Practical Synthesis of 5-Substituted Tetrazoles under Microwave Irradiation

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Abstract: 5-Substituted tetrazoles were prepared by treatment of nitriles with sodium azide and triethylammonium chloride in nitrobenzene in a microwave reactor. This practical method combines the advantages of previous procedures, including good-to-excellent yields, short reaction times, and easy isolation of the product. Moreover, sterically hindered tetrazoles, as well as those deactivated by electron-donating groups, can be prepared.

Key words: tetrazoles, microwave irradiation, sodium azide, heterocycles, nitriles

The preparation of variously substituted tetrazoles has been the subject of intense investigation, especially over the past few decades. These heterocycles have found widespread use as ligands in coordination chemistry, in the photographic industry, as components of special explosives,[1] and, above all, in pharmaceutical chemistry. The first attempts to optimize their preparation were made by Finnegan and coworkers[2] 50 years ago, and various modifications of their method, which is based on the reaction of nitriles with sodium azide in *N*,*N*-dimethylformamide, have been used. However, this method is not optimal, particularly when sterically hindered nitriles or those with electron-donating substituents are used as starting materials, or when the tetrazoles that are obtained are very hydrophilic. In such cases, difficulties in isolating the products or the extreme duration of the reaction can be serious drawbacks.

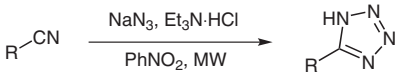
Wiberg and Michaud were the first to use a Lewis acid in a nonaqueous medium for tetrazole synthesis,[3] but this modification did not make the procedure more economical. Later, Demko and Sharpless[4] published an improved method, but they did not succeed in shortening the reaction times; also, the reaction of less-reactive nitriles required temperatures as high as 170 °C in an autoclave.

The latest reports describe the use of organometallic reagents that serve as donors of the azide anion.[5] However, not even the use of these reagents markedly decreases the reaction times that are necessary to obtain good yields of tetrazoles; furthermore, the reagents suffer the combined disadvantages of being both costly and toxic. Moreover, because of the production of equimolar amounts of organometallic side products, problems can occur in purifying the products.

Microwave (MW) irradiation of the reactants in hydrophilic media (water, *N*,*N*-dimethylformamide, dioxane, 1,2-dimethoxyethane, or ionic liquids) has also been used recently, but with the exception of shorter reaction times, substantial optimization has not been achieved.[7] All the methods are efficient only for the preparation of tetrazoles from sterically unhindered nitriles or those bearing an electron-accepting substituent attached to the nitrile group. Otherwise, long reaction times and more-forcing reaction conditions have to be used to achieve reasonable yields.

The aim of this study was to find a practical method for synthesis of tetrazoles that combines the advantages of previous procedures, namely good yields in short times, versatility, and easy isolation of the products.

The general reaction is outlined in Scheme 1. To take advantage of MW irradiation, we focused our attention on the use of hydrophobic solvents with large dipole moments. Toluene, as employed by Koguro et al.,[8] is unsuitable because of its low absorption of MW radiation ($\mu = 1.0 \times 10^{30}$ Cm). Chlorobenzene and anisole gave slightly higher yields. As shown in Table 1, nitrobenzene was found to be the solvent of choice because of its high dipole moment and its minimal water solubility, which facilitates the extraction of tetrazoles, in the form of their salts, into aqueous solution. Moreover, there is no need to use dried solvents, as shown by entry 7 in Table 1.



Scheme 1

The reactions were carried out in a microwave reactor at a constant temperature, as measured at the surface of the reaction flask by an external infrared thermometer (see Table 2 and Table 3). The average MW power values are given in Tables 2 and 3, which present an overview of the preparation of water-insoluble and water-soluble tetrazoles, respectively. The advantages of this method are a substantial decrease in reaction times compared with the method of Koguro et al.,[8] good-to-excellent yields, and, in most cases, isolation of the products by simple aqueous

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Table 1 Conversion of Benzonitrile into 5-Phenyl-1*H*-tetrazole (**1a**) in the Presence of Sodium Azide (1.3 equiv) and Triethylammonium Chloride (1.3 equiv) under Microwave Irradiation

Entry	Solvent	μ (10^{30} Cm)[a]	Temp (°C)	Time (h)	Yield (%)
1	PhCl	5.6	100	0.5	49
2	PhOMe	4.2	100	0.5	56
3	$PhNO_2$	14.0	100	0.5	56
4	PhCl	5.6	100	2	83
5	PhOMe	4.2	100	2	87
6	$PhNO_2$	14.0	100	2	93
7	$PhNO_2$[b]	–	100	2	88

[a] See reference [6].
[b] Saturated with H_2O.

extraction with recycling of the solvent and without the need for column chromatography.

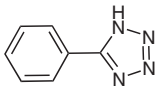
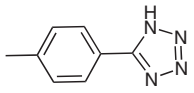
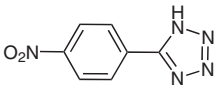
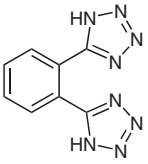
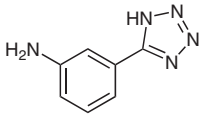
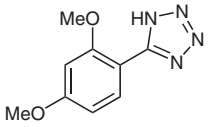
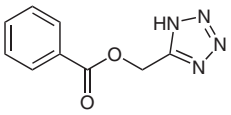
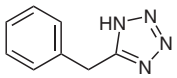
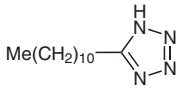
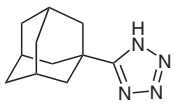
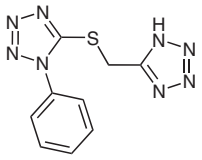
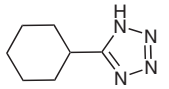
The second notable advantage of this method is the possibility of converting electron-rich nitriles (alkyl or cycloalkyl nitriles) or sterically hindered nitriles (e.g., adamantane-1-carbonitrile) into the corresponding tetrazoles. For example, 5-undecyl-1*H*-tetrazole (**1i**), the conventionally preparation of which requires refluxing for three days in toluene,[9] was obtained in 60% yield in 12 hours (Table 2). 2,4-Dimethoxybenzonitrile, a nitrile whose reactivity is decreased by both steric hindrance and the presence of electron-donating groups, was successfully converted into 5-(2,4-dimethoxyphenyl)-1*H*-tetrazole (**1f**) (Table 2). Tetrazoles **1g**, **1o**, and **1p**, which contain chemically sensitive ester bonds, could also be prepared (Tables 2 and 3); interestingly, no hydrolysis products were detected in the reaction mixtures.

It should also be emphasized that previously described methods for the synthesis of 5-substituted tetrazoles that use ammonium azide suffer from the problem of sublimation of the highly explosive and toxic salt from the reaction mixture and its crystallization in the condenser. With our method, this sublimation does not occur even at longer reaction times, thereby increasing the overall safety of the procedure.

In conclusion, a practical method has been developed for the preparation of 5-substituted tetrazoles that combines the advantages of previous methods. Note that the procedure can be scaled up to 100-gram amounts of the starting nitriles without decreasing the yields.

Reactants for the preparation of tetrazoles **1g**, **1k**, and **1p** were prepared according to known procedures.[10,11] All other chemicals were purchased from Sigma-Aldrich (Schnelldorf, Germany). Melting points were recorded on a Kofler apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury-Vx BB 300 spectrometer. Microwave reactions were conducted in a Milestone MicroSYNTH Ethos 1600 URM apparatus.

Table 2 Water-Insoluble Tetrazoles

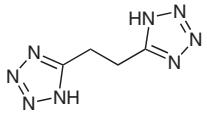
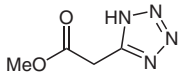
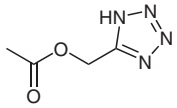
	Set temp (°C)	Average power (W)	Time (h)	Tetrazole	Yield (%)[a]
1a	100	75	2		93
1b	100	75	3		91
1c	100	75	1		92
1d	100	75	6		90
1e	100	75	4		81
1f[b]	125	100	4		30
1g	100	75	3		85
1h	100	75	2		80
1i	100	75	12		60
1j[b]	100	75	8		32
1k	80	50	4		83
1l	100	75	8		54

[a] Isolated yields.
[b] 2 equiv each of NaN_3 and $Et_3N{\cdot}HCl$ were used.

Tetrazoles 1a–p: General Procedure

$Et_3N{\cdot}HCl$ (10.5 mmol) and NaN_3 (10.5 mmol) were added to the solution of the nitrile (8 mmol) or dinitrile (4 mmol) in $PhNO_2$ (30 mL), and the mixture was heated with continuous stirring in the microwave reactor under the conditions summarized in Tables 2 and 3.

Table 3 Water-Soluble Tetrazoles

	Set temp (°C)	Average power (W)	Time (h)	Tetrazole	Yield (%)[a]
1m	100	75	4		78
1n	80	50	8		59
1o	100	75	4		69
1p	100	75	4		71

[a] Isolated yields.

Water-Insoluble Tetrazoles

The mixture was extracted with H_2O or 2% aq NaOH (3 × 20 mL). The combined aqueous extracts were extracted with Et_2O (2 × 20 mL) and then acidified with aq HCl. The resultant precipitate was filtered off and crystallized. In some cases, the reaction mixture became dark, and consequently the isolated product was yellow-brown. Simple crystallization with charcoal afforded pure products.

5-Phenyl-1*H*-tetrazole (1a)

Yield: 93%; mp 217–218 °C (H_2O–EtOH).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.54–7.64 (m, 3 H), 7.98–8.06 (m, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 124.3, 127.2, 129.6, 131.5, 155.4.

5-(4-Tolyl)-1*H*-tetrazole (1b)

Yield: 91%; mp 244–245 °C (H_2O–EtOH).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.37 (s, 3 H), 7.39 (d, *J* = 8.0 Hz, 2 H), 7.91 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 21.2, 121.5, 127.1, 130.2, 141.4, 155.3.

5-(4-Nitrophenyl)-1*H*-tetrazole (1c)

Yield: 92%; mp 218–219 °C (H_2O–EtOH).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.28 (d, *J* = 9.0 Hz, 2 H), 8.42 (d, *J* = 9.0 Hz, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 124.8, 128.4, 130.8, 148.9, 155.6.

5,5'-(1,2-Phenylene)bis(1*H*-tetrazole) (1d)

Yield: 90%; mp 232–233 °C (EtOH).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.76–7.85 (m, 2 H), 7.86–7.95 (m, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 124.7, 131.0, 131.6, 155.0.

3-(1*H*-Tetrazol-5-yl)aniline (1e)

Yield: 81%; mp 199–201 °C (H_2O).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.74 (d, *J* = 8.0 Hz, 1 H), 7.08–7.28 (m, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 112.0, 114.4, 116.8, 124.7, 130.1, 149.7, 155.8.

5-(2,4-Dimethoxyphenyl)-1*H*-tetrazole (1f)

Yield: 30%; mp 175 °C (EtOAc).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.84 (s, 3 H), 3.95 (s, 3 H), 6.70–6.77 (m, 2 H), 8.02 (d, *J* = 8.5 Hz, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 55.8, 56.0, 98.7, 105.1, 106.7, 130.7, 151.2, 158.1, 163.4.

Anal. Calcd. for $C_9H_{10}N_4O_2$: C, 52.42; H, 4.89; N, 27.17; O, 15.52. Found: C, 51.97; H, 4.59; N, 26.90.

1*H*-Tetrazol-5-ylmethyl Benzoate (1g)

Yield: 85%; mp 120–122 °C (no recrystallization).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 5.68 (s, 2 H), 7.51–7.59 (m, 2 H), 7.65–7.73 (m, 1 H), 8.00–8.05 (m, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 56.1, 128.9, 129.1, 129.7, 134.1, 153.3, 165.4.

5-Benzyl-1*H*-tetrazole (1h)

Yield: 80%; mp 121–123 °C (H_2O).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.28 (s, 2 H), 7.22–7.37 (m, 5 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 29.1, 127.2, 128.8, 128.9, 136.1, 155.4

5-Undecyl-1*H*-tetrazole (1i)

Yield: 60%; mp 72–73 °C (MeCN).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.83 (t, *J* = 6.5 Hz, 3 H), 1.15–1.30 (m, 16 H), 1.58–1.73 (m, 2 H), 2.84 (t, *J* = 7.5 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 22.3, 22.9, 27.2, 28.5, 28.8, 28.9, 29.1, 29.2, 31.5, 156.1.

Anal. Calcd for $C_{12}H_{24}N_4$: C, 64.24; H, 10.78; N, 24.97. Found: C, 64.26; H, 10.82; N, 24.93.

5-(Adamantan-1-yl)-1*H*-tetrazole (1j)

Yield: 32%; mp 250 °C (EtOAc).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.68–1.78 (m, 6 H), 1.96 (m, 6 H), 2.00–2.08 (m, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 27.6, 32.3, 36.0, 40.7, 163.2.

Anal. Calcd for $C_{11}H_{16}N_4$: C, 64.68; H, 7.89; N: 27.43. Found: C, 64.29; H, 7.73; N: 27.15.

1-Phenyl-5-[(1*H*-tetrazol-5-ylmethyl)sulfanyl]-1*H*-tetrazole (1k)

Yield: 83%; mp136–137 °C (EtOH).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.90 (s, 2 H), 7.60–7.75 (m, 5 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 153.9, 153.3, 133.1, 131.0, 130.3, 124.7, 25.3

5-Cyclohexyl-1*H*-tetrazole (1l)

Yield: 54%; mp 131 °C (H_2O).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.1–2.1 (m, 10 H), 2.90–3.05 (m, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 25.2, 25.4, 30.9, 32.9, 159.8.

Water-Soluble Tetrazoles

The mixture was extracted with H_2O (3 × 15 mL). The resulting aqueous phase was washed with Et_2O (2 × 20 mL) then acidified with HCl, saturated with NaCl, and extracted with EtOAc (3 × 20

mL). The combined organic extracts were evaporated, and the crude product was crystallized.

5,5′-Ethane-1,2-diylbis(1*H*-tetrazole) (1m)
Yield: 78%; mp 247 °C (*i*-PrOH or EtOH).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.38 (s).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 21.0, 155.0.

Anal Calcd for $C_4H_6N_8$: C, 28.92; H, 3.64; N, 67.44. Found: C, 28.90; H, 3.46; N, 67.26.

5-Methyl-1*H*-tetrazole (1n)
Yield: 59%; mp 147 °C (EtOAc).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.47 (s).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 8.6, 152.4.

Methyl 2-(1*H*-Tetrazol-5-yl)acetate (1o)
Yield: 69%; mp 153–155 °C (EtOAc).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.66 (s, 3 H), 4.18 (s, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 29.5, 52.6, 150.7, 168.4.

(1*H*-Tetrazol-5-yl)methyl Acetate (1p)
Yield: 71%; oil.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.1 (s, 3 H), 5.4 (s, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 20.6, 55.1, 153.3, 170.1.

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