Facile Synthesis of 5-Substituted 1*H*-Tetrazoles Catalyzed by Tetrabutylammonium Hydrogen Sulfate in Water

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Facile synthesis of 5-substituted 1*H*-tetrazoles was achieved by treating nitriles with NaN_3 in water or toluene in the presence of tetrabutylammonium hydrogen sulfate (TBAHS). The reaction could be carried out in water as well as in toluene. The procedure is environment-friendly, practical, and provides excellent yield of tetrazoles.

Keywords: [3 + 2] Cycloaddition, Nitrile, Sodium azide, Tetrabutylammonium hydrogen sulfate, Tetrazoles

Introduction

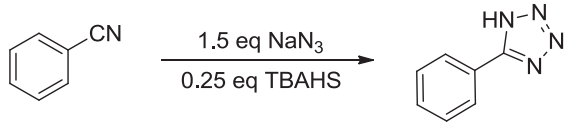
Tetrazoles, an important class of heterocyclic compounds, have attracted much attention because of their wide range of pharmacological and therapeutic activities that include antiproliferative,[1] antitumor,[1] anti-inflammatory,[2] antibacterial,[2] anticonvulsant,[3] and antiallergic activities[4]. As a bioisostere of carboxylic acid, tetrazoles have better pharmacokinetic profiles including metabolic stability, which confer longer bioavailability.[5,6] Tetrazoles are also a main constituent used in explosives, agriculture, and photography.[7] In addition, they have an important role as oxidizers and plant growth regulators.[8] Many of these derivatives are key precursors for the synthesis of various nitrogen-containing heterocyclic compounds and many useful transformations.[9] Herein, we report a facile synthesis of 5-substituted 1*H*-tetrazole derivatives from nitrile and sodium azide in water or toluene in the presence of tetrabutylammonium hydrogen sulfate (TBAHS).[10]

Several methods for the synthesis of tetrazoles have been reported. Earlier protocols suffered from one or several drawbacks including the use of expensive and/or toxic metal organic azide complexes, such as tin or silicon,[11] and the use of amine salts and hydrazoic acid that are extremely toxic, water-sensitive, explosive, and volatile.[12] Later, Demko and Sharpless[13] reported a relatively simple and safe procedure for the synthesis of tetrazoles by the addition of sodium azide to nitriles using zinc salt. However, for less-reactive nitriles, a long reaction time and high temperature were required. In order to overcome these disadvantages, new pathways have been developed, such as using a stoichiometric amount of inorganic salts[13] and transition metal complexes[14] as catalysts. In addition, various catalysts including $AlCl_3$,[15] $Pd(OAc)_2$/$ZnBr_2$,[16] Pd-$(PPh_3)_4$,[17] and $Zn(OTf)_3$[18] were also used for this purpose. However, these catalytic processes have limitations in separation, recovery, and reusability of the catalyst. Alternatively several heterogeneous catalysts, such as γ-Fe_2O_3,[19] Zn/Al hydrotalcite,[20] and Cu_2O[21] have also been used in the synthesis of tetrazoles.

In this article, in light of improving the eco-compatibility of tetrazole synthesis, we focused our attention in finding a green catalyst and environmentally benign solvent, such as water. TBAHS is a readily available solid-acid catalyst that is inexpensive, water-soluble, easy to handle, thermally stable, and environment-friendly. Moreover, TBAHS could be easily separated and recovered,[22] and has been used as an efficient catalyst for the synthesis of aryl vinyl ether,[23] alkaloids,[24] glycosylation of hydroxamic acid,[25] and dihydropyridines.[26,27] Moreover, some important organic transformations, such as selective oxidation of benzyl alcohols,[28] have been performed successfully in the presence of TBAHS. Versatility and favorable properties of TBAHS prompted us to investigate its possible role as a catalyst for the synthesis of 5-substituted 1*H*-tetrazoles from nitriles and sodium azide.

Results and Discussion

In order to determine the effects of solvent and temperature in a [3 + 2] cycloaddition reaction of benzonitrile and sodium azide in the presence of TBAHS, a series of reactions were carried out by varying the solvent and temperature (Scheme 1). The results are summarized in Table 1; the best conversion was obtained when the reaction was performed at 85–100 °C in toluene or water using 1 equiv of nitrile and 1.5 equiv of sodium azide in the presence of 0.25 equiv of TBAHS. The amount of TBAHS and sodium azide did not appear to be critical, as we ran successful experiments also in high yield with 3 equiv of sodium azide and 2 equiv of TBAHS per 1 equiv of the nitrile. TBAHS was recovered during work-up from aqueous phase by evaporating the water under reduced pressure followed by washing the evaporation residue with hexane.



Scheme 1. Reaction of benzonitrile and sodium azide with TBAHS.

A series of 5-substituted 1*H*-tetrazoles was prepared from various organic nitriles (aromatic, heteroaromatic, and aliphatic) in either toluene (Table 2, Method I) or in water (Table 2, Method II). Benzonitrile (**1a**) and sodium azide in the presence of TBAHS in toluene were allowed to react at 85 °C to give, after work-up, a 93% yield of compound **2a** (Table 2, entry 1). Similarly, compounds **2b–2l** were synthesized and characterized (Table 2). All the products were known compounds, and the spectral data (IR, ^{1}H-NMR, and ^{13}C-NMR) and melting points were same as 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 characteristics of the formation of 5-substituted 1*H*-tetrazoles. Interestingly, electron-donating or electron-withdrawing substituent at *para*- or *meta*-position does not have significant influence on the product yield (Table 2 entries 2–6, 9). Substitution of either electron-donating or electron-withdrawing group at position 2 gave comparatively lower yields, perhaps due to steric effects (Table 2, entries 7–8). Products with indole and naphthalene moiety were obtained in good yields (Table 2, entries 10–11); however, a tetrazole containing a cyclopentane ring was formed in a lower yield (Table 2, entry 12).

To compare the solvent effect in this method, these reactions were carried out in water solvent. Most of the reactions (Table 2, Method II) required a shorter reaction time for completion in water compared to toluene as a solvent. In particular, 3-(trifluoromethyl)benzonitrile exhibited the highest reactivity, afforded the product **2i**, within 3 h in 98% yield compared to 12 h reaction time with 81% yield in toluene. However, 1-cyanonaphthalene required much longer reaction time (20 h) in water compared to toluene solvent. High hydrophobicity of the naphthalene ring may hinder the reaction in the aqueous solution. Electrostatic effect of the substituent displayed similar results in water as in toluene (Table 2, entries 2–9).

In conclusion, we report a facile synthesis of 5-substituted 1*H*-tetrazoles catalyzed by recyclable green TBAHS in toluene or water in high yield. The significant advantages of this methodology are good yields, avoidance of toxic and expensive reagents, a simple work-up procedure, easy handling of the catalyst, and readily available water as the solvent. This new process may be especially suitable for industrial scale production of 5-substituted 1*H*-tetrazoles in a green and practical manner.

Experimental Section

Melting points were determined in capillary tubes using a capillary melting point apparatus and were not corrected. IR spectra were recorded on JASCO (Tokyo, Japan) FT/IR 300E Fourier transform infrared spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) and carbon nuclear magnetic resonance (^{13}C-NMR) spectra were recorded on a Varian (Palo Alto, CA, USA) Unity 300 using dimethyl sulfoxide (DMSO) as the solvent. All solvents were purchased from OCI Company Ltd. (Seoul, Korea), and reagents were all obtained from Alfa Aesar (Lancashire, UK) or Aldrich (Milwaukee, WI, USA), and used without further purification. Silica gel plates Merck (Darmstadt, Germany F254) and silica gel 60 (Merck, 70–230 mesh) were used for analytical and column chromatography, respectively. Compounds were visualized by ultraviolet light.

Table 1. Effects of temperature and solvent on the formation of 5-substituted 1*H*-tetrazole.

Entry	*T* (°C)	Solvent	Yield (%)
1	RT	PhMe	5
2	40	PhMe	21
3	60	PhMe	52
4	85	PhMe	93
5	100	PhMe	93
6	65	MeOH	67
7	85	H_2O	87
8	85	DMSO	71

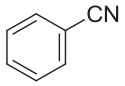
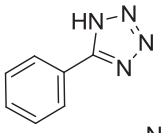
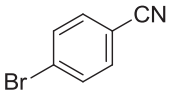
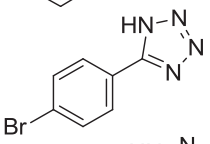
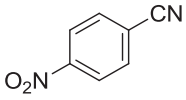
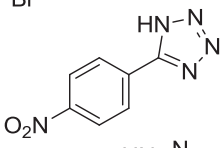
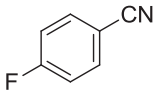
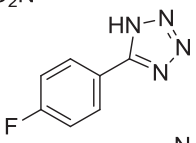
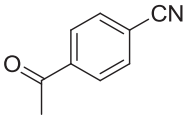
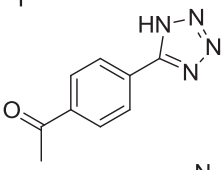
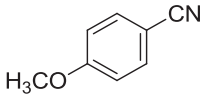
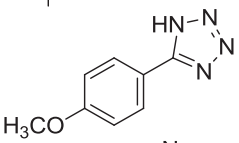
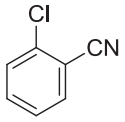
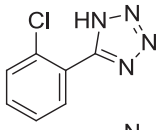
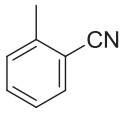
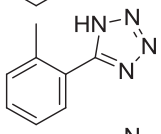
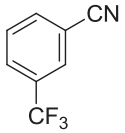
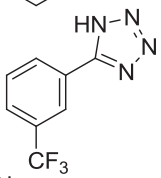
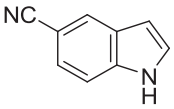
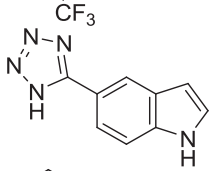
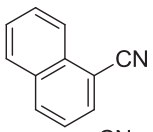
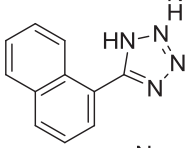
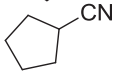
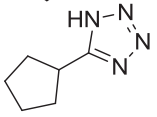
RT, room temperature; PhMe, toluene; MeOH, methanol; DMSO, dimethyl sulfoxide.

General Procedure for Preparation of Tetrazoles in Toluene (Method I). Nitrile (1 mmol) was added to sodium azide (1.5 mmol), PhMe (2 mL), and TBAHS (0.25 mmol) in a round-bottomed flask. The reaction mixture was stirred at 85 °C. After completion of the reaction (as indicated by thin-layer chromatography [TLC]), the crude reaction mixture was treated with ethyl acetate (15 mL) and 1 N HCl (15 mL) and stirred vigorously. The resultant organic layer was separated and the aqueous layer was extracted with ethyl acetate (10 mL × 5). The combined organic layer was washed with water and concentrated to give pure 5-substituted-1*H*-tetrazole.

General Procedure for Preparation of Tetrazoles in Water (Method II). TBAHS (0.25 mmol) was added to a mixture of nitrile (1 mmol), sodium azide (1.5 mmol), and 2 mL H_2O in a round-bottomed flask. The reaction mixture was heated to 85 °C. After completion of the reaction (as monitored by TLC), the crude reaction mixture was transferred into a separatory funnel, to which was added 1 N HCl (15 mL) extracted by ethyl acetate (EtOAc, 10 mL × 5). The combined organic layers were washed with H_2O and dried over anhydrous sodium sulfate, and were evaporated under reduced pressure to give pure 5-substituted-1*H*-tetrazole.

At the end of the reaction in toluene, extracted by ethyl acetate, combined water layers were evaporated, washed with hexane, and dried under vacuum. The recycled catalyst was used for three reactions without observation of appreciable loss in its catalytic activities. In the case of water as solvent, evaporated and washed with hexane, and dried under vacuum,

Table 2. TBAHS catalyzed synthesis of 5-substituted 1*H*-tetrazole.

					Method I[a]		Method II[b]	
Entry	Substrate	**1**	Product	**2**	Time (h)	Yield (%)	Time (h)	Yield (%)
1		**1a**		**2a**	12	93	6	87
2		**1b**		**2b**	15	80	9	72
3		**1c**		**2c**	12	81	10	77
4		**1d**		**2d**	11	72	9	69
5		**1e**		**2e**	9	91	5	90
6		**1f**		**2f**	12	87	7	88
7		**1g**		**2g**	15	61	6	53
8		**1h**		**2h**	24	68	7	57
9		**1i**		**2i**	12	81	3	98
10		**1j**		**2j**	18	76	8	81
11		**1k**		**2k**	12	82	20	85
12		**1l**		**2l**	20	67	9	77

[a] Method I: Nitrile (1 mmol), sodium azide (1.5 mmol), and TBAHS (0.25 mmol) in 2 mL of toluene.
[b] Method II: Nitrile (1 mmol), sodium azide (1.5 mmol), and TBAHS (0.25 mmol) in 2 mL of water.

the catalyst was obtained and could be reused in another reaction (see Supporting Information).

5-Phenyl-1*H*-tetrazole (2a):[13] White solid; mp: 214–216 °C (215–216 °C). IR (KBr, cm^{-1}): 3200–2300 (br, NH), 3129, 3055, 1608, 1564, 1486, 1465, 1410, 688. ^{1}H-NMR (300 MHz, DMSO): δ 8.00–8.08 (m, 2H), 7.54–7.63 (m, 3H). ^{13}C-NMR (75 MHz, DMSO): δ 155.32, 131.24, 129.42, 126.98, 124.17.

5-(4-Bromophenyl)-1*H*-tetrazole (2b):[29] White solid; mp: 259–261 °C (261 °C). IR (KBr, cm^{-1}): 3200–2400 (br, NH), 3089, 3064, 1604, 1558, 1482, 1454, 828. ^{1}H-NMR (300 MHz, DMSO): δ 7.96–8.00 (m, 2H), 7.81–7.85 (m, 2H). ^{13}C-NMR (126 MHz, DMSO): δ 155.00, 132.49, 128.87, 124.68, 123.62.

5-(4-Nitrophenyl)-1*H*-tetrazole (2c):[30] Yellow solid; mp: 218–220 °C (218–219 °C). IR (KBr, cm^{-1}): 3200–2300 (br, NH), 3091, 2925, 2852, 2728, 2673, 1611, 1571, 1487, 1428, 1320, 807. ^{1}H-NMR (300 MHz, DMSO): δ 8.42–8.47 (m, 2H), 8.28–8.32 (m, 2H). ^{13}C-NMR (75 MHz, DMSO): δ 155.43, 148.74, 130.64, 128.22, 124.64.

5-(4-Fluorophenyl)-1*H*-tetrazole (2d):[31] Yellow solid; mp: 112–114 °C (114–116 °C). IR (KBr, cm^{-1}): 3200–2300 (br, NH), 3084, 3019, 1611, 1567, 1471, 1443, 1407, 816. ^{1}H-NMR (300 MHz, DMSO): δ 8.03–8.11 (m, 2H), 7.40–7.48 (m, 2H). ^{13}C-NMR (75 MHz, DMSO): δ 163.7 (d, J = 248 Hz), 154.8, 129.5 (d, J = 8.9 Hz), 120.9 (d, J = 3.0 Hz), 116.6 (d, J = 22.1 Hz).

1-(4-(1*H*-Tetrazol-5-yl)phenyl)ethanone (2e):[32] White solid; mp: 189–191 °C (191.7–192.3 °C). IR (KBr, cm^{-1}): 3100–2800 (brs, NH), 1685, 1614, 1575, 1464, 803. ^{1}H-NMR (300 MHz, DMSO): δ 8.15–8.17 (m, 2H), 8.10–8.12 (m, 2H), 2.61 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 202.77, 160.62, 143.79, 134.53, 133.68, 132.59, 32.27.

5-(4-Methoxyphenyl)-1*H*-tetrazole (2f):[13] White solid; mp: 229–230 °C (231–232 °C). IR (KBr, cm^{-1}): 3200–2200 (brs, NH), 3074, 1617, 1584, 1468, 1406, 1267, 1020, 834. ^{1}H-NMR (300 MHz, DMSO): δ 7.95–8.00 (m, 2H), 7.11–7.16 (m, 2H), 3.82 (s, 3H). ^{13}C-NMR (75 MHz, DMSO): δ 161.47, 154.76, 128.65, 116.30, 114.84, 55.44.

5-(2-Chlorophenyl)-1*H*-tetrazole (2g):[33] White solid; mp: 172–174 °C (176–177 °C). IR (KBr, cm^{-1}): 3200–2400 (br, NH), 3045, 3020, 1602, 1563, 1470, 1441, 1407,747. ^{1}H-NMR (300 MHz, DMSO): δ 7.80–7.83 (m, 1H), 7.69–7.72 (m, 1H), 7.52–7.65 (m, 2H). ^{13}C-NMR (75 MHz, DMSO): δ 153.47, 132.63, 132.02, 131.77, 130.45, 127.80, 124.17.

5-(*O*-Tolyl)-1*H*-tetrazole (2h):[33] White solid; mp: 151–153 °C (150–151 °C). IR (KBr, cm^{-1}): 3200–2400 (br, NH), 2969, 1607, 1563, 1491, 1465, 1405, 746. ^{1}H-NMR (300 MHz, DMSO): δ 7.67–7.70 (m, 1H), 7.36–7.50 (m, 3H), 2.48 (s, 3H). ^{13}C-NMR (75 MHz, DMSO): δ 155.30, 137.15, 131.35, 130.75, 129.43, 126.32, 123.87, 20.52.

5-(3-(Trifluoromethyl)phenyl)-1*H*-tetrazole (2i):[34] White solid; mp: 156–157 °C (155–156 °C). IR (KBr, cm^{-1}): 3200–2300 (br, NH), 3083, 1600, 1561, 1492, 1460, 906, 810, 763. ^{1}H-NMR (300 MHz, DMSO): δ 8.33–8.35 (m, 2H), 7.95–7.97 (m, 1H), 7.85–7.88 (m, 1H). ^{13}C-NMR (75 MHz, DMSO): δ 155.03, 130.86 (d, J = 10.5 Hz), 130.09 (d, J = 32.1 Hz), 129.32 (d, J = 19.1 Hz), 127.70 (q, J = 3.6 Hz), 125.56, 123.41 (q, J = 3.9 Hz), 121.97.

5-(1*H*-Tetrazol-5-yl)-1*H*-indole (2j):[35] Yellow solid; mp: 212–213 °C (216–217 °C). IR (KBr, cm^{-1}): 3295, 3200–2300 (br, NH), 3085, 1619, 1566, 1481, 1464, 875, 810. ^{1}H-NMR (300 MHz, DMSO): δ 16.53 (s, br, 1H), 11.47 (s, br, 1H), 8.28 (d, J = 0.6 Hz, 1H), 7.78 (dd, J = 8.6, 1.8 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.49 (t, J = 2.7 Hz, 1H), 6.60 (t, J = 2.1 Hz, 1H). ^{13}C-NMR (75 MHz, DMSO): δ 152.13, 137.25, 127.79, 127.29, 119.89, 119.53, 114.53, 112.39, 102.07.

5-(Naphthalen-1-yl)-1*H*-tetrazole (2k):[36] White solid; mp: 212–214 °C (216–218 °C). IR (KBr, cm^{-1}): 3100–2200 (br, NH), 3047, 1599, 1568, 1464, 1393, 772, 735. ^{1}H-NMR (300 MHz, DMSO): δ 8.56–8.59 (m, 1H), 8.19 (d, J = 8.4 Hz, 1H), 8.06–8.10 (m, 1H), 7.99 (dd, J = 7.2, 1.2 Hz, 1H), 7.62–7.73 (m, 3H). ^{13}C-NMR (126 MHz, DMSO): δ 155.10, 133.40, 131.50, 129.94, 128.66, 128.45, 127.73, 126.77, 125.34, 125.10, 121.41.

5-Cyclopentyl-1*H*-tetrazole (2l): White solid; mp: 109–111 °C. IR (KBr, cm^{-1}): 3100–2300 (br, NH), 1564, 1410, 925. ^{1}H-NMR (300 MHz, DMSO): δ 3.28–3.40 (m, 1H), 2.00–2.11 (m, 2H), 1.64–1.77 (m, 6H). ^{13}C-NMR (75 MHz, DMSO): δ 159.83, 33.97, 31.69, 24.88.

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Supporting Information. The spectral data (IR, ^{1}H-NMR, and ^{13}C-NMR) and melting points can be found via the "Supplementary Content" section of this article's webpage.

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