Research Article

Silica Sulfuric Acid as an Efficient Heterogeneous Catalyst for the Solvent-Free Synthesis of 1-Substituted 1H-1,2,3,4-Tetrazoles

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Silica sulfuric acid (SSA) was found to be an efficient heterogeneous catalyst for the synthesis of 1-substituted 1H-1,2,3,4-tetrazoles from the reaction of primary amines with triethyl orthoformate and sodium azide under thermal and solvent-free conditions.

1. Introduction

Application of the tetrazole compounds including 1-substituted tetrazoles [1–3] has increased rapidly over the past few years for different purposes. For example they have been used in coordination chemistry, medicinal chemistry, agriculture, photography, and preparation of nitrogen-containing compounds [4, 5].

In general, the most direct and versatile method of the synthesis of tetrazoles is the cycloaddition between nitriles, cyanates and cyanamides, and azides [4, 6–11].

1-substituted tetrazoles are generally synthesized by reaction of isocyanides with large excess amounts of dangerous and harmful hydrazoic acid [12, 13] or trimethyl azide [14]. The other methods include addition of amines or their salts to sodium azide and orthocarboxylic acid ester in acetic acid or trifluoroacetic acid [15, 16]. Su and coworkers have reported the synthesis of 1-substituted tetrazoles using $\text{Yb}(\text{OTf})_3$ in volatile organic solvents [17].

All of these known methods suffered from some limitations such as low yields, drastic reaction conditions, the use of expensive and toxic metal catalysts, tedious workup, complex isolation and recovery procedures, the use of excessive amounts of glacial acetic acid or trifluoroacetic acid (an expensive solvent), the use of high boiling point solvent such as DMF (which is soluble in both organic solvents and water; thus its removing from the reaction mixture is difficult) and even the need for excess amounts of dangerous and harmful hydrazoic acid [4, 6–8, 15, 16]. Therefore, the development

of a more efficient and convenient method for the synthesis of 1-substituted tetrazoles under solvent-free conditions still remains an active research area.

During the last decade many academic and industrial processes shifted towards the development of new technologies in synthetic organic chemistry using solid acid catalysts [18–22]. Among various silica-based heterogeneous catalysts, silica sulfuric acid (SSA) has advantages of low cost, ease of preparation and recyclability, and is insoluble in all organic solvents.

2. Experimental

2.1. General Procedure for Preparation of the 1-Substituted Tetrazoles. A mixture of amine (2.0 mmol), NaN_3 (2.0 mmol), triethyl orthoformate (2.4 mmol), and SSA (0.02 g) was taken in a 25 mL round bottom flask equipped with a condenser under a well-ventilated fume hood and heated at 120°C for the appropriate time with vigorous stirring (Table 1). After completion (as monitored by TLC), the reaction mixture was diluted with cold water (5 mL) and extracted with ethyl acetate (3×10 mL). The catalyst was removed by filtration, and the combined organic layers were washed with brine and dried over anhydrous Na_2SO_4 . After concentration, a crystallization step was performed using EtOAc-hexane to afford the pure product. All the products are known compounds, and the spectral data and melting points were identical to those reported in the literature [14–16, 23, 24].

TABLE 1: Synthesis of 1-substituted 1H-1,2,3,4-tetrazoles from the reaction of primary amines, sodium azide, and triethyl orthoformate in the presence of SSA at 120°C and in solvent-free conditions.

Entry	Substrate	Product	Time (h)	Yield% ^a	Literature reference
1			4	90	[17, 23, 24]
2			5	88	[17, 24]
3			5	95	[17, 23, 24]
4			5	95	[24]
5			8	89	[17, 23, 24]
6			6	94	[17, 24]
7			6	95	[24]
8			2.5	96	[24]
9			3.5	93	[24]
10			5	95	[17, 23]

^aYield refers to the pure isolated product.

SCHEME 1

3. Results and Discussion

In continuation of our researches on the synthesis of nitrogen-containing compounds [10, 11, 24–31], we put forward a mild, efficient, and convenient method for the synthesis of 1-substituted 1H-1,2,3,4-tetrazoles from a wide variety of primary amines with sodium azide and orthoformate in the presence of SSA as an efficient heterogeneous catalyst at 120°C for appropriate time in solvent-free condition (Scheme 1).

First, we examined a variety of structurally divergent aniline possessing a wide range of functional groups to understand the scope and generality of the SSA-promoted cycloaddition reaction to form the 1-substituted tetrazoles, and the results are summarized in Table 1.

Treatment of the heteroaromatic 3-aminopyridine with orthoformate and sodium azide at 120°C for 5 h also afforded the corresponding tetrazole in an excellent yield (Table 1, entry 10). Due to the presence of two NH₂ groups, **1h** interestingly afforded the double-addition product (Table 1, entry 8).

In a typical experiment, after completion of the reaction, SSA was isolated from the reaction mixture by simple filtration. The reusability of the catalyst was assessed after activating the catalyst at 80°C for 5 h. Then it was reused three times successively with consistent activity, indicating high activity of the catalyst. This reusability demonstrates the high stability and turnover of SSA under operating condition.

The products were characterized by NMR, FT-IR, elemental analysis (CHN), and melting points. The 1-substituted tetrazoles are generally acidic substances and the relevant proton signal will be shifted to downfield (see ¹H NMR data), so the peak at $\delta = 7.80\text{--}8.30$ ppm can be attributed to the proton of the tetrazole ring. ¹³C NMR spectra displayed signals about $\delta = 147\text{--}157$ ppm for C5 of the tetrazole ring [10, 11, 24].

4. Conclusion

We applied an efficient methodology for synthesis of the 1-substituted tetrazoles using SSA as a heterogeneous catalyst. All reactions were performed under solvent-free conditions (from the standpoint of green chemistry and industry, both are important due to the reduced pollution, low cost, and simplicity in processing and handling) with high yields and a simple workup that no chromatographic procedure is necessary to get the pure compounds. The SSA catalyst can be recovered by simple filtration and reused without the loss of activity. This methodology may find widespread application in organic synthesis for preparation of the tetrazoles. Further studies are in progress.

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