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REVIEW ARTICLE

Michael Addition of Imidazole to *α, β* -Unsaturated Carbonyl/Cyano Compound

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Abstract:

Introduction:

Aza-Michael addition is an important reaction for carbon-nitrogen bond formation in synthetic organic chemistry.

Explaination:

Conjugate addition of imidazole to *α,β*-unsaturated carbonyl/cyano compounds provides significant numbers of the biologically and synthetically interesting products, such as *β*-amino acids and *β*-lactams, which have attracted great attention for their use as key intermediates of anticancer agents, antibiotics and other drugs.

Conclusion:

This review addresses most significant method for the synthesis of N-substituted imidazole derivatives following Michael addition reaction of imidazole to *α,β*-unsaturated carbonyl/cyano compounds using ionic liquid/base/acid/enzyme as catalysts from year 2007-2017.

Keywords: Michael addition, Imidazole derivative, Methyl acrylate, Silica sulfuric acid, Heterocycles, Ionic liquids.

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1. INTRODUCTION

Michael Addition Reaction [1] is one of the most powerful methods in organic synthesis for C–C and C–X (X=O, N, S) bond formation (Fig. **1**). Michael addition of imidazoles to *α,β*-unsaturated carbonyls/cyano compound represents a powerful synthetic approach in the area of synthetic heterocyclic chemistry and have attracted the attention of many chemist and biologists due to its applications in pharmaceutical research, agriculture science, and drug discovery.
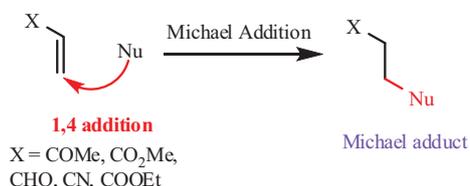

X = COMe, CO$_2$Me, CHO, CN, COOEt

Fig. (1). Michael addition reaction.

Imidazole ring is a constituent of several important natural products, including purine, histamine, histidine and nucleic acid. Being a polar and ionisable aromatic compound, it improves pharmacokinetic characteristics of lead molecules and thus used as a remedy to optimize solubility and bioavailability parameters of proposed poorly soluble

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lead molecules. The imidazole derivatives possess extensive spectrum of biological activities such as antibacterial, anticancer, antitubercular, antifungal, analgesic, and anti-HIV activities [2 - 8].

Some representative molecules of these structural motifs such as 1,2-Arylimidazole derivatives[I], Metronidazole[II], Complexes of Co(II) and Cu(II) with 3-(2-nitroimidazol-1-yl)propanoic acid[III], Tinidazole[IV] are shown in Fig. (**2**) [9 - 12]. Therefore, synthetic methodologies allowing rapid access to these heterocycles are highly desirable in organic synthesis and chemical biology/medicinal chemistry. Michael addition [13 - 24] is the most potent and economic method for the synthesis of *β*-amino carbonyl/cyano compound [25 - 29]. The conjugate addition of imidazole to *α,β*-unsaturated compounds for making *β*-amino carbonyl/cyano functionalities have been attracted target for synthetic chemistry . In this review we have sumerized various catalytic methods using Michael addition reaction for the synthesis of *β*-amino carbonyl/nitrile covering literature upto 2017. This review is systematized under the headings (1) Ionic liquid catalysed (2) Base catalyzed (3) Acid catalyzed (4) Enzyme catalyzed (5).
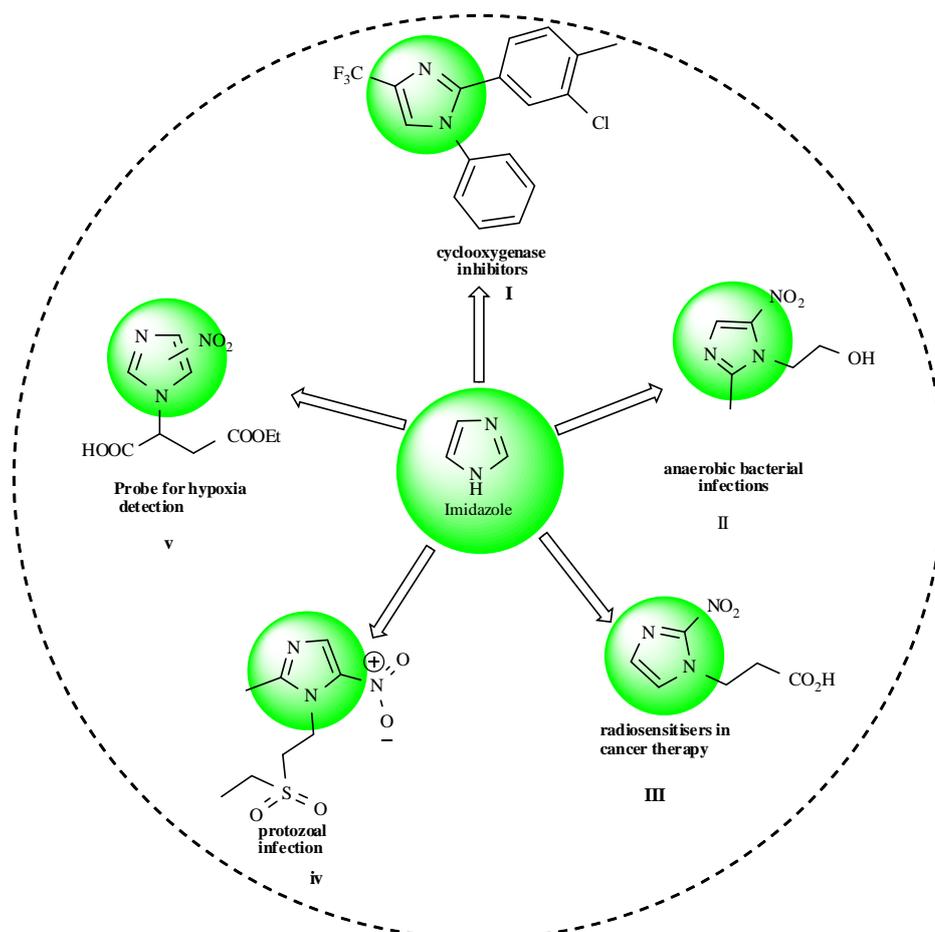

Fig. (2). Imidazole based bio active molecules.

2. IONIC LIQUID CATALYSED MICHAEL ADDITION REACTION

2.1. Michael Addition Using Copper(II)Acetylacetonate (Cu(acac)$_2$)Immobilized in Ionic Liquids

Michael type addition of *N*-substituted imidazoles **1** to *α,β*-unsaturated compounds **2** using Cu(acac)$_2$ immobilized in ionic liquids([bmim]BF$_4$ and [bmim]PF$_6$) under ambient conditions has been reported by Kantam *et al.* [30] in 2007. The conjugate addition of imidazole with acrylonitrile using Cu(acac)$_2$ provided *N*-substituted imidazoles in poor yield whereas using Cu(acac)$_2$ in ionic liquid, best yield of product obtained. The use of organic solvents such as toluene and chloroform were less effective in place of ionic liquids, whereas the use of a hydrophilic high polar solvent (such as Dimethyl Sulfoxide, DMSO) resulted in 80% product conversion in the same length of time. Both [bmim] [BF$_4$] and

[bmim][PF6] were equally effective as ionic liquids for the reaction.Temperature of the reaction also affected the yield of the reaction. Above or below 60 °C poor yield of product obtained. Different *α, β*-unsaturated compounds (such as acrylates, nitriles, and cyclic enones) underwent reaction with imidazole to give the corresponding addition products in good yields. Both simple acrylates and long-chain acrylates were equally effective for the conjugate additions with imidazole. Bulky esters such as *tert*-butyl acrylate afforded the product in good yield (Scheme. **1**).
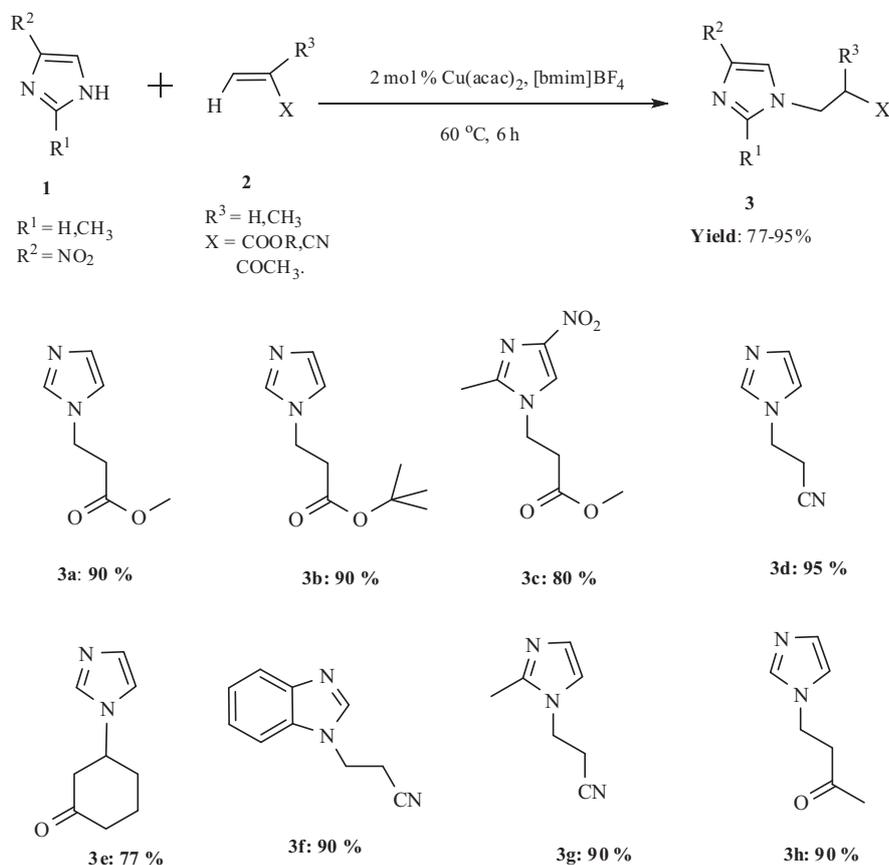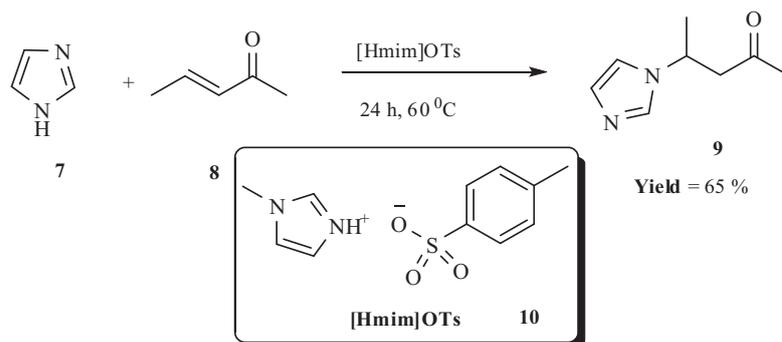

Scheme (1). Michael addition of imidazoles to *α,β*-unsaturated compounds using copper(II) acetylacetonate immobilized in ionic liquids.

2.2. Michael Addition Using Basic Ionic Liquid [bmIm]OH as Catalyst

A fast and green protocol for the Michael addition of *N*-heterocycles **4** to *α, β* -unsaturated carbonyl compounds **5**, catalysed by a basic ionic liquid, 1-methyl-3-butylimidazolium hydroxide [bmIm]OH at room temperature in short reaction times (0.5–3 h) was developed by Lin *et al*. [31] in 2007. A variety of structurally diverse imidazoles (4-nitro imidazole, 2-methyl-4-nitro-imidazole, 2-methyl imidazole, 4-methyl imidazoles) and *α,β* -unsaturated carbonyl compounds (ester, nitrile, ketone) underwent Michael additions smoothly without any other catalyst to generate the corresponding imidazole derivatives in moderate to good yields. Generally, the reactivity decreased with increasing chain length of acceptor. Vinyl acrylate showed higher reactivity than methyl acrylate. Michael acceptors like methyl methacrylate and methyl crotonate showed lower reactivity with 4-nitro imidazole because of the strong steric hindrance, whereas imidazole/substituted imidazoles underwent Michael addition with methyl acrylate favourably and all substituted imidazoles obtained in good yields in short reaction time. The reactivity was in accordance with the nucleophilicity of imidazole derivatives. Sterically hindered imidazole underwent Michael addition much more slowly. In this reaction no Markovnikov addition product was observed only Michael adduct was obtained because vinyl acrylate was used in excess in the reaction. This method is quite general and works with a broad range of *N*-heterocycles, including five-membered *N*-heterocycles, pyrimidines and purines. Also, in this reaction the recovered ionic liquid was reused for several cycles with consistent activity (Scheme **2**).

6a: 95 %   **6b: 92 %**   **6c: 94 %**   **6d: 90%**

6e: 96%   **6f: 60 %**   **6g: 85 %**   **6h: 92 %**
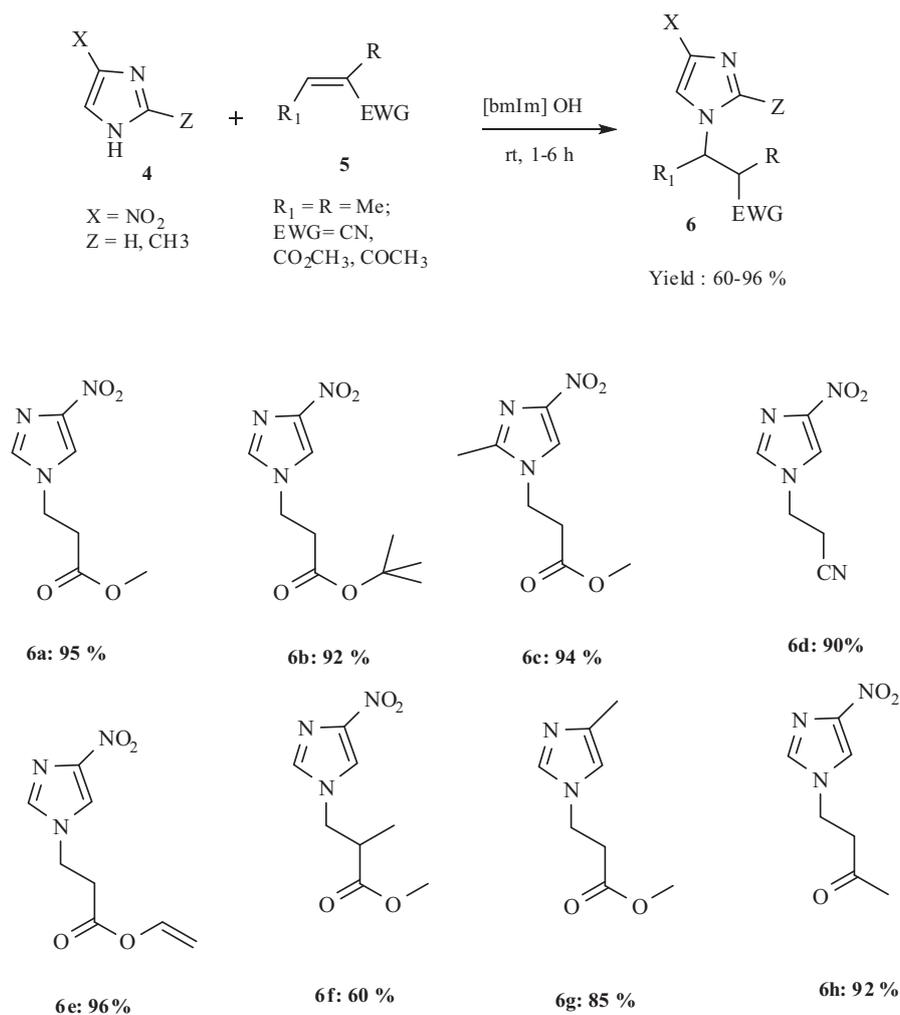
Scheme (2). Michael addition of Imidazole using basic ionic [bmIm]OH as catalyst.
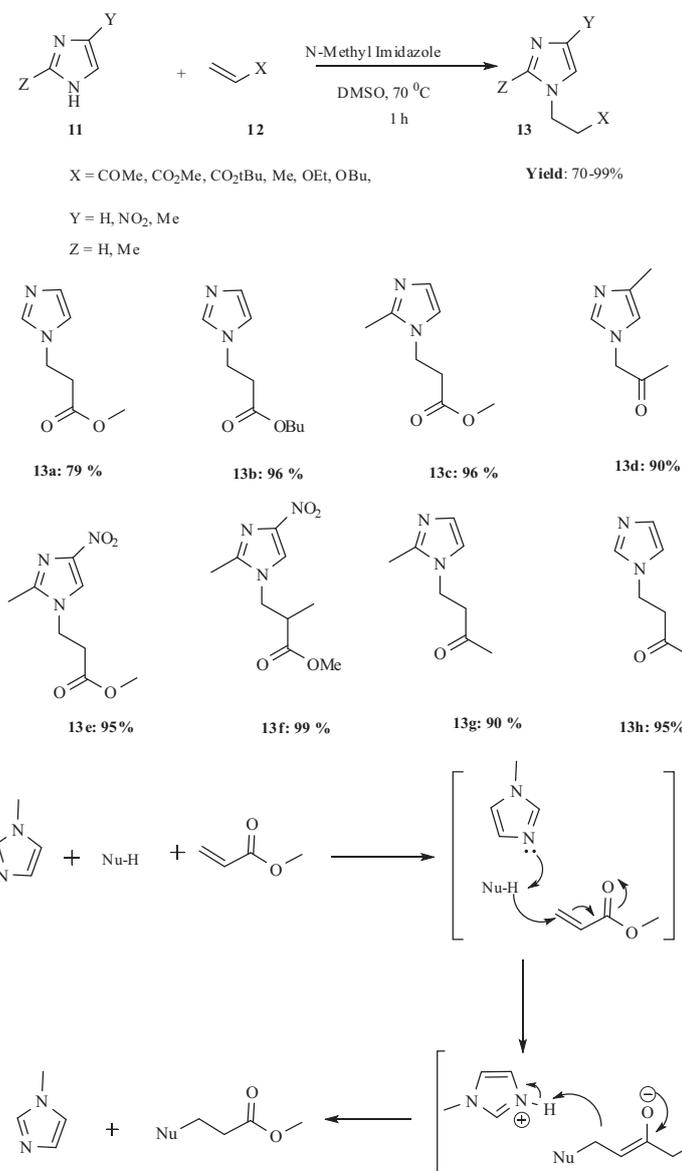

[Hmim]OTs **10**

Scheme (3). Michael addition of imidazole to *α,β*-unsaturated substrates catalyzed by [Hmim]OTs.

2.3. Michael Addition Catalyzed by [Hmim]OTs

Xia *et al*. [32] in 2012 reported the synthesis of various *N*-substituted carbonyl derivatives **9** by Michael addition of imidazole **7** to α, β-unsaturated ketone/nitro **8** catalysed by 1-methylimidazolium *p*-toluenesulfonic ([Hmim]OTs) **10** in good to excellent yield at 60∘C. The reactions did not work at room temperature. Michael addition reactions of various imidazole derivatives were performed using pent-3-en-2-one and (*E*)-(2-nitrovinyl)benzene as electrophiles. Quantitative yield of product (92-95%) was obtained when tetrazole/triazole was reacted with pent-3-en-2-one in 1-3h whereas moderate yield (65-79%) of product was obtained with imidazole/diazole in 12-24h. Better yield of the product was obtained when pent-3-en-2-one was used as electophile in comparision to (*E*)-(2-nitrovinyl)benzene (yield 82%).

No product formation was observed when the reaction was carried out using other α,β-unsaturated electrophiles such as methyl acrylate, acrylamide, acrylonitrile and (*E*)-(2-nitrovinyl)benzene using ethyl carbamate or 1*H*-benzo [1 - 3] triazole as the acceptor respectively (Scheme **3**).

X = COMe, CO$_2$Me, CO$_2$tBu, Me, OEt, OBu,

Y = H, NO$_2$, Me

Z = H, Me

Yield: 70-99%

13a: 79 %   **13b: 96 %**   **13c: 96 %**   **13d: 90%**

13e: 95%   **13f: 99 %**   **13g: 90 %**   **13h: 95%**

Scheme (4). Michael addition of Imidazole and its derivatives to acrylate and methyl vinyl ketone.
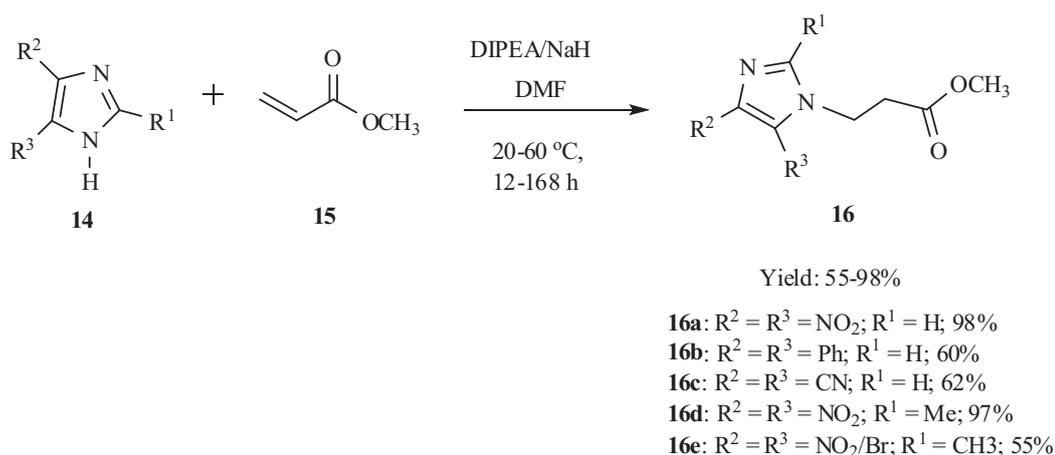
3. BASE CATALYZED REACTIONS

3.1. *N*-Methylimidazole as Catalyst for the Michael Addition Reaction

In 2007 Lin *et al*. [33] developed aza-Michael reaction imidazole **11** to α,β-unsaturated compounds **12** using *N*-methyl imidazole as catalyst. The reaction proceeds in a highly efficient and rapid manner with high yield by mixing 4-nitroimidazole and methyl acrylate with *N*-methylimidazole in dimethyl sulfoxide at 70 °C for 1 h (Scheme **4**). In the absence of catalyst reaction was gone but very poor yield was observed. 4-nitroimidazole gave superior results, compared with imidazole in the reaction with methyl acrylate. Presence of electron-withdrawing groups enhanced the nucleophilicity and reactivity of the *N*-heterocycles. Triazole was found to be more reactive than imidazole, 2-methylimidazole and 4-methylimidazole, both in the aza-Michael addition to methyl vinyl ketone and to methyl acrylate. Also the reaction was studied with a range of acrylates revealed that the chain length of the ester played a minimal role in governing the reactivity of the conjugate addition. As the carbon chain of the alcohol moiety was

increased in length, a slight decrease in yield was observed. In case of michael acceptors either α-methyl or β-methyl substituted acrylates reaction proceeded more slowly due to steric hindrance. Compared with 4-nitroimidazole, 2-methyl-4-nitroimidazole gave slightly lower yields upon reaction with both methyl vinyl ketone and methyl acrylate due to the substitution at the 2-position.

3.2. Diisopropylethylamine catalyzed Michael addition Reaction

Michael-type addition of azoles, inter aliaimidazole and 1,2,4-triazole derivatives of high acidity (pKa ≤6.05), to methyl acrylate **15** was carried out regioselectively by Boncel *et al*. [34] in 2011. The optimisation process involved the use of an appropriate basic catalyst (DBU, DIPEA, NaOH, NaH, TEDA), a donor/base/acceptor ratio. The reactions were carried out in DMF. The adducts formed were used as biologically active intermediates (Scheme **5**).

Yield: 55-98%

16a: $R^2 = R^3 = NO_2$; $R^1 = H$; 98%
16b: $R^2 = R^3 = Ph$; $R^1 = H$; 60%
16c: $R^2 = R^3 = CN$; $R^1 = H$; 62%
16d: $R^2 = R^3 = NO_2$; $R^1 = Me$; 97%
16e: $R^2 = R^3 = NO_2/Br$; $R^1 = CH3$; 55%

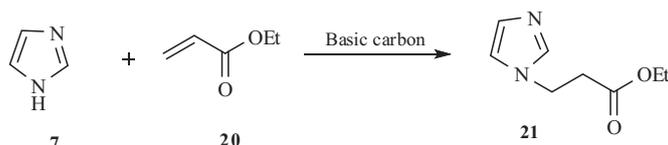**Scheme (5).** Michael-type addition of imidazole with methyl acrylate under basic conditions.
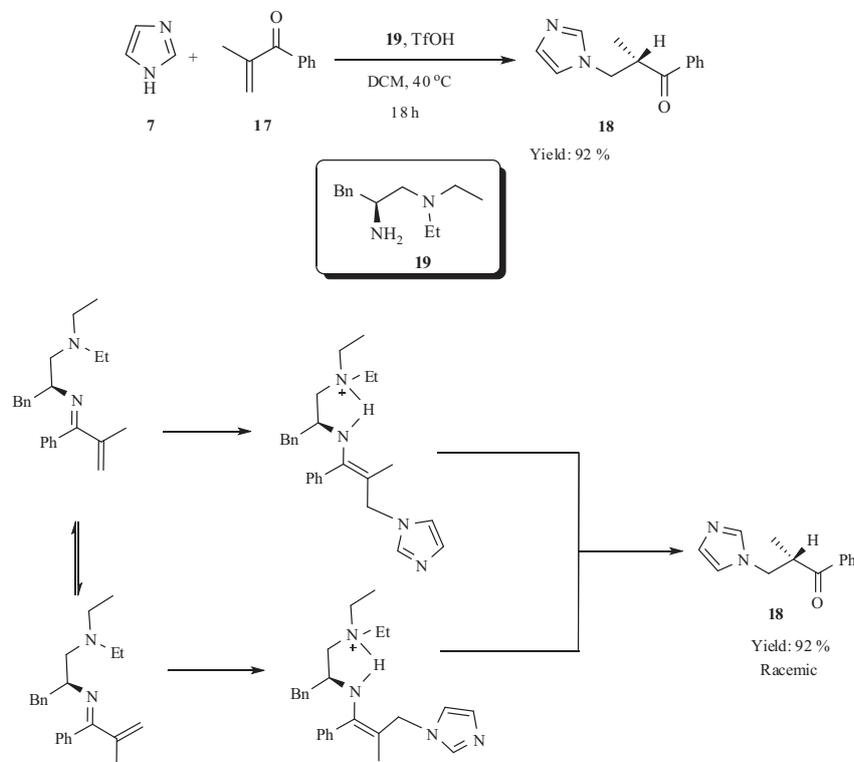
Scheme (6). The reactions of vinyl ketone with imidazole.

3.3. Chiral Primary Amine Catalyzed Michael Addition

Luo *et al*. [35] has developed an aza-Michael addition–protonation reactions using **19**, TfOH as the catalyst. Michael addition of imidazole **7** to α-branched vinyl ketone **17** provided Michael adduct with good yield without enatioselectivity (Scheme **6**).

V. Calvino-Casilda *et al*. [36] in 2011 reported the *in situ* raman monitoring durrng Michael addition reaction of imidazole **7** and ethyl acrylate **20** at moderate reaction temperatures in dry media using basic carbon as catalyst to produce *N*-substituted imidazoles **21** with 100% selectivity. This non-invasive methodology provides molecular information on the reaction mechanism and possible species as intermediates of the reaction (Scheme **7**).
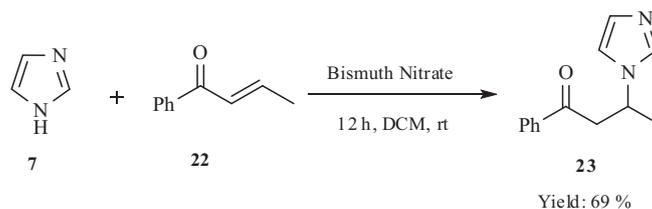

Scheme (7). Michael addition of imidazole and ethyl acrylate catalysed by basic carbon.

4. ACID CATALYZED REACTIONS

### 4.1. Bismuth Nitrate-Catalysed Versatile Michael Reactions

Banik *et al*. in 2003 [37] developed Michael addition reaction of imidazole **7** with acyclic/cyclic enones **22** catalyzed by bismuth nitrate. This method was very general, simple, high yielding, environmentally friendly and oxygen tolerant (Scheme **8**).

Scheme (8). Michael addition of imidazole catalyzed by bismuth nitrate.

4.2. Highly Efficient KF/Al$_2$O$_3$-Catalyzed Versatile Michael Addition

Xia and his group [38] introduced first hetero Michael addition reactions of imidazole **7** to α,β-unsaturated ester **20** catalyzed by KF/Al$_2$O$_3$ in acetonitrile 18h stirring provided Michael adduct **21** in 96% yield. In contrast with the existing methods using much acid catalyst, this method was very general, simple, high-yielding and environmentally friendly. This catalytic system was also exhibited efficient catalytic activity in the hetero-Michael addition reaction of α,β-unsaturated compounds with other nitrogen, oxygen, and sulphur nucleophiles (Scheme **9**).
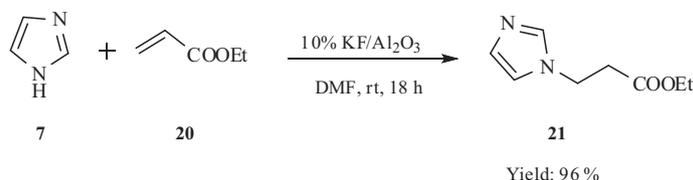
**Scheme (9).** KF/Al$_2$O$_3$catalysed hetero-Michael addition of ethyl acrylate with imidazole.

Uxue Uria *et al*. [39] in 2007 reported the asymmetric organocatalytic aza-Michael addition reaction of substituted imidazole **25** with α,β-unsaturated aldehydes **24** using imidazole based chiral catalyst **27** and TFA in ethyl nitrile at low temperature. When R = CN best yield was obtained with 31% ee whereas when R = H the yield of the product was negligible (Scheme **10**).
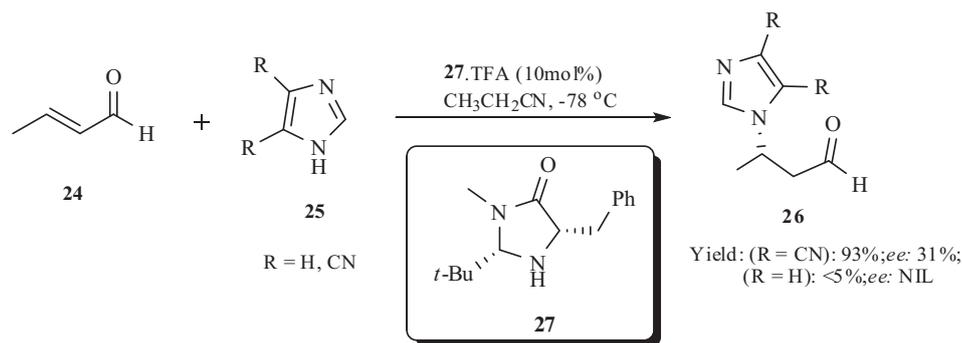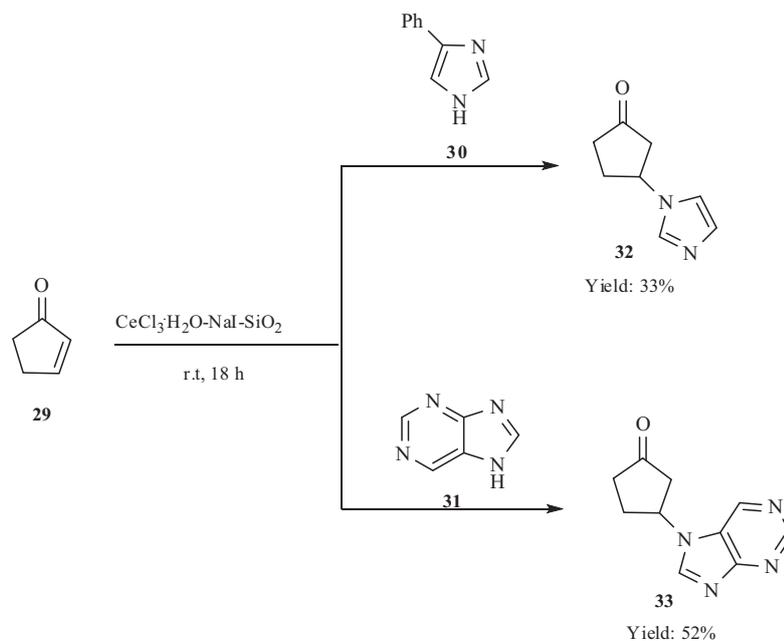
Scheme (10). Aza Michael addition of imidazole catalysed TFA.

4.3. Addition of Silica Sulfuric Acid Promotes Michael Addition

Guo *et al*. in 2009 [40] reported the silica supported sulphuric acid catalysed aza-Michael addition reaction of imidazole **7** to acrylic acid 2-phenylsulfanyl-ethyl ester (PTEA) **27** in solvent free condition. The disadvantage associated with the reaction was more time and lower yield of product which might be due to the weak nucleophilicity of the imidazole molecule steming from its aromaticity (Scheme **11**).
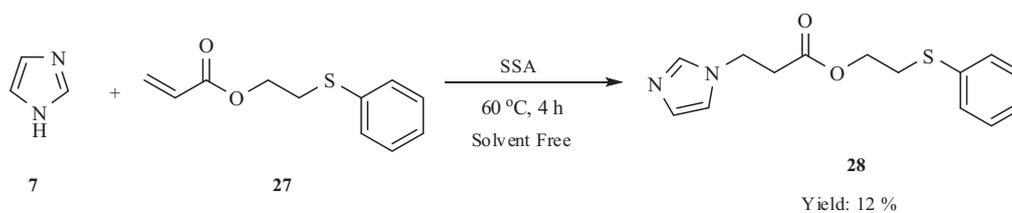
Scheme (11). Michael addition of amines catalysed by SSA under solvent-free conditions.

**Scheme (12).** CeCl$_3$·7H$_2$O-NaI-SiO$_2$ catalysed Michael reaction of enones with imidazole/purine.

4.4. CeCl$_3$·7H$_2$O-NaI-SiO$_2$ Catalyzed Michael Addition

Lee *et al*. [41] in 2012 developed an efficient one-pot protocol for Michael addition of imidazole/purine **30/31** to enones **29** catalysed by CeCl$_3$·7H$_2$O-NaI-SiO$_2$ at room temperature. The reaction took long time as well as the yield of the product was very poor (Scheme **12**).

5. ENZYME CATALYZED AND MISCELLANEOUS

### 5.1. Sonocatalysis and Basic Clay Catalysed Michael Addition

Martin-Aranda *et al*. [42] in 2002 took the advantage of sonication reaction and developed a novel methodology for the synthesis of *N*-substituted imidazole derivatives **21** by the Michael addition of imidazole **7** to ethylacrylate **20** catalysed by basic clays (Li$^+$ and Cs$^+$ montmorillonites). Alkaline clays are active and very selective catalyst under sonication and employs positive effect for Michael addition of imidazole to ethyl acrylate also enhances the formation of *N*-substituted imidazole derivatives in comparision to other conventional thermal heating reactions. The conversion increases with the basicity of clays and ultrasonic exposition time. The yield was maximum when Cs$^+$ montmorillonites was used in comparision to Li$^+$ which might be due to higher basicity. (Scheme **13**).
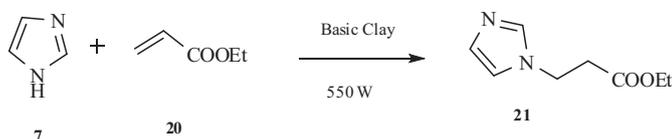
Scheme (13). Michael addition Imidazole to ethyl acrylate.

5.2. Michael addition Catalysed by Alkaline Protease

Catalytic Activity of alkaline protease for Michael addition reaction of imidazole **34** to *α,β*-unsaturated acrylate **35** in pyridine at 50 $^\circ$C for 72h was studied by Lin *et al*. [43] in 2004. The reaction proceeded well and provided the *N*-substituted imidazole derivative **36** up to a satisfactory yield (62-76%). Catalyst plays a significant role for the progress of the reaction. When the enzyme was changed to lipase the yield of the product decreases to 10-25%. Structure of Michael donor as well as acceptor also affect the yield of the reaction. With increasing the chain length of Michael acceptor the yield of the reaction decreased (Scheme **14**).
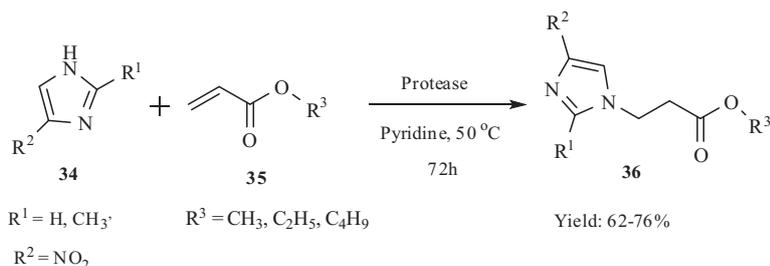

Scheme (14). Michael addition of substituted Imidazole with acrylates, catalysed by alkaline protease.

Cai *et al*. in 2006 [44] described Michael addition reaction of imidazole derivatives **37** to acrylic monomers **38** in organic medium. A serial of *N*-substituted imidazole derivatives **39** were successfully synthesized in moderate yields (32-76%) by the catalysis of hydrolases in organic medium. Non-polar solvents was more favorable to the hydrolase-catalyzed Michael addition reaction than polar solvents. Solvents with higher log *P* value gave higher yield of product. The acceptor with shorter alcohol chain afforded a higher yield. More rapid conversion was observed when the donor had an electron-withdrawing group whereas presence of elctron donating groups decreases the yield of the reaction to 28-31% (Scheme **15**).

Scheme (15). Michael addition of imidazoles and acrylic monomers catalyzed by alkaline protease from *Bacillus subtilis* at 50 °C.

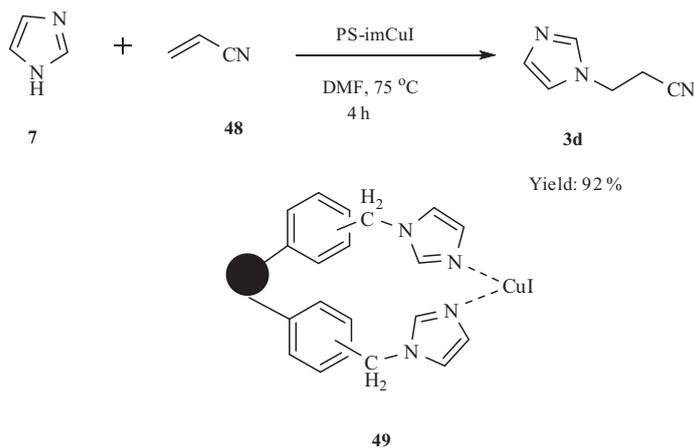**Scheme (16).** Michael addition of imidazole with unsaturated ester.

Lin and co-workers disclosed [45] a regioselective one-pot synthesis of *N*-substituted imidazole derivatives **43** and **44** by Michael addition reaction of imidazole **40** to sugar conjugated *α,β*-unsaturated ester **42**/2-vinyloxycarbonyl-ethyl ester **41** catalysed by alkaline protease from *bacillus subtilis* in anhydrous pyridine. The imidazole-sugar conjugates derivatives **44** were obtained in good yield (69-80%) in comparision to imidazole ethyl ester **43** (yield 44%) (Scheme **16**).

5.3. Michael Addition on Thermal Catalyzed Michael Reactions

Ballesteros and his research group in 2006 [46] reported an easy and efficient synthetic approach for the synthesis of *N*-substiuted imidazole derivatives **47** by the Michael addition reaction of imidazole **45** to *α,β*-unsaturated ester **46** in DMF at 100 °C in moderate yield (Scheme **17**).
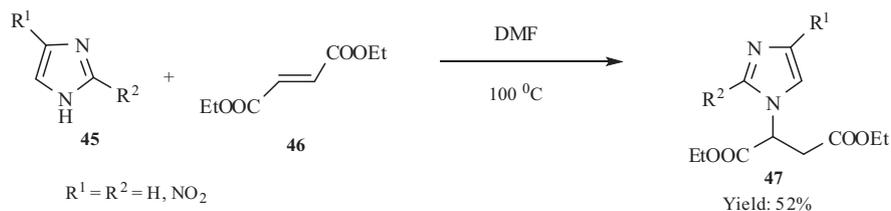
Scheme (17). Efficient synthesis of the first (Nitro imidazoyl) Succinic ester.

Scheme (18). Polystyrene-supported CuI–imidazole complex for the aza Michael reactions.

Xing *et al*. in 2012 [47] reported PS–imCuI catalyst **49** (polystyrene-supported CuI–imidazole complex) supported aza-Michael addition reaction of imidazole **7** to *α,β*-unsaturated nitrile **48** with good yields in 4-8 h. The catalyst had significant role for the progress of the reaction. No product formation was observed in the absence of catalyst in DMF. Very low amount of product formation was observed when homogeneous CuI was used instead of PS-imCuI catalyst. Temperature had a great role on the yield of the reaction. Higher reaction temperature resulted better yields. With the increase of the catalyst dosage, the yields increase quickly whereas the increase slows down when the catalyst usage was over. Best yield of product formation was observed with acrylonitrile whereas yield was poor with methyl methacrylate which might be due to the electronegativity of cyano group is bigger than that of ester group in DMF so that the reaction of imidazole with acrylonitrile is easier than with acrylate. Imidazole with electron donating methyl was also less active than simple imidazole which could be due to the stieric hindrance of the 2-methyl imidazole (Scheme **18**).

CONCLUSION

After intense investigations in the last decade, impressive advances in organocatalytic aza-Michael reactions have been achieved in every branch of organocatalysis (proline, hiourea, cinchona, and phosphoric acid catalysis), providing a simple, direct, and highly stereoselective way to access both cyclic and acyclic, chiral, nitrogen-containing compounds under mild reaction conditions. Especially, cascade processes show the specific advantage in efficiently

constructing complex nitrogen-containing heterocycles in one single operation. Furthermore, the aza-Michael addition has been successfully applied in total synthesis of biologically active natural products. Further findings and contributions in this attractive field are expected to extend the scope of nitrogen nucleophiles and Michael acceptors and to design new domino processes as well as to explore the total syntheses of complex molecules using aza-Michael reactions as a key step After intense investigations in the last decade, impressive advances in organocatalytic aza-Michael reactions have been achieved in every branch of organocatalysis (proline,thiourea, cinchona, and phosphoric acid catalysis), providing a simple, direct, and highly stereoselective way to access both cyclic and acyclic, chiral, nitrogen-containing compounds under mild reaction conditions. Especially, cascade processes show the specific advantage in efficiently constructing complex nitrogen-containing heterocycles in one single operation. Furthermore, the aza-Michael addition has been successfully applied in total synthesis of biologically active natural products. Further findings and contributions in this attractive field are expected to extend the scope of nitrogen nucleophiles and Michael acceptors and to design new domino processes as well as to explore the total syntheses of complex molecules using aza-Michael reactions as a key step.

After intense literature investigations on last ten years, impressive advances in aza-Michael reactions of imidazole to *α,β*-unsaturated carbonyls/cyano compound have been achieved which provided a simple, direct way to access nitrogen containing heterocycles under mild conditions. Especially, the present reports show the specific advantage in efficient construction of imidazole containing nitrogen heterocycles in one single operation which can further be used as potential candidate for the synthesis of valuable synthetic intermediates of natural as well as unnatural products.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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