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FULL PAPER

Boron sulfuric acid as an efficient heterogeneous catalyst for the synthesis of 1-substituted 1*H*-1,2,3,4-tetrazoles in polyethylene glycol

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Boron sulfuric acid (BSA) is an efficient heterogeneous catalyst for the synthesis of 1-substituted 1*H*-1, 2, 3, 4-tetrazoles from the reaction of aryl and alkyl amines with triethyl orthoformate and sodium azide at 120 °C in polyethylenglicole (PEG).

KEYWORDS

Boron sulfuric acid (BSA); heterogeneous catalyst; aryl and alkyl amines; triethyl orthoformates; 1-substituted 1*H*-1,2,3,4-tetrazole; green chemistry.

Introduction

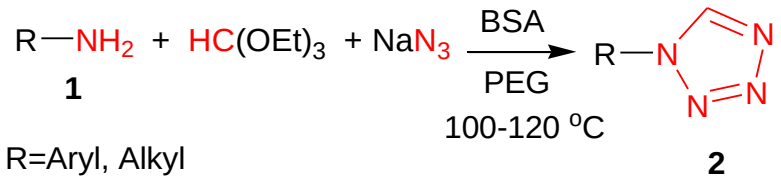
Over the years, multicomponent reactions (MCRs) have become increasingly popular tools to ensure sufficient molecular diversity. They have gained significant popularity in recent years due to their atom-economy and straightforward reaction design due to the substantial minimization of waste, labor, time, and cost [1,2]. Tetrazole derivatives are important synthons in synthetic organic chemistry [3]. Tetrazoles are used for a variety of different useful purposes [4-15].

In general, the most direct and versatile method of the synthesis of tetrazoles is the cyclization between nitriles, cyanates, cyanamides and azides [12,16-19]. 1-Substituted tetrazoles are generally synthesized by the reaction of isocyanides with large excess amounts of dangerous and harmful hydrazoic acid [20,21] or trimethyl azide [22]. The other methods include the addition of amines or their salts to sodium azide and orthocarboxylic acid ester in acetic acid or trifluoroacetic acid [23,24]. Su and co-workers have reported the synthesis of 1-substituted tetrazoles using $Yb(OTf)_3$ in volatile organic solvents [25]. Although many synthetic protocols for 1- substituted tetrazoles have been reported, there is still a need for more efficient processes for the synthesis of 1-aryl tetrazoles, and this 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-phase acid catalysts [26-29]. Among various silica-based heterogeneous catalysts, SiO_2/boron sulfuric acid (BSA) [30-36], has particular advantages of low cost, ease of preparation and recyclability. Usefully, it is insoluble in all organic solvents.

In continuation of our researches on the synthesis of nitrogen-containing compounds and application of solid acids [30-37], we here put forward a mild, efficient and convenient method for the synthesis of 1-substituted 1*H*-

1, 2, 3, 4-tetrazoles from primary amines with sodium azide and ethyl orthoformate in the presence of BSA as an efficient heterogeneous catalyst at 120 °C over 6-8 h in polyethyleneglycol (PEG) (Scheme 1).



SCHEME 1

To determine the best conditions (Table 1), we examined the cyclization between *p*-methoxyaniline **5a** (Table 2), sodium azide and ethyl orthoformate using several different solvents, various mole ratios of catalyst and different temperatures. The best results were obtained under the conditions noted in entry 16 of Table 1. We obtained the optimum yield using BSA (5 mol%) in PEG at 120°C, with a reaction time of 6-8 hours.

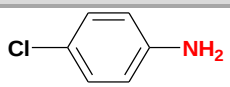
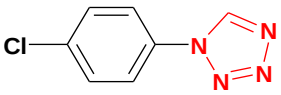
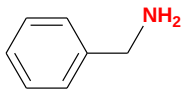
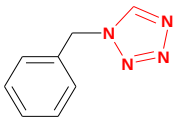
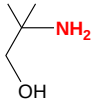
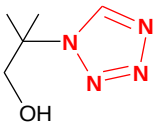
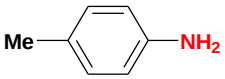
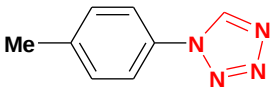
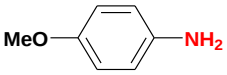
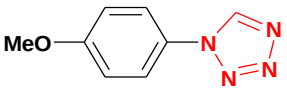
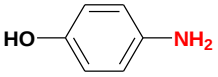
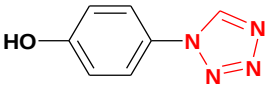
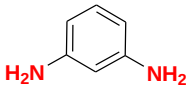
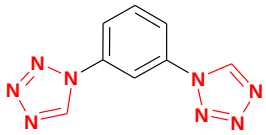
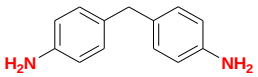
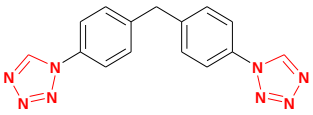
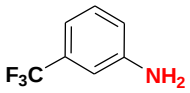
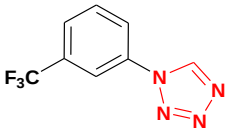
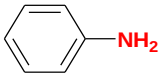
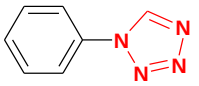
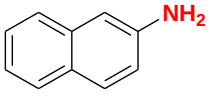
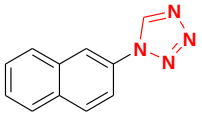
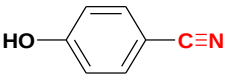
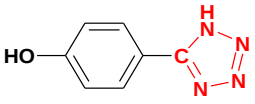
TABLE 1 Optimization of conditions for the reaction condition

Entry	Conditions	Catalyst, %	Conversion, %
1	Solvent-Free, rt	5	Trace[a]
2	Solvent-Free, 100 °C	10	30[a]
3	MeOH, reflux	5	35[a]
4	MeOH, reflux	10	35[a]
5	Ethanol, rt	5	Trace[a]
6	Ethanol, reflux	5	60[a]
7	Ethanol, reflux	3	50[a]
8	H_2O, reflux	5	40[a]
9	THF, reflux	5	30[a]
10	EtOAc, reflux	5	50[a]
11	*n*-Hexane, reflux	5	Trace[a]
12	Diethyl ether, reflux	5	Trace[a]
13	PEG, rt	5	Trace[a]
14	PEG, 100 °C	5	80[b]
15	PEG, 120 °C	10	89[b]
16	**PEG, 120 °C**	**5**	**95[b]**
17	PEG, 120 °C	3	90[b]
18	PEG, 150 °C	5	92[b]

[a]Estimated by TLC. [b]Isolated yield.

Having determined the best conditions, we next examined a variety of structurally divergent anilines possessing a range of functional groups to understand the scope and generality of the BSA-promoted cyclization reaction, and the results are summarized in **Table 2**. The procedure was tolerant of the presence of the alcohol and phenol functions.

TABLE 2 Synthesis of 1-substituted 1*H*-1,2,3,4-tetrazoles

Entry	Aryl & Alkyl Amines (a)	Product (T)	Yield %[a]	m.p °C Found	[ref.]
1	 **1a**		89	195-198	25,38
2	 **2a**		65	121-123	25, 38
3	 **3a**		64	134-136	
4	 **4a**		73	92-94	25, 39
5	 **5a**		95	117-119	39
6	 **5a**		75	164-166	38
7	 **7a**		93	156-158	40
8	 **8a**		87	139-141	40
9	 **9a**		94	184-186	40
10	 **10a**		78	75-77	
11	 **11a**		89	103-105	25, 39
12	 **12a**		81	194-196	
13	 **13a**		67	232-234	22, 24

[a]Isolated yield

In the development of these investigations and to broaden the preparative possibilities of this reaction, the heterocyclization of several amines has been studied in this work. It was discovered that primary amines **1** react with sodium azide

and triethyl orthoformate at a molar ratio of reactants of 1:1.1:1.5 in PEG using BSA, forming the corresponding 1-monosubstituted tetrazoles **2** (Scheme 1).

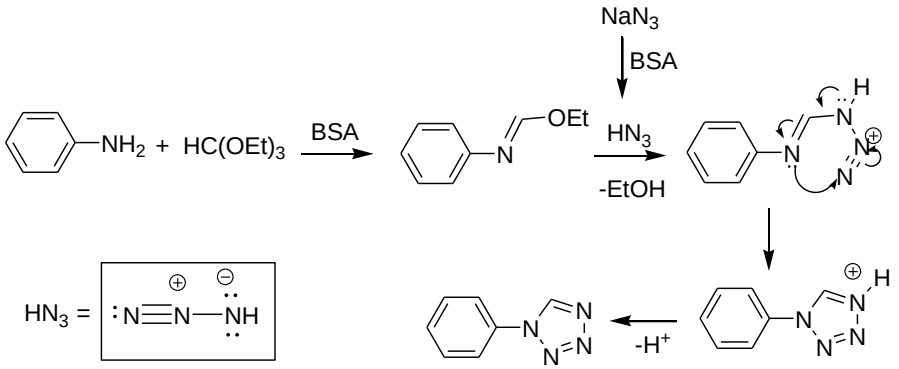
Treatment of the benzylamine and 2-amino-2-methylpropan-1-ol as aliphatic amines with orthoformate and sodium azide at 120 °C for 5 h also afforded the corresponding tetrazole and respectively in high yield (Table 2, Entries 2-3).

Difunctional amines afforded the expected double-addition products (Table 2, Entries 7-9, stoichiometry adjusted to permit full reaction).

The reaction procedure applied to 4-hydroxybenzonitrile afforded the corresponding 5-substituted tetrazole (**T13**) in good yield (Table 2, Entry 13).

The 1-substituted tetrazoles are generally acidic substances and the relevant proton signal will be shifted downfield. The peak at δ=8.30-9.30 ppm can be attributed to the proton of the tetrazole ring. ^{13}C NMR spectra displayed signals near δ 150 ppm for C5 of the tetrazole ring.

A proposed mechanism for the 1-substituted tetrazole-forming reaction in the presence of BSA is shown in Scheme 2.



SCHEME 2

In this study, we found that the 1-substituted tetrazole **1T** was produced in a low yield when the reaction of **1a** with sodium azide was carried out in the presence of $AlCl_3$, instead of the BSA catalyst.

In a typical experiment, after completion of the reaction, BSA was isolated from the reaction mixture by the simple filtration, separation of the aqueous layer and evaporation of water. The reusability of the catalyst was assessed after activating the catalyst at 80 °C for 8 h. Then it was reused four times successively with consistent activity, indicating high activity of the catalyst. This reusability, demonstrates the high efficiency of BSA under the reaction conditions.

The BSA catalyst can be recovered by simple filtration, separation of aqueous layer and reused after evaporation of solvent without the loss of activity. This methodology may find widespread application in organic synthesis for the preparation of the tetrazoles. Further studies are in progress.

Now, we are in a position to report the convenient synthesis of the 1-substituted tetrazoles in good to excellent yields through the BSA-catalyzed cyclization reaction between primary amines, triethyl orthoformate and sodium azide in PEG.

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 ^{1}H NMR data), so the peak at=8.30-9.30 ppm can be attributed to the proton of the tetrazole ring. ^{13}C NMR spectra displayed signals about=147-157 ppm for C5 of the tetrazole

ring. ^{1}H NMR shifting of C-H(C5) show at 8.30-9.30 ppm (Figure 1).

In summary, we have applied an efficient methodology for the synthesis of 1-substituted tetrazoles in PEG using BSA as a heterogeneous catalyst. Pure products are obtained in good to excellent yields through a simple work-up without need to the chromatographic purification way.

Experimental section

All reagents were purchased from Merck and Aldrich and used without further purification. ^{13}C NMR and ^{1}H NMR spectra were recorded on a Brucker (author supply model number and operating frequency) using TMS as an internal standard. Chemical shifts are reported in ppm, and coupling constants are reported in Hz. IR spectra were recorded on a Shimadzu 470 spectrophotometer. TLC was performed on Merck-precoated silica gel 60-F254 plates, using ethylacetate:*n*-hexane (1:10) as the solvent phase.

Safety Notes: sodium azide is toxic and explosive. Along with the appropriate personal safety gear, all reactions should be carried out in a well-ventilated hood behind a safety shield. Workers should be thoroughly trained in the use of sodium azide before performing reactions. The reactions were done on the small scale. Any attempt at scaling up should be done with due caution and with safety in mind.

General procedure for preparation of the 1-substituted tetrazoles

A mixture of amine (2.0 mmol), NaN_3 (2.2 mmol. CAUTION! See *Safety Notes* above), triethyl orthoformate (3 mmol) and SiO_2/BSA (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 ^{o}C with vigorous stirring for the appropriate time (Table 1). Completion of the reaction was followed by TLC method. After completion, the reaction mixture was diluted with cold water (50 mL) and extracted with ethyl acetate (3×50 mL). The catalyst was removed by filtration and the organic layer was dried over anhydrous Na_2SO_4 and filtered. After concentration, a crystallization step was performed using EtOAc:*n*-hexane to afford the pure product. All the products are known compounds and the spectral data and melting points were compatible with those reported in the literature [22-24, 38,40].

Preparation of boron sulfonic acid (BSA)

Catalyst 1 is synthesized based on the method reported in our previous articles [30-36].

1-(4-Chlorophenyl)-1H-tetrazole (1T)

White solid, ^{1}H NMR (FT-400 MHz, $CDCl_3$/TMS): δ_{ppm} 9.03(s, 1H, C-H) 7.68(d, 2H, *J*=8.7) 7.54(d, 2H, *J*=6.9); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_{ppm} 121.12, 122.46, 129.10, 130.47, 140.49; MS: *m/z*=180 (M^+).

1-Benzyl-1H-tetrazole (2T):

White solid, m.p 121-123 ^{o}C; ^{1}H NMR (FT-400 MHz, $CDCl_3$/TMS): δ_{ppm} 8.672 (s, 1H, C-H) 7.304 (t, 3H, *J*=2.7, Ar-H) 7.50 (d, 2H, *J*=3.6, Ar-H) 5.561 (s, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ_{ppm} 142.79, 133.11, 129.31, 129.21, 128.32, 52.07; MS: *m/z*=160 (M^+).

2-Methyl-2-(1H-tetrazole-1-yl) propan-1-ol (3T):

White solid, m.p 134-136 ^{o}C; ^{1}H NMR (FT-400 MHz, $CDCl_3$/TMS): δ_{ppm} 8.764 (s, 1H, C-H) 8.721 (s, 1H, O-H) 3.764 (s, 2H, CH_2) 1.706 (s, 6H, $2CH_3$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_{ppm} 141.18, 141.81, 68.78, 63.86, 24.35; MS: *m/z*=142 (M+).

1-(4-Methylphenyl)-1H-tetrazole (4T):

White solid, m.p 92-94 ^{o}C; ^{1}H NMR (FT-400 MHz, $CDCl_3$/TMS): δ_{ppm} 8.161 (s, 1H, C-H) 7.101 (d, *J*=7.8, 2H) 6.941 (d, *J*=8.1, 2H)

2.231(s, 3H, Ar-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_{ppm} 149.31, 142.58, 132.82, 129.93, 118.98, 70.56; MS: *m/z*=160 (M+).

1-(4-Methoxyphenyl)-1H-tetrazole (5T):

White solid, m.p 117-119 °C; ^1H NMR (FT-400 MHz, $CDCl_3$/TMS): δ_{ppm} 8.948 (s, 1H, C-H) 7.582 (d, *J*=7.2, 2H, Ar-H) 7.038 (d, *J*=7.2, 2H, Ar-H) 3.85 (s,3H, CH_3); MS: *m/z*=177 (MH^+).

5-(4-Hydroxyphenyl)-1H-tetrazole (13T)

White solid, m.p 232-234 °C; ^1H NMR (FT-400 MHz, $CDCl_3$/TMS): δ_{ppm} 7.551 (d, *J*=8.7, 2H, Ar-H) 7.259 (s, 1H, N-H) 6.938 (d, *J*=8.4, 2H, Ar-H) 6.683 (bs, 1H, O-H); ^{13}C NMR (100 MHz, $CDCl_3$): 160.236, 134.1515(br) 119.280, 116.489, 103.025; MS: *m/z*=163 (MH^+).

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