Trifluoromethanesulfonimide catalysed synthesis of 1-substituted-1*H*-1,2,3,4-tetrazoles using glycerol as green solvent at room temperature

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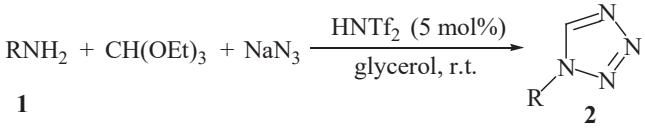
A direct synthetic protocol is developed for the synthesis of 1-substituted-1*H*-1,2,3,4-tetrazoles *via* a three-component condensation of primary amines, triethyl orthoformate and sodium azide in the presence of 5 mol% of trifluoromethanesulfonimide ($HNTf_2$) in glycerol at room temperature with good to excellent yields.

Keywords: 1-substituted-1*H*-1,2,3,4-tetrazoles, trifluoromethanesulfonimide, glycerol, primary amines

Tetrazoles are an important class of heterocycles which exhibit a wide range of applications for different purposes. Among tetrazole derivatives, 1-substituted tetrazoles have received much attention and have been used in the fields of synthetic and medicinal chemistry[1,2] as well as in material science including propellants and explosives.[3,4] They are also regarded as biologically equivalent to carboxylic acid group.[5] The routes to 1-substituted tetrazoles include acid-catalysed cycloaddition between hydrozoic acid and isocyanides,[6] acid-catalysed cycloaddition between isocyanides and trimethyl azide,[7] acetic acid or trifluoroacetic acid-catalysed cyclisation reaction of amines or its hydrochloride salt with an orthocarboxylic acid ester and a hydrazoic acid metal salt[8] and cyclisation from an amine, orthoformate, and sodium azide using $In(OTf)_3$,[9] $Yb(OTf)_3$,[10] ionic liquids,[11,12] salen Cu(II),[13] terpyridine copper complex,[14] Fe_3O_4@SiO_2/ligand/Cu(II),[15] $HClO_4$–SiO_2,[16] natrolite zeolite,[17] $CoFe_2O_4$ nanoparticles,[18] silica sulfuric acid,[19] P_2O_5–SiO_2,[20] ZnS nanoparticles[21] and methanesulfonic acid[22] as a catalyst. The cyclisation of amines, orthoformates and sodium azide is known as one of the most conventional pathways for the synthesis of 1-substituted tetrazoles. Most of the catalysts in previous works are not available commercially and involve a high cost for their preparation and therefore are not a good contender for general use, and have other drawbacks such as high reaction temperatures, low yields and the use of a large amount of catalysts. $In(OTf)_3$ and $Yb(OTf)_3$ are expensive and contain polluted metals. In view of these, the search for finding a more efficient and convenient protocol for the synthesis of 1-substituted tetrazoles is still relevant.

In recent years, metal bistrifluoromethanesulfonimides[23,24] and $HNTf_2$[25,26] have been used in various organic transformations. $HNTf_2$ as a catalyst has several advantages over metal bistrifluoromethanesulfonimides: no metals are required and therefore, no metallic waste remains after the reaction, $HNTf_2$ is commercially available and many of metal bistrifluoromethanesulfonimides are not available commercially. Our many efforts have been recently done in the synthesis of tetrazoles, which can be used for the energetic materials. In continuation to our work,[27] we herein report an efficient synthesis of 1-substituted-1*H*-1,2,3,4-tetrazoles from amines, triethyl orthoformate and sodium azide in the presence of 5 mol% of $HNTf_2$ using glycerol as a green solvent at room temperature (Scheme 1).



Scheme 1 Synthesis of 1-substituted-1*H*-1,2,3,4-tetrazoles catalysed by $HNTf_2$.

Results and discussion

The reaction of aniline, triethyl orthoformate and sodium azide was chosen as a model reaction. The reaction was optimised for various reaction parameters such as solvent and catalyst loading. Low yield was obtained under solvent-free conditions (Table 1, entry 1). The use of organic solvents such as CH_3CN, 1,2-dichloroethane, DMSO, toluene and 1,4-dioxane afforded the desired product **2a** in lower yields (Table 1, entries 2–6). Glycerol proved to be the most effective solvent (Table 1, entry 7).

With respect to the catalyst loading (Table 2, entries 2–6), 5 mol% of $HNTf_2$ was found to be optimal. No product was detected in the absence of the catalyst (Table 2, entry 1). The desired product **2a** was isolated in lower yield using a lower loading of $HNTf_2$ and there was no observed improvement with a higher loading of 10 mol% of $HNTf_2$.

Table 1 Effect of solvent on the reaction of aniline, triethyl orthoformate and sodium azide[a]

Entry	Solvent	Yield/%[b]
1	None	46
2	CH_3CN	52
3	1,2-Dichloroethane	49
4	DMSO	73
5	Toluene	47
6	1,4-Dioxane	37
7	Glycerol	92

[a]The reactions were performed in the presence of 5 mol% of $HNTf_2$ at room temperature for 3 h.

[b]Isolated yield.

Table 2 Effect of catalyst loading on the reaction of aniline, triethyl orthoformate and sodium azide[a]

Entry	Catalyst/mol%	Yield/%[b]
1	0	0
2	1	51
3	3	78
4	5	92
5	7	92
6	10	92

[a]The reactions were performed in the presence of $HNTf_2$ in glycerol at room temperature for 3 h.

[b]Isolated yield.

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Table 3 Synthesis of 1-substituted-1*H*-1,2,3,4-tetrazoles catalysed by $HNTf_2$[a]

Entry	R	Product	Time/h	Yield/%[b]	m.p./°C	
					Found	Lit.
1	C_6H_5	**2a**	3	92	65–66	64–65[10]
2	4-MeC_6H_4	**2b**	3.5	90	91–93	93–94[21]
3	2-MeC_6H_4	**2c**	3	87	152–154	153–155[21]
4	4-ClC_6H_4	**2d**	3.5	90	155–157	157–158[10]
5	3-$NO_2C_6H_4$	**2e**	3	95	100–102	101–102[14]
6	3-$MeOC_6H_4$	**2f**	3.5	87	68–70	68–69[14]
7	3-BrC_6H_4	**2g**	3	91	76–78	77–79[14]
8	4-$MeCOC_6H_4$	**2h**	3	92	146–148	148–150[21]
9	2-ClC_6H_4	**2i**	3.5	85	127–129	129–131[21]
10	3-HOC_6H_4	**2j**	3	87	166–168	168–170[14]
11	2,4-$Cl_2C_6H_3$	**2k**	3	89	146–148	146[10]
12	2-Me-5-ClC_6H_3	**2l**	3.5	87	55–56	54–55[10]
13	2-pyridyl	**2m**	3	94	126–128	129–130[10]
14	$C_6H_5CH_2$	**2n**	4	91	59–60	57–58[10]
15	$CH_3(CH_2)_3$	**2o**	5	84	142–143	143[15]

[a]All reactions were conducted in the presence of 5 mol% of $HNTf_2$ in glycerol at room temperature.
[b]Isolated yield.

To expand the efficiency and generality of this methodology, additional reactions of triethyl orthoformate and NaN_3 with a variety of amines (aromatic, heteroaromatic, and aliphatic) were next attempted in the presence of 5 mol% of $HNTf_2$ in glycerol at room temperature. The results are summarised in Table 3. Aromatic amines including both electron-donating and electron-withdrawing groups on the aromatic ring provided the corresponding products in excellent yields. Interestingly, electron-donating or electron-withdrawing at para-, ortho- or meta-position does not have significant influence on the product yield (Table 3, entries 2–12). The heterocyclic based 1-substituted tetrazole was also formed with high yield (Table 3, entry 13). Aliphatic amines such as benzylamine and butylamine furnished the corresponding products in good yields, but longer reaction times were required (Table 3, entries 14 and 15).

In conclusion, glycerol was found to be an effective and environmentally benign medium for the synthesis of 1-substituted-1*H*-1,2,3,4-tetrazoles from amines, triethyl orthoformate and sodium azide catalysed by $HNTf_2$. The advantages of this protocol include the use of a metal-free and commercially available catalyst, ease of experimentation (room temperature) and green solvent.

Experimental

Melting points were determined on an XT4A electrothermal apparatus equipped with a microscope and are uncorrected. NMR spectra were recorded on a Bruker Avance 400 spectrometer in DMSO-d_6. IR spectra were recorded on a Nicolet FTIR-750 spectrometer. Elemental analyses were performed on a Perkin Elmer 240-C instrument. All solvents were dried by standard procedures.

Synthesis of 1-substituted-1H-1,2,3,4-tetrazoles (**2a**–**o**)*; general procedure*

A mixture of amine (2 mmol), sodium azide (2 mmol), triethyl orthoformate (2.4 mmol), glycerol (8 mL) and $HNTf_2$ (5 mol%) was taken in a round bottomed flask and stirred at room temperature. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with cold water (5 mL) and extracted with a mixture of hexane/ethyl acetate 95:5 (3 × 10 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The residue was concentrated and recrystallised from ethyl acetate/hexane 2:1 to afford the pure product.

All the products are known compounds and the spectral data and melting points were in agreement with those reported in the literature. Selected spectral data for **2c** and **2d** is given below.

*1-(2-Methylphenyl)-1*H*-tetrazole* (**2c**): White solid; m.p. 152–154 °C (lit.[21] 153–155 °C); IR (ν_{max}, cm^{-1}) KBr: 3011, 2868, 1661, 1594, 1483 1179, 1166, 1093; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.33 (s, 3H, CH_3), 7.02–7.09 (m, 2H, ArH), 7.20–7.25 (t, *J* = 7.6 Hz, 2H, ArH), 8.16 (s, 1H, tetrazole); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.9, 117.8, 123.6, 127.1, 128.5, 130.2, 144.6, 147.9; Anal. calcd for $C_8H_8N_4$: C, 59.98; H, 5.03; N, 34.98; found: C, 60.13; H, 5.11; N, 34.86%.

*1-(4-Chlorolphenyl)-1*H*-1,2,3,4-tetrazole* (**2d**): White solid; m.p. 155–157 °C (lit.[10] 157–158 °C); IR (ν_{max}, cm^{-1}) KBr: 3052, 2915, 2850, 1498, 1385, 1201, 992, 833; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.53 (d, *J* = 8.6 Hz, 2H, ArH), 7.75 (d, *J* = 8.6 Hz, 2H, ArH), 8.41 (s, 1H, tetrazole); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 122.9, 123.8, 129.5, 136.1, 150.9; Anal. calcd for $C_7H_5ClN_4$: C, 46.55; H, 2.79; N, 31.03; found: C, 46.41; H, 2.63; N, 31.16%.

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