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Applications of microwave technology to rapid synthesis of substituted imidazoles on silica-supported $SbCl_3$ as an efficient heterogeneous catalyst

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Abstract

One-pot cyclo-condensation of benzil, aldehydes, ammonium acetate and primary amines were used to synthesize 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted-1*H*-imidazole derivatives under microwave irradiation with silica-supported $SbCl_3$ ($SbCl_3/SiO_2$) as a heterogeneous catalyst. The operational simplicity, practicability and applicability of this protocol to various substrates make it an interesting alternative to previous procedures. From the environmental stand-point, this eco-friendly, green catalyst is stable, highly active, easy to prepare and handle.

Keywords: $SbCl_3/SiO_2$; Lewis acid; Heterogeneous catalyst; Imidazoles; Microwave irradiation; Solvent-free condition

1. Introduction

Microwave-assisted organic synthesis results in spectacular acceleration of many chemical reactions as a consequence of three-dimensional heating of the reaction mass, which cannot be reproduced by classical heating methods. High yields, simple work-up, improved selectivity and clean reaction pathways are additional advantages of this synthetic technique [1]. Moreover, even reactions that do not occur with conventional heating can be performed with microwave irradiation. In most cases, microwave irradiation coupled with solvent-free techniques represents a powerful, eco-friendly, green alternative to conventional synthesis. Theoretical calculations also suggest that reactions with high activation energies can be performed under microwave conditions without the use of harsh organic solvents [2].

Numerous important heterocycle compounds have been synthesized under solvent-free conditions accelerated by microwave technology. Nitrogen-containing heterocyclics are widespread in nature, and their applications in agrochemicals, pharmaceuticals and functional materials are gaining importance [3,4]. A wide variety of N-containing heterocyclic imidazole ring systems have received considerable attention because of their pharmacological properties and roles in biochemical processes [4,5].

Multi-substituted imidazoles are known to possess NO synthase inhibition and antifungal, antibacterial, antiulcerative, antibiotic, antitumour, antimycotic, and CB1 receptor antagonistic activities [6,7]. Various

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substituted imidazoles act as inhibitors of p38 MAP kinase [8] and B-Raf kinase [9], glucagon receptors [10], plant growth regulators [11] and pesticides [12]. Accordingly, a number of synthetic methods have been reported for the construction of substituted imidazoles.

In 1882, Radziszewski and Japp [13,14] reported the first synthesis of a highly substituted imidazole from a 1,2-dicarbonyl compound, aldehydes and ammonia. A number of synthetic processes have also been developed for the synthesis of 1,2,4,5-tetrasubstituted imidazole and 2,4,5-trisubstituted imidazole derivatives. Syntheses of 1,2,4,5-tetrasubstituted imidazoles are carried out by four-component cyclo-condensation of a 1,2-diketone/α-hydroxyketone with various aldehydes, primary amine and ammonium acetate with molecular HBF_4-SiO_2 [15], $FePO_4$ [16], $BF_3{\cdot}SiO_2$ [17], sulfuric acid ([3-(3-silicapropyl)sulfanyl]propyl] ester [18], cyclic phosphoric acid [19], silica-supported Wells–Dawson acid [20], heteropolyacid [21,22], ionic liquids [23,24], SBA-15/2,2,2-trifluoroethanol [25] and clay-supported titanium [26]. 1,2,4,5-Tetrasubstituted imidazoles can also be obtained by condensation of a 1,2-diketone, aryl nitrile and primary amine under microwave conditions [27], by N-alkylation of trisubstituted imidazoles and by hetero-cope rearrangement [5]. 2,4,5-Trisubstituted imidazole derivatives are generally synthesized by three-component condensation of a 1,2-diketone/α-hydroxyketone with various aldehydes and ammonium acetate, including ionic liquids [28], refluxing in acetic acid [29], silica-immobilized sulfuric acid [30], $InCl_3{\cdot}3H_2O$ [31], ceric ammonium nitrate [32], $NiCl_2{\cdot}6H_2O/Al_2O_3$ [33] and microwave irradiation [34].

Although these protocols are suitable for certain synthetic conditions, many have one or more disadvantages, such as long reaction times, expensive reagents and catalysts, low selectivity, tedious work-up procedure and large amounts of catalysts, which eventually results in the generation of large amounts of toxic waste.

Use of Lewis acids supported on "inert" carriers as catalysts has received considerable interest for organic synthesis [35]. The features of supported Lewis acids, such as ease of handling, enhanced reaction rates, greater selectivity, simple workup and recoverability of catalysts make them attractive alternatives to conventional reagents [36]. Although there is a large variety of supported Lewis acids, silica-supported antimony (III) chloride is a recoverable, reusable heterogeneous catalyst in organic synthesis [36–39], making the processes truly eco-friendly, green methods [35]. $SbCl_3$ has been studied for its catalytic activity in only one study [35], while this compound is not only commercially available and inexpensive, but is also easier to handle than other metal halides. Reports on the safety of $SbCl_3$, however, show that it is highly toxic. Therefore, immobilized antimony (III) chloride has recently received considerable importance. This catalyst can be easily separated from the reaction products by simple filtration and recovered quantitatively in the active form. Supported $SbCl_3$ can be recycled, making the preparation of sophisticated fine chemicals less expensive and, at the same time, avoiding contamination of the products by trace amounts of catalyst [40].

In this context and in continuation of our studies on the applications of new catalysts for the synthesis of heterocyclic compounds [41–43] and to extend them to cleaner processes, we herein report a facile, efficient synthetic strategy for obtaining multi-substituted imidazoles in excellent yield with $SbCl_3/SiO_2$ under microwave irradiation and solvent-free conditions. Although the use of various solid heterogeneous catalysts has been reported in literature, silica-supported heterogeneous Lewis acid catalysts like $SbCl_3/SiO_2$, have not yet been explored for the preparation of imidazoles under solvent-free conditions and microwave irradiation (Scheme 1).

2. Experimental

2.1. Chemicals and apparatus

Chemical reagents of high purity were purchased from Merck, and all materials were of commercial reagent grade. Melting-points were determined in open capillaries on an Electrothermal Mk3 apparatus and are uncorrected. ^1H nuclear magnetic resonance (NMR) and ^{13}C NMR spectra were recorded on a Bruker DRX-400 spectrometer at 400 and 100 MHz, respectively, and are reported as parts per million (ppm) downfield from tetramethylsilane as the internal standard. Fourier transform (FT)–infrared (IR) spectra were obtained with potassium bromide pellets in the range 400–4000 cm^{-1} on a Perkin-Elmer 550 spectrometer. A domestic microwave oven (Bajaj, ET–B at 2450 MHz, 100% power, 1300 W) was used in all experiments.

2.2. Preparation of $SbCl_3/SiO_2$ catalyst

The catalyst was prepared as reported elsewhere [35]. Thus, 20 g of silica gel (80–200 mesh) were activated by refluxing with 150 mL of 6 mol/L hydrochloric acid under stirring for 24 h. The activated silica gel was filtered and washed with double-distilled water to neutral and dried overnight at 70 °C under vacuum to give preconditioned silica gel. Antimony trichloride (1.99 g) was