Efficient synthesis of 5-substituted 1*H*-tetrazoles catalysed by silver(I) bis(trifluoromethanesulfoyl)nimide

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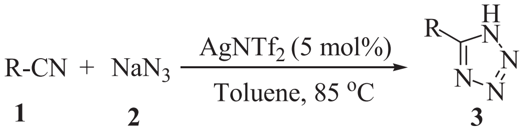
An efficient method is developed for the synthesis of 5-substituted 1*H*-tetrazoles through the [3 + 2] cycloaddition reaction of nitriles with sodium azide using silver(I) bis(trifluoromethanesulfonyl)imide ($AgNTf_2$) as a catalyst. This procedure provides mild reaction conditions, short reaction times and high yields.

Keywords: 5-substituted 1*H*-tetrazoles, silver bistrifluoromethanesulfonimide, nitriles, sodium azide

Tetrazoles are a class of heterocyclic compounds with a wide range of applications in pharmaceuticals,[1,2] energetic materials,[3,4] and coordination chemistry.[5,6] Because of their importance and usefulness, various synthetic methods have been developed for the construction of tetrazole frameworks. These include the reactions of nitriles with $TMSN_3$,[7,8] aldehydes with hydroxylamine and $[bmim]N_3$,[9] aldehydes with acetohydroxamic acid and sodium azide[10] and nitriles with boron-azides.[11] The [3+2] cycloaddition of nitriles with NaN_3 is one of the most conventional pathways for the synthesis of 5-substituted 1*H*-tetrazoles. Sharpless and co-workers[12] reported an innovative procedure for the synthesis of tetrazoles by the addition of nitriles to NaN_3 using either a stoichiometric amount, or 50 mol % of Zn(II) salts. Since then, many methods for the synthesis of 5-substituted 1*H*-tetrazoles have been reported in the presence of catalysts such as nanocrystalline ZnO,[13] $FeCl_3$–SiO_2,[14] tungstates,[15] Zn/Al hydrotalcite,[16] $NaHSO_4{\cdot}SiO_2$ or I_2,[17] $ZnCl_2$,[18] a terpyridine copper complex,[19] $AgNO_3$,[20] TBAHS,[21] 4-(dimethylamino)pyridinium acetate,[22] $Ln(OTf)_3$-SiO_2,[23] $B(C_6F_5)_3$,[24] CAN/HY-zeolite[25] and $Yb(OTf)_3{\cdot}xH_2O$.[26] Although each of the above methods has its own merit, most of these are associated with drawbacks such as long reaction times, high reaction temperatures and the use of a large amount of catalysts.

In recent years, metal bis(trifluoromethanesulfonyl)imides have been successfully used for the acetylation of phenols and alcohols,[27] [2+2] cycloadditions of siloxy alkynes with carbonyl compounds,[28] Friedel–Crafts acylation reactions,[29] cycloisomerisation of 1,6-dienes[30] and intermolecular hydroamination of alkynes with anilines.[31] However, many metal bis(trifluoromethanesulfonyl)imides are not available commercially and involve a high cost for their preparation and therefore are not good contenders for general use. $AgNTf_2$ is commercially available and therefore better suited for catalytic use. Previously, we have reported the use of $Mg(NTf_2)_2$[32] and $LiNTf_2$[33] as efficient catalysts for the organic reactions. In continuation of our work, we now report an efficient procedure for the synthesis of 5-substituted 1*H*-tetrazoles from nitriles with NaN_3 in the presence of 5 mol% of $AgNTf_2$ in toluene at 85 °C (Scheme 1).



Scheme 1 Synthesis of 5-substituted 1*H*-tetrazoles catalysed by $AgNTf_2$.

The reaction of benzonitrile with NaN_3 was first examined in the presence of various silver-based catalysts (Table 1). With Ag_2CO_3, $AgNO_3$ and AgOAc, compound **3a** was produced in only 34, 25 and 30% yields, respectively. The reaction of benzonitrile with NaN_3 in DMF at 100 °C in the presence of 10 mol% of $AgNO_3$ was completed in 12 h affording the corresponding tetrazole **3a** in 49% yield.[20] With Ag_2O and AgOTf, the desired product **3a** was isolated in 56 and 71% yields, respectively. Importantly, the best yield (92%) was obtained in the presence of 5 mol% of $AgNTf_2$.

The reaction was optimised for various reaction parameters such as temperature, solvent, and catalyst loading. When the reaction was carried out at room temperature, **3a** was obtained in only 8% yield (Table 2, entry 1). The effect of temperature on the yield of product was monitored from 45 to 100 °C (Table 2, entries 2–5). However, no further increase in the yield was obtained by increasing the temperature from 85 to 100 °C. Therefore, 85 °C was chosen as the optimum temperature for all further reactions.

The reaction afforded the corresponding product in a very low yield in the absence of solvent (Table 3, entry 1). Among the various solvents studied, toluene was found to be the most effective solvent (Table 3, entries 2–5).

With respect to the catalyst loading, 5 mol % of $AgNTf_2$ was found to be optimal. The desired product **3a** was isolated in lower yield using a lower loading of $AgNTf_2$ (Table 4, entries 1 and 2). However, no improvement was observed with 10 mol % of $AgNTf_2$ (Table 4, entry 4).

Table 1 Effect of catalysts on the reaction of benzonitrile with NaN_3[a]

Entry	Catalyst	Yield/%[b]
1	Ag_2CO_3	34
2	$AgNO_3$	25
3	AgOAc	30
4	Ag_2O	56
5	AgOTf	71
6	$AgNTf_2$	92

[a] The reactions were performed in the presence of 5 mol% of catalyst in toluene at 85 °C for 3 h.
[b] Isolated yield.

Table 2 Effect of temperature on the reaction of benzonitrile with NaN_3[a]

Entry	Temperature/°C	Yield/%[b]
1	r.t.	8
2	45	33
3	60	61
4	85	92
5	100	92

[a] The reactions were performed in the presence of 5 mol% of $AgNTf_2$ in toluene for 3 h.
[b] Isolated yield.

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Table 3 Effect of solvent on the reaction of benzonitrile with NaN_3[a]

Entry	Solvent	Yield/%[b]
1	None	22
2	CH_3CN	46
3	DMF	84
4	DMSO	75
5	H_2O	26
6	Toluene	92

[a] The reactions were performed in the presence of 5 mol% of $AgNTf_2$ at 85 °C for 3 h.

[b] Isolated yield.

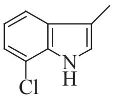
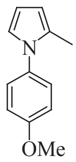
Table 4 Effect of catalyst loading on the reaction of benzonitrile with NaN_3[a]

Entry	Catalyst/mol%	Yield/%[b]
1	1	20
2	3	41
3	5	92
4	10	92

[a] The reactions were performed in the presence of $AgNTf_2$ in toluene at 85 °C for 3 h.

[b] Isolated yield.

Table 5 Synthesis of 5-substituted 1*H*-tetrazoles catalysed by $AgNTf_2$[a]

Entry	R	Product	Time/h	Yield[b]/%	M.p./°C	
					Found	Reported (lit.)
1	C_6H_5	**3a**	3	92	214–216	215–216[7]
2	$4\text{-}ClC_6H_4$	**3b**	3	93	256–258	258–260[11]
3	$3\text{-}BrC_6H_4$	**3c**	3	84	149–151	149–150[19]
4	$4\text{-}OHC_6H_4$	**3d**	3	90	234–236	234–235[8]
5	$4\text{-}NO_2C_6H_4$	**3e**	2.5	96	218–220	219–221[7]
6	$4\text{-}MeOC_6H_4$	**3f**	3.5	87	231–233	231–233[8]
7	$3\text{-}MeOC_6H_4$	**3g**	3	88	157–159	156–157[7]
8	$4\text{-}MeC_6H_4$	**3h**	3	90	248–250	248–249[8]
9	$2\text{-}ClC_6H_4$	**3i**	4	81	173–174	172–174[21]
10	$2\text{-}MeC_6H_4$	**3j**	5	78	152–154	151–153[21]
11	2-Furanyl	**3k**	1	96	202–204	204–205[7]
12	3-Pyridyl	**3l**	2	92	236–238	239–240[7]
13	$CH_3(CH_2)_3$	**3m**	5	86	42–44	41–42[7]
14	Cyclopentyl	**3n**	5	84	110–112	109–111[21]
15		**3o**	3	94	257–259	256–258[34]
16		**3p**	4	89	190–192	191–193[35]

[a] All reactions were conducted in the presence of 5 mol% of $AgNTf_2$ in toluene at 85 °C.

[b] Isolated yield.

To expand the efficiency and generality of this methodology, additional reactions of NaN_3 with a variety of nitriles (aromatic, heteroaromatic, and aliphatic) were next attempted in the presence of 5 mol% of $AgNTf_2$ in toluene at 85 °C. The results are summarised in Table 5. Treatment of NaN_3 with aryl nitriles including both electron-donating and electron-withdrawing groups on the aromatic ring provided the corresponding products in high yields. Interestingly, either an electron-donating or an electron-withdrawing substituent at a *para-* or a *meta-*position does not have a significant influence on the product yield (Table 5, entries 2–8). Introduction of either an electron-donating or an electron-withdrawing group at position 2 gave good to moderate yields, perhaps due to steric effects (Table 5, entries 9 and 10). The heterocyclic based tetrazoles were formed in shorter reaction times with excellent yields (Table 5, entries 11 and 12). The reaction of NaN_3 with aliphatic nitriles furnished the desired tetrazoles in high yields, but longer reaction times were needed (Table 5, entries 13 and 14). The reactions were completed in 3 or 4 h affording the corresponding tetrazoles **3o** and **3p** in 94% and 89% yields, respectively (Table 5, entries 15 and 16).

In conclusion, $AgNTf_2$ was found to be a highly efficient catalyst for the synthesis of 5-substituted 1*H*-tetrazoles from nitriles with NaN_3. The advantages of this protocol include high yields, short reaction times, low reaction temperatures and the use of a catalytic amount and commercially available catalyst.

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 for solutions in DMSO-d_6. IR spectra were recorded on a Nicolet FTIR-750 spectrometer. Elemental analyses were performed on a PerkinElmer 240-C instrument. All solvents were dried by standard procedures.

Synthesis of 7-chloro-1H-indole-3-carbonitrile

A mixture of 7-chloro-1*H*-indole-3-carboxaldehyde[36] (3.6 g, 20 mmol), hydroxylamine hydrochloride (1.40 g, 20 mmol), sodium acetate (1.60 g, 20 mmol), glacial acetic acid (63 g, 60 mL) and acetic anhydride (2.2 g, 2 mL) was placed in a round bottomed flask and heated under reflux for 4 h. Then the reaction mixture was cooled and poured into ice water. The resulting precipitate was filtered, washed with water, dried and recrystallised from methanol to give the pure product 7-chloro-1*H*-

indole-3-carbonitrile (3.1 g, 88% yield): m.p. 180–182 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.19–7.35 (m, 2H), 7.58–7.64 (m, 1H), 8.32 (d, $J = 5.0$ Hz, 1H), 12.61 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 113.5, 115.7, 118.3, 119.6, 120.1, 122.2, 123.4, 127.9, 137.4. IR (KBr) ν_{max}/cm^{-1} 3272, 3124, 2240, 1583, 1441, 1352, 1300, 1211.

Synthesis of 1-(4-methoxyphenyl)pyrrole-2-carbonitrile

A mixture of 4-methoxyaniline (2.50 g, 20 mmol), 2,5-dimethoxytetrahydrofuran (3.20 g, 24 mmol) and bismuth(III) nitrate pentahydrate (0.6 g) was placed in a three-necked flask in a microwave oven equipped with a temperature sensor and a reflux condenser. Then the mixture was irradiated for 10 min (300W) at 90 °C. After completion of the reaction, the mixture was cooled and extracted with diethyl ether (3 × 50 mL). The combined organic layers were dried with anhydrous magnesium sulfate. The solvent was removed and the crude product was purified by column chromatography on silica gel using petroleum ether and acetone (10:1, v/v) as the eluent to give the pure product 1-(4-methoxyphenyl)pyrrole (3.20 g, 93% yield): m.p. 108–112 °C (lit.[37] 104–108 °C).

Trimethylsilyl cyanide (4.50 g, 45 mmol) was added to a stirred solution of phenyliodine bis(trifluoroacetate) (12.9 g, 30 mmol) and $BF_3·Et_2O$ (8.5 g, 60 mmol) in CH_2Cl_2 (15 mL) at room temperature. After stirring for 30 min, 1-(4-methoxyphenyl)pyrrole (2.6 g, 15 mmol) was added in one portion, and the mixture was stirred for additional 7 h under the same conditions whilst the reaction progress was monitored by TLC. After the reaction was complete, saturated aqueous sodium thiosulfate (80 mL) was added to the mixture. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined extracts were dried with anhydrous magnesium sulfate and evaporated to dryness. The crude product was purified by column chromatography on silica gel using petroleum ether and ethyl acetate (5:1, v/v) as the eluent to give the pure product 1-(4-methoxyphenyl)pyrrole-2-carbonitrile[38] (1.1 g, 38% yield): m.p. 162–164 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.79 (s, 3H), 6.34 (t, J =3.0 Hz, 1H), 6.91–6.98 (m, 1H), 7.04 (d, $J = 4.6$ Hz, 1H), 7.18 (t, $J = 3.9$ Hz, 2H), 7.42–7.46 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 63.5, 104.4, 110.7, 113.6, 116.4, 116.8, 122.1, 126.0, 126.1, 127.2, 134.3, 160.4, 163.7. IR (KBr) ν_{max}/cm^{-1} 3111, 2920, 2211, 1512.

Synthesis of 5-substituted 1H-tetrazoles; general procedure

A mixture of the appropriate nitrile (1 mmol), NaN_3 (1.5 mmol), toluene (2 mL) and $AgNTf_2$ (5 mol%) was placed in a round bottomed flask and heated at 85 °C. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was cooled and treated with ethyl acetate (15 mL) and 1M HCl (15 mL) and stirred vigorously. The resultant organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with water and concentrated to give the pure tetrazole.

All the products are known compounds and the spectral data and melting points were identical to those reported in the literature. The disappearance of one strong and sharp absorption band (CN stretching band), and the appearance of an NH stretching band in the IR spectra, were characteristic of the formation of 5-substituted 1*H*-tetrazoles.

*5-(7-Chloroindol-3-yl)-1*H*-tetrazole* (**3o**): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.26 (s, 1H), 7.39 (d, $J = 7.6$ Hz, 1H), 8.12–8.20 (m, 2H), 12.28 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 111.3, 114.2, 118.0, 118.7, 120.6, 122.8, 127.2, 136.5, 152.8. IR (KBr) ν_{max}/cm^{-1} 3302, 1635, 1610, 1453, 1412, 1200, 741. Anal. calcd for $C_9H_6N_5Cl$: C, 49.20; H, 2.73; N, 31.89; found: C, 49.35; H, 2.68; N, 31.76%.

*5-[1-(4-Methoxyphenyl)pyrrol-2-yl]-1*H*-tetrazole* (**3p**): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.75 (s, 3H), 6.36–6.41 (m, 1H), 6.82–6.87 (m, 1H), 6.95 (d, $J = 8.7$ Hz, 2H), 7.17–7.20 (m, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 63.1, 110.4, 114.2, 114.6, 117.9, 127.6, 128.7, 132.8, 149.8, 159.3. IR (KBr) ν_{max}/cm^{-1} 2936, 1738, 1604, 1512, 951. Anal. calcd for $C_{12}H_{11}N_5O$: C, 59.75; H, 4.56; N, 29.05; found: C, 59.92; H, 4.60, N, 28.96%.

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