



ORIGINAL ARTICLE

One-pot synthesis of 1,2,4,5-tetra substituted imidazoles using sulfonic acid functionalized silica (SiO₂-Pr-SO₃H)



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Tetrasubstituted imidazoles;
Benzil;
1,2-Diketones;
One-pot reaction

Abstract SiO₂-Pr-SO₃H has been used as an efficient catalyst for an improved and rapid synthesis of 1,2,4,5-tetrasubstituted imidazoles, by four-component, one-pot reaction of 1,2-diketones, aryl aldehydes, ammonium acetate and substituted aromatic amines in excellent yields under solvent-free conditions.

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1. Introduction

The imidazoles constitute an important class of compounds with profound interest to medicinal chemists, as these compounds exhibit diverse biological properties such as anti-allergic, analgesic (Chary et al., 2008), antifungal (Ballard et al., 1988), antibacterial, antiprotozoal, anthelmintic (Venkatesan et al., 2009), anti-tuberculosis, and anti-inflammatory (Gupta et al., 2004). They act as glucagon receptor, kinase inhibitor, antagonist of CB1 cannabinoid (Nshimyumukiza et al., 2010)

and possess many other activities (Bellina et al., 2008). A large class of imidazoles emerges as ionic liquid in green chemistry and organometallic catalysis (Zang et al., 2010). They also have optical absorption and bright luminescence (Kumar and Thomas, 2011). They have been applied as ligands in coordination chemistry (Fulwa et al., 2009). They are also an active backbone in existing drugs such as candesartan (Alonen et al., 2008), losartan (Polevaya et al., 2001) and eprosartan (Grange et al., 2008) (Scheme 1).

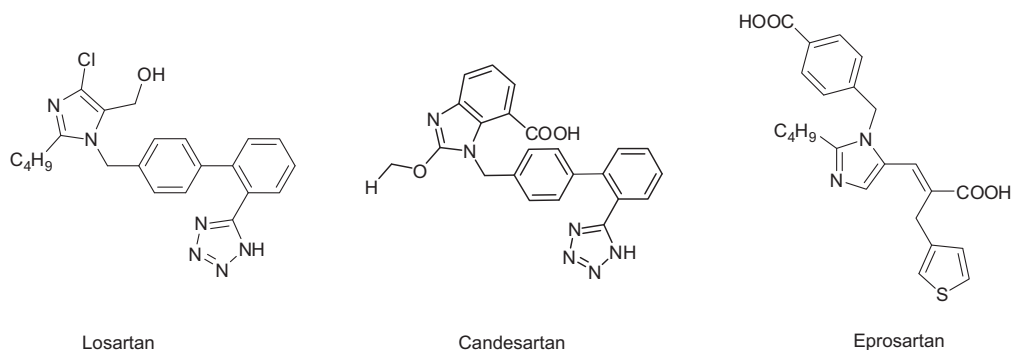
1,2,4,5-Tetra-substituted imidazoles are synthesized by four-component condensation of a 1,2-diketone, a hydroxyketone or a ketomonoxime with an aldehyde, primary amine and ammonium acetate using HY zeolite (Balalaei and Arabanian, 2000), silica gel/NaHSO₄ (Karimi et al., 2006), HClO₄-SiO₂ (Kantevari et al., 2007), molecular iodine (Kidwai et al., 2007), BF₃-SiO₂ (Sadeghi et al., 2008), InCl₃·3H₂O (Das Sharma et al., 2008), potassium dodecatungstocobaltatetratehydrate (K₅CoW₁₂O₄₀·3H₂O) (Nagarapu et al., 2007), and

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Scheme 1 Some drugs with imidazole structure.

Keggin-type heteropolyacids (Heravi et al., 2007). In addition, they can also be synthesized by N-alkylation of tri-substituted imidazoles (Uçucu et al., 2001), hetero-Cope rearrangement (Lantos et al., 1993), condensation of 1,2-diketone with an aryl nitrile and primary amine under microwave irradiation (Balalaie et al., 2003).

In this paper, we want to report the application of SiO₂-Pr-SO₃H as a highly active heterogeneous solid acid catalyst in the preparation of 1,2,4,5-tetrasubstituted imidazoles.

2. Result and discussion

The condensation reaction of benzil (**1**), aromatic aldehydes (**2**), ammonium acetate as ammonia source (**3**) and substituted amine (**4**) in the presence of SiO₂-Pr-SO₃H produced 1,2,4,5-tetra-substituted imidazoles (**5**) in excellent yields under solvent-free conditions at 140 °C (Scheme 2) in 10 min to 2.5 h. The results are demonstrated in Table 1. After completion of the reaction (monitored by TLC), water was added for removing any excess ammonium acetate, then the crude product was dissolved in ethyl acetate and the heterogeneous solid acid catalyst was removed easily by simple filtration, and after cooling of the filtrate, the pure crystals of products were obtained. It can be seen when the electron-withdrawing substituents exist in the aromatic ring of the aldehydes, increased yields of products were observed, whereas the effect was reverse with the electron-donating substituent.

For the preparation of catalyst, at first, the surface of silica was grafted with (3-mercapto-propyl)trimethoxysilane (MPTS) and then the thiol functionalities were oxidized into sulfonic acid groups by hydrogen peroxide to give SiO₂-Pr-SO₃H as solid heterogeneous catalyst (Scheme 3) (Mohammadi Ziarani et al., 2011, 2014).

The suggested mechanism for the SiO₂-Pr-SO₃H catalyzed transformation is shown in Scheme 4. Concerning the reaction mechanism, we suggest that initially, the solid acid catalyst

protonates the carbonyl group of aromatic aldehyde which then condenses with ammonium acetate and substituted aromatic amine (**4**) to produce the adduct products (**7**). Nucleophilic reaction of compound (**7**) with protonated benzil (**1**) creates intermediate (**8**). In the presence of catalyst, ring closure followed by dehydration, gives 1,2,4,5-tetra-substituted imidazoles (**5**). The product structure was confirmed by IR, ¹H NMR and GC–Mass data.

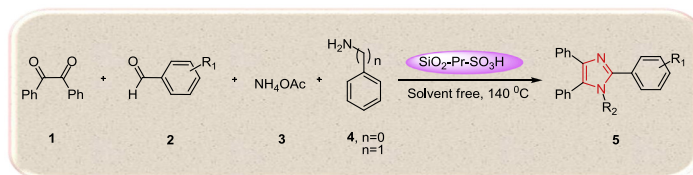
The efficiency of various catalysts in the synthesis of imidazole derivatives has been compared in Table 2. The mentioned method has several advantages, such as excellent yields, simple procedure, and use of an eco-friendly and recyclable catalyst.

3. Experimental section: general information

IR spectra were recorded from KBr disk using a FT-IR Bruker Tensor 27 instrument. The NMR was run on a Bruker DPX, 250 MHz. Melting points were measured using the capillary tube method with an electro thermal 9200 apparatus.

3.1. Preparation of catalyst

To SiO₂ (20 g) in dry toluene (50 ml), (3-mercaptopropyl)trimethoxysilane (25 ml) was added and the reaction mixture was refluxed for 24 h. After this period, the mixture was filtered to obtain 3-mercaptopropylsilica which was washed with acetone and dried. 3-mercaptopropylsilica (MPS) (20 g) was oxidized with H₂O₂ (50 ml) and one drop of H₂SO₄ in methanol (20 ml) for 24 h at room temperature and then the mixture was filtered and washed with H₂O and acetone to obtain SiO₂-Pr-SO₃H catalyst. The modified SiO₂-Pr-SO₃H was dried and used as solid acid catalyst in the synthesis of 1,2,4,5-tetra substituted imidazoles.



Scheme 2 Synthesis of 1,2,4,5-tetra-substituted imidazoles (**5**) in the presence of SiO₂-Pr-SO₃H.

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