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# Simple and efficient method for the synthesis of highly substituted imidazoles using zeolite-supported reagents

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ABSTRACT

Cu(II) nitrate impregnated zeolite has been used as an efficient supported reagent for an improved and rapid one-pot synthesis of 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazoles in excellent yields. Condensation in the presence of supported reagents with operational simplicity, inexpensive reagents, high yield of products, and the use of non-toxic reagents makes this synthetic protocol, an attractive one.


The imidazole ring system is one of the most important substructure found in a large number of natural products and pharmacologically active compounds[1–5] and the members of this class of compounds are known to possess NO synthase inhibition and antifungal, antimycotic, antibiotic, antiulcerative, antibacterial, antitumor, and CB1 receptor antagonistic activities.[6,7] Various substituted imidazoles act as inhibitors of p38 MAP kinase[8a] and B-Raf kinase,[8b] glucagon receptors,[9] plant growth regulators,[10] therapeutic agents,[11] and pesticides.[12] Accordingly, a number of synthetic methods have been reported for the construction of this important structure.

Recently, multi-component reactions (MCRs) have attracted considerable attention since they are performed without the need to isolate any intermediate and save both energy and raw materials and also reduce time.[13] In 1882, Radziszewski and Japp reported the first synthesis of the highly substituted imidazole from a 1,2-dicarbonyl compound, different aldehydes, and ammonia.[14,15] Also a number of methods have been developed for the synthesis of 1,2,4,5-tetrasubstituted imidazoles and 2,4,5-trisubstituted imidazoles. The syntheses of 1,2,4,5-tetrasubstituted imidazoles are carried out by four-component condensation of a 1,2-diketone/α-hydroxyketone with an aldehyde, primary amine, and ammonium acetate using microwaves,[16a] molecular iodine,[16b] $HClO_4$–$SiO_2$,[16c] heteropolyacid,[16d,e] silica gel/$NaHSO_4$,[16f] L-proline,[17] $FeCl_3{\cdot}6H_2O$,[18] $BF_3{\cdot}SiO_2$,[19] and silica-supported Wells-Dawson acid.[20] In addition, they can also be accessed by the condensation of a 1,2-diketone with an aryl nitrile and primary amine under microwave irradiation,[21a] by hetero-Cope rearrangement,[21b] and by N-alkylation of trisubstituted imidazoles.[21c] On the other hand, 2,4,5-trisubstituted imidazoles are generally synthesized by three-component cyclo-condensation of a 1,2-diketone/α-hydroxyketone with an aldehyde and ammonium acetate, which comprise the use of microwaves,[22a–d] refluxing in acetic acid,[22e–g] silica sulfuric acid,[22h] $NiCl_2{\cdot}6H_2O/Al_2O_3$,[22i] ZrCl4,[22j] ionic liquids,[22k] and CAN.[22l]

These methods are suitable for certain synthetic conditions, however, many of these procedures are associated with one or more disadvantages such as expensive reagents, longer reaction times, tedious work-up procedure, low selectivity, and large amounts of catalysts which would eventually result in the generation of large amounts of toxic waste.

Many organic reactions have been devised in which reagents are supported on various inorganic solid supports. These solid-supported reagents have several advantages over various conventional reagents. Laszlo and co-workers have successfully investigated reagents like iron(III) nitrate supported on K-10 montmorillonite and copper(II) nitrate supported on K-10. The variety and versatility of these supported reagent-based organic synthesis reported in recent years are the formation of new carbon–carbon bonds in cycloaddition reaction,[23] porphyrin synthesis by condensation of pyrrole with aldehydes,[24] oxidation of alcohols to aldehydes or ketones,[25] benzoins to benzils,[26] hydrolytic cleavage of thioacetals,[27] preparation of azides from hydrazines,[28] and nitration of phenols.[29]

In this Letter, we have presented a novel, mild, and efficient method for the synthesis of tri and tetrasubstituted imidazoles

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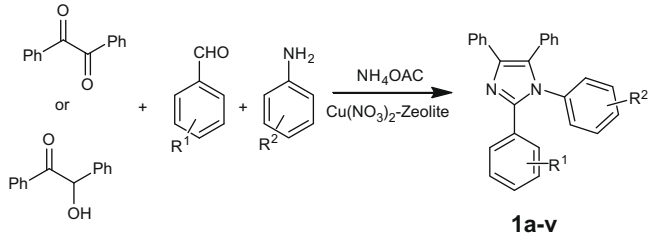
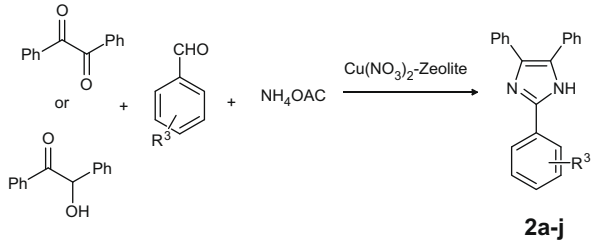



**Scheme 1.**




**Scheme 2.**

**Table 1**
Synthesis of 1-(4-chlorophenyl)-2,4,5-triphenylimidazole **1a** using $Cu(NO_3)_2$–zeolite in different solvents

| Entry | Solvent | Temperature °C | Time (h) | Yield[a] (%) |
|---|---|---|---|---|
| 1 | Methanol | 65 | 3 | 56 |
| 2 | Ethanol | 70 | 3 | 53 |
| 3 | Acetonitrile | 70 | 3 | 41 |
| 4 | Chloroform | 50 | 6 | 22 |
| 5 | Dichloromethane | 45 | 6 | 12 |
| 6 | Solvent-free | 80 | 0.5 | 96 |

[a] Yields refer to isolated products.

using supported reagents (Schemes 1 and 2). Out of range of zeolite supported metal nitrates, $Cu(NO_3)_2$ has attracted much attention because of its suitable acidity, eco-friendliness, easy availability, and low cost thereby acting as a promising table top reagent.

The typical procedure for 1,2,4,5-tetrasubstituted imidazoles involves impregnating the mixture of zeolite-supported metal nitrate (supported reagent) and ammonium acetate (ammonia source) with a dichloromethane solution of benzil, benzaldehyde, and 4-chloroaniline and was used as a model reaction to optimize the reaction conditions.[30,31] Among the tested solvents such as methanol, ethanol, acetonitrile, chloroform, dichloromethane, and solvent-free system, the formation of product **1a** was more facile and proceeded to give highest yield, only under solvent-free reaction conditions (Table 1).

To evaluate and optimize the catalytic system, four-component condensation to give **1a** was examined with different solid acids and supported Lewis acid catalysts (Table 2). Interestingly, it was found that $Cu(NO_3)_2$ supported on zeolite-HY with low loading [one gram of zeolite-HY-supported copper(II) nitrate reagent contains about 0.241 g of $Cu(NO_3)_2$ (1 mmol)] was proved to be an efficient catalyst and gave exclusively 1-(4-chlorophenyl)-2,4,5-triphenylimidazole **1a** in 96% yield in 30 min under solvent-free conditions (Table 2).

From these experiments it was clearly demonstrated that the zeolite-supported cupric nitrate was indeed an effective catalyst and was convincingly superior to the reported procedures (Table 2, entries 16–18) with respect to reaction time, amount of catalyst and yields; and under solvent-free conditions. In order to

**Table 2**
Synthesis of 1,2,4,5-tetraphenylimidazole (**1a**) using different supported reagents under classical heating condition[a]

| Entry | Catalyst | Temp (°C)/time (min) | Yield[b] (%) |
|---|---|---|---|
| 1 | $Cu(NO_3)_2$/zeolite-HY | 80/30 | 96 |
| 2 | $Fe(NO_3)_3$/zeolite-HY | 60/30 | 91 |
| 3 | $Bi(NO_3)_3$/zeolite-HY | 120/30 | 88 |
| 4 | $Co(NO_3)_2$/zeolite-HY | 120/60 | 45 |
| 5 | $Mn(NO_3)_2$/zeolite-HY | 120/60 | 19 |
| 6 | $Ni(NO_3)_2$/zeolite-HY | 120/60 | 18 |
| 7 | $Cu(NO_3)_2$/MCM-41 | 80/30 | 89 |
| 8 | $Fe(NO_3)_3$/MCM-41 | 60/30 | 77 |
| 9 | $Bi(NO_3)_3$/MCM-41 | 120/60 | 56 |
| 10 | $Co(NO_3)_2$/MCM-41 | 120/90 | 11 |
| 11 | $Mn(NO_3)_2$/MCM-41 | 120/90 | — |
| 12 | $Ni(NO_3)_2$/MCM-41 | 120/90 | — |
| 13 | $ZnCl_2$/MCM-41 | 80/90 | 56 |
| 14 | Zeolite-HY | 120/90 | 31 |
| 15 | $Cu(NO_3)_2$ | 80/60 | Charred |
| 16 | $SiO_2/NaHSO_4$ (400 mg) | 140/120 | 92[16f] |
| 17 | $SiO_2/HClO_4$ (1 mol %) | 140/6 | 90[16c] |
| 18 | $BF_3/SiO_2$ (21 mol %) | 140/120 | 92[19] |

[a] The reaction condition: benzaldehyde (1 mmol), benzil (1 mmol), 4-chloro aniline (1 mmol), ammonium acetate (1 mmol), and catalyst (0.03 g) (metal salt loading = 1 mmol $g^{-1}$ of solid support).
[b] Yields refer to isolated products.

**Table 3**
$Cu(NO_3)_2$–zeolite catalyzed synthesis of 1,2,4,5-tetrasubstituted imidazoles

| Entry | Product | $-R_1$ | $-R_2$ | Reaction time | | Yield[a] | |
|---|---|---|---|---|---|---|---|
| | | | | Benzil | Benzoin | Benzil | Benzoin |
| 1 | **1a** | –H | 4-Cl | 0.5 | 1.0 | 96 | 92 |
| 2 | **1b** | 2-Cl | 4-$OCH_3$ | 0.5 | 1.0 | 92 | 80 |
| 3 | **1c** | 2-OH | 4-Cl | 0.5 | 1.0 | 76 | 72 |
| 4 | **1d** | 2-$NO_2$ | 2-Cl | 0.5 | 1.0 | 86 | 73 |
| 5 | **1e** | 4-$NO_2$ | 2-$NO_2$ | 0.5 | 1.0 | 93 | 82 |
| 6 | **1f** | –H | –H | 0.5 | 1.0 | 96 | 94 |
| 7 | **1g** | 4-$OCH_3$ | –H | 0.5 | 1.0 | 95 | 92 |
| 8 | **1h** | 4-Cl | 4-Cl | 0.5 | 1.0 | 86 | 79 |
| 9 | **1i** | 2-Cl | 4-$CH_3$ | 0.5 | 1.0 | 94 | 90 |
| 10 | **1j** | 2-OH | 4-$CH_3$ | 0.5 | 1.0 | 86 | 75 |
| 11 | **1k** | 4-$NO_2$ | –H | 0.5 | 1.0 | 97 | 82 |
| 12 | **1l** | 4-$NO_2$ | 4-$CH_3$ | 0.5 | 1.0 | 93 | 87 |
| 13 | **1m** | 4-Cl | –H | 0.5 | 1.0 | 86 | 72 |
| 14 | **1n** | 4-$OCH_3$ | 2-Cl | 0.5 | 1.0 | 86 | 82 |
| 15 | **1o** | 4-Cl | 2-$NO_2$ | 0.5 | 1.0 | 95 | 79 |
| 16 | **1p** | 2-Cl | 4-$NO_2$ | 0.5 | 1.0 | 86 | 80 |
| 17 | **1q** | 2-OH | –H | 0.5 | 1.0 | 84 | 77 |
| 18 | **1r** | 3-$NO_2$ | 4-$CH_3$ | 0.5 | 1.0 | 79 | 80 |
| 19 | **1s** | 4-Cl | 4-$CH_3$ | 0.5 | 1.0 | 86 | 82 |
| 20 | **1t** | Furfural | 2-$NO_2$ | 0.5 | 1.0 | 63 | 52 |
| 21 | **1u** | Furfural | 4-$NO_2$ | 0.5 | 1.0 | 67 | 62 |
| 22 | **1v** | Furfural | –H | 0.5 | 1.0 | 77 | 72 |

[a] Yields refer to pure isolated solid products, characterized by mp, spectral (IR, $^1H$, $^{13}C$ NMR, and mass) data.

evaluate the generality of the process, several diversified examples illustrating the present method for the synthesis of 1,2,4,5-tetrasubstituted imidazoles **1a–v** were studied (Table 3).

The cyclo-condensation of benzil/benzoin with various aromatic aldehydes bearing electron-withdrawing groups (such as nitro and halide) or electron-releasing groups (such as methyl, hydroxyl, mono, di, or tri methoxy groups), substituted anilines, and ammonium acetate was carried out in the presence of $Cu(NO_3)_2$–zeolite as a catalyst. The yields obtained were good to excellent without the formation of any side products such as the formation of 2,4,5-trisubstituted imidazoles, oxidized products of anilines, and aldehydes , which are normally observed under the influence of strong acids. The results obtained in the current method are illustrated in Table 3. All the products obtained were fully