Review Article

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Synthesis of imidazole derivatives in the last 5 years: An update

https://doi.org/10.1515/hc-2022-0173
received November 22, 2023; accepted February 19, 2024

Abstract: Imidazole and its derivatives possess remarkable versatility, finding applications in medicine, synthetic chemistry, and industry. This review explores the latest advancements observed over the last few years (2018–2022), focusing on diverse multicomponent reactions conducted under different conditions. It highlights the role of catalysts and diverse conditions, optimizing synthetic efficiency. The review offers concise insights into emerging trends, making it a valuable resource for researchers and practitioners seeking greener and more efficient imidazole synthesis.

Keywords: imidazoles, water, two components, biological activities, heterocycles

1 Introduction

Nitrogen-containing aromatic heterocyclic compounds, particularly imidazoles, have garnered significant attention in research and industrial chemistry in recent years, mainly due to their versatile range of biological and pharmacological activities [1]. They play a pivotal role in the synthesis of biologically active molecules [2,3], such as anticancer, anti-aging, anticoagulant, anti-inflammatory, antimicrobial, antitubercular, antidiabetic, antimalarial, antiviral drugs, and enzyme inhibitors [4–6]. They also act as selective plant growth regulators, fungicides, herbicides, and therapeutic agents [7]. Nowadays, green chemistry and organometallic catalysis have extended the application of imidazoles as ionic liquids and *N*-heterocyclic carbenes (NHCs) [8,9]. Therefore, imidazole derivatives have become more popular due to the demand for environmentally friendly methods in chemical organic synthesis. There are several approaches for the synthesis of substituted imidazoles by condensation [10], ring cyclization [11], oxidation conversion [12], solid face analysis [13], flash vacuum pyrolysis [14], microreactor [15] and ionic liquid promoted technique [16]. In most cases, tri and tetra-substituted imidazoles are synthesized by three or four components of cyclo-condensation of 1,2-diketones, ammonium acetate with aldehydes, and anilines using a variety of different catalysts under efficient green method or solvent-based conditions [17]. Some of the well-known methods for the synthesis of substituted imidazoles are Van Leusen [18], Debus-Radziszewski [19], Marckwald [20], and Wallach [21] in the last few decades [22].

Continuing our interest in *N*-containing heterocycles [23–25], we propose this review, which comprehensively explores recent advancements in imidazole synthesis. We emphasize reviewing critical strategies, catalytic approaches, and sustainable methodologies based on two, three, and four components. As imidazole derivative synthesis continues to evolve, it promises scientific innovation while addressing environmental sustainability concerns in the chemical industry.

2 Two-component methods

2.1 Synthesis of imidazoles using water as a solvent

Zhaojun et al. explored the synthesis of 1-benzyl-2-aryl-1*H*-benzo[*d*]imidazole derivatives **1**[a] via 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP)-copper supported by hydrotalcite ([Cu(binap)I]$_2$@HT) as a heterogeneous catalyst in water. The reaction between diamines **2** and various alcohol **3**, which undergoes dehydrogenative cyclization in the presence of the [Cu(binap)I]$_2$@HT catalyst, and K_2CO_3 in water at 90°C gives the expected products in high yield (Scheme 1).

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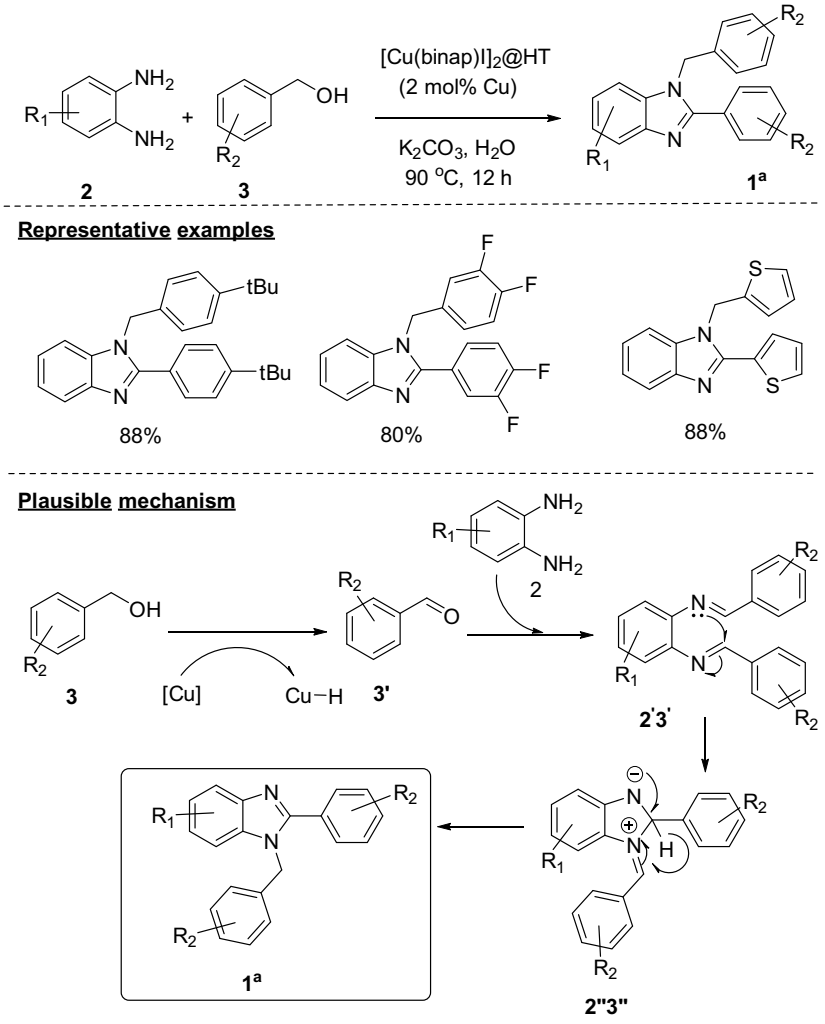
This BINAP-Cu complex, which is supported by hydrotalcite, exhibits exceptional air stability and can be recycled at least five times in an environment free of solvents [26].

2.2 Synthesis of imidazoles under solvent-free conditions

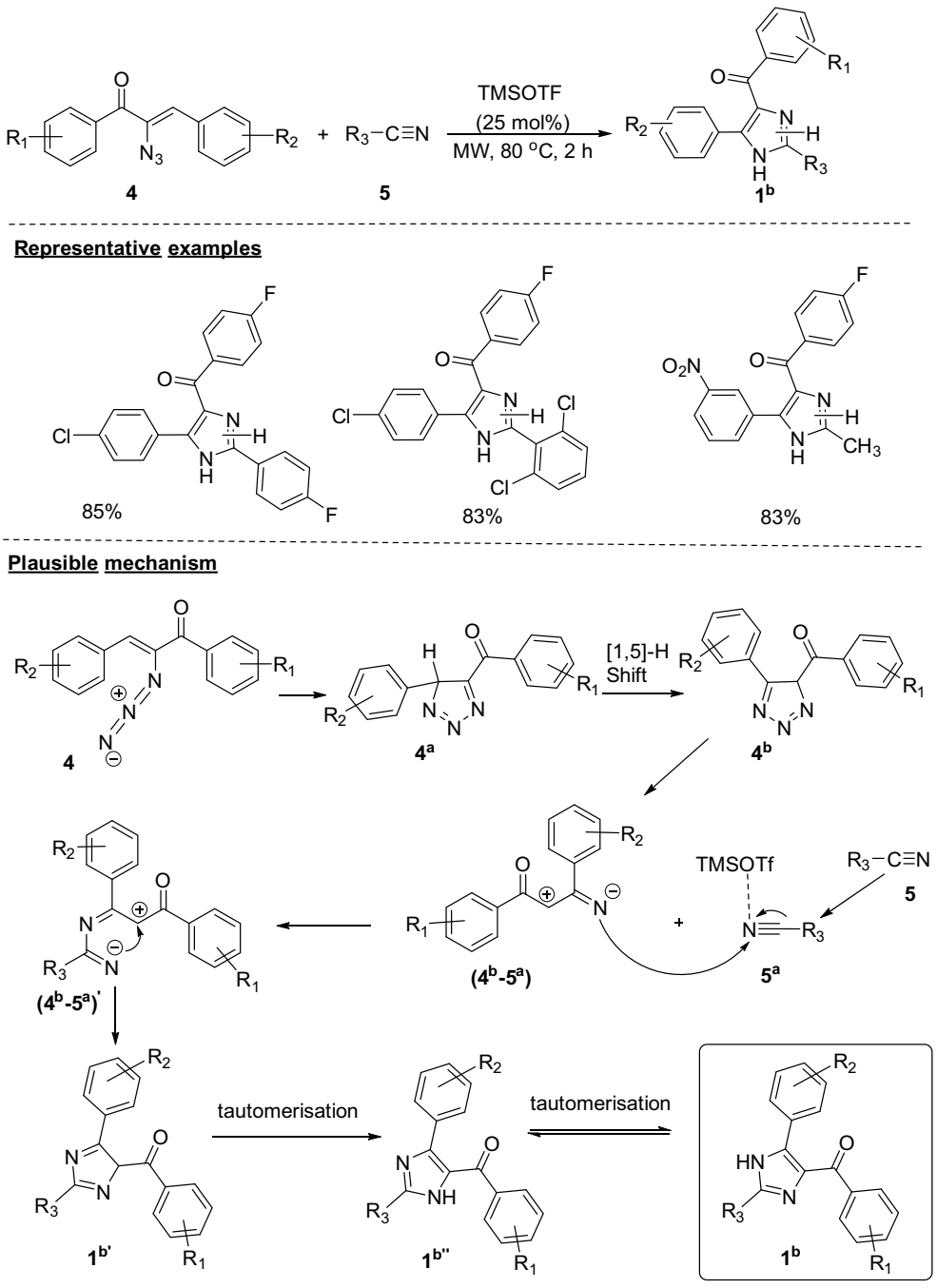
An efficient synthesis of 2,4,5-trisubstituted imidazoles **1[b]** by the intermolecular [3 + 2] cycloaddition reaction between azido chalcones **4** and organic nitriles **5** using trimethylsilyl-trifluoromethanesulfonate (TMSOTF) as a catalyst under microwave radiation, resulted in a high yield (85%) under a short reaction time (Scheme 2), as reported by Mysore et al. This method has a simple and straightforward procedure for synthesizing substituted imidazole derivatives **1[b]** for future purposes [27].

Anitha and Sankari reported a novel NHC catalyst for synthesizing substituted imidazole derivatives **1[c]**. An NHC catalyzed the reaction between acetophenones **6** and benzylamines **7** with *t*-BuOK, and BF_3OEt_2 as a Lewis acid in the presence of aq. *tert*-butyl hydroperoxide (TBHP) as an oxidant at 80°C under solvent-free conditions and a plausible mechanism is shown in Scheme 3. It is a convenient method for synthesizing substituted imidazoles **1[c]** in high yields under solvent-free conditions without using transition metals and the pre-functionalization of substrates [28].

Ali et al. recently prepared a novel nanoparticle (Co/Mn)-supported graphene oxide (GO) nanocatalyst for the synthesis of benzimidazoles **1[d]**. The reaction started with aldehydes **8** and 1,2-benzenediamine **2** in the presence of GO(Co/Mn) catalyst (0.1 g) under thermal conditions at 80°C. In the same manner, they also performed the reaction under ultrasonic irradiation in the presence of water.



Scheme 1: Synthesis of 1*H*-benzo[*d*]imidazoles using the $[Cu(binap)I]_2$@HT catalyst.

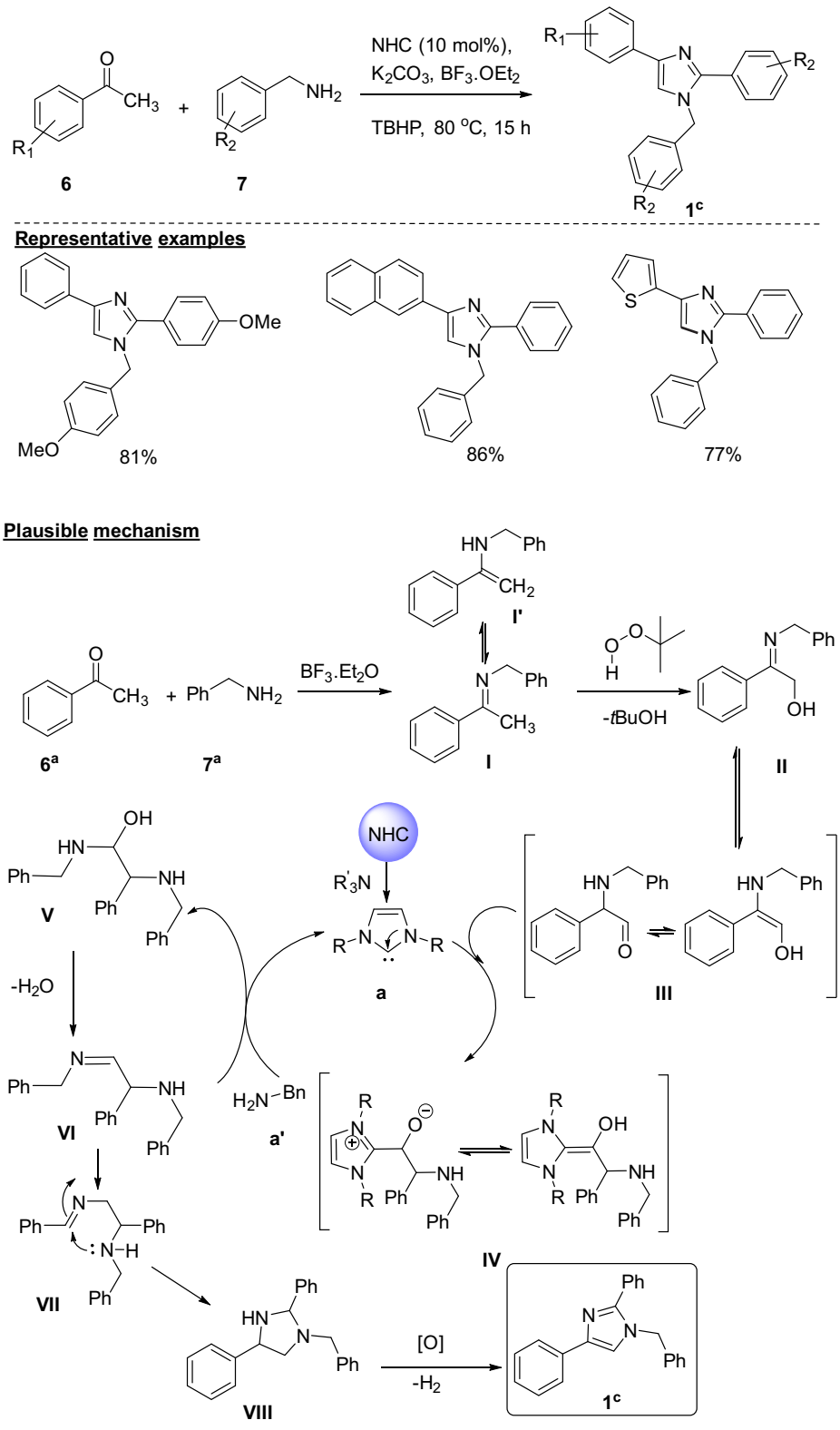


Scheme 2: Synthesis of 2,4,5-trisubstituted imidazoles using the TMSOTF catalyst.

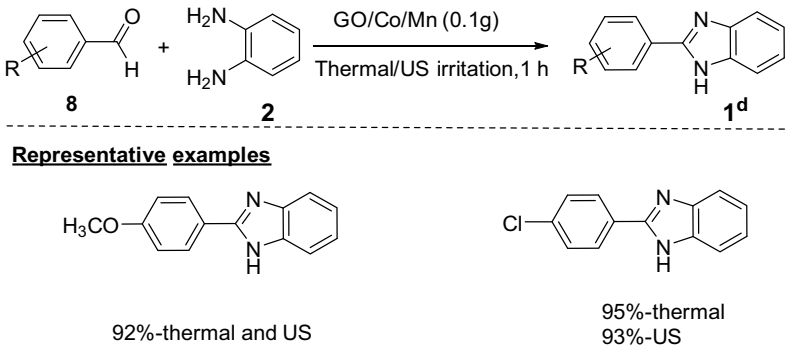
The thermal and ultrasonic conditions give high yields of up to 95% benzimidazoles **1[d]** (Scheme 4). This is an efficient method due to the short reaction time, easy procedure, and reuse of the catalyst, and it is performed under solvent-free conditions [29].

2.3 Synthesis of imidazoles using an organic solvent

A new novel phosphine-free Ru(II)-NNN pincer complex ([RuCl(L)(MeCN)$_2$]Cl), L = 2,6-bis(1*H*-imidazole-2-yl)pyridine,



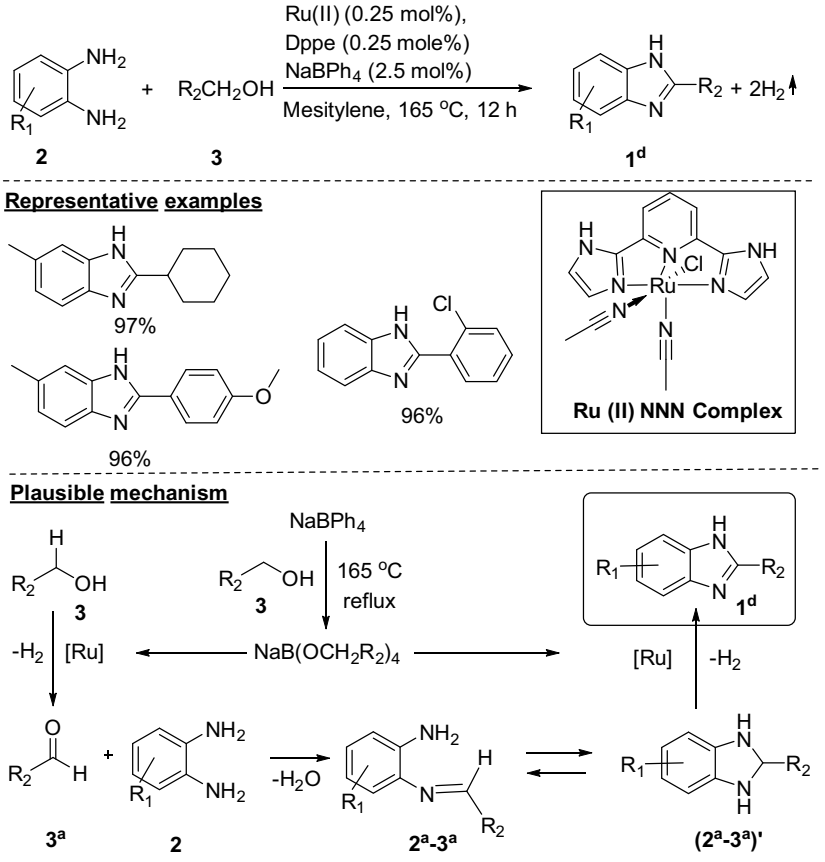
Scheme 3: Synthesis of imidazole derivatives using the NHC catalyst.



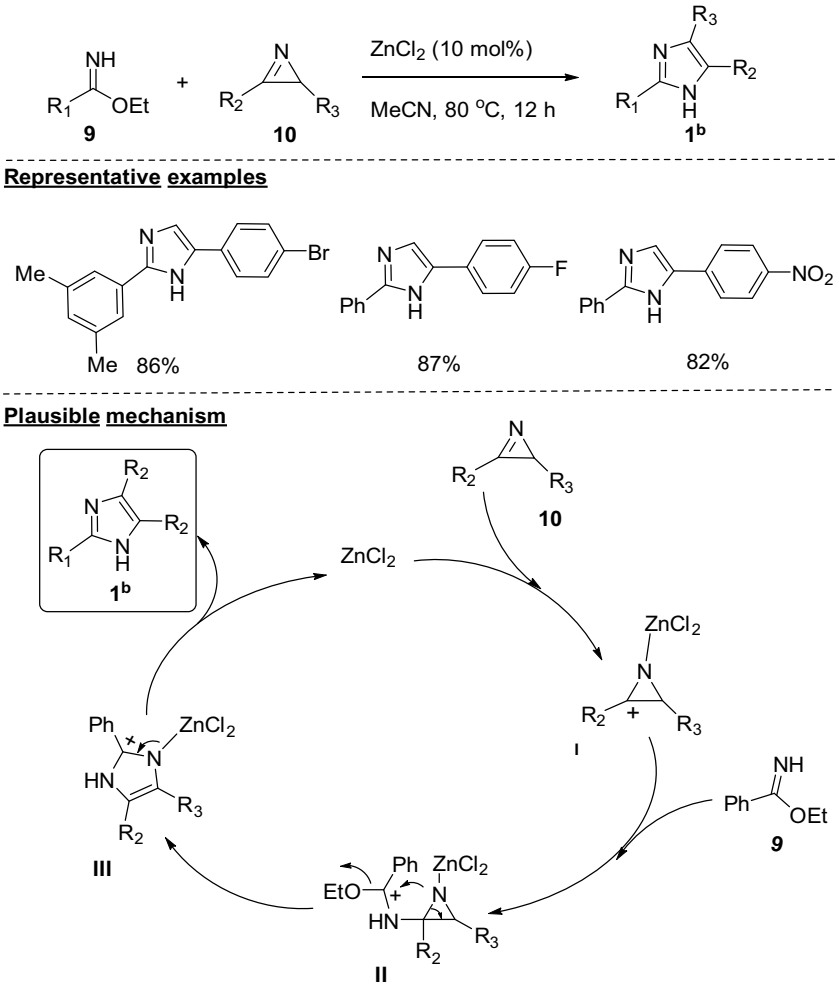
Scheme 4: Synthesis of imidazoles using the GO/Co/Mn catalyst.

developed by Lin et al. was used as a homogenous catalyst for the synthesis of 1*H*-benzo[*d*]imidazoles **1**^{d}. The reaction proceeds between benzene-1,2-diamines **2** and primary alcohols **3** that dehydrogenation condensation with the Ru(II) complex as a catalyst with additive $NaBPh_4$ and 1,2-bis(diphenylphosphanyl)ethane (DPPE) in mesitylene was heated at 165°C for 12 h in an open system and gives a high yield of 2-substituted 1*H*-benzo[*d*]imidazole **1**^{d} (95%) and released H_2 (Scheme 5). A strong electro-donor ligand DPPE was coordinated to the Ru center, which improved the catalytic reactivity. Both electron-donating and electron-withdrawing groups of alcohols or diamines give excellent yields (97%) of the products [30]. Compared to other reported homogeneous systems, it is an excellent example of a one-step synthesis of imidazole derivatives from alcohols without using an oxidant and the stoichiometric amounts of inorganic bases.

Shoujie et al. developed a $ZnCl_2$-catalyzed one-pot [3 + 2] cycloaddition reaction between benzimidates **9** and



Scheme 5: Synthesis of 1*H*-benzo[*d*]imidazole derivatives using the Ru(II) catalyst.



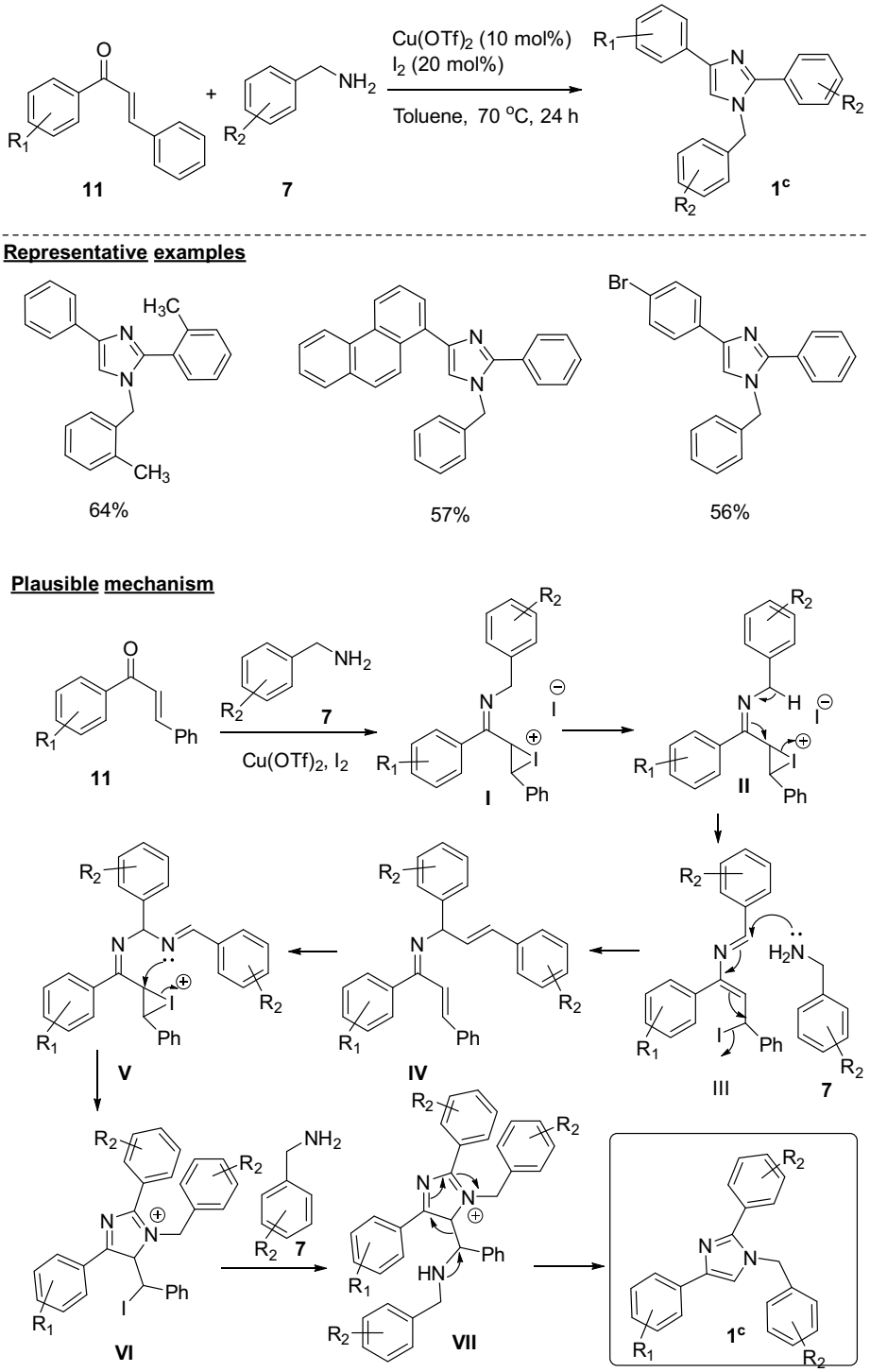
Scheme 6: Synthesis of imidazoles using the $ZnCl_2$ catalyst.

2*H*-azirines **10** in MeCN for the synthesis of substituted imidazoles **1[b]** (Scheme 6). The substrates of electron-withdrawing groups, such as F– and NO_2– groups, afford the products **1[b]** in good yields (87 and 82%). In the mechanism, $ZnCl_2$ activates azirine **10,** which undergoes nucleophilic attack by benzimidate **9**, and then subsequent ring opening and intramolecular cyclization occur to give the desired products. The reaction exhibits exceptional reactivity and favorable tolerance towards various functional groups and produces a good yield in the afforded period [31].

1,2,4-Trisubstituted-(1*H*)-imidazoles **1[c]** was successfully synthesized through the unconventional C–C bond cleavage of chalcones **11** and benzylamine **7**, catalyzed by Cu $(OTF)_2$ and I_2 in toluene at 70°C for 24 h in the presence of air, developed by Chettiyan et al. (Scheme 7). In this reaction, a variety of aryl- and heteroaryl-substituted chalcones **11** and benzylamines **7** afforded a good yield. This protocol was applicable in medicinal chemistry approaches, such as scaffold hopping, molecular hybridization, and other related techniques to achieve selectivity [32].

Lucas et al. developed the synthesis of 2-aminoimidazole derivatives **1[b]** using [3 + 2] dipolar cycloaddition of vinyl azides **12** (1 eq.) and cyanamide **13** (3 eq.) in the presence of potassium acetate as a base under both microwave and visible light-mediated conditions with *t*-butanol and ethanol as solvents, respectively (Scheme 8). Microwave and thermal conditions give a high yield of 2-aminoimidazoles **1[b]** under a short reaction time. The photoactivation of vinyl azides gives a remarkable outcome through visible light. In the photochemical reaction, blue light (456 nm) alone generated photolysis of the azide without the addition of a photocatalyst [33].

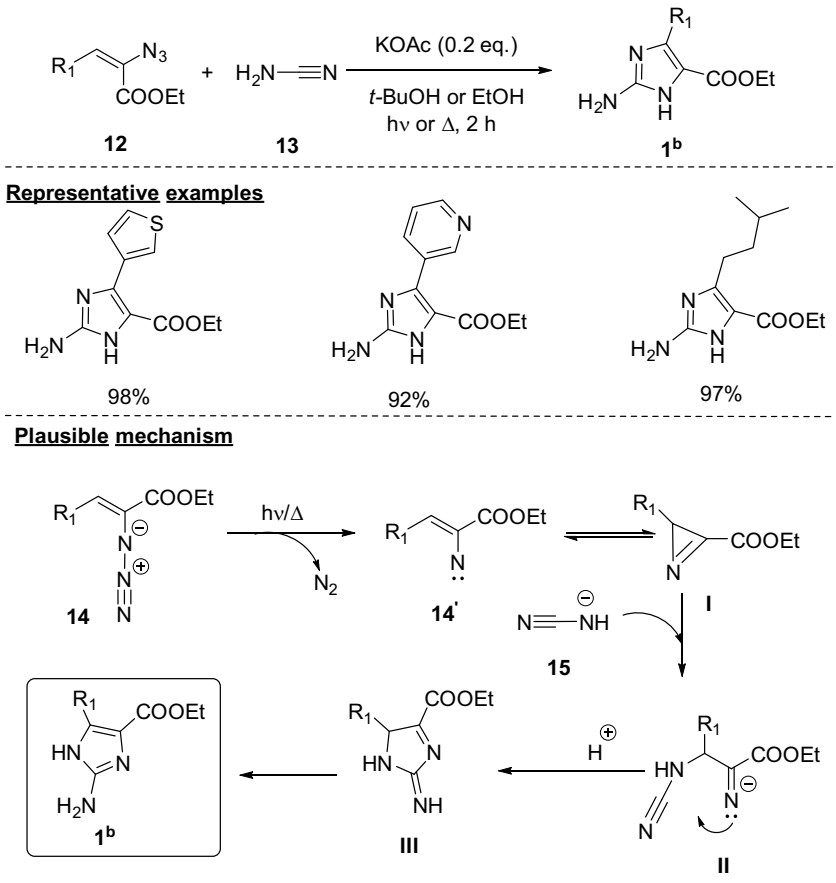
An efficient base-promoted metal-free cyclization reaction for the synthesis of 2,4,5-trisubstituted imidazoles **1[b]** using substituted alkynes **14** (1 eq.), benzonitrile **5** (3 eq.), and *t*-BuOK (2.5 eq.) as a base at 100°C in cyclohexane for



Scheme 7: Synthesis of trisubstituted-(1*H*)-imidazoles using $Cu(OTf)_2$ and I_2 catalysts.

11 h under Ar atmosphere was developed by Qiang et al. (Scheme 9). The best result was obtained with up to 93% yield when using cyclohexane as a solvent, but the reaction still obtained a 43% yield without a solvent. This approach directly contributes to the achievement of synthesizing valuable imidazole derivatives using easily accessible raw materials [34].

The synthesis of 2-amido-substituted benzimidazoles **1[d]**, from benzene-1,2-diamine **2** and 2-bromo-2,2-difluoro-*N*-isopropylacetamides **15** using S_8 and Na_2CO_3 in MeCN



Scheme 8: Synthesis of 2-aminoimidazole derivatives using KOAc as a base.

at 130°C for 16 h was reported by Shuilin et al. (Scheme 10) [35]. This method successfully obtained S_8-catalyzed selective cleavage of three halogen carbon bonds of the halogenated difluoro compounds and 2-amido-substituted benzimidazoles **1[d]** with a high yield.

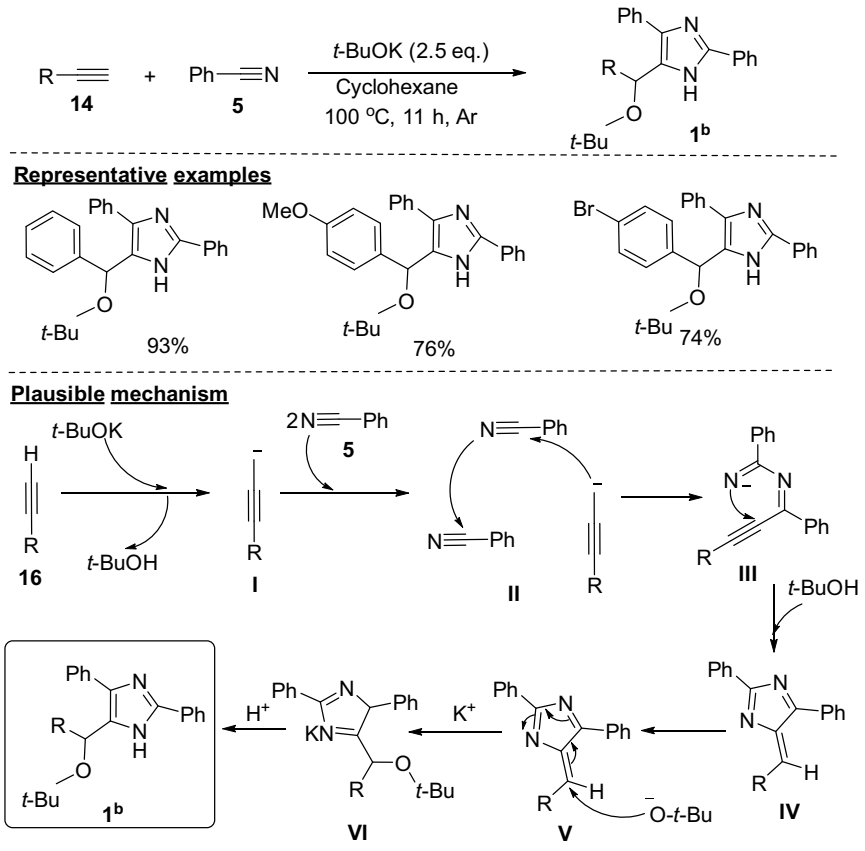
Erfei et al. reported a single-step synthesis of 2-aminoimidazole derivatives **1[e]** by a cyclization between unsymmetrical carbodiimides **16** and propargylic amines **17** with Cs_2CO_3 in dioxane at room temperature for 8 h and afforded the product in moderate to good yield (Scheme 11). The regio-divergent cyclization is observed when they change the base and temperature [36].

Lan et al. developed substituted imidazoles **1[b]** using trimethylsilylethynyl benzoxazinanones **18** and benzimidamides hydrochloride **19**, which undergo S_N2 reaction followed by decarboxylation in the presence of K_2CO_3 (2 eq.) in MeCN as a solvent at 80°C for 5 h and afforded the corresponding imidazole derivatives in high yield of up to 90% (Scheme 12) [37].

3 Three-component methods

3.1 Synthesis of imidazoles using a green solvent

Mohd and Zeba described a practical and ecofriendly process for the synthesis of isatin-based imidazole derivatives **1[d]** using cerium-immobilized silicotungstic acid nanoparticle-impregnated zirconia (Ce@STANPs/ZrO_2) as a catalyst in water. A mixture of isatin **20**, aliphatic/aromatic/heteroaromatic aldehydes **8**, ammonium acetate **21**, and Ce@STANPs/ZrO_2 in water was heated at 100°C under MW condition and obtained a high yield of products up to 94% (Scheme 13). In this reaction, the Ce@STANPs/ZrO_2 catalyst was used to activate the carbonyl bond, and they optimized several organic solvents; among them, using water as a solvent gave a high yield under a short reaction time [38]. The protocol provides various advantages, including the catalyst's ability to be



Scheme 9: Synthesis of 2,4,5-trisubstituted imidazoles from alkyne and benzonitrile.

reused several times, a high product yield, and environmentally conscious conditions.

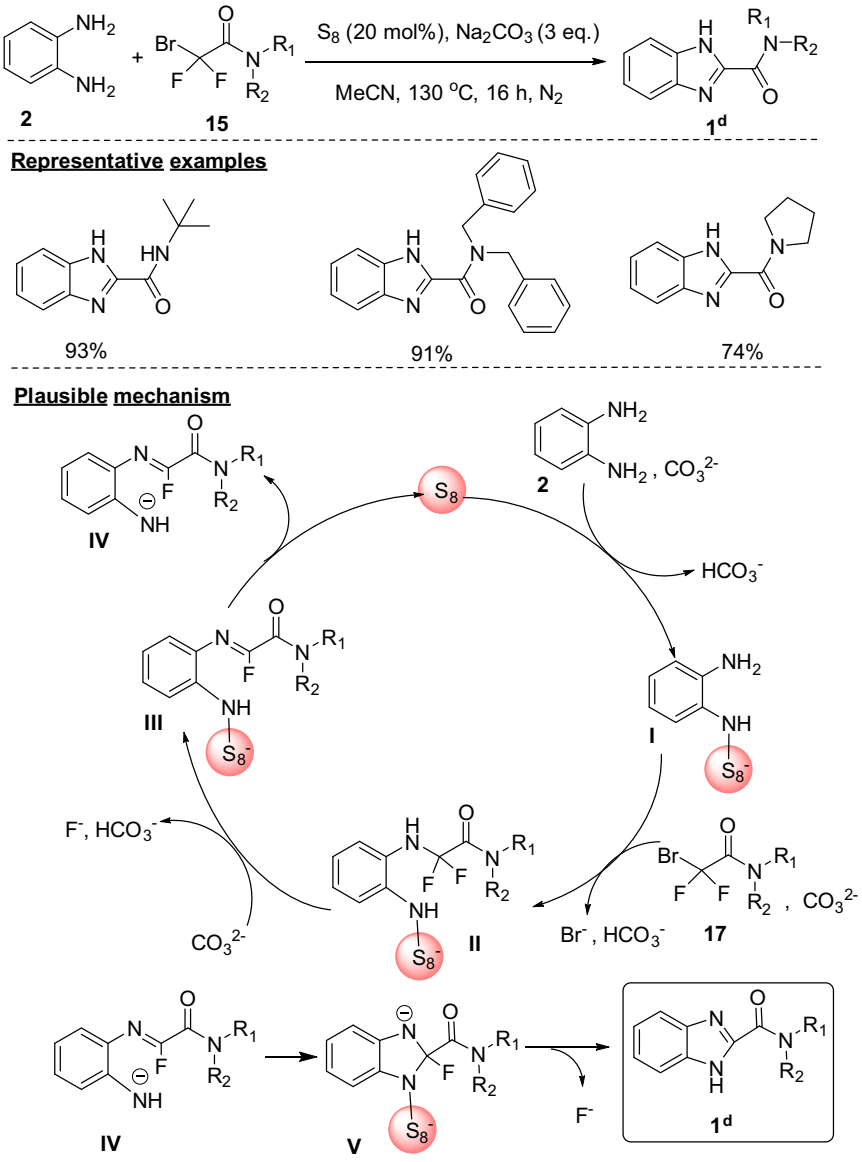
Leila et al. recently prepared a zingiber extract based on the Cr_2O_3 nanocatalyst, used as a precursor for the synthesis of polysubstituted imidazoles **1[b]** from aromatic aldehydes **8**, ammonium acetate **21**, and benzil **22** under microwave irradiation in the presence of H_2O as a solvent for 4–5 min, which gave a high yield of up to 98% (Scheme 14). When aldehyde has electron-donating groups, yields are higher than those with electron-withdrawing groups. This methodology is a simple and efficient route for synthesizing imidazole derivatives without using other inorganic solvents [39].

Natalia and Diana reported an efficient and environmentally friendly method for the synthesis of triaryl-1*H*-imidazoles or 2-aryl-1*H*-phenanthro[9,10-*d*]imidazoles **(1[d]/1[d']**) using dicarbonyl compound **22/23**, ammonium acetate **21**, and aromatic aldehydes **8** in the presence of the urea–$ZnCl_2$ deep eutectic solvent (DES) as a precursor at 110°C under 30 min. They afforded imidazole derivatives in good to excellent yield (Scheme 15) [40].

3.2 Synthesis of imidazoles under solvent-free conditions

Zeinab and Mohammad prepared a new magnetic polymer catalyst named cross-linked poly(4-vinylpyridine)-supported Fe_3O_4 nanoparticles ([P_4-VP]-Fe_3O_4NPs) for the synthesis of 2,4,5-trisubstituted imidazole derivatives **1[b]**. The one-pot condensation reaction was between benzil **22**, aldehydes **8**, and ammonium acetate **21** in the presence of [P_4-VP]-Fe_3O_4 catalyst under short reaction time (20–80 min) at 100°C [method a] (Scheme 16). The best result (yield: 99%) was obtained with 100 mg of the catalyst under solvent-free conditions [41]. The catalyst exhibits commendable catalytic efficiency when employed to synthesize imidazole derivatives.

Leila et al. also described the synthesis of 2,4,5-trisubstituted imidazoles **1[b]** using benzil **22**, ammonium acetate **21**, and aryl aldehydes **8** in the presence of amino glucose-functionalized silica-coated $NiFe_2O_4$ nanoparticles ($NiFe_2O_4$@SiO_2@amino glucose) as a catalyst under solvent-free conditions at rt for 10 min (method b) (Scheme 16) [42].

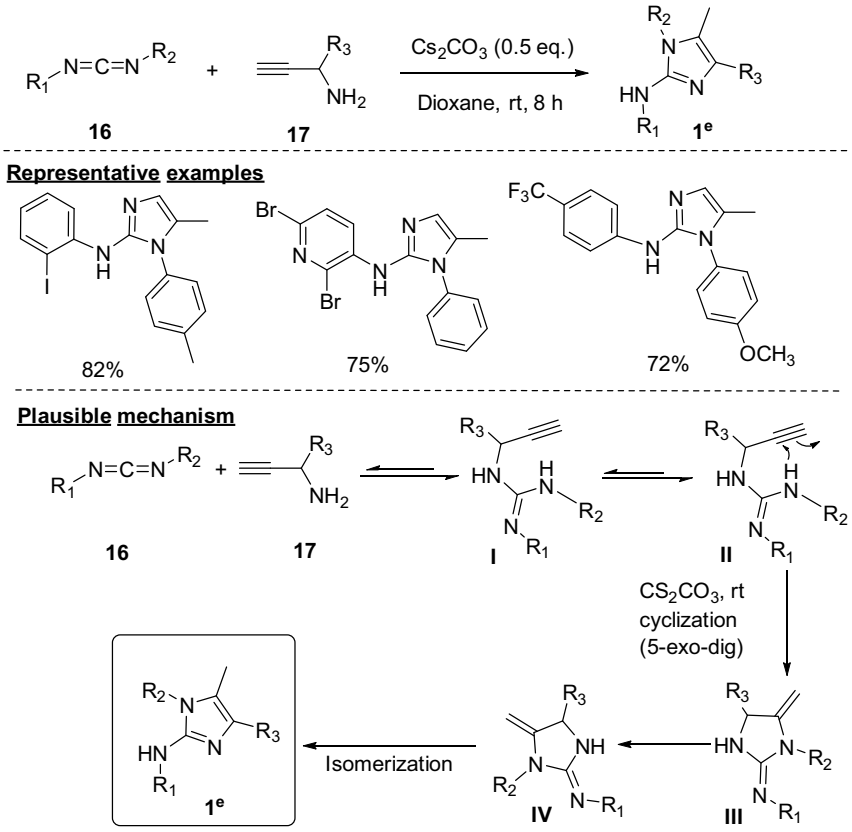


Scheme 10: Synthesis of 2-amido-substituted benzimidazoles using S_8.

Jayant et al. also reported another route for the synthesis of 2,4,5-trisubstituted imidazole derivatives **1[b]** using aromatic aldehydes **8**, benzil **22**, and ammonium acetate **21** in lactic acid as a precursor at 160°C (method c) (Scheme 16) [43].

Faranak et al. recently described one-pot synthesis of 2,4,5-trisubstituted imidazoles **1[b]** under solvent-free conditions [44]. The reaction between benzil **22**, aldehydes **8**, and ammonium acetate **21** in the presence of MIL-101 (chromium(III) benzene-1,4-dicarboxylate) catalyst at 120°C gave excellent yield (method d) (Scheme 16). There are several advantages of the above method, such as short reaction time and simple procedure, and the catalyst could be reused several times without loss in its activity.

A one-pot reaction between benzil **22**, ammonium acetate **21,** and aromatic aldehydes **8** in the presence of LADES@MNP catalyst under solvent-free sonication conditions gave an excellent yield of 2,4,5-trisubstituted imidazoles **1[b]** was also developed by Nguyen et al. (method e) (Scheme 17) [45]. In the reaction, the Lewis acid properties of the LADES@MNP catalyst activate the oxygen atoms of carbonyl groups to accept nucleophiles and intramolecular cyclization to form the expected product. The depicted mechanism is shown in Scheme 17.



Scheme 11: Synthesis of 2-aminoimidazoles from carbodiimides and propargylic amines.

3.3 Synthesis of imidazoles using an organic solvent

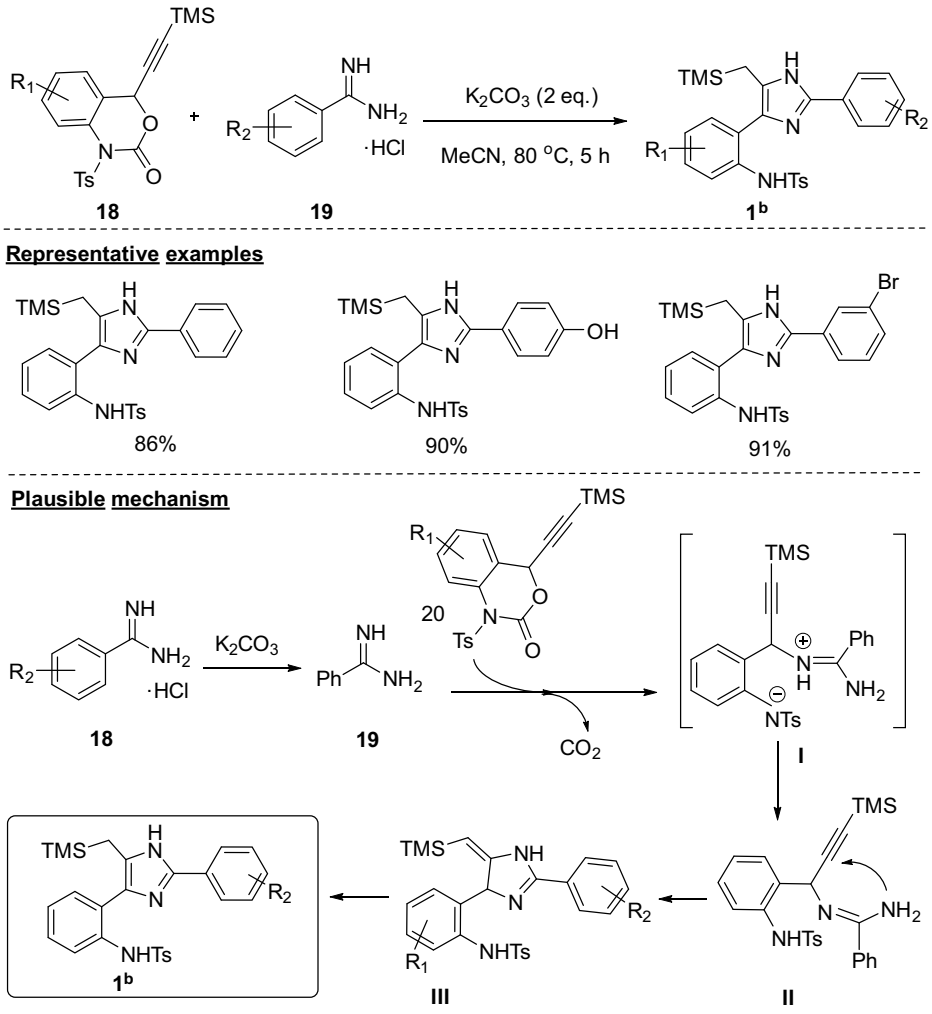
Wei et al. described the two routes for synthesizing substituted imidazoles **1[c]/1[f]** under metal-free three-component between amidines **25**, ynals **26**, and sodium sulfonates **27** as a substrate. They generate sulfonylated imidazoles **1[c]** in the first route, using AcOH as a promoter in EtOH at 70°C, and the other route generates 1f in the presence of TBHP in MeCN at 70°C and gives excellent yield in both conditions (Scheme 18). This transition-metal-free protocol is an efficient and environmentally friendly procedure for synthesizing substituted imidazoles for future purposes [46].

A three-component reaction between amidines **25**, ynals **26**, and boronic acids **28** for the synthesis of imidazole derivatives **1[f]** through transition metal-free C–B bond cleavage was reported by Changcheng et al. The reaction proceeded in the presence of PivOH as a catalyst in *n*-hexane at 80°C under mild conditions (Scheme 19). In the reaction, various functional groups could afford an excellent yield of imidazole-containing triarylmethanes **1[f]** [47].

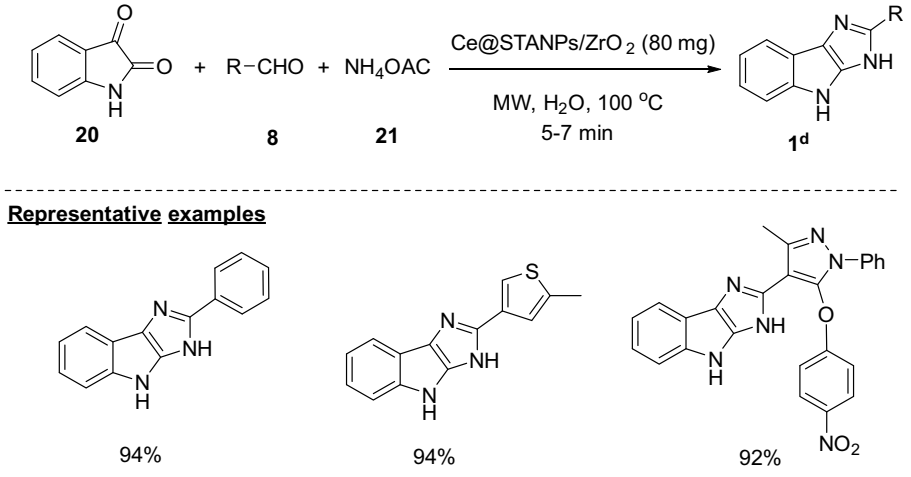
The synthesis of 4- and 5-hydroxyalkyl substituted imidazoles **1[c]/1[f]** under a three-component reaction of amidines **25**, ynals **26**, and water as a substrate was established by Wei et al. The best result of 4-hydroxyalkyl-substituted imidazoles **1[c]** was obtained when $NaSO_2CF_3$/TsOH was used as an additive in toluene at 80°C for 4 h. Meanwhile, they also synthesized 5-hydroxyalkyl-substituted imidazoles **1[b]** using the same starting material in the presence of CuI in DMSO at 80°C for 4 h (Scheme 20) [48].

Stefanie et al. reported a three-component synthesis of 1,4,5-trisubstituted imidazoles **1[g]** via Van Leusen cyclization using primary amines **7**, toluenesulfonyl isocyanides **29,** and aldehyde-functionalized DNA conjugate molecule **30**, under basic conditions and afforded a high yield of up to 97% (Scheme 21). They optimized various organic bases but obtained a low yield and oxazol formation as a side product. The best result was obtained when morpholine was used as a base under a high percentage of dimethylacetamide (DMA, 62%) under mild heating (45°C) conditions [49].

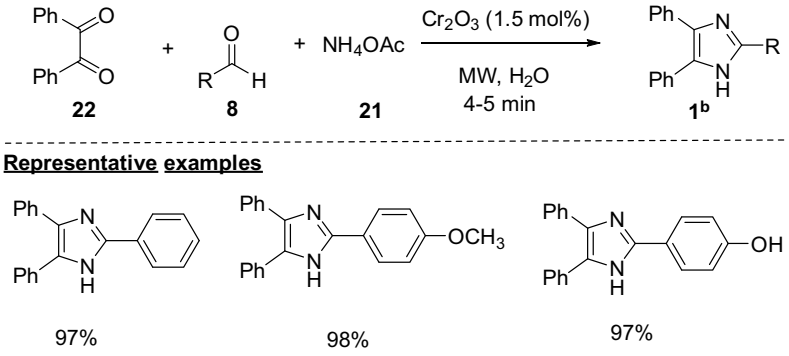
A one-pot multicomponent reaction for the synthesis of substituted imidazoles **1[h]**, under Van Leusen [2 + 2 + 1] cyclization between aryl methyl ketones **6**,2-aminobenzyl alcohols **31**, and *p*-toluene sulfonyl methyl isocyanide (TosMIC) **32** in the presence of $I_2/FeCl_3$ as a co-catalyst in DMSO at 110°C was



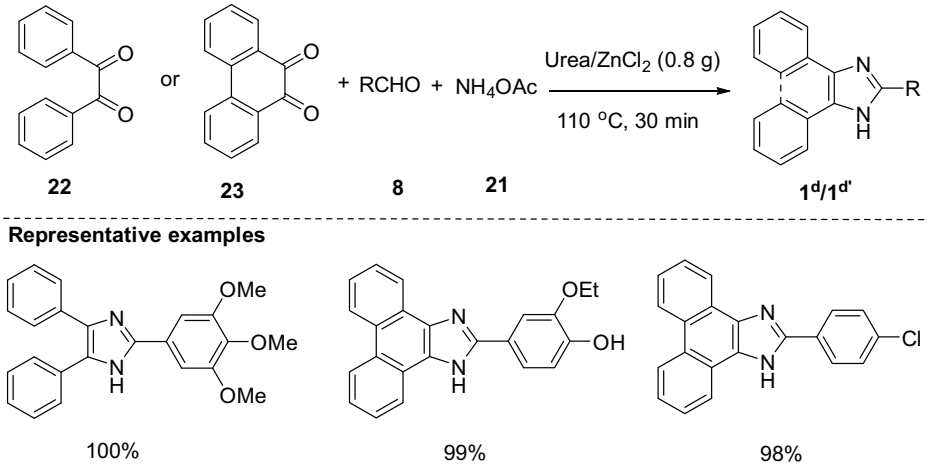
Scheme 12: Synthesis of imidazoles using benzoxazinanones and benzimidamides.



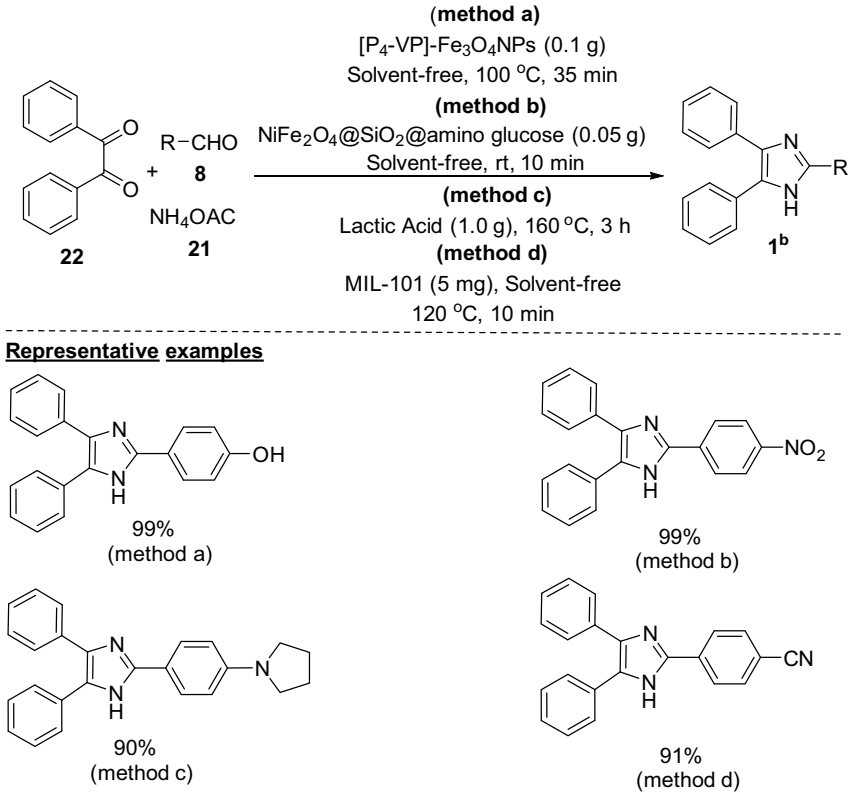
Scheme 13: Synthesis of imidazole derivatives using the Ce@STANPs/ZrO_2 catalyst in water.



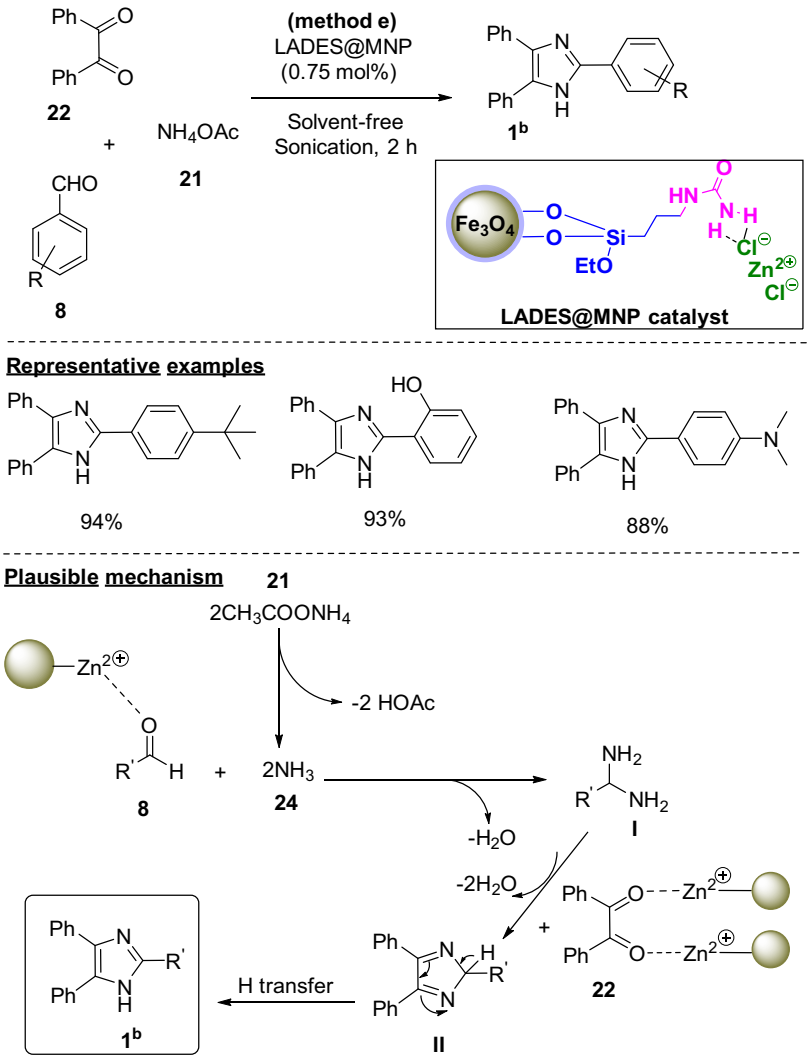
Scheme 14: Synthesis of trisubstituted imidazoles using the Cr_2O_3 nanocatalyst in water.



Scheme 15: Synthesis of trisubstituted imidazoles using DES.



Scheme 16: Synthesis of trisubstituted imidazoles under solvent-free conditions.



Scheme 17: Synthesis of trisubstituted imidazoles using LADES@MNP catalyst under solvent-free sonication.

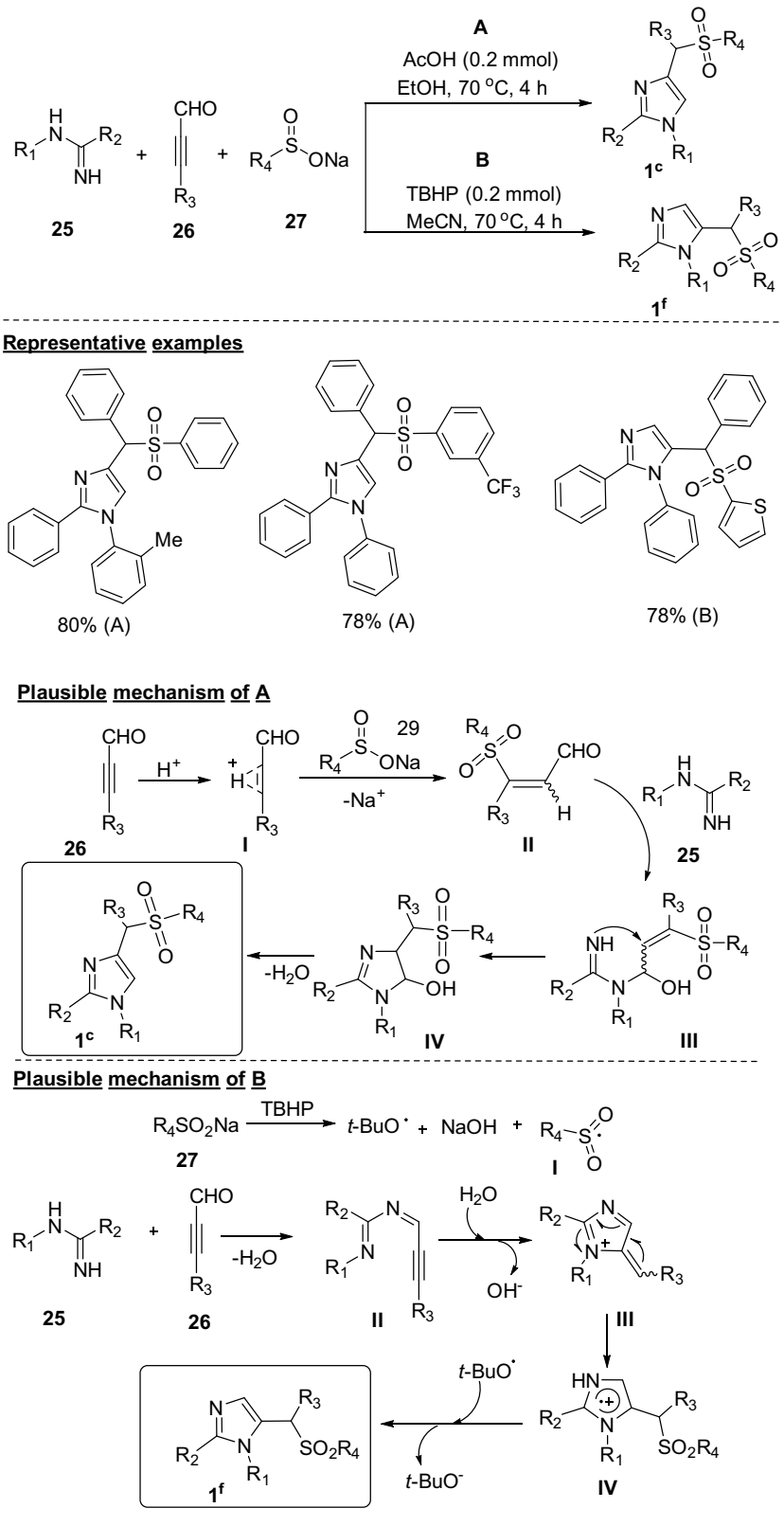
developed by Xiao et al. [50]. In this reaction, they introduced a neighboring-assisted group (−CH_2OH) to avoid imine intermediate formation and then *in situ*-generated intermediate $TsCH_2NH_2$ **35** by hydrolysis and further underwent cyclization and ring opening to obtain a high yield of 1,4-disubstituted imidazole derivatives **1[d]**; the possible mechanism is shown in Scheme 22.

The Radziszewski reaction was used to create new porphyrin-imidazole derivatives **1[b]/1[b']** from 2-formyl-5,10,15,20-tetraphenylporphyrin **36**, heteroaromatic 1,2-diones **37/38**, and ammonium acetate **21** in the presence of toluene/acetic acid as a solvent under reflux for 3 h and obtained a high yield up to 99% (Scheme 23), as reported by Xavier et al. [51].

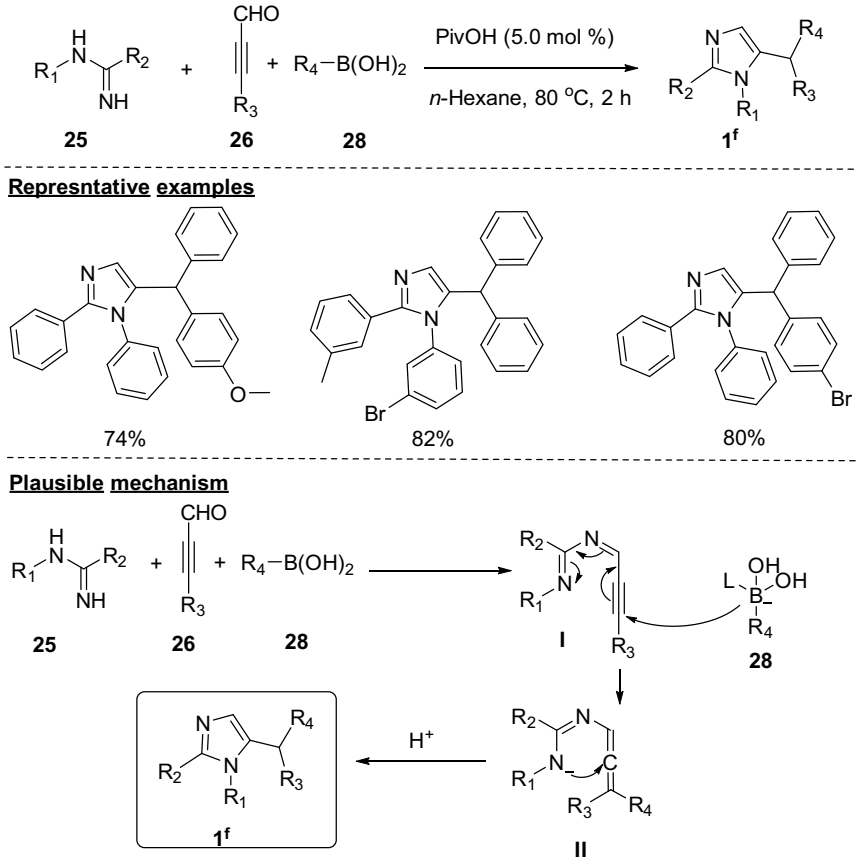
Mansouria et al. synthesized fatty imidazoles **1[b]/1[i]** using fatty 1,3-diketones **39** (derived from methyl oleate), ammonium acetate **21**, and various aldehydes **8** through the Debus–Radziszewski reaction. The reaction proceeded under microwave irradiation in AcOH at 180°C under 5 min and produced a high yield of fatty imidazole derivatives **1[b]/1[i]** (Scheme 24) [52].

Amol et al. described a one-pot, three-component synthesis of substituted imidazole derivatives **1[d]** using isatin **20**, aromatic aldehydes **8**, and ammonium acetate **21** as a substrate, which was catalyzed by *β*-cyclodextrin (*β*-CD) (15 mol %) using H_2O/EtOH as a solvent. The mixture was refluxed at 80°C (Scheme 25). During optimization, they used H_2O, EtOH, and various organic solvents, but the best yield of the desired 1,8-dihydroimidazo[2,3-*b*]indoles **1[d]** (95% of yield) was obtained when H_2O/EtOH (9:1) was used as a solvent [53].

A one-pot three-component reaction was used for the synthesis of trisubstituted imidazole derivatives **1[b]** using benzil/benzoin **22/22"**, various aldehydes **8**, and ammonium acetate **21** in the presence of newly synthesized



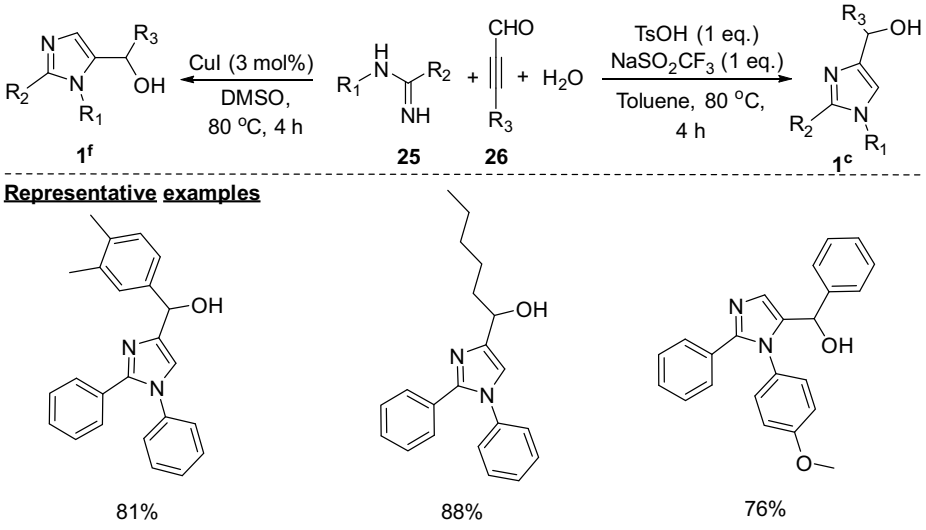
Scheme 18: Synthesis of imidazoles from amidines, ynals, and sodium sulfonates.



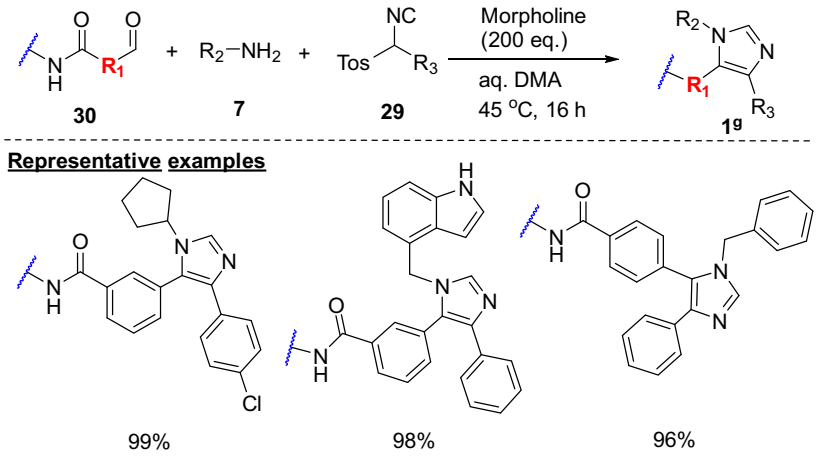
Scheme 19: Synthesis of imidazole derivatives using metal-free PivOH catalyst.

supermagnetic heterogenous Bronsted acidic sulfonated nanocomposite (Fe_3O_4@PVA–SO_3H) as a catalyst in EtOH at room temperature, as described by Ali et al. (method f) (Scheme 26) [54].

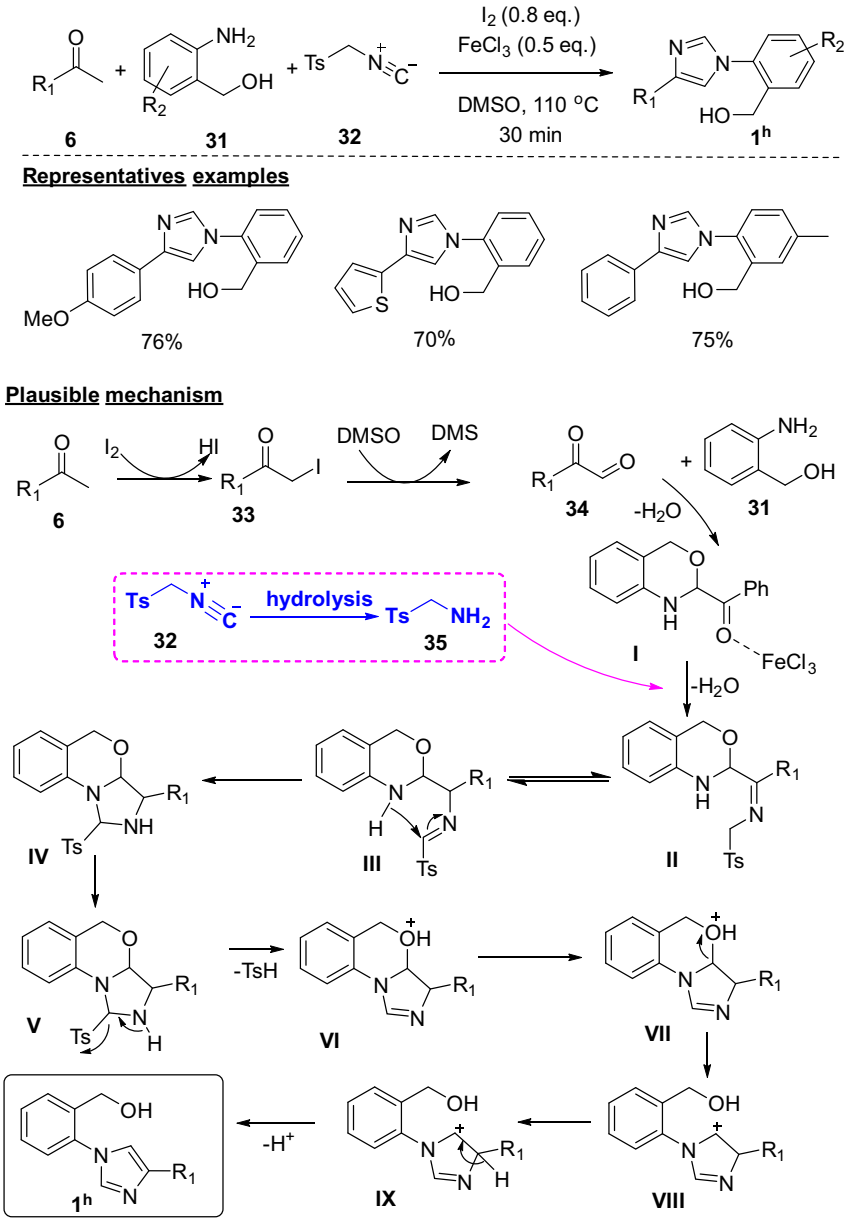
Zahra and Ali designed an efficiently mixed transition metal oxide (MTMO) nanocatalyst, ZnS-$ZnFe_2O_2$, by the chemical co-precipitation method. They also described the one-pot synthesis of 2,4,5-triaryl-1*H*-imidazole derivatives



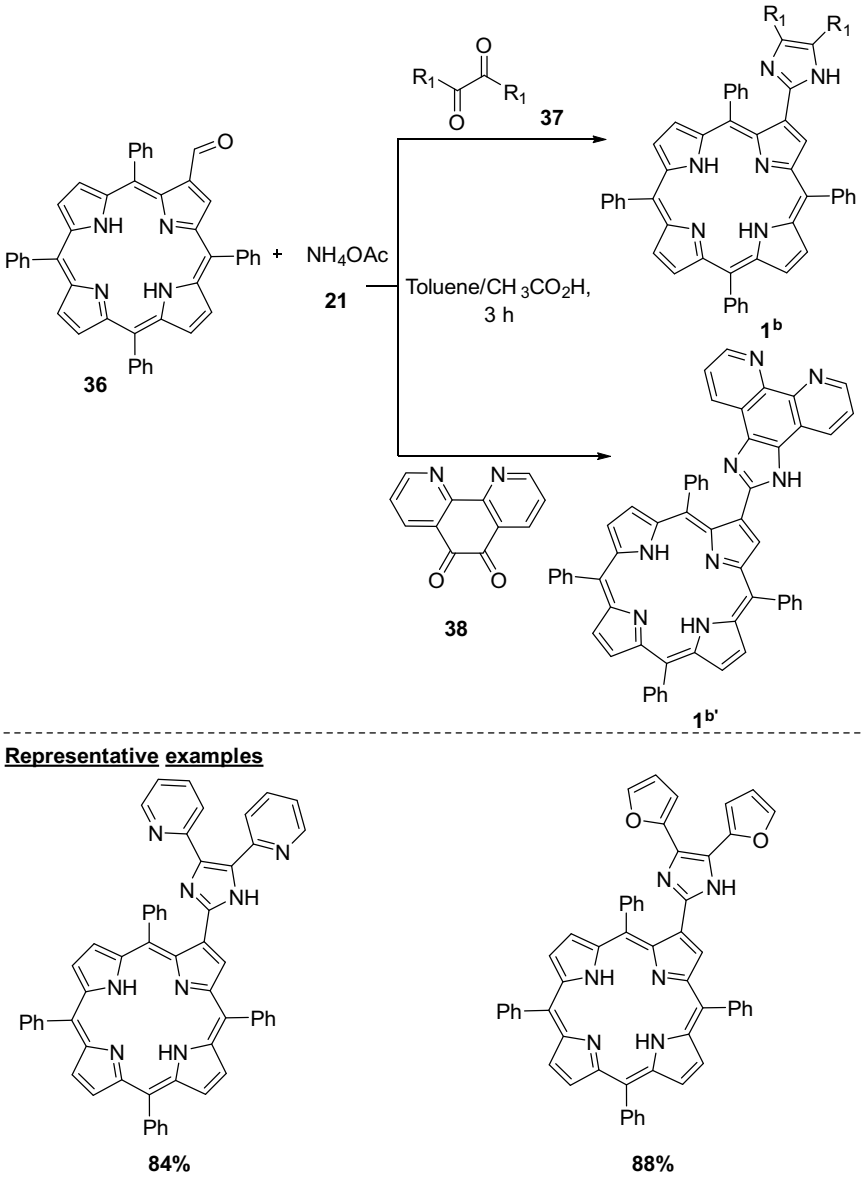
Scheme 20: Synthesis of 4- and 5-hydroxyalkyl-substituted imidazole derivatives.



Scheme 21: Synthesis of imidazole derivatives from aldehyde DNA conjugate molecules.



Scheme 22: Synthesis of imidazole derivatives using TosMIC.

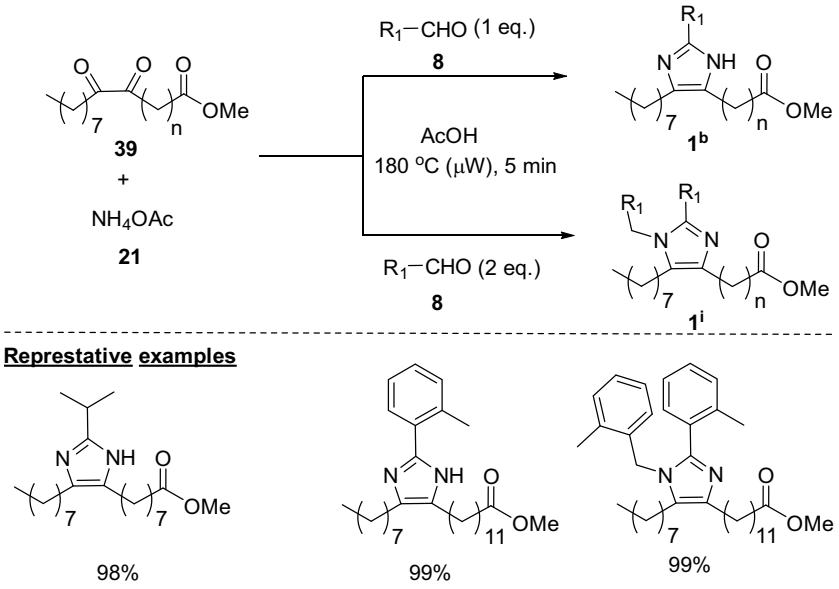


Scheme 23: Synthesis of porphyrin-imidazole derivatives.

1[b] by cyclic condensation of benzil **22**, various aldehydes **8**, and ammonium acetate **21** using ZnS-$ZnFe_2O_2$ (2 mg) as a catalyst in ethanol under ultrasonic irradiation at 70°C. They obtained excellent yields of up to 95% under short reaction time (method g) (Scheme 26). The yield was not affected when the amount of catalyst was increased. The ZnS-$ZnFe_2O_4$ MTMO catalyst acts as a Lewis acid, which interacts with the oxygen of the carbonyl group of benzaldehyde [55]. The benefits of this methodology are mild reaction conditions, high product yields, simple recyclability, high atom economy, and environmentally benign conditions.

For the synthesis of 2,4,5-trisubstituted imidazoles **1[b]**, Mehdi and Zohre also reported using the same substrates of benzil **22**, aldehydes **8**, and ammonium acetate **21** in the presence of magnetic SO_3H@zeolite-Y nanocomposite-supported nano-Fe_3O_4 (Fe_3O_4/SO_3H@zeolite-Y) as a catalyst in ethanol at 80°C (method h) (Scheme 26) [56].

Gyanendra et al. designed an efficient and eco-friendly nanocatalyst of graphene oxide/NiO nanocomposites (rGO-NiO-NCs), which was used as a promoter for the synthesis of imidazole derivatives **1[b]** using benzil **22**, aldehydes **8**, and ammonium acetate **21** in ethanol at 55°C under 60 min and obtained a high yield (86–96%) (method i) (Scheme 26) [57].



Scheme 24: Synthesis of imidazole derivatives from fatty 1,2-diketones.

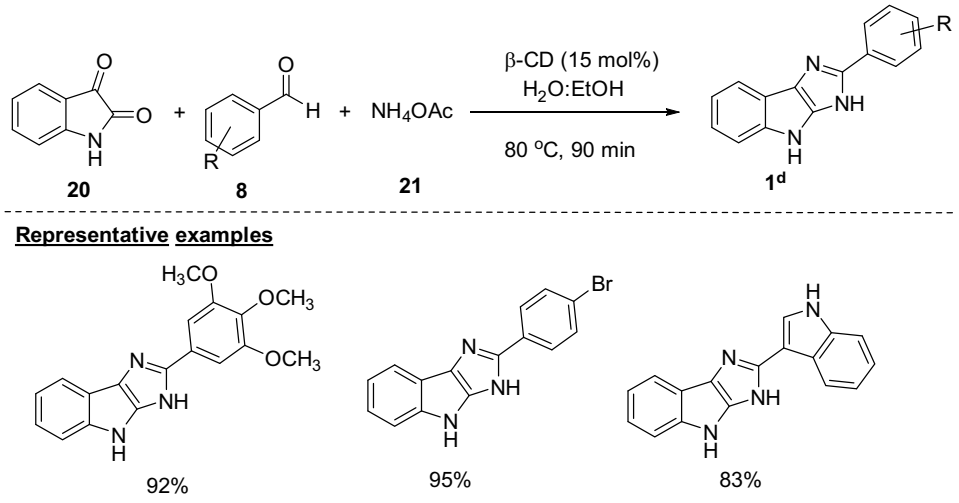
A novel pyromellitic diamide–diacid-bridged mesoporous organosilica (PMAMOS) nanosphere with different morphologies and Bronsted acid catalytic centers was prepared under green conditions by Ehsan and Mohammad. Recently, they synthesized substituted imidazoles **1[b]** from benzyl/benzoin **22/22′**, ammonium acetate **21**, and different aldehydes **8** in the presence of PMAMOS as a catalyst in EtOH under reflux conditions (method j) (Scheme 26). The best yield of 2,4,5-trisubstituted imidazole derivatives **1[b]** was obtained when 15 mg of PMAMOS was used as a nanocatalyst. This heterogeneous catalyst can be reused several times without loss of any catalytic activity [58].

Babak and Mohammad also synthesized the trisubstituted imidazoles **1[b]** using the three components of benzil/benzoin **22/22″**, aldehydes **8**, and ammonium acetate **21** with a newly prepared supramolecular Fe_3O_4/SiO_2-decorated trimesic acid-melamine (Fe_3O_4/SiO_2-TMA-Me) nanocomposite as a catalyst in EtOH (method k) (Scheme 26) [59].

4 Four-component methods

4.1 Synthesis of imidazoles using water as a solvent

Ravi et al. reported a one-pot four-component reaction for the synthesis of 1,2,4,5-tetrasubstituted imidazoles **1[i]** using



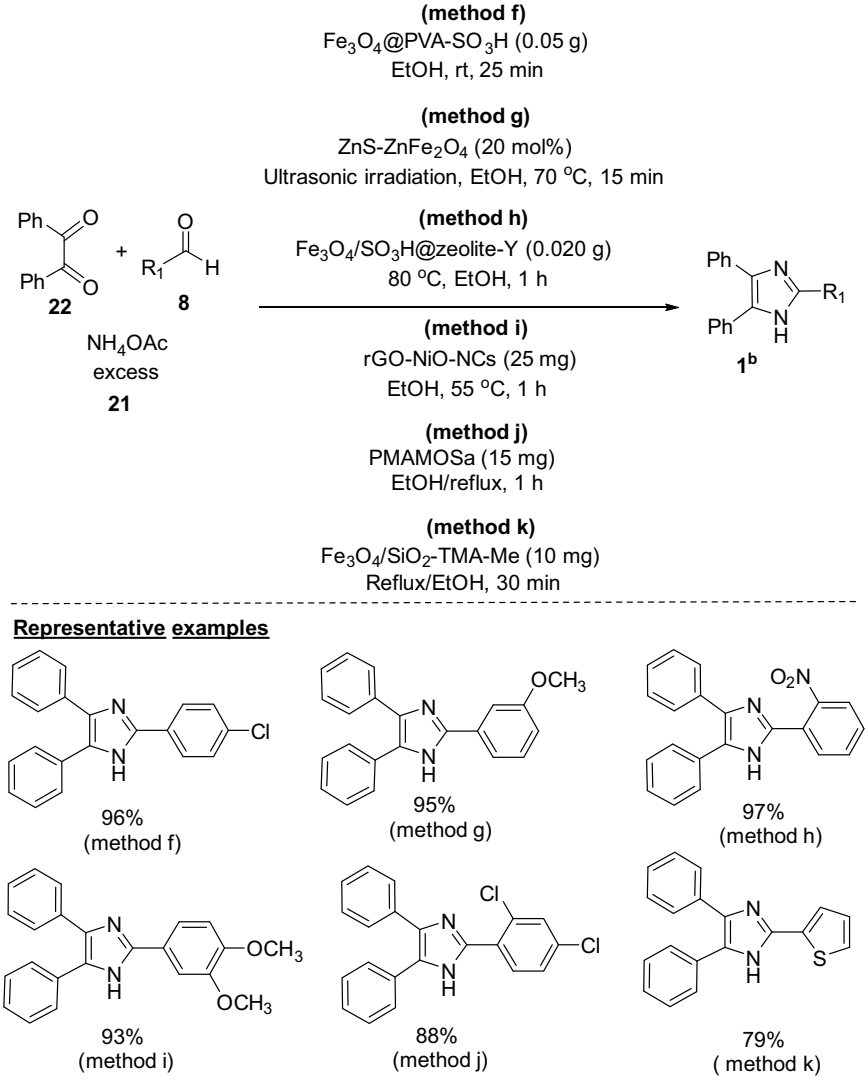
Scheme 25: Synthesis of 2-phenyl-3,4-dihydroimidazo[4,5-*b*]indoles using *β*-CD catalyst.

benzil **22**, aldehydes **8**, anilines **7**, and ammonium acetate **21** in the presence of sodium lauryl sulfate (SLS) as a catalyst in water under reflux at 80°C; after 1 h, the desired product was obtained in up to 95% yield (Scheme 27). It is an efficient and convenient method for synthesizing substituted imidazoles under simple and environmentally friendly conditions [60].

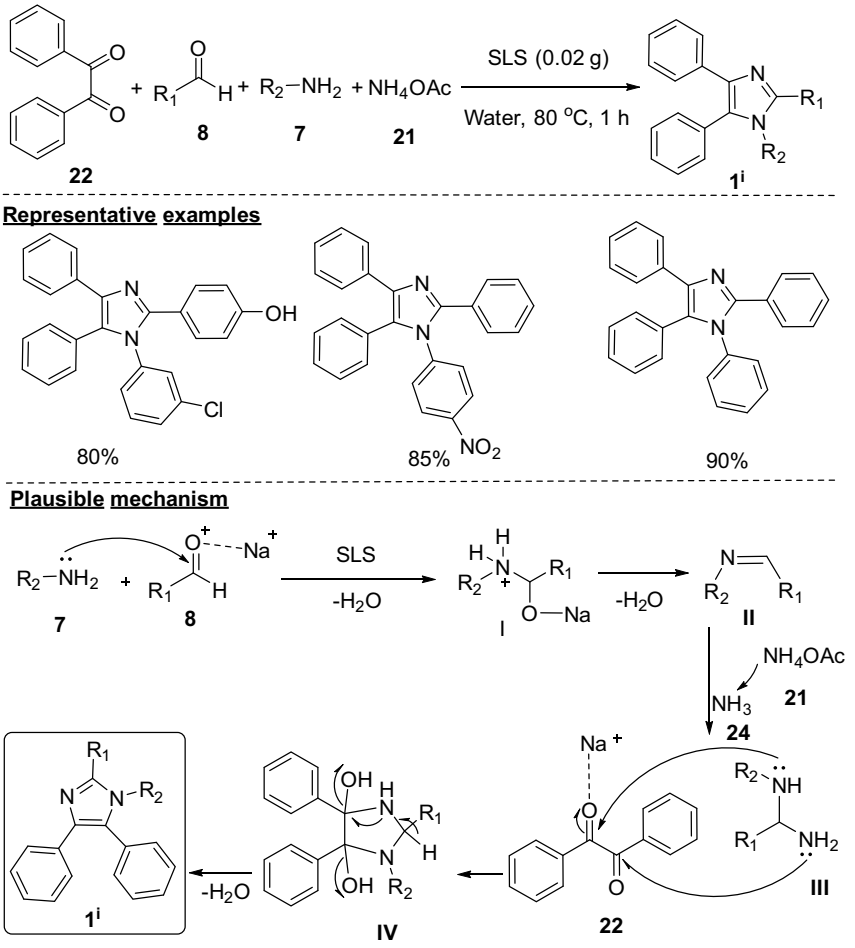
4.2 Synthesis of imidazoles under solvent-free conditions

Maryam et al. prepared a new nano-Fe_3O_4@$Ca_3(PO_4)_2$ catalyst synthesized from an eggshell as a solid waste with Fe_3O_4 nanoparticles. The newly synthesized nano-Fe_3O_4@$Ca_3(PO_4)_2$ catalyst was used as a promoter for the synthesis of 1,2,4,5-tetra-substituted imidazole derivatives **1**^{i} via a one-pot four component of benzaldehydes **8**, anilines **7**, benzoin **22″,** and ammonium acetate **21** at 95°C (method l) (Scheme 28). The best yield of up to 90% was obtained using 0.05 g of the synthesized catalyst under solvent-free conditions [61].

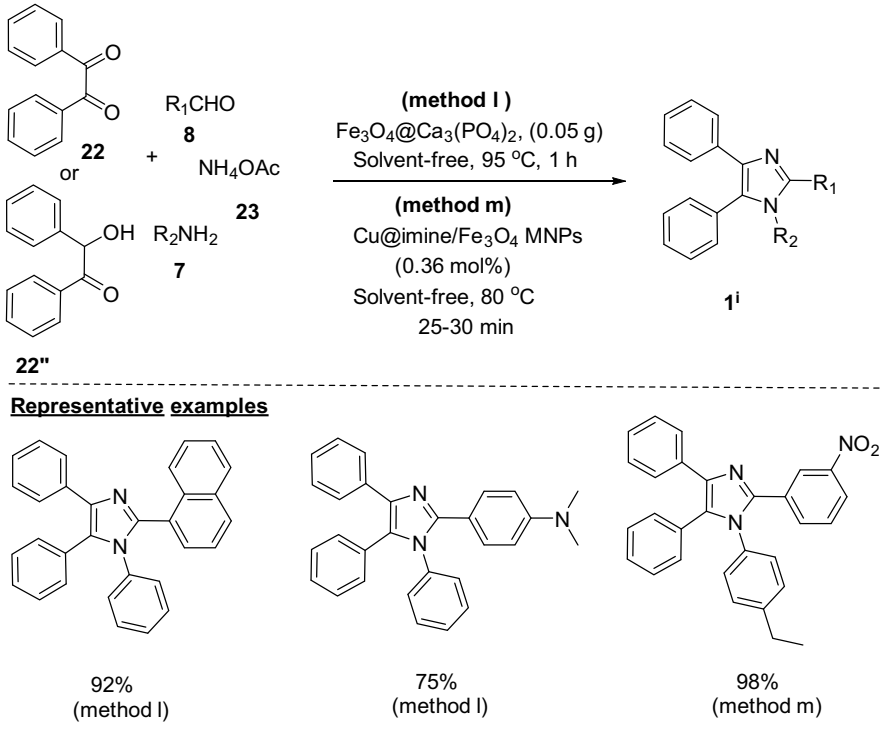
Myo et al. also reported the synthesis of 1,2,4,5-tetra-substituted imidazole derivatives **1**^{i} using benzil **22**, benzaldehydes **8**, benzalamines **7**, and ammonium acetate **21** in the presence of Cu@imine/Fe_3O_4 MNPs as a catalyst at 80°C under solvent-free conditions (method m) (Scheme 28). Both electrons, the donating and withdrawing groups, at the meta and para positions of the benzene ring of aldehydes and amines, gave an excellent yield of the desired imidazole derivatives (up to 95%) [62].



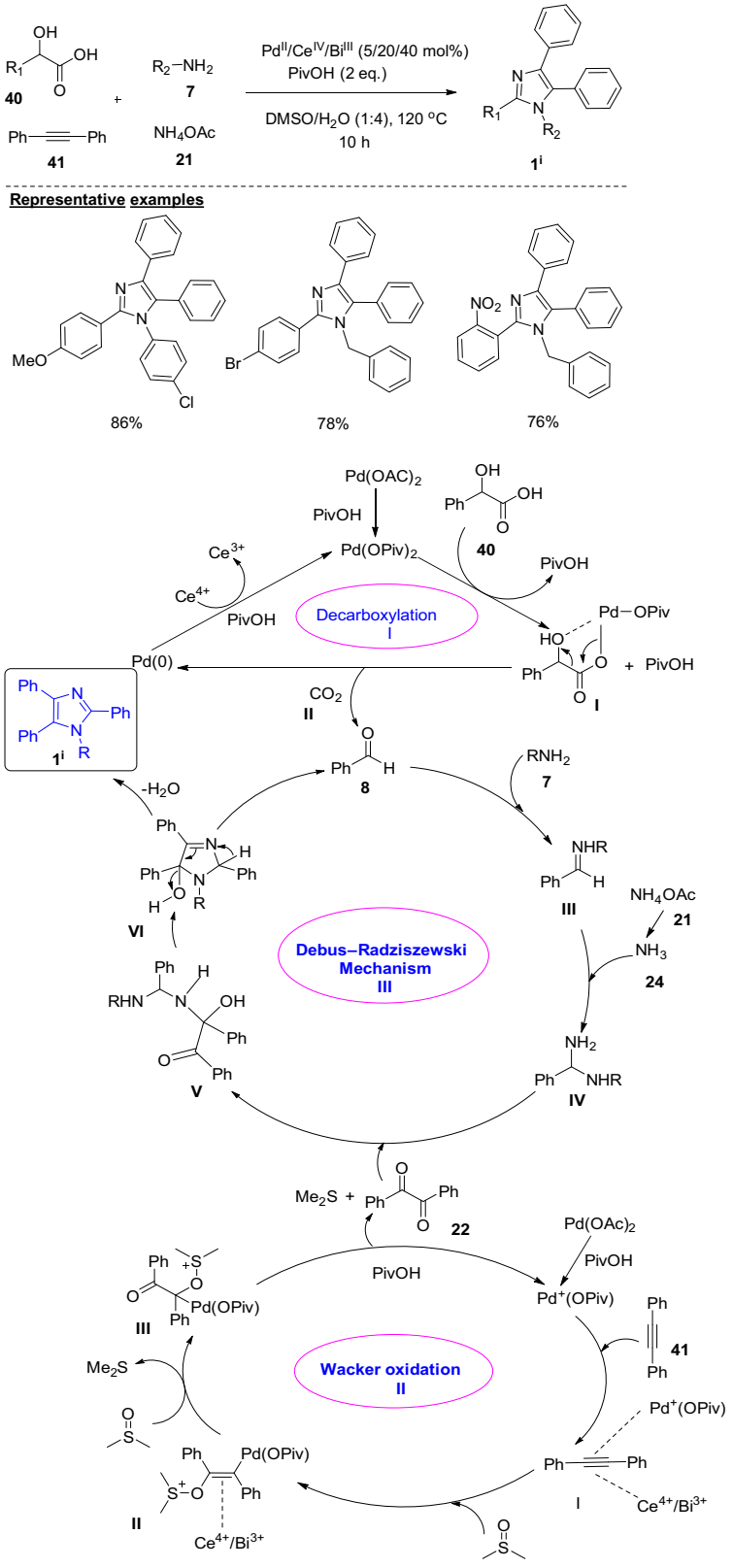
Scheme 26: Synthesis of 2,4,5-trisubstituted imidazoles in ethanol as a solvent.



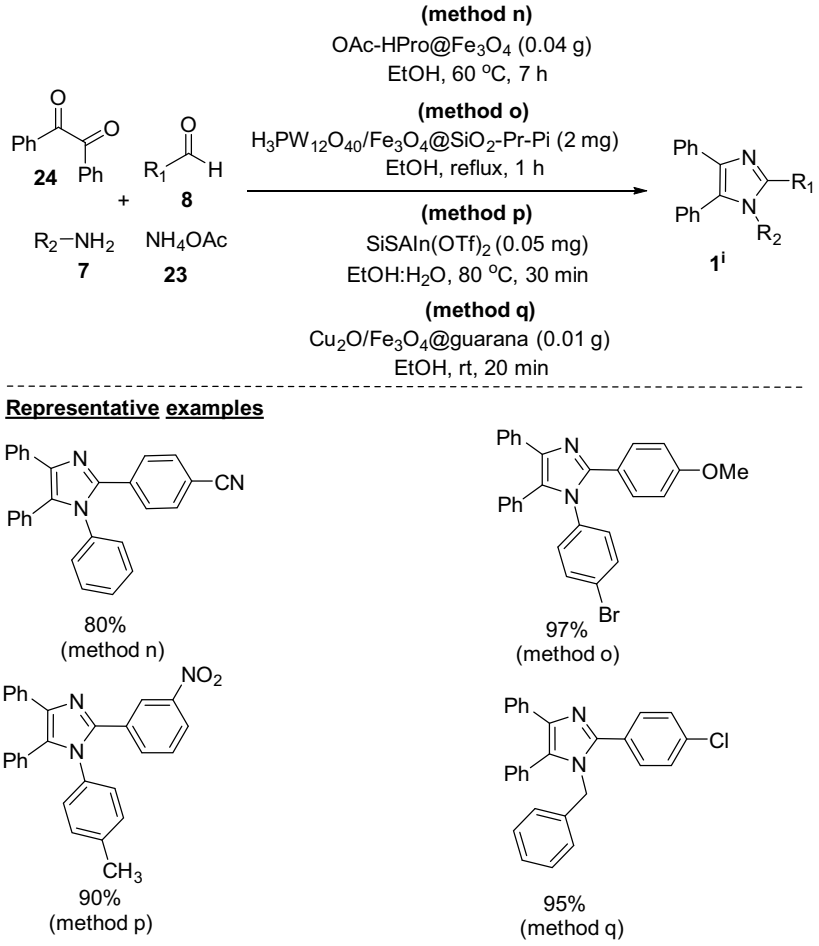
Scheme 27: Synthesis of 1,2,4,5-tetrasubstituted imidazoles using SLS catalyst.



Scheme 28: Synthesis of tetrasubstituted imidazoles under solvent-free conditions.



Scheme 29: Synthesis of tetrasubstituted imidazoles using $Pd^{II}/Ce^{IV}/Bi^{III}$ catalyst.



Scheme 30: Synthesis of tetrasubstituted imidazoles using various catalysts in EtOH.

4.3 Synthesis of imidazoles using organic solvents

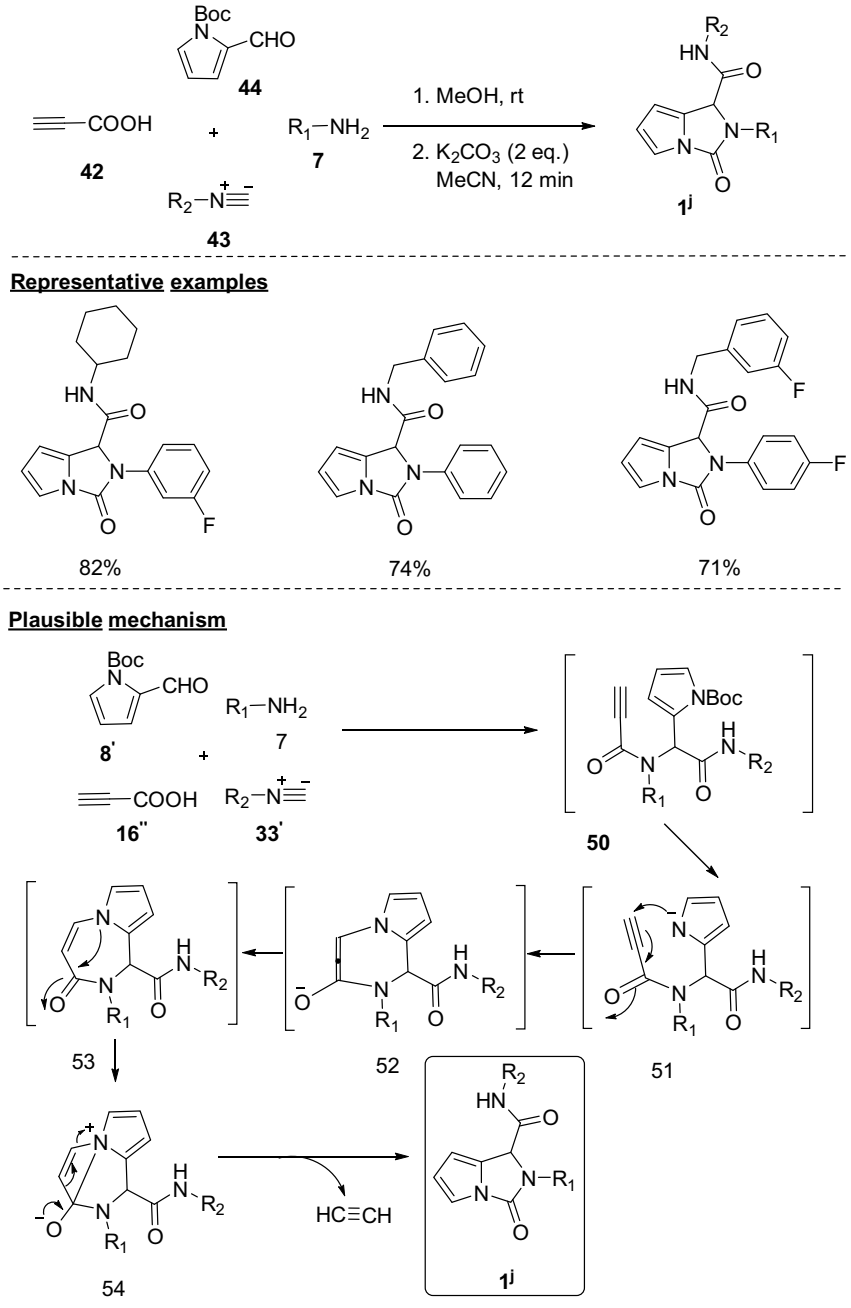
An efficient synthesis of tetra-substituted imidazoles **1**^{i} from *α*-hydroxyphenyl-acetic acids **40**, diphenylacetylene **41**, primary amines **7**, and ammonium acetate **21** was catalyzed by $Pd(OAc)_2/Ce(SO_4)_2/Bi(NO_3)_3$ (tri-metallic system) in DMSO/H_2O at 120°C, as described by Wei et al. The reaction proceeds via decarboxylation of α-hydroxyphenylacetic acid oxidation of diphenylacetylene through the Wacker process, followed by Debus–Radziszewski annulation. The plausible mechanism of the reaction is shown in Scheme 29 [63].

A one-pot four component of benzils **22**, aldehydes **8**, amines **7**, and ammonium acetate **21** was used as a substrate to synthesize 1,2,4,5-tetrasubstituted imidazoles **1**^{i} in the presence of a newly derived magnetic bifunctional L-proline artificial enzyme (OAc-HPro@Fe_3O_4) that acts as a catalyst in ethanol at 60°C and obtained a high yield in the range 70–90%, as described by Hamideh et al. (method n) (Scheme 30) [64].

Ramin et al. also synthesized tetra-substituted imidazole derivatives **1**^{i} under *in situ* oxidation–condensation between benzoin **22″**, aldehydes **8**, amines **7,** and ammonium acetate **21** in the presence of $H_3PW_{12}O_{40}/Fe_3O_4@SiO_2$–Pr–Pi magnetic nanoparticles as a catalyst in EtOH under reflux conditions (method o) (Scheme 30) [65].

Rupali and Monika also developed another route for the synthesis of tetrasubstituted imidazoles **1**^{i} from benzil **22**, aldehydes **8**, amines **7**, and ammonium acetate **21** catalyzed by sulfoacetate-modified silica-supported indium(III) triflate ($SiSAIn(OTf)_2$) in EtOH/H_2O at 80°C (method p) (Scheme 30). Different amounts of the synthesized catalyst were used in the reaction, but the best yield of 80–85% was obtained when 0.05 mg of catalyst was used [66].

Moreover, recently, Zahra et al. also reported the efficient synthesis of 1,2,4,5-tetrasubstituted imidazoles **1**^{i} using a newly synthesized hybrid nanocatalyst of guar gum with iron oxide and copper oxide nanoparticles (Cu_2O/Fe_3O_4@guarana) as a catalyst under one-pot multicomponent of benzil **22**, aldehydes **8**, amines **7,** and ammonium acetate **21** in EtOH under



Scheme 31: Synthesis of pyrrole-imidazole derivatives at room temperature.

ultrasonication at room temperature. After 20 min, a yield of up to 97% was obtained (method q) (Scheme 30) [67].

Ming et al. developed a one-pot, four-component synthesis of pyrrole-imidazoles derivatives **1j** followed by a post-Ugi cascade reaction. In the reaction, the mixture of *tert*-butyl 2-formyl-1*H*-pyrrole-1-carboxylate **44**, anilines **7**, propionic acid **42**, and benzyl isocyanides **43** in methanol, stirred at room temperature overnight gave an intermediate. Then, the intermediate mixture was further heated at high temperature under microwave conditions with an additive K_2CO_3 (2 eq.) and MeCN for 20 min and obtained the desired product **1j** in high yield. The plausible mechanism is shown in Scheme 31 [68].

5 Conclusions

This review has provided a comprehensive overview of recent advancements in imidazole synthesis, demonstrating

a solid commitment to efficiency and versatility. They were based on solvents and solvent-free conditions while effectively employing catalysts in multicomponent reactions. These innovations hold great promise for sustainable and adaptable imidazole synthesis, impacting various applications from pharmaceuticals to materials science. The dynamic evolution of imidazole synthesis signifies a bright future, marked by more efficient and versatile pathways for imidazole derivative production, ensuring the continued advancement of the field.

Acknowledgment: Mayanglambam Maneeta Devi is grateful to UGC, Govt. of India, for the fellowship provided.

Funding information: Authors state no funding involved.

Author contributions: Mayanglambam Maneeta Devi designed this article and wrote the manuscript. Dr. Keisham Subarani Devi contributed to designing the schemes. Professor Okram Mukherjee Singh and Dr. Thokchom Prasanta Singh provided technical guidance and overall modifications.

Conflict of interest: Authors state no conflict of interest.

Data availability statement: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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