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An efficient synthesis of 5-substituted 1*H*-tetrazoles via $B(C_6F_5)_3$ catalyzed [3+2] cycloaddition of nitriles and sodium azide

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ABSTRACT

A simple and efficient protocol is developed for the synthesis of 5-substituted 1*H*-tetrazole derivatives from various nitriles and sodium azide (NaN_3) via [3+2] cycloaddition reaction using $B(C_6F_5)_3$ as a catalyst. The present synthetic method displayed significant advantages such as low catalyst loading, mild reaction conditions, low toxicity, easy work-up, high yields, and compatibility with other functional groups.

Tetrazoles are an important class of heterocycles with a wide range of application in the field of medicinal chemistry.[1] The tetrazoles are representative of active pharmacophores for several therapeutic active molecules such as antiallergic,[2a] anti-inflammatory,[2b] antibiotic,[2c] antihypertensive,[2d] antineoplastic,[2e,f] antiviral, and receptor modulator activities.[2g] Angiotensin II receptor blockers belonging to the sartan family often contain tetrazole as their active moiety, for example losartan, and candesartan.[3] Tetrazole derivatives have potential in drug development for HIV and other immune diseases[4] and also play an important role in metabolically stable surrogate for a carboxylic acid group in biologically active molecules.[5] Tetrazoles are found to be useful in various material sciences, including photography, and explosive.[6] In addition to this, tetrazoles have a wide range of application in coordination chemistry as well as in the preparation of imidoylazides.[7]

This broad utility provoked significant effort toward the tetrazole synthesis. Various methods have been reported for the synthesis of 5-substituted 1*H*-tetrazoles, most of which are based on [3+2] cycloaddition of azide ion to corresponding organic nitriles. The reactions were carried out by using numerous catalysts such as copper triflates,[8a] $CdCl_2$,[8b] $Fe(OAc)_2$,[8c] $ZnBr_2$,[8d] triethyl amine hydrochloride,[8e] Bronsted acid catalyst,[8f] various Lewis acid catalysts such as $AlCl_3$,[2f,9a] BF_3-OEt_2,[9b] $FeCl_3$,[9c] TBAF,[9d] $InCl_3$,[9e] I_2,[9f] $(CH_3)_2SnO$[9g] and by using some heterogeneous catalysts such as $NaHSO_4{\cdot}SiO_2$,[9f] COY zeolites,[10a] Zn/Al hydrotalcite,[10b] nanocrystalline ZnO,[10c] mesoporous ZnS nanospheres,[10d] Zn hydroxyapatite,[10e] $Pd(PPh_3)_4$,[10f] Cu_2O,[10g] and $CuFe_2O_4$ nanoparticles.[10h] Acid catalysts are also employed for the synthesis of tetrazoles via cycloaddition of isocyanide to hydrazoic acid.[11a] Very recently, $AgNO_3$ has also been described for the same purpose.[11b] However, some of the reported methods suffer from drawbacks such as harsh reaction condition, inferior yields of the desired product, formation of side product, stoichiometric amount of catalyst, water sensitivity, use of organic azide complexes such as tin or silicon organic azides, and the in situ generated hydrazoic acid, which is toxic, volatile, and explosive.[9g]

In view of the demands of organic syntheses, there is still need to develop new catalytic, environmentally benign and efficient protocol for the preparation of tetrazoles. In this regard, tris(pentafluorophenyl)borane [$B(C_6F_5)_3$] has been explored as non conventional Lewis acid of comparable strength to BF_3, but without the problem associated with reactive B—F bond.[12a] $B(C_6F_5)_3$ gained prominence because of its thermal stability, less toxicity than other Lewis acids, air stable, and water tolerant Lewis acid.[12b] Numerous research groups are actively involved to explore the potential utility of $B(C_6F_5)_3$ in modern organic synthesis, such as ring-opening of epoxides,[13a] aza-Ferrier glycosylation,[13b] hydrosilylation of imines,[14] reduction of alcohols with silane,[15] and hydrogenation of imines.[16] $B(C_6F_5)_3$ was utilized in the regio- and stereo-selective cyclizations of unsaturated alkoxysilanes.[17a] $B(C_6F_5)_3$ was also used as an efficient activator of polymethoxyhydrosiloxane in the reduction of various functional groups,[17b,c] and Friedel–Crafts alkylation of activated arenes and heteroarenes.[18]

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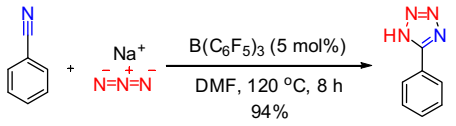

Scheme 1. Synthesis of 5-phenyl 1*H*-tetrazole.

Recently, $B(C_6F_5)_3$ catalyzed Sakurai allylation of *N*-benzyloxycarbonylamino *p*-tolylsulfone is also reported with allyltrimethylsilane.[19]

In continuation of our research in the development of novel synthetic methodology,[20] herein we wish to report a remarkable activity of tris(pentafluorophenyl)borane [$B(C_6F_5)_3$] to catalyze [3+2] cycloaddition reaction between organic nitriles and sodium azide to corresponding 5-substituted 1*H*-tetrazoles in high yields and purity. To the best of our knowledge, $B(C_6F_5)_3$ has not previously been reported for the preparation of 5-substituted 1*H*-tetrazole.

Initially, we screened the reaction conditions for [3+2] cycloaddition reaction of benzonitrile with sodium azide in the absence and presence of tris(pentafluorophenyl)borane [$B(C_6F_5)_3$] (Scheme 1). In the absence of catalyst at 120 °C, no reaction occurred after 10 h (Table 1, entry1). When benzonitrile was treated with sodium azide using 1 mol % $B(C_6F_5)_3$ in DMF, the 5-phenyl 1*H*-tetrazole was isolated in 33% yield (Table 1, entry 2). The yield was improved to 72% when the reaction was carried out in the presence of 3 mol % of $B(C_6F_5)_3$ (Table 1, entry 3). In an attempt to improve the conversion and yield, the reaction was repeated using 5 mol % of $B(C_6F_5)_3$ as a catalyst. Pleasingly, this resulted in complete conversion of benzonitrile into 5-phenyl 1*H*-tetrazole within 8 h in excellent yield (Table 1, entry 4). Further improvement of yields was not observed on increasing the loading of the catalyst (Table 1, entry 5). Hence 5 mol % of catalyst was considered as an optimum catalyst concentration. Furthermore, the reaction was carried out in different solvents (Table 1, entries 6–8). Among the various solvents tested, DMF was found to be the best solvent giving maximum yields of the desired product.

We also investigated the reaction by using $TMSN_3$ as azide source in DMF at 120 °C and the desired product was obtained in 92% yield (Table 1, entry 9). Interestingly, no silylated product was observed in present reaction conditions. An attempt was also made to catalyze the reaction in the absence of solvent but outcome was not promising (Table 1, entry 10). We also tried reaction in water and EtOH, but the yields of the desired products were inferior (Table 1, entries 11 and 12). Thus, 5 mol % of $B(C_6F_5)_3$ and DMF were selected as the optimized condition for the synthesis of 5-substituted 1*H*-tetrazoles (Table 1, entry 4). We also compared the catalytic efficiency of $B(C_6F_5)_3$ with other Lewis acids (Table 1, entries 13–16). Among the Lewis acid catalysts, $B(C_6F_5)_3$ was found to be superior in terms of yield and reaction time. We next examined a variety of structurally diverse organic nitriles to understand the scope and generality of the $B(C_6F_5)_3$ promoted [3+2] cycloaddition reaction to form 5-substituted 1*H*-tetrazoles and results are summarized in Table 2.

It was observed that, by using 5 mol % of $B(C_6F_5)_3$ in solution of organic nitriles and NaN_3 in DMF at 120 °C, the desired 5-substituted 1*H*-tetrazoles were obtained in admirable yields (Table 2, entries 1–18).[21] In case of aromatic nitriles, electron donating and electron withdrawing groups have a significant influence on the reaction times and product yields. The aromatic nitriles containing electron withdrawing substituents took less time for complete conversion of starting material relatively and the desired products were obtained in excellent yields (Table 2, entries 2–4), while bromo substitution at *ortho* position had given comparatively lower yield and longer reaction time due to steric effect (Table 2, entry 5). Moreover, electron donating groups at *para* position of aromatic ring gave the corresponding tetrazoles in high yields, although longer reaction times were required (Table 2, entries 6 and 7). Aryl nitrile containing a free hydroxy group at *para* position also gave desired product in high yield after 12 h (Table 2, entry 8). Similarly, 4-(allyloxy)benzonitrile and ethyl 2-(4-cyanophenoxy)acetate gave corresponding 1*H*-tetrazoles in excellent yields after 12 and 14 h, respectively. Other aryl nitriles such as 3,4-(methylenedioxy) phenyl acetonitrile and phenyl acetonitrile also reacted smoothly to give the corresponding tetrazoles in 89% and 84%, respectively (Table 2, entries 11 and 12).

We next examined the reactivity of heterocyclic nitriles. 6-Chloronicotinonitrile was found to be extremely reactive substrate, affording the relative tetrazole in 90% yield after 4 h (Table 2, entry 13), while furan-2-carbonitrile gave respective 1-*H* tetrazole in 89% yield in 6 h (Table 2, entry 14). Indole 3-acetonitrile and indole 5-carbonitrile produced corresponding tetrazoles in good yields after 14 and 20 h, respectively (Table 2, entries 15 and 16). Furthermore, [3+2] cycloaddition reaction was also extended to 1-adamantyl carbonitrile and butyronitrile under standard

Table 1
Optimization of various reaction parameters for the synthesis of 5 substituted 1*H*-tetrazole[a]

Entry	Catalyst (mol %)	Solvent	Azide source	Time (h)	Yield[b] (%)
1	Nil	DMF	NaN_3	10	NR[c]
2	$B(C_6F_5)_3$ (1)	DMF	NaN_3	12	33
3	$B(C_6F_5)_3$ (3)	DMF	NaN_3	12	72
4	$B(C_6F_5)_3$ (5)	DMF	NaN_3	8	94
5	$B(C_6F_5)_3$ (7)	DMF	NaN_3	8	93
6	$B(C_6F_5)_3$ (5)	EtOH	NaN_3	48	20
7	$B(C_6F_5)_3$ (5)	EtOH/water (8:2)	NaN_3	48	20
8	$B(C_6F_5)_3$ (5)	THF	NaN_3	48	Trace
9	$B(C_6F_5)_3$ (5)	DMF	$TMSN_3$	10	92[d]
10	$B(C_6F_5)_3$ (5)	Neat	$TMSN_3$	24	25[d]
11	$B(C_6F_5)_3$ (5)	Water	$TMSN_3$	18	15[d]
12	$B(C_6F_5)_3$ (5)	EtOH	$TMSN_3$	48	40[d]
13	BF_3-OEt_2 (5)	DMF	NaN_3	20	80
14[9f]	I_2	DMF	NaN_3	10	89
15[8c]	$Fe(OAc)_2$	DMF/water (9:1)	$TMSN_3$	24	56
16[9g]	$(CH_3)SnO$	Toluene	$TMSN_3$	72	60

[a] Reaction and conditions: benzonitrile (1 mmol), NaN_3 (1.5 mmol) are used at 120 °C.
[b] Isolated yield.
[c] In the absence of catalyst, no reaction occurred after 10 h.
[d] $TMSN_3$ (1.5 mmol) was used as azide source.

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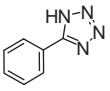
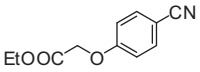
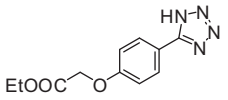
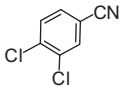
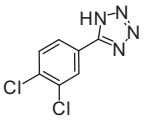
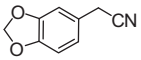
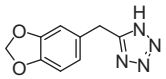
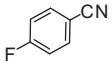
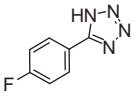
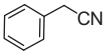
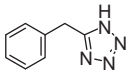
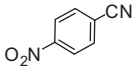
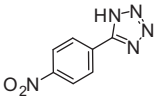
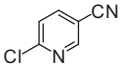
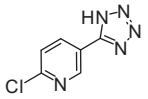
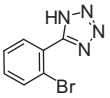
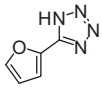
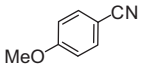
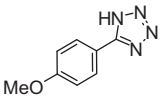
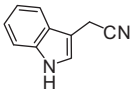
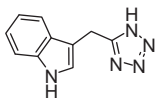
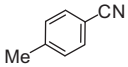
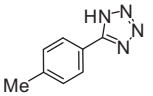
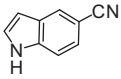
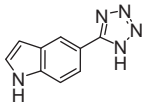
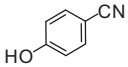
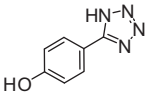
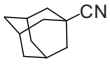
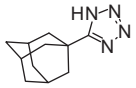
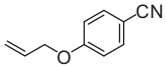
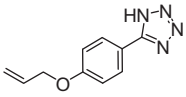
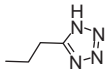
Table 2
$B(C_6F_5)_3$ catalyzed synthesis of 5-substituted 1*H*-tetrazole[a]

Entry	Substrate	Time (h)	Product	Yield[b] (%)	Entry	Substrate	Time (h)	Product	Yield[b] (%)
1[9d]		8		94	10[22]		14		90
2[22]		6		96	11[8d]		12		89
3[9e]		7		90	12[9c,9d]		12		84
4[9d]		6		95	13[8e]		4		90
5[11a]		15		82	14[9d]		6		89
6[10g]		14		84	15[2f]		14		78
7[10g]		12		88	16[9d]		20		80
8[10g]		12		87	17[8e]		14		87
9[22]		12		92	18[10g]		16		76

[a] Reaction and conditions: nitriles (1 mmol), NaN_3 (1.5 mmol), $B(C_6F_5)_3$ (5 mol %), DMF (5 mL), and temperature (120 °C).
[b] Isolated yield.

reaction condition, the corresponding 1*H*-tetrazoles were produced in 87% and 76% yields, respectively (Table 2, entries 17 and 18). The above results clearly indicate the scope and generality of catalyst for the synthesis of 5-substituted 1*H*-tetrzoles using a wide range of organic nitriles without affecting the presence of other functional groups and [3+2] cycloaddition proceeds well, irrespective of the electronic nature and position of the substituents of aromatic ring. Presumably, the mechanism of reaction instigates through co-ordination of nitriles with $B(C_6F_5)_3$, resulting in enhancement of its reactivity with NaN_3, which may facilitate the cycloaddition reaction to yield 5-substituted 1*H*-tetrazole products.

In summary, we have demonstrated a novel and an efficient protocol for the synthesis of 5-substituted 1*H*-tetrazole by using organic nitriles and NaN_3 via [3+2] cycloaddition reaction in the presence of $B(C_6F_5)_3$ as a catalyst.

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21. *Typical experimental procedure:* $B(C_6F_5)_3$ (67.3 mg, 0.13 mmol, 5 mol %) was added to a stirred solution of 3,4-dichlorobenzaldehyde (172 mg, 1 mmol) and NaN_3 (97.5 mg, 1.5 mmol) in DMF (5 mL) and was heated at 120 °C. After completion of reaction (as monitored by TLC), the reaction mixture was cooled to room temperature and was added 5 mL of cold water followed by 10 mL of 2 N HCl and 10 mL of ethyl acetate. The resulting mixture was stirred vigorously for 15 min. The organic layer was separated and aqueous layer was again extracted with ethyl acetate (3 × 15 mL). The combined organic layer was washed with water and dried over anhydrous sodium sulfate and was evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, EtOAc/hexane 9:1) to obtain pure 5-(3,4-dichlorophenyl)-1*H*-tetrazole. The known compounds were characterized and confirmed by comparison of their spectral data and physical properties with reported literature.
22. *Spectroscopic data of representative novel compounds:* 5-(3,4-Dichlorophenyl)-1*H*-tetrazole (entry 2): off white solid, mp 150–152 °C; (KBr) ν_{max} 3481, 2923, 1610, 1425, 1243, 1124, 1096, 886 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 8.25 (1H, d, J = 1.51 Hz), 8.03 (1H, dd, J = 1.51 Hz, J = 8.30 Hz), 7.70 (1H, d, J = 8.30 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) 154.7, 133.3, 132.3, 131.6, 128.5, 126.8, 125.1; HRMS m/z calcd for $C_7H_4Cl_2N_4^+$ $[M+H]^+$: 214.9891; found: 214.9881. 5-(4-(Allyloxy)phenyl)-1*H*-tetrazole (entry 9): pale yellow solid, mp 181–183 °C; (KBr) ν_{max} 3400, 2921, 1613, 1508, 1500, 1262, 1181, 989, 835 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.97 (2H, d, J = 8.87 Hz), 7.17 (2H, d, J = 8.87 Hz), 6.05 (1H, m), 5.45 (1H, d, J = 17.18 Hz), 5.38 (1H, d, J = 10.57 Hz), 4.66 (2H, d, J = 5.09 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) 160.1, 154.8, 133.1, 128.4, 117.7, 116.6, 115.37, 68.2; HRMS m/z calcd for $C_{10}H_{10}N_4O^+$ $[M+H]^+$: 203.0933; found: 203.0922. Ethyl 2-(4-(1*H*-tetrazol-5-yl)phenoxy)acetate (entry 10): pale brown solid, mp 154–156 °C; (KBr) ν_{max} 3410, 2982, 2920, 1751, 1614, 1500, 1208, 1077, 835 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.98 (2H, d, J = 8.87 Hz), 7.17 (2H, d, J = 8.87 Hz), 4.89 (2H, s), 4.21 (2H, q, J = 7.17 Hz), 1.24 (3H, t, J = 6.98 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) 168.2, 159.6, 154.6, 128.4, 116.9, 115.3, 64.6, 60.6, 13.9; HRMS m/z calcd for $C_{11}H_{12}N_4O_3^+$ $[M+H]^+$: 249.0988; found: 249.0982.