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Lewis acid catalyst free synthesis of substituted imidazoles in 2,2,2-trifluoroethanol

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Abstract A simple, inexpensive, environmentally friendly, and efficient route for the synthesis of highly substituted imidazoles by the condensation of 1,2-dicarbonyl compounds, aldehydes, and ammonium acetate using 2,2,2-trifluoroethanol as a solvent is described. The solvent can be readily separated from reaction products and recovered in excellent purity for direct reuse.

Keywords Imidazole · Hydrogen bonding · Fluorinated solvent

Introduction

Imidazoles are important heterocyclic compounds which influence numerous cellular processes [1]. They display a broad range of biological, medicinal, and pharmacological properties and are constituents of antitumor, antifungal, antimycotic, antibiotic, antiulcerative, antibacterial, and CB_1 receptor antagonistic activities [2, 3]. Various substituted imidazoles act as inhibitors of p38 MAP kinase [4], B-Raf kinase [5], glucagon receptors [6], plant growth regulators [7, 8], therapeutic agents [9], and also pesticides [10, 11]. In particular, imidazole drugs such as losartan, omeprazole, olmesartan, eprosartan, and trifenagrel are some of the leading drugs on the market with diverse functionalization around the imidazole motif (Fig. 1).

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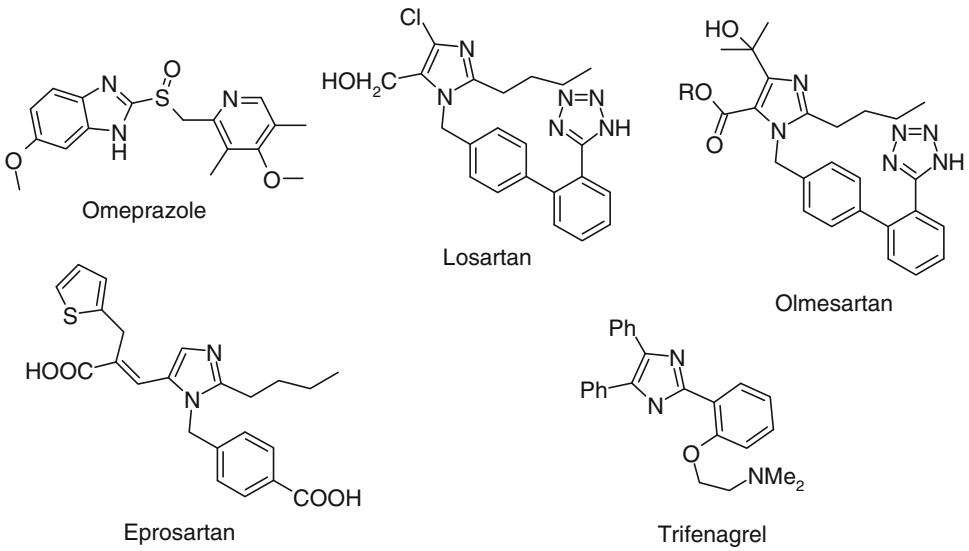
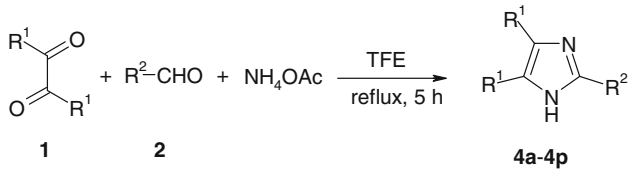
Recent development of green chemistry and organometallic chemistry has expanded the utility of imidazoles as ionic liquids [12, 13] and N-heterocyclic carbenes [14–16]. The classical method for the synthesis of 2,4,5-trisubstituted imidazoles is the one-pot condensation of benzil with aryl aldehyde in alcoholic ammonia solution [17]. The procedure was later modified by refluxing benzil with substituted aldehydes and ammonium acetate in glacial acetic acid [18]. However, this method involves long reaction times, harsh reaction conditions, use of a large quantity of volatile organic solvents and generally gives low yields. In recent years, several new efficient methods have been developed including the use of silica gel [19], zeolite [19], alumina [20], $NaHSO_4/SiO_2$ [21], $HClO_4/SiO_2$ [22], molecular iodine [23, 24], $FeCl_3{\cdot}6H_2O$ [25], $BF_3{\cdot}SiO_2$ [26], $InCl_3{\cdot}3H_2O$ [27], $K_5CoW_{12}O_{40}{\cdot}3H_2O$ [28], copper acetate [29], trifluoroacetic acid [30], L-proline [31], zeolite-supported reagents [32], mercaptopropyl silica (MPS) [33], Brønsted acidic ionic liquid [34], MCM-41 or *p*-TsOH [35], DABCO [36], silica-bonded propylpiperazine *N*-sulfamic acid [37], and 1-butyl-3-methylimidazolium bromide [38]. Despite their potential utility, most of these methods are not environmentally friendly. They require high temperature (180–200 °C), created by microwave irradiation, complex work-up and purification, strong acidic conditions, use of toxic metal catalysts, and suffer from poor yields, occurrence of side reactions, and use of expensive reagents. Hence, the development of clean, high-yielding, and environmentally benign approaches is still desirable and much in demand.

Over the last decade, significant progress has been made in the application of fluorinated solvents as catalysts and alternative solvents in organic synthesis given their unique advantages of low nucleophilicity, high polarity, strong hydrogen-bond-donating ability and ability to solvate water [39, 40]. The use of fluorinated solvents as reaction media

Fig. 1 Typical imidazole drugs





Scheme 1

and/or catalysts for clean catalytic transformations would have profound effects on reaction rates and product selectivity [41–54]. Additionally, if the synthesis is carried out with a fluorinated solvent as the catalyst and the product is immiscible, separation and recycling of the catalyst is facile. In response to the current challenges of developing environmentally benign synthetic processes and in continuation of our interest in the application of fluorinated solvents for various organic transformations [55–59], we report a new, convenient, mild, and efficient procedure for the synthesis of highly substituted imidazole derivatives via a four-component, one-pot reaction in refluxing 2,2,2-trifluoroethanol (TFE) (Scheme 1).

Results and discussion

In an initial endeavor, we started the condensation of benzil (1 mmol), benzaldehyde (1 mmol), and ammonium acetate (2 mmol) in TFE at room temperature for 24 h, which led to very poor yield (10 %) of 2,4,5-trisubstituted imidazole. When we attempted the same reaction in TFE at reflux the reaction proceeded to completion within 5 h and yielded the corresponding imidazole in 95 % yield. Further experiments revealed that a similar procedure is applicable for the preparation of a wide range of compounds analogous to adduct **4a** (Table 1). In order to evaluate the efficiency of this methodology, a wide range of aromatic aldehydes were employed and all imidazoles were obtained in high to excellent yields, which demonstrated that this is a general method that tolerates both electron-withdrawing and electron-donating constituents. It is noteworthy to mention that the structural variation of the aldehyde and substituents on the aromatic ring did not show any obvious effect on this conversion, because the desired products were obtained in high yields in relatively short reaction times. In contrast, aliphatic aldehydes such as *n*-hexanal and cyclohexanecarboxaldehyde did not provide the desired products. The experimental procedure is very efficient, convenient, rapid, and has the ability to tolerate a variety of other functional groups, such as alkyl, methoxy,

Table 1 Synthesis of 2,4,5-trisubstituted imidazoles (Scheme 1)

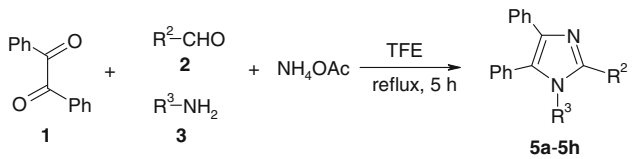
Entry	R^1	R^2	Product	Yield/%	References
1	Ph	Ph	**4a**	95	[31]
2	Ph	4-Cl-Ph	**4b**	97	[31]
3	Ph	2-Cl-Ph	**4c**	97	[31]
4	Ph	2,4-Cl_2-Ph	**4d**	85	[36]
5	Ph	4-Br-Ph	**4e**	90	[36]
6	Ph	4-F-Ph	**4f**	90	[36]
7	Ph	4-NO_2-Ph	**4g**	92	[31]
8	Ph	3-NO_2-Ph	**4h**	95	[36]
9	Ph	4-Me-Ph	**4i**	96	[36]
10	Ph	4-MeO-Ph	**4j**	90	[36]
11	Ph	3,4-$(MeO)_2$-Ph	**4k**	95	[36]
12	Ph	2-Furanyl	**4l**	95	[32]
13	4-Me-Ph	4-Br-Ph	**4m**	85	[36]
14	4-Me-Ph	Ph	**4n**	85	[36]
15	4-Cl-Ph	Ph	**4o**	80	[36]
16	2-Furanyl	Ph	**4p**	85	[36]

nitro, and halides under these reaction conditions. This method not only affords the products in excellent yields but also avoids the problems associated with catalyst cost, handling, safety, and pollution. One of the major advantages of this protocol is the isolation and purification of the products, which have been achieved by simple filtration and crystallization of the crude products. The results illustrate the suitability of this method for the synthesis of substituted imidazoles with different groups. Interestingly, the reaction did not proceed to completion when either ethanol or water alone was used as solvent, even at reflux.

In order to explore the applicability of this method, the same reaction conditions were applied for the synthesis of 1,2,4,5-tetrasubstituted imidazoles via the one-pot, four-component condensation of 1,2-diketone (1 mmol), aldehyde (1 mmol), primary amine (1 mmol), and ammonium acetate (1 mmol) as depicted in Scheme 2. As expected, these substrates underwent smooth, one-pot conversion to give the corresponding 1,2,4,5-tetrasubstituted imidazoles **5a–5h** in excellent yields. The substrate scope of the reaction was then evaluated using a variety of structurally diverse aldehydes and primary amines (Table 2).

After the reaction, TFE can be easily separated (by distillation) and reused without decrease in its activity. For example, the reaction of benzil, benzaldehyde, and ammonium acetate afforded the corresponding substituted imidazole derivative in 90, 90, and 88 % isolated yield over three cycles. When we carried out the reaction in TFE at room temperature, the reaction proceeded very slowly to give very poor yields.

In summary, we described herein a highly efficient, one-pot, three-component protocol for the synthesis of 2,4,5-trisubstituted imidazoles **4a–4p** by the condensation of an aldehyde, benzil, and ammonium acetate in refluxing TFE in excellent yields. This protocol offers many attractive features such as (1) avoiding the use of any base, metal, or Lewis acid catalyst, (2) short reaction times, (3) ease of product isolation/purification by non-aqueous work-up, (4) high chemoselectivity, (5) no side reaction, and (6) low costs and simplicity in process and handling. The recovered TFE can be reused. Further studies and efforts to extend the scope of this method for other useful reactions are currently underway.



Scheme 2

Table 2 Synthesis of 1,2,4,5-tetrasubstituted imidazoles in TFE (Scheme 2)

Entry	R^2	R^3	Product	Yield/%	References
1	Ph	Ph	**5a**	90	[31]
2	4-Cl-Ph	Ph	**5b**	95	[37]
3	4-Me-Ph	Ph	**5c**	90	[31]
4	4-NO_2-Ph	Ph	**5d**	93	[37]
5	Ph	$PhCH_2$	**5e**	90	[31]
6	4-Cl-Ph	$PhCH_2$	**5f**	95	[37]
7	4-MeO-Ph	$PhCH_2$	**5g**	85	[31]
8	4-CN-Ph	$PhCH_2$	**5h**	92	[31]

Experimental

NMR spectra were determined on a Bruker AV-400 Fourier transform NMR spectrometer in $CDCl_3$ or dimethyl sulfoxide (DMSO-d_6) and are expressed in δ values relative to tetramethylsilane; coupling constants (J) are measured in hertz. Melting points were determined on an Electrothermal 9100 instrument. Infrared spectra were recorded on a Rayleigh WQF-510 Fourier transform instrument. Commercially available reagents were used throughout without further purification.

Typical experimental procedure

Benzil (1 mmol), aldehyde (1 mmol), and ammonium acetate (2 mmol) were dissolved in 2 cm^3 TFE and stirred at reflux until complete dissolution of the reagents was observed. After 10–15 min the precipitation of light-yellow crystals occurred gradually and precipitation continued for 5 h. The mixture was cooled to room temperature and the was precipitate filtered. The crude product was purified by recrystallization from ethanol to yield the highly pure 2,4,5-trisubstituted imidazoles. The physical data (m.p., IR, NMR) of known compounds were found to be identical with those reported in literature [36].

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