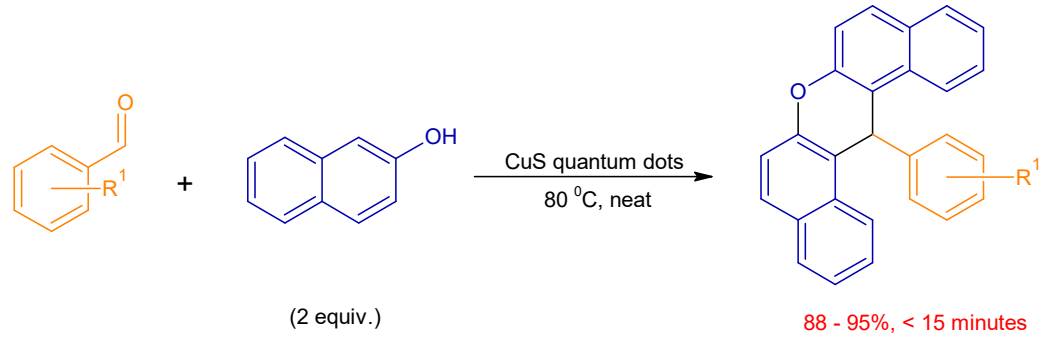


Figure 13. Xanthene synthesis using two equivalents of 2-naphthol and an aldehyde.

A high temperature was required when the same reaction scope was studied using graphene oxide supported on copper ferrite. In addition, excellent yields were obtained (84–96%) in a maximum of 15 min [47].

2.2. Heterocycles Containing 2 Heteroatoms

2.2.1. Pyrazoles

Pyrazole is a 5-membered heterocyclic aromatic compound that is present in several notable drugs, principal amongst them being celecoxib (Celebrex®, a nonsteroidal anti-inflammatory drug–NSAID, Figure 14) [48].

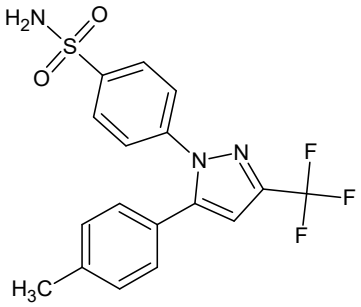


Figure 14. The structure of celecoxib, a pyrazole-containing NSAID drug.

Meanwhile, pyranopyrazoles are molecules with a pyran ring fused to a pyrazole ring. They exhibit a wide range of activities because they can act as Chk1 kinase inhibitors as well as acting as anticancer and antimicrobial agents [49,50]. One of the contemporary methodologies to synthesize dihydropyrano [2,3-*c*]pyrazole derivatives involves a 4CR between a β-dicarbonyl, a malononitrile, an aldehyde, and a hydrazine hydrate (Figure 15). A case in point is silver–titania nanofilms being utilized in ethanol/water solvent at 70 °C to collect products in a maximum of 55 min at yields of 75–93% [51].

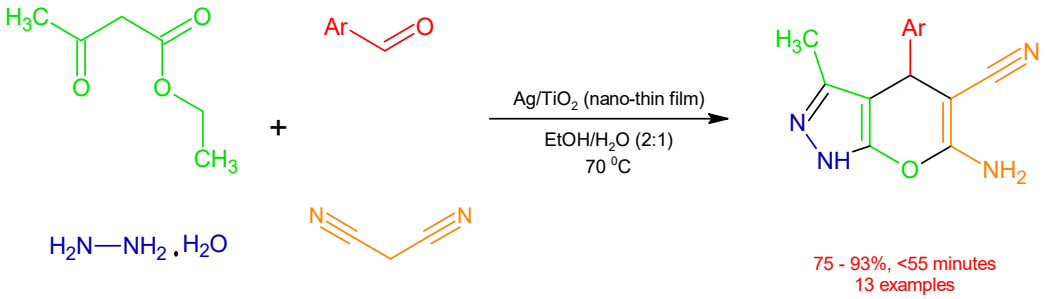


Figure 15. Pyranopyrazole synthesis using a β-dicarbonyl compound, an aldehyde, a malononitrile, and a hydrazine hydrate.

An alternative method requires the combination of 3-methyl-1-phenyl-2-pyrazoline-5-one, aldehydes, and malononitrile (Figure 16). A recently developed catalyst, cobalt Schiff base complex immobilized on magnetic iron oxide nanoparticles, gave impressive results in very short reaction times. Moreover, the catalyst could be reused for up to eight runs with the yield decreasing from 95 to 88% for the chosen reaction [52].

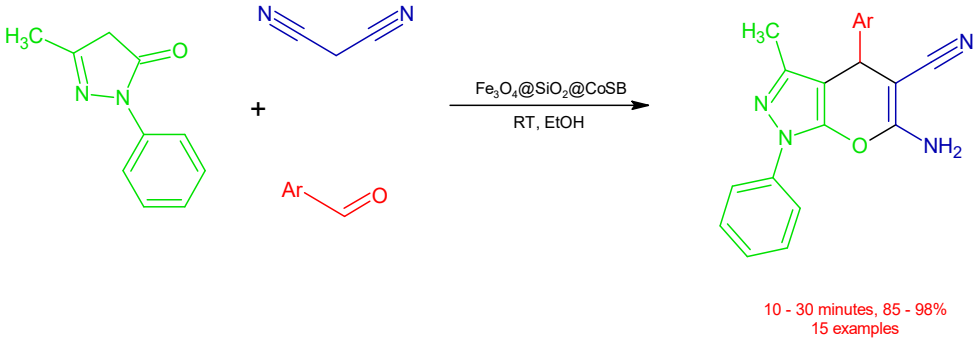


Figure 16. Pyranopyrazole synthesis via 3-methyl-1-phenyl-2-pyrazoline-5-one, aldehydes, and malononitrile.

2.2.2. Imidazoles

Isomeric with pyrazoles, imidazoles are heterocycles that have a 1,3-nitrogen arrangement instead of 1,2. The imidazole moiety is present in histidine (an α-amino acid), histamine (a hormone, Figure 17), and a sedative (midazolam), apart from other natural products and drugs [53].

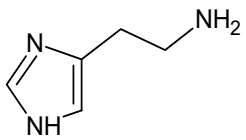


Figure 17. Histamine, an imidazole-containing hormone that regulates action in the gut and acts as a neurotransmitter for nerve impulses in the brain.

A novel catalyst, composed of iron oxide and copper(I) oxide nanoparticles suspended on guarana, was used successfully for the reaction of aldehydes with benzyl to produce imidazole derivatives, specifically, 2,4,5-triaryl-1*H*-imidazoles (Figure 18). It is pertinent to note that the reaction was carried out under ultrasonication, leading to very short reaction times (20 min) and excellent yields (75–97%) [54].

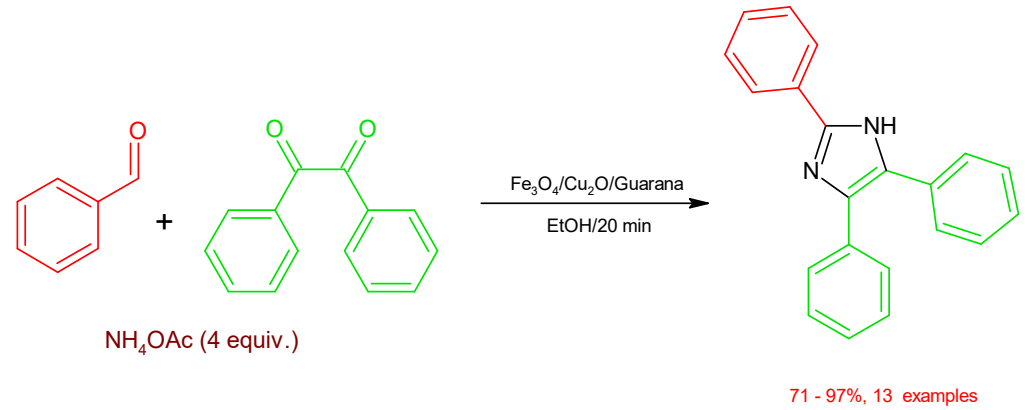


Figure 18. Copper(I) oxide–magnetite suspended on guarana nanocatalyst used to catalyse the formation of 2,4,5-triaryl-1*H*-imidazoles.

2.2.3. Thiazolines

Thiazolines (also known as dihydrothiazoles), are penta-membered heterocyclic compounds containing both a sulphur and a nitrogen atom in their ring. A notable life example of a molecule consisting of such rings is luciferin, the compound which allows for the emission of light in fireflies. Vitamin B1 (Figure 19) has been reported to be an efficient catalyst in the formation of trisubstituted 1,3-thiazoles after having been supported on magnetite in a research study by Shaterian et al. The reaction entailed a one-pot combination of arylglyoxals monohydrate, cyclic 1,3-dicarbonyls, and thiobenzamides in aqueous conditions at 80 °C (Figure 20) [55].

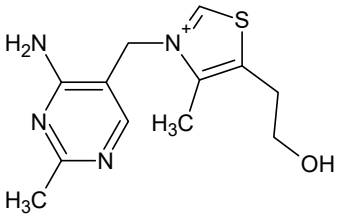


Figure 19. Vitamin B1, also known as thiamine.

Yields were superb (78–93%) and reactions took less than 45 min. Lastly, the catalyst could be easily removed by a magnet and reused for up to five times [55].

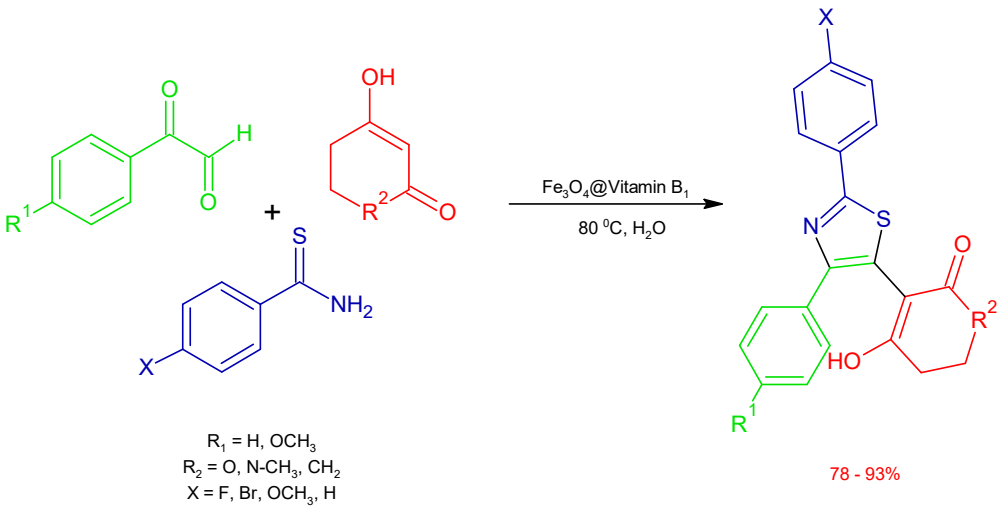


Figure 20. Synthesis of trisubstituted 1,3-thiazole derivatives.

In a related approach, a glycine–proline–glutamine tripeptide was supported on silica-encapsulated-γ-iron(III) oxide nanoparticles to act as a catalyst in aqueous conditions. Impressively, reaction times were even lower (maximum of 15 min) and yields were generally slightly better (91–98%). Even better, the catalyst was reused 10 times, with the yield dropping from 98 to 91% for the chosen model reaction [56].

2.2.4. Thiazolidinones

The ketone analogues of thiazoles are the thiazolidinones and these are synthesized in a completely different manner from the above. One method involves the Mannich-type attack of a thiol followed by amide formation. An approach by Kumar et al. involved the use of supported perchloric acid on silica for the reaction of various aromatic aldehydes and amines with thioglycolic acid at 100 °C (Figure 21). Impressively, the study encompassed 43 reactant combinations and all yields were within the range of 70–87%. Despite this, toluene, a nonenvironmentally benign solvent, was required [57].

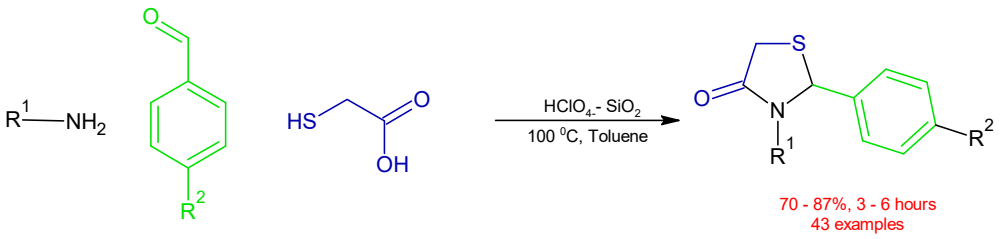


Figure 21. Synthesis of 4-thiazolidinones using perchloric acid–silica catalyst.

Recently, an alternative approach was taken in which, instead of using benzaldehyde, benzyl alcohol was utilised. The catalyst, cobalt–aluminium hydrotalcite, allowed for the air oxidation of the benzyl alcohol to the aldehyde before inducing the same reaction described above (Figure 22). All trials were concluded within 2 h in methanol solvent, with yields being in the range of 75–85%. It is well worth mentioning that in this study, unlike the previous one, no aliphatic amines were trialled and only 12 products were ultimately obtained [58].

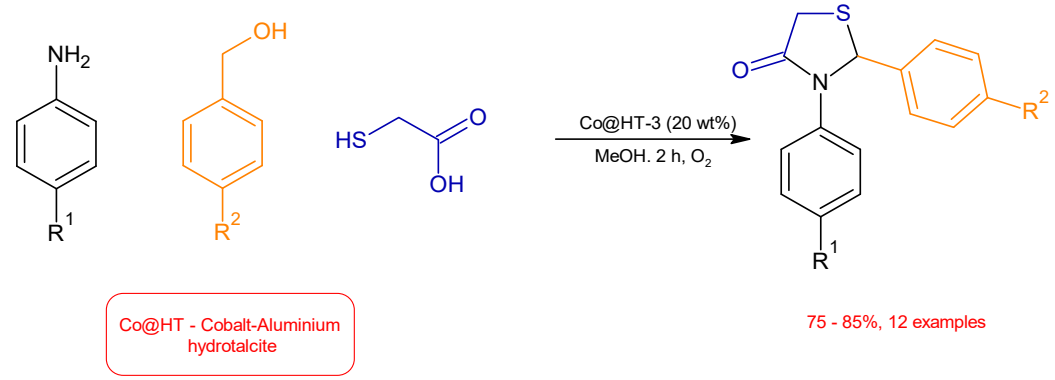


Figure 22. 4-Thiazolidinone derivative synthesis via benzyl alcohols.

2.2.5. Pyrimidines

The magnitude of the importance of pyrimidines in everyday life cannot be underlined enough. It suffices to say that pyrimidines are structural motifs found in nucleic acids such as thymine, cytosine, and uracil. In addition, there are several established drugs which have a pyrimidine nucleus, including 5-fluoruracil—an anticancer drug (Figure 23) [59,60].

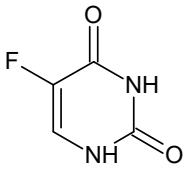


Figure 23. 5-fluorouracil—an anticancer drug usually used to treat colon tumours.

In a novel method by Nimkar et al., guanidine hydrochloride, aldehydes, and acetophenone (Figure 24) were reacted in the presence of caesium hydroxide supported on γ-alumina after mixing for 1 h at room temperature and then refluxing for 4 h. Ethanol solvent was used, and yields varied from 72 to 80% [59].

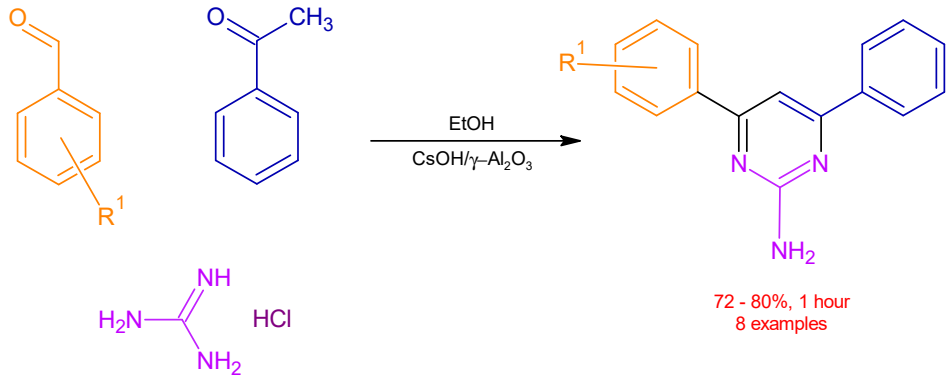


Figure 24. Synthesis of pyrimidines from aldehydes, acetophenone, and guanidine hydrochloride.

2.2.6. Pyrimidinones

Discovered in approximately the same period as the Hantzsch synthesis, the Biginelli reaction provides 3,4-dihydropyrimidin-2-(1*H*)-ones (Figure 25). The latter have been investigated as potential Adenosine A2b receptor antagonists, ergo, they can be potentially used for the treatment of diabetes, asthma, and other inflammations [61].

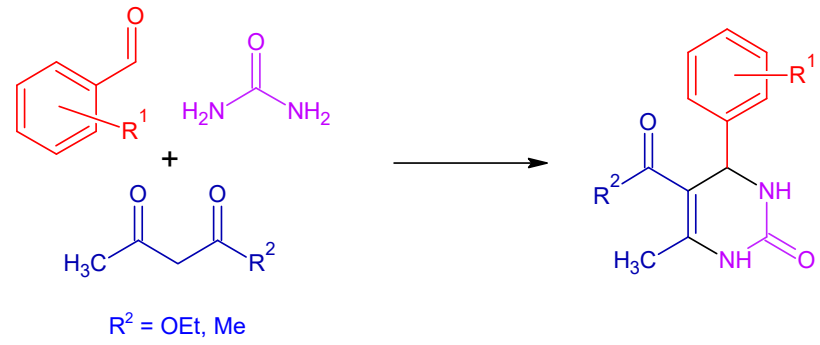


Figure 25. Biginelli reaction between an aldehyde, urea, and a β-dicarbonyl compound.

Amongst the most recent catalysts employed for the reaction, those listed in the Table 4. are heterogeneous and recoverable in nature and gave good to excellent yields.

Table 4. Recent catalysts employed in the Biginelli reaction.

Author (Date) Reference	Catalyst and Conditions	Reaction times, Yields, Recycling Runs
Patel et al. (2017) [62]	13 mol% PANI-$FeCl_3$ Acetonitrile solvent Reflux	24 h, 61–90%, 19 examples No recycling runs specified
Alonso et al. (2020) [63]	5 mol% Nb_2O_5 Neat	38–70 min, 60–94%, 9 examples Recycling runs: 4 (3% yield drop)

	130 °C	
Ali et al. (2021) [64]	Pumice stone (0.4 g) Neat Heat (Temperature not specified)	2–3 min, 91–97%, 18 examples No recycling runs specified
Bosica et al. (2021) [65]	Silicotungstic acid on Amberlyst 15 (40% w/w) (0.05 g per mmol) Neat 92 °C	4.5–23 h, 37–86%, 17 examples Recycling runs: 5 (12% yield drop)

Ketones have also been explored in the synthesis of pyrimidinones, a version which is often described as being Biginelli-like. In fact, they are synthesized by the reaction between aldehydes, acetophenones, and urea (Figure 26).

Because most contemporary synthetic studies are looking into the possibility of using nanomaterials as catalysts, Safari et al. utilised titania–multiwalled carbon nanotube composites to drive the reactions [66]. Yields were excellent (80–98%) and reaction times were not longer than 35 min. Positively, the catalyst could be reused for five cycles with only a two percent drop in activity.

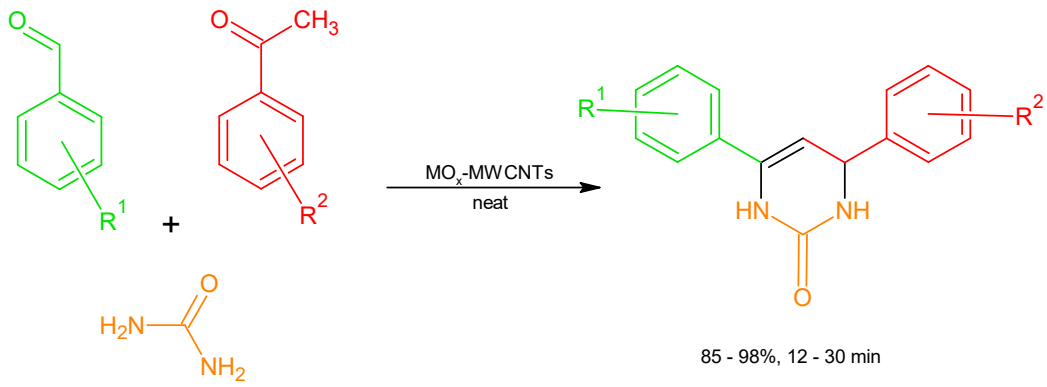


Figure 26. Synthesis of pyrimidinones via a Biginelli-like reaction of aldehydes, acetophenone, and urea.

2.3. Fused Heterocycles

2.3.1. Indolizine

Indolizines are *N*-fused heterocycles with a significant level of pharmacological relevance owing to their antimicrobial, antileishmanial, antihistaminic, antitubercular, and herbicidal activity [67]. One simple method which can be employed to synthesize them involves the A^3 coupling–cyclization tandem reaction of an alkyne, an amine, and 2-pyridinecarboxaldehyde (Figure 27**)**. In fact, copper(I) iodide, supported on glucose-derived and hydrothermally obtained carbon spheres, was used as a catalyst in ethylene glycol or in neat conditions at 60 °C to obtain a wide range of indolizine derivatives (yields: 75–95%) [68].

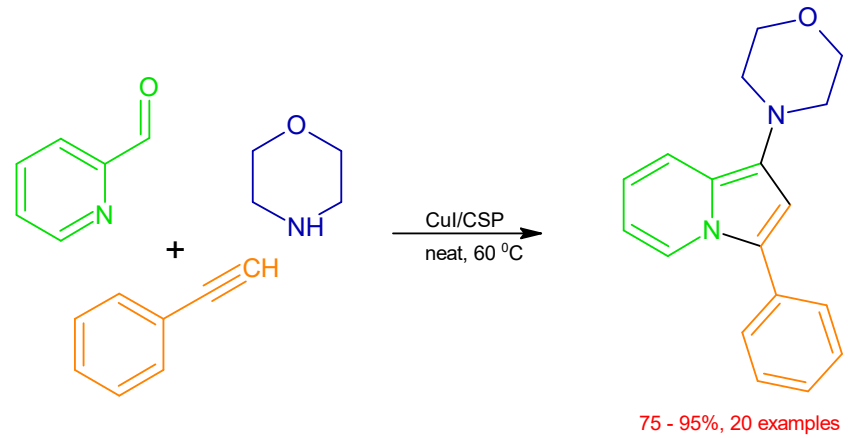


Figure 27. Synthesis of indolizine derivatives via A^3 coupling–cyclization tandem reaction of an alkyne, an amine, and 2-pyridinecarboxaldehyde.

The Lewis acid of choice was also copper iodide when the latter was supported on porous cross-linked poly(ethyleneamine)polysulfonamide gel to serve as a recyclable nanocatalyst. Most importantly, the reaction was also carried out in neat conditions and yields were very good (70–95% in 1–3 h). On the other hand, the number of conducted trials was only nine [69].

2.3.2. Benzofurans

Although quite diverse from the just-mentioned class of compounds, benzo[*b*]furans can be synthesized via a very similar route, replacing pyridine-2-carboxaldehyde with salicylaldehyde (Figure 28). Their pharmacological properties are just as diverse with, for instance, some exhibiting antitumour capabilities and others being used in cosmetic formulations [70,71]. Copper iodide nanoparticles were employed by Safaei-Ghomi et al. in the aforementioned reaction, which required water as solvent and an equivalent of potassium carbonate as a base. The reaction had to take place at 100 °C but was ready in 1–2 h to give products in excellent yields (82–95%) [72].

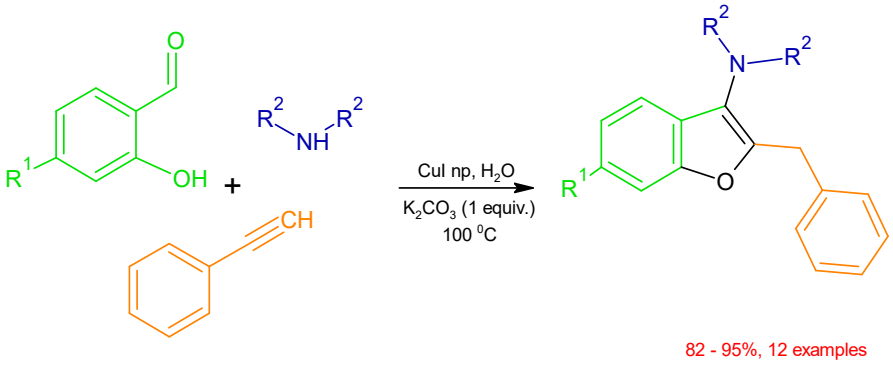


Figure 28. Benzo[*b*]furan synthesis via A^3 coupling of aldehydes, amines, and alkynes.

In a separate study by Purohit et al., it was remarkably established that, in the absence of potassium carbonate as base and using hierarchically porous copper(II) oxide (HS-CuO) as a heterogeneous catalyst, salicylaldehydes with electron-withdrawing groups gave benzo[*b*]furans, whereas salicylaldehyde itself gave dihydrobenzo[*b*]furans (Figure 29) [73].

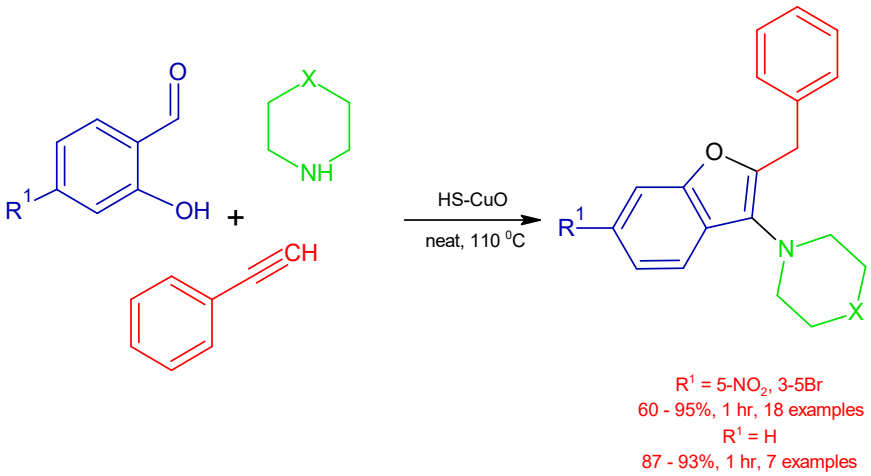


Figure 29. Selective synthesis of benzofurans and dihydrobenzofurans depending on the salicylaldehyde used.

2.3.3. Pyrimidobenzoimidazoles

Amongst recently synthesized antitumour agents are the pyrimido [1,2-*b*]benzoimidazoles, which have been found to exhibit activity against breast MCF7 cancer, and for some of which the compounds are equipotent to other drugs such as Tamoxifen® [74]. One of the diverse synthetic pathways that one can follow to obtain these compounds involves the combination of aldehydes, β-dicarbonyl compounds, and 2-aminobenzoimidazole (Figure 30). A novel catalyst composed of hafnium metal–organic frameworks drove the formation of several pyrimido [1,2-*b*]benzoimidazole derivatives to high yields (60–96%) in 3 h at 100 °C [75].

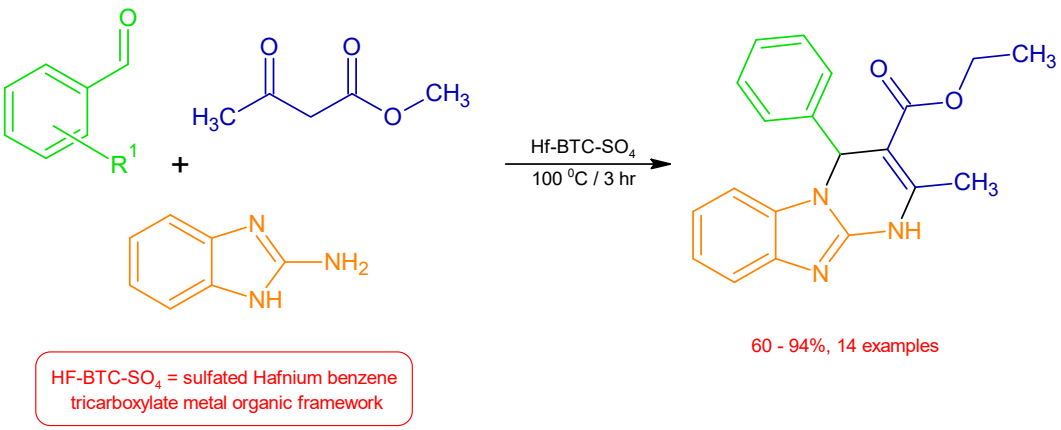


Figure 30. Synthesis of pyrimido [1,2-*b*]benzoimidazoles via the combination of aldehydes, 2-aminobenzoimidazole, and ethyl acetoacetate.

An alternative catalyst that was used was a Brønsted acidic ionic liquid supported on nanoporous sodium montmorillonite (Na^+-MMT-[pmim][HSO_4]). Impressively, the 22 reaction trials conducted were finalised in less than 50 min and gave yields between 87 and 95% [76].

2.3.4. Chromenopyridines

Replacing the aldehyde with salicylaldehyde for the previously mentioned reaction of an aldehyde, malononitrile, and thiophenol (Table 2) furnishes a diverse class of pyridine-3-carbonitriles, specifically called chromeno [2,3-*b*]pyridines, which have a chromene ring fused to the pyridine ring (Figure 31).

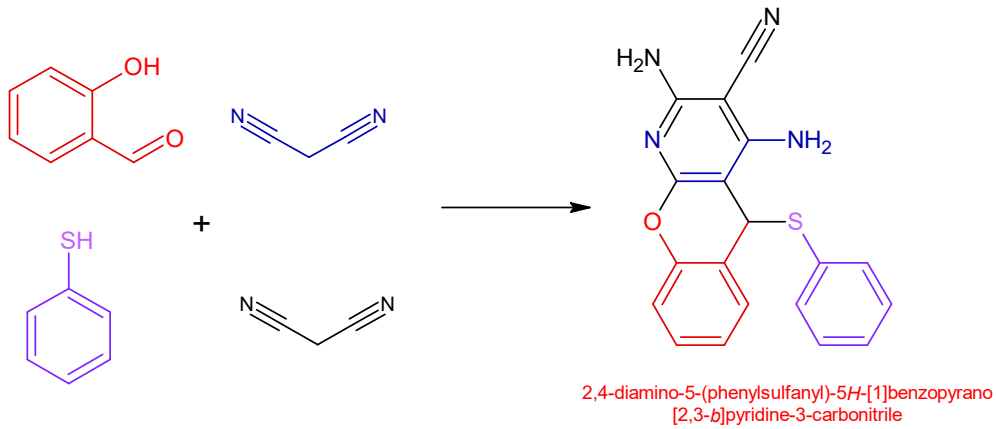


Figure 31. Synthesis of chromeno [2,3-*b*]pyridines from salicylaldehyde, thiophenol, and two equivalents of malononitrile.

In a study by Safaei-Ghomi et al., amongst various other trialled metal oxides, tin(II) oxide was found to be the ideal one [29]. In fact, at only 6 mol%, tin(II) oxide yielded the products in 54–63 min in very good yields (80–88%, six examples). More so, it could be recycled five times with a total yield drop of six percent. The same research group synthesized citric acid-functionalized chitosan polymeric beads as catalysts for the reaction and obtained excellent yields (84–92%) in 35–40 min whilst refluxing in ethanol [77]. Furthermore, the catalyst could be reused for five consecutive reaction cycles with only a minor two percent yield drop registered between the first and fifth run.

2.3.5. Chromenopyrimidines

Delving deeper into the possibilities that chromene products demonstrate, one would encounter another pseudo-four-component reaction involving salicylaldehyde (two equivalents), malononitrile, and amines or alcohols to yield chromeno [2,3-*d*]pyrimidine derivatives (Figure 32). A summary of some of the recent results is tabulated in Table 5.

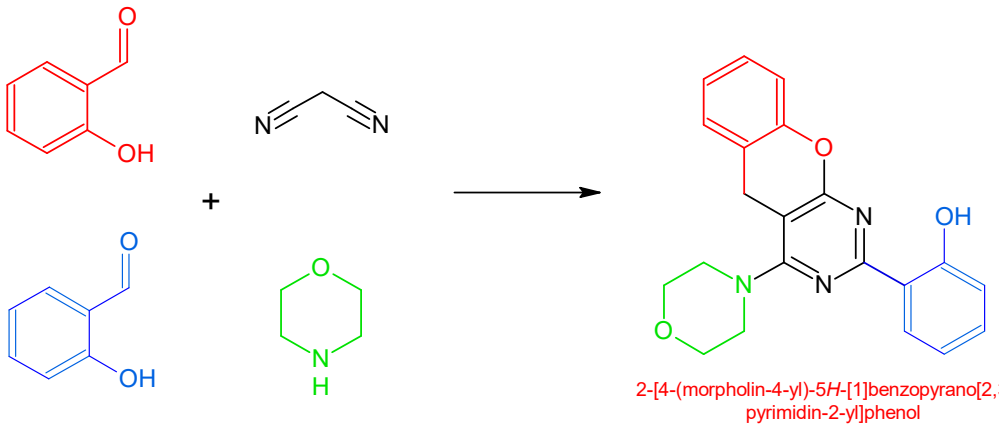


Figure 32. Synthesis of chromeno [2,3-*d*]pyrimidine from salicylaldehyde, thiophenol, and two equivalents of malononitrile.

Table 5. Recent catalysts employed in the synthesis of chromeno [2,3-*d*]pyrimidines.

Author (Date) Reference	Catalyst and Conditions	Reaction Times, Yields, Recycling Runs
Kour et al. (2017) [78]	0.1 g of nano-silver-xerogel 60 °C Ethanol solvent (2 mL per mmol) 45 min	79–93%, 7 examples (secondary amines); 63%—using 1 primary amine

Kabeer et al. (2017) [79]	Titania–silica (5 mol%) 80 °C Neat 10–20 min	89–94%, 12 examples Catalyst reused 3 times (92 → 85%)
Sadjadi, S. et al. (2017) [80]	Heteropolyacid@creatin-halloysite clay (0.03 g per mmol) Ultrasound radiation RT Water solvent (10 mL per mmol) 4 min	78-92%, 8 examples Catalyst reused 5 times (95 → 88%)
Mostafavi et al. (2019) [81]	Sulfamic acid-functionalized magnetic IRMOF-3 nano-composite (10 mg per mmol) RT 4 mL EtOH (per mmol)	78–97%, 21 examples 3 h Catalyst reused 5 times (95 → 93%)

2.4. Spiro Compounds

A spiro compound is one which has at least two rings joined by one common atom. In the literature, there are a plethora of reported syntheses of such compounds and amongst these there are methods involving the formation of spirooxindole derivatives. Interestingly, in a study by Liang et al., the enzyme papain was effectively used to catalyse the reaction between isatin, cyclic-1,3-diketones, and 3-methyl-5-aminopyrazole in ethanol solvent at 50 ^{0}C (Figure 33). Even if no recycling trials were performed, the enzyme did not dissolve and could be recovered by filtration. Although ultimately the obtained yields were poor to average (27–71%), and reaction times were comparatively long (48 h), no metals or toxic chemicals were needed in the creation of a catalyst, and papain itself is easily extracted from the raw fruit of the papaya plant [82].

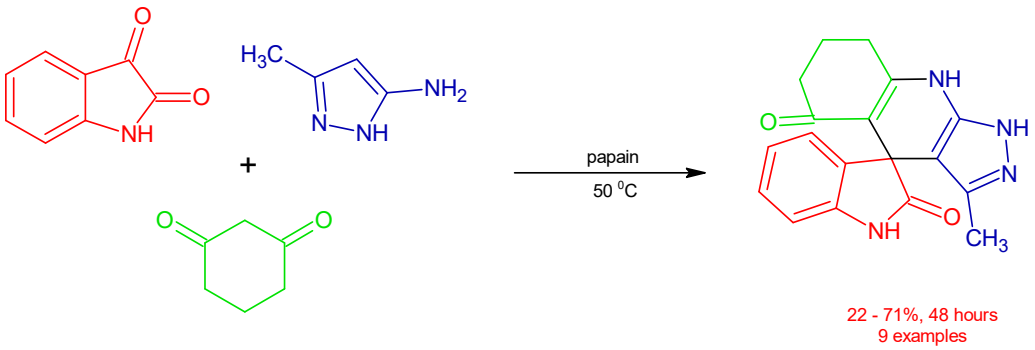


Figure 33. Formation of spirooxindole backbone via a papain-catalysed reaction.

Meanwhile, Arya et al. developed a ZSM-5 zeolite-supported Brønsted acid ionic liquid to catalyse the reaction of isatins, 2-mercaptopyridine-3-carboxylic acid, and various amines under ultrasonication (Figure 34) [83]. Reactions were very fast and yielded excellent results (80–92%). Meanwhile, conventional heating was also tried but yields were poor (0–35% in 46–50 h).

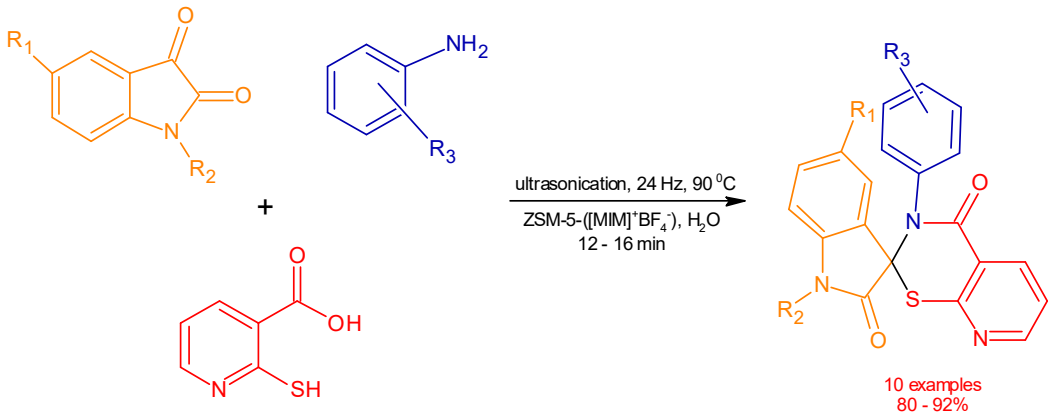


Figure 34. Synthesis of spiro[indole-pyrido [3,2-e]thiazine] under ultrasound radiation.

The nanocatalyst alum–silica was used to prepare spirooxindole derivatives via β-ketoesters, malononitrile, and isatins in ethanol solvent under reflux conditions (Figure 35) [84].

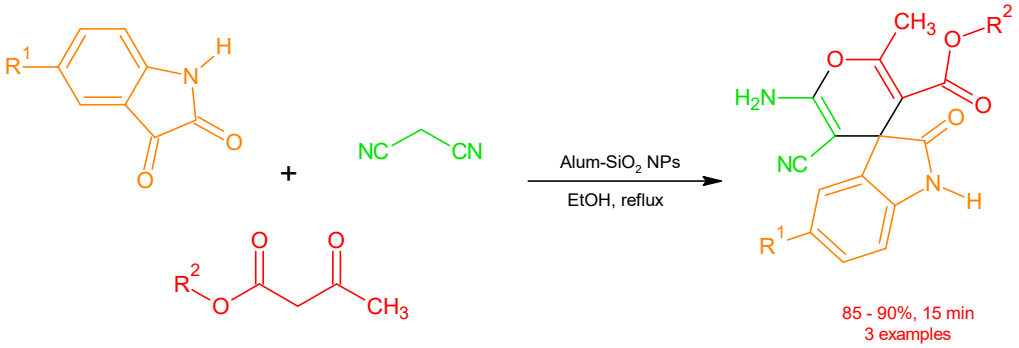


Figure 35. Spirooxindole synthesis via malononitrile, isatins, and β-ketoesters using alum–silica as a catalyst under reflux conditions.

Recently, an attractive approach was undertaken by Sadeghi et al., who developed nano-sulfonic acid-derivatised coconut shell powder to catalyse the just-mentioned reaction to obtain products (12 examples, 87–95%) in ethanol solvent after refluxing for only 15 min [85].

3. Acyclic Multicomponent Reactions

3.1. Mannich-Type Reactions

The classic Mannich reaction involves a C-C bond formation after the reaction of an aldehyde and an amine (to form an imine) with a resonance-stabilised carbon nucleophile [86]. With time, several variants have been discovered and established by replacing the carbon nucleophiles with others.

Two related variants of such aforementioned reactions are the A^3 and KA^2 coupling reactions, which involve the combination of an aldehyde (or ketone for the KA^2), a primary/secondary amine, and a terminal alkyne. The diversity of catalysts tried for this reaction is vast, to say the least. Amongst these, copper(I) has been employed in various forms and supported on numerous heterogeneous supports. For example, Bosica et al. used copper(I) iodide supported on Amberlyst A21 polymeric beads to catalyse the reaction between various secondary aliphatic amines, aromatic aldehydes, and different aromatic and silyl terminal alkynes in neat conditions at 100 °C in 2–3 h, with yields ranging from 70 to 98% (Figure 36). Positively, the catalyst could be reused for up to six cycles [87].

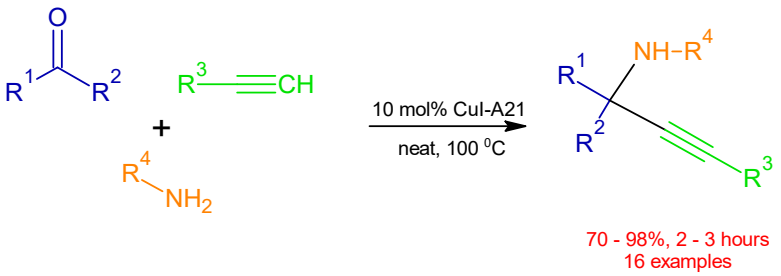


Figure 36. The A³coupling reaction catalysed by 10 mol% CuI/A21.

The same catalyst was used in a separate study to instead investigate its feasibility in reactions involving ketones (KA²). Yields were overall lower, but still acceptable considering the relative unreactivity of ketones. When the alkyne used was phenylacetylene, yields ranged between 62 and 98% in 1.5–48 h at 98 °C. The use of 1-octyne resulted in poorer yields (49–81% in 2–15 h) [88]. Metal–organic frameworks (MOFs), porous hybrid materials composed of metals ions linked together by organic molecules, are other versatile catalysts or supports being developed in the field of heterogeneous chemistry. In fact, a silver(I)-functionalised metal–organic framework (MIL-101-SO_3Ag) was demonstrated to be an efficient and environmentally friendly catalyst in the A³ coupling reaction, giving the products in excellent yields (>92%) after 4–10 h, under solvent-free conditions at 100 °C [89].

If the alkyne is replaced with an electron-rich alcohol, i.e., 2-naphthol, the Mannich-type reaction is termed as the Betti synthesis, and the products are specifically 1-aminoalkyl-2-naphthols (Figure 37). For instance, nano-silica boric acid was utilised in a neat reaction environment at 40 °C to drive the reaction in 30–40 min, and to give the products in excellent yields (88–94%). Furthermore, the catalyst was recyclable for up to five runs, with yield decreasing by 5–10% between the first and fifth trial [90].

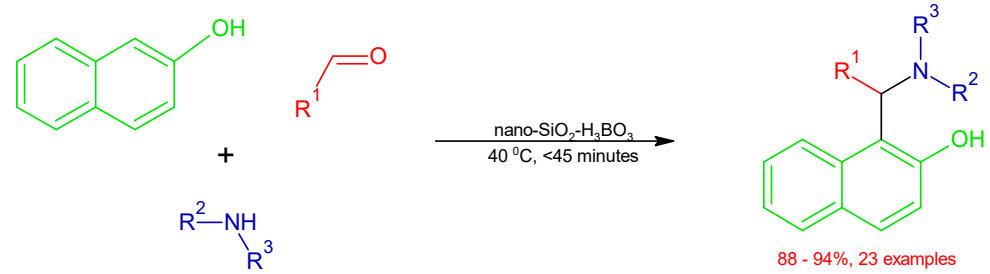


Figure 37. The Betti synthesis via the reaction of 2-naphthol, aldehydes, and amines.

This reaction can also be easily catalysed by the commercially available Montmorillonite K30 clay catalyst. Reactions were conducted at 60 °C in neat conditions. The use of proline as an amine resulted in yields ranging from 50 to 91% in 2–6 h. Morpholine and piperidine also worked to give the products in 4–12 h, at yields of 86–90% [91]. It is also possible to use amides instead of amines, as Lei et al. did when they succeeded in making use of graphite-supported perchloric acid (Figure 38). The reaction required higher temperatures (125 °C) than the amine-analogues due to the relative unreactivity of amides. Just the same, yields were moderate to very good (68–88%) and products were collected after 2 h of reaction time [92].

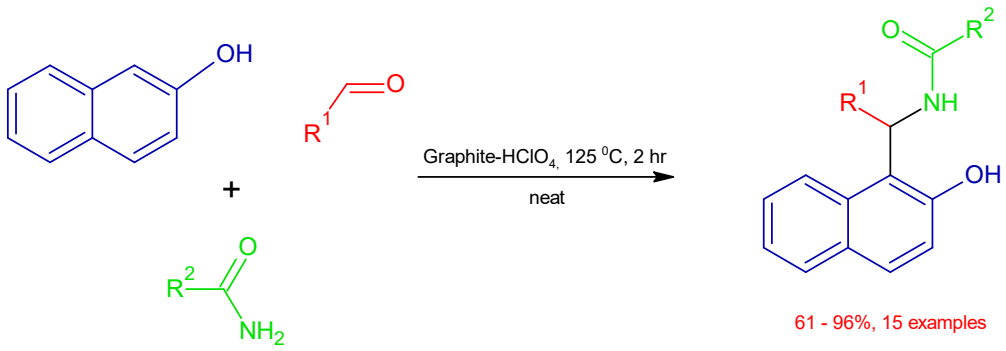


Figure 38. The Betti synthesis via the reaction of 2-naphthols, aldehydes, and amides.

The heteroaromatic compound, indole, behaves similar to 2-naphthol and carries out the so-called aza-Friedel–Crafts reactions to form 3-substituted indoles. Ganesan et al. reported the use of magnetite-sulfonic acid for the synthesis of aza-Friedel–Crafts products, using either secondary or tertiary amines (Figure 39). In the case of the former, the reactions were performed in neat conditions at room temperature for 3 h to collect products originating from a C-N bond forming in very good yields (78–90%, four examples only). On other hand, tertiary amines required a higher temperature (100 °C, 1 h) and gave products that resulted only from C-C bond formation (82–88%) [93]. Interestingly, as reported by Bosica et al., the products which were obtained from primary, secondary, and tertiary aromatic amines were all only via C-C bond formation. The catalyst of choice was silicotungstic acid supported on Amberlyst 15, sulfonic acid-functionalized polymeric beads. The reactions involving secondary aromatic amines (25 examples) took 4–24 h, with yields of 40–99%. Primary amines gave products in 6 h at yields of 41–84%, (18 examples). Lastly, tertiary amines performed poorly, and heating was needed (33–47%,18–24 h) [94].

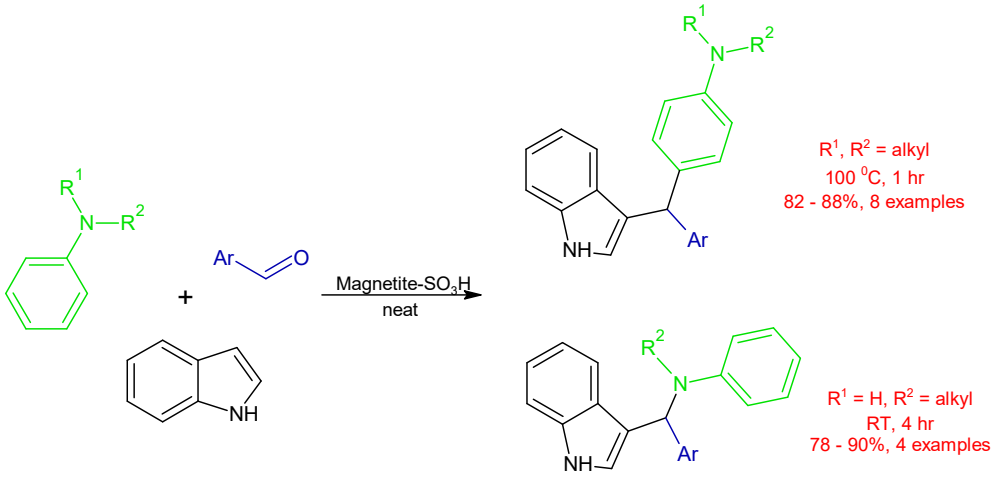


Figure 39. Aza-Friedel–Crafts reaction for secondary and tertiary aromatic amines gives two different products.

Another member of the Mannich-type reaction is the aza-Henry, or nitro-Mannich reaction, which involves the combination of aldehydes, amines, and nitroalkanes (Figure 40) [95]. The use of copper(I) iodide supported on Amberlyst A21 was reported for such a reaction, and did not require the addition of other solvents (even if nitromethane was used in large excess to act as a reactant and solvent simultaneously). Reaction times varied between 2 and 10 h, with yields occupying the range of 38–98% (in truth, only one result was below 50% in 27 trials).

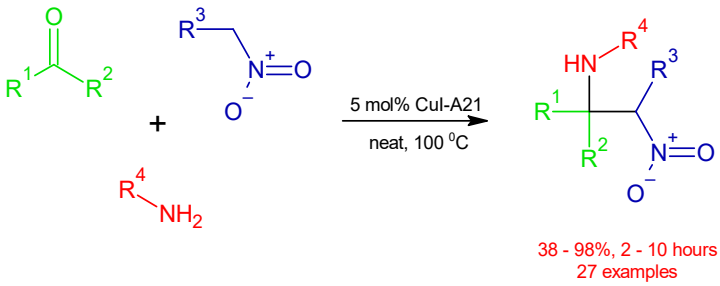


Figure 40. The nitro-Mannich reaction catalysed by copper(I) iodide supported on Amberlyst A21.

Even if not encountered in the final product itself, boron, or more precisely boronic acids, are involved reactions falling within the same reaction family. The borono–Mannich reaction (also known as the Petasis reaction) entails the reaction of an aldehyde and an amine to form an imine that gets attacked by an alkyl/aryl boronic acid which transfers an alkyl/aryl group to it (Figure 41). Recently, cobalt ferrite was selected to catalyse the reaction in acetonitrile solvent at 80 °C for 2.5–6 h. Yields were very good (72–90%) and it was observed that the catalyst could be reused for up to five times with no apparent decrease in activity [96].

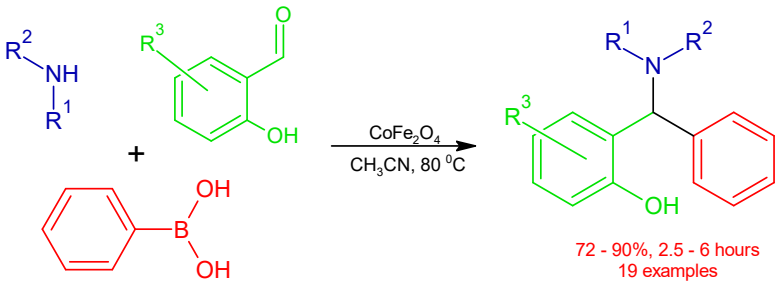


Figure 41. Borono–Mannich reaction using cobalt ferrite as a catalyst.

One of the most important routes to synthesize α-aminophosphonates is the Kabachnik–Fields reaction which, similar to the above, requires the formation of an imine before the latter gets attacked by dialkyl phosphites [97]. In a novel approach by Sobhani et al., phosphoric acid was supported on magnetic nanoparticles coated with silica (γ-Fe_3O_4@SiO_2-PA) to obtain products in 1–4 h (85–96% yields, Figure 42). All reactions were performed in water at 80 °C and at the end of each reaction, the catalyst could be easily separated by a magnet before being reused for up to a total of five times.

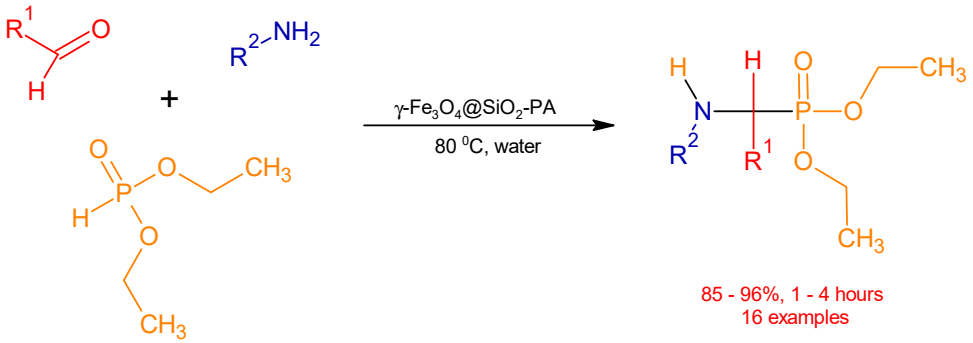


Figure 42. The Kabachnik–Fields reaction catalysed by phosphoric acid (PA) supported on magnetic core nanoparticles (γ-Fe_3O_4@SiO_2-PA).

β-Aminocarbonyl compounds are useful building blocks in the synthesis of pharmaceuticals and natural products such as β-amino acids. They can also be synthesized via

the classical Mannich reaction, in which an aldehyde and an amine react together to form the imine, which then gets attacked by acetophenone (Figure 43). Amongst the wide range of catalysts attempted and tested for this reaction, recently, nano-sulphated zirconia was also discovered to give very good results (71–88%) at room temperature in ethanol solvent in 4.5–5 h [98].

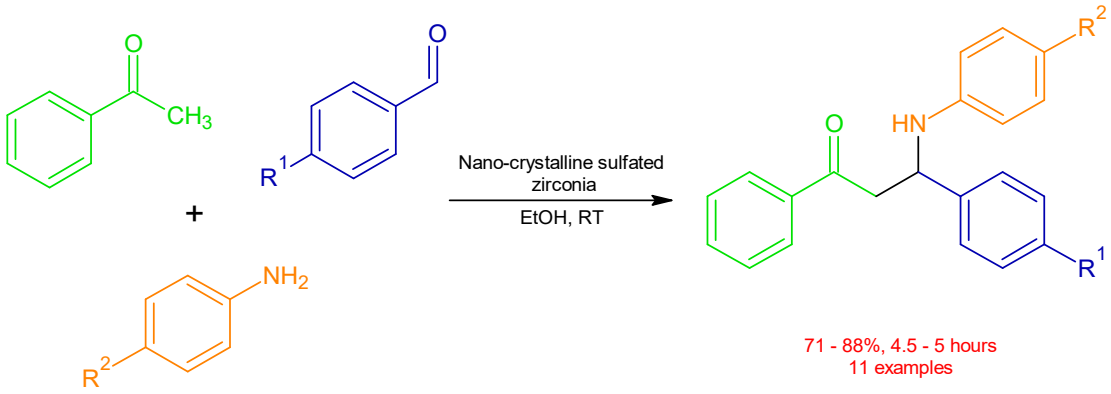


Figure 43. β-amino carbonyl compound synthesis via a Mannich-type reaction of an aldehyde, an amine, and acetophenones.

Liu et al. managed to obtain similar products using cyclohexanone instead of acetophenone via the use of silica-supported phenylphosphinic acid in ethanol solvent at room temperature. Reactions were much faster (30–70 min), and yields were similarly high (67–96%) [99].

Lastly, if the imine-attacking nucleophile is cyanide, the end products of the Mannich-type reaction are specifically called α-aminonitriles (Figure 44). Whereas, in the past, the latter were obtained by the use of ionic cyanides, nowadays, alternative cyanide sources, such as trimethylsilyl cyanide (TMSCN), are sought [100]. One novel and heterogeneous approach established in recent years requires the use of nano-copper ferrite [101]. The reactions were performed at room temperature in ethanol/water (50:1) solvent to give the end products in 50–81 min at yields of 72–98%.

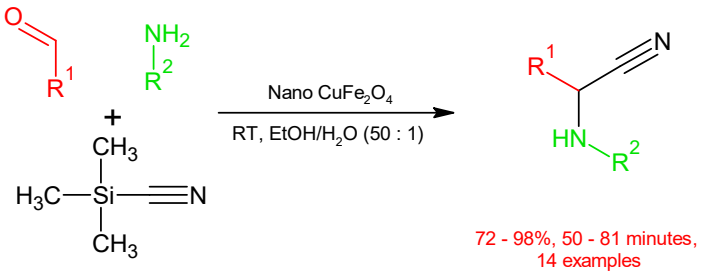


Figure 44. Synthesis of α-aminonitriles using trimethylsilyl cyanide as the CN^- source.

3.2. Knoevenagel-Type Reactions

The classical Knoevenagel condensation reaction is the nucleophilic addition of an active methylene-containing compound to a carbonyl-containing compound followed by condensation to form an α,β-unsaturated derivative [102].

With time, several Knoevenagel-type reactions have been established, which involve first the formation of an α,β-unsaturated carbonyl compound that could then be attacked by a nucleophile. For example, zeoltic imidazolate frameworks were found to be worthy catalysts for the Knoevenagel–phospha-Michael reaction (as shown in Figure 45), whereby the dialkyl phosphite ($HPO(OEt)_2$) attacks the Knoevenagel product formed earlier from the aldehyde and malononitrile. In the six trials carried out, the products were

obtained after 5 h (at 50 °C in 1,4-dioxane solvent in air) at yields of 98–100%. When malononitrile was replaced by ethyl cyanoacetate, the reaction time increased to 10 h but the yield remained at 98% [103].

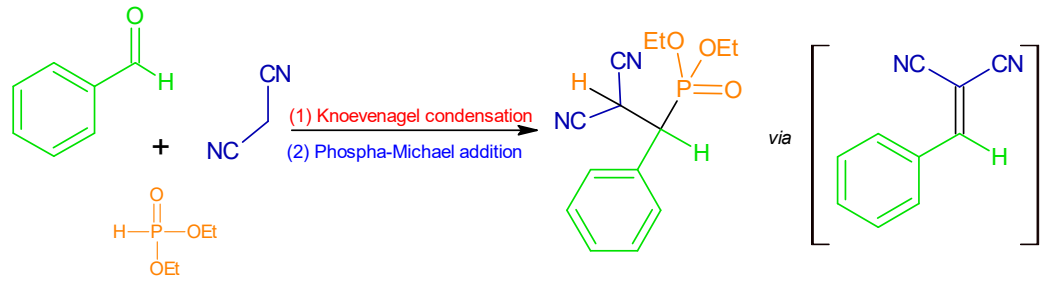


Figure 45. Tandem Knoevenagel condensation phospha-Michael reaction.

3-Aminopropylated silica is a recently developed, efficient, and reusable catalyst that was also put into use for the synthesis of bis(pyrazolyl)methanes via a three-component tandem Knoevenagel–Michael reaction of 1-phenyl-3-methylpyrazolone with aldehydes (Figure 46) [104]. The formation of these products was very rapid (<45 min) and efficient (90–98% yields at room temperature).

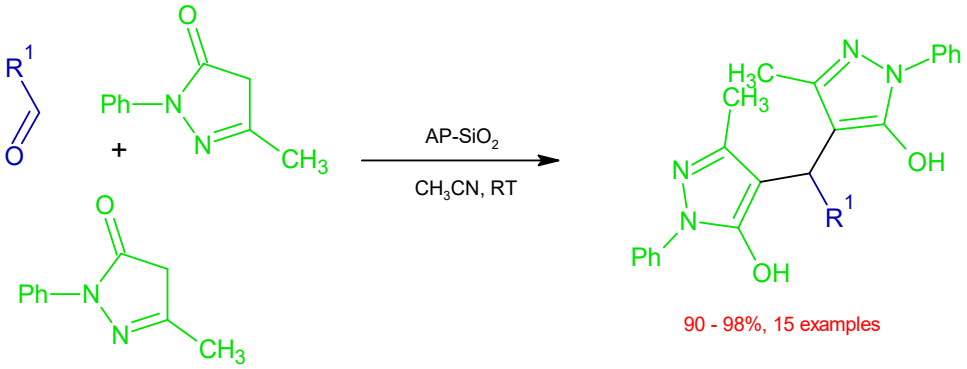


Figure 46. Synthesis of bis(pyrazolyl)methanes via a Knoevenagel–Michael reaction.

3.3. Isocyanide-Type

The wide range of starting materials that can be used in isocyanide-based MCRs makes it one of the most researched families of reactions. There are various ways in which the isocyanide derivatives can react, but the most important one is the α-addition of electrophiles and nucleophiles at the isocyanide carbon [105]. The earliest studied reaction that falls into this category is the Passerini three-component reaction (3CR) between an aldehyde, a carboxylic acid, and an isocyanide to yield α-acyloxycarboxamides (Figure 47). A recently developed and successfully employed heterogeneous catalyst for the reaction is silica gel-immobilised 1,2-benzenedisulfonimide [106]. This catalyst gave the products in excellent yields (78–93%) in 20–30 h and, most importantly, at an enantiomeric excess, surpassing 92.7% in all trials. The carboxylic acids that were used were both aromatic and aliphatic, the aldehydes were mainly aromatic in nature, and the isocyanides were either *t*-butyl or naphthyl isocyanides. The catalyst could also be reused for five consecutive runs with a 3% reduction in yield.

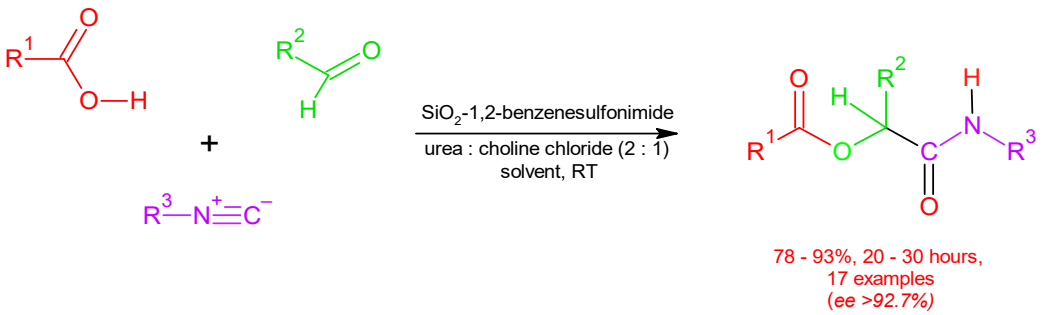


Figure 47. The Passerini three-component reaction results in the formation of α-acyloxycarboxamides via the combination of isonitriles, aldehydes, and carboxylic acids.

Later on, it was postulated that if the aldehyde were to be replaced by an imine that can itself be formed in situ by the reaction of an amine and an aldehyde, the reaction mechanism should be followed in a similar manner to that of the Passerini reaction and result in similar products. In fact, the reaction worked to form peptide-like structures and became known as the Ugi reaction (first reported in 1959) [107]. A modern heterogeneous catalyst that could be used was fluorite which, in the presence of microwaves and ethanol solvent, yielded 2-chloroquinoline-3-carbaldehyde derivatives in excellent yields (Figure 48) [108].

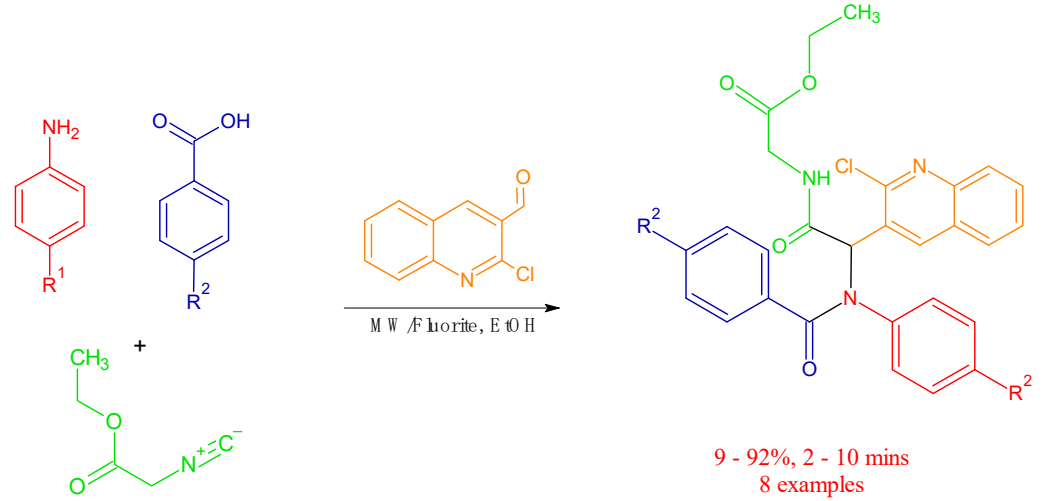


Figure 48. The Ugi reaction, a modification of the Passerini reaction.

4. Conclusions

As can be discerned, the diversity of multicomponent reactions is particularly broad, owing to the fact that if one reactant is replaced by one or more others, a completely new set of products will end up being produced, thus confirming the high versatility of this useful synthetic approach. All the catalysts that were employed in the selected multicomponent reactions could be reused at the end of the reaction, making them operationally heterogeneous. In mechanistic terms, some were homotopic and others were heterotopic, but few studies actually delved into such details. This is because the determination of the catalyst functionality needs to be coupled with detailed mechanistic studies which, in truth, fall outside of the scope of the studies for which the aim was simply to obtain products in an environmentally benign manner.

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