One-Step Synthesis of 5-Substituted 1*H*-Tetrazoles from an Aldehyde by Reaction with Acetohydroxamic Acid and Sodium Azide under $Bi(OTf)_3$ Catalysis

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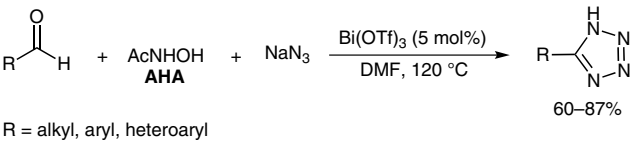
Abstract: An efficient one-step method for the synthesis of 5-substituted 1*H*-tetrazoles from aldehydes by reaction with acetohydroxamic acid and sodium azide using bismuth(III) triflate as the catalyst is described.

Key words: aldehydes, 5-substituted 1*H*-tetrazoles, sodium azide, bismuth(III) triflate, catalysis

5-Substituted 1*H*-tetrazoles are an important class of nitrogen heterocycles that have applications as propellants[1] and specialty explosives.[2] These compounds also exhibit important pharmacological properties as antiviral,[3] anti-inflammatory,[4] antifungal,[5] and antiulcer[6] agents. In medicinal chemistry, the tetrazole functionality is a known bioisosteric replacement for the carboxylic group[7] and also exhibits good metabolic stability and high lipophilicity. Hence, the presence of this functionality was often found to improve *in vivo* half-life, oral bioavailability, and cell penetration ability of several bioactive molecules.[8]

The synthesis of 5-substituted 1*H*-tetrazoles is a widely studied subject in the literature,[9] and in existing studies 5-substituted 1*H*-tetrazoles are generally prepared from nitriles by reaction with a metal azide in the presence of a base or acid catalyst. However, there are no methods in the literature for the preparation of 5-substituted 1*H*-tetrazoles directly from aldehydes in a single step. We consider that development of a simple method for preparation of 5-substituted 1*H*-tetrazoles from aldehydes is highly desirable as it reduces the number of steps and minimizes effluents.

Acetohydroxamic acid (AHA) is simple organic compound that can be easily prepared by reaction of hydroxylamine and ethyl acetate in the presence of a base. Acetohydroxamic acid, which is also known as Lithostat®, is a known drug for treatment of urinary tract infections.[10] Acetohydroxamic acid is a widely used chelating agent in the UREX process for the separation of uranium from spent nuclear fuel.[11] However, acetohydroxamic acid has not received much attention in organic chemistry and its applications in organic synthesis are scarcely known. Recently, we developed new methods for the selective preparation of oximes[12] and nitriles[13] from aldehydes using acetohydroxamic acid. In continuation of our research interest in the development of new synthetic applications of acetohydroxamic acid, we report here an efficient and simple method for the preparation of 5-substituted 1*H*-tetrazoles in high yields (60–87%) directly from aldehydes by reaction with acetohydroxamic acid and sodium azide using bismuth(III) triflate as the catalyst as shown in Scheme 1.



Scheme 1 One-step synthesis of 5-substituted 1*H*-tetrazoles from aldehydes

In our preliminary experiments, we found benzaldehyde (**1a**) reacted with acetohydroxamic acid and sodium azide under bismuth(III) triflate catalysis upon heating in *N*,*N*-dimethylformamide at 120 °C producing 5-phenyl-1*H*-tetrazole (**2a**) in 87% yield. Under similar conditions, this reaction was found to proceed well also with aldehydes **1b**–**l**, which gave the corresponding 5-substituted 1*H*-tetrazoles **2b**–**l** in 60–87% yields; the results are shown in Table 1. Tetrazoles **2a**–**c**,**e**–**g**,**k**,**l** are known compounds and they gave characteristic and spectroscopic data identical to that reported in the literature (Table 1). Tetrazoles **2d**,**h**–**j** are novel compounds and their characteristic and spectroscopic data are provided.

In this study, the solvent was found to play an important role in promoting the reaction. For example, in acetonitrile, the reaction proceeds only up to the stage of the formation of the intermediate nitrile and no tetrazole formation was observed. Whereas in *N*,*N*-dimethylformamide we observed efficient completion of the reaction with exclusive formation of tetrazoles in high yields (Scheme 1).

In conclusion, this work shows an efficient and simple one-step method for the preparation of 5-substituted 1*H*-tetrazoles from aldehydes by reaction with acetohydroxamic acid and sodium azide under bismuth(III) triflate catalysis.

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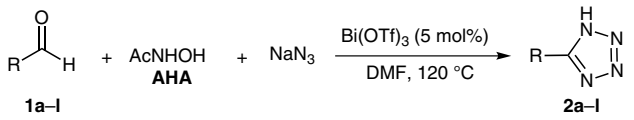
Table 1 Synthesis of 5-Substituted 1*H*-Tetrazoles from Aldehydes Using Acetohydroxamic Acid



1a–l 2a–l

Entry	Aldehyde	Time (h)	Tetrazole	Yield[a] (%)	Mp (°C)
1	**1a**	24	**2a**	87	215–216[9e]
2	**1b**	24	**2b**	85	264–266[9g]
3	**1c**	24	**2c**	70	218–219[9o]
4	**1d**	24	**2d**	80	198–200
5	**1e**	28	**2e**	60	219–220[9e]
6	**1f**	24	**2f**	83	234–235[9o]
7	**1g**	24	**2g**	79	154–156[9o]
8	**1h**	25	**2h**	76	120–121
9	**1i**	28	**2i**	65	145–146
10	**1j**	24	**2j**	79	127–128
11	**1k**	22	**2k**	86	204–205[9g]
12	**1l**	15	**2l**	84	242–244[9e]

[a] Isolated yields. All products gave satisfactory ^{1}H and ^{13}C NMR, IR, and mass spectral data.

All reagents were procured from commercial sources and used without further treatment. Melting points were recorded on Casiae-Siamia (VMP-AM) melting point apparatus and are uncorrected. IR spectra were recorded on a PerkinElmer FT-IR 240-C spectrophotometer using KBr optics. ^{1}H NMR spectra were recorded on Bruker AV 300 MHz in $CDCl_3$–DMSO using TMS as internal standard. Electron Spray Ionization (ESI) and HRMS were recorded on QSTARXL hybrid MS/MS system (Applied Biosystems, USA) under electrospray ionization.

All the reactions were monitored by TLC on precoated silica gel 60 F254 (mesh); spots were visualized with UV light. Merck silica gel (100–200 mesh) was used for column chromatography.

5-Phenyl-1*H*-tetrazole (2a); Typical Procedure

Benzaldehyde (**1a**, 0.5 g, 4.7 mmol), acetohydroxamic acid (0.42 g, 5.7 mmol), NaN_3 (0.4 g, 6.1 mmol), DMF (5 mL), and $Bi(OTf)_3$ (0.15 g, 0.23 mmol) were taken into a 25-mL round-bottomed flask fitted with a condenser and $CaCl_2$ guard tube. The mixture was heated at 120 °C for 24 h. After completion of the reaction (TLC), the

mixture was cooled to r.t. and neutralized (pH 7) with 5% HCl. Next, the mixture was extracted with EtOAc and the organic layer was separated, dried (anhyd Na_2SO_4), and concentrated under reduced pressure. The crude product obtained was purified by column chromatography (silica gel 100–200 mesh, EtOAc–hexane, 1:2) to obtain **2a** as a white solid; yield: 0.6 g (87%); mp 215–216 °C (Lit.[9e] 215–216 °C).

IR (KBr): 3448, 3128, 3055, 1853, 1638, 1562, 1485, 1407, 1254, 1056 cm^{-1}.

^1H NMR (300 MHz, DMSO): δ = 8.10–8.05 (m, 2 H), 7.57–7.50 (m, 3 H).

^{13}C NMR (75 MHz, DMSO): δ = 154.2, 129.5, 127.7, 125.6, 123.0.

MS (ESI): *m*/*z* = 147 [M + H].

HRMS (ESI): *m*/*z* [M + H] calcd for $C_7H_7N_4$: 147.0671; found: 147.0665.

5-(4-Chlorophenyl)-1*H*-tetrazole (2b)
Brown solid; yield: 0.55 g (85%); mp 264–266 °C (Lit.[9g] 265–266 °C)

IR (KBr): 3423, 3066, 2924, 1908, 1608, 1558, 1433, 1256, 1094 cm^{-1}.

^1H NMR (300 MHz, DMSO): δ = 10.20 (br s, 1 H), 8.10 (d, *J* = 8.5 Hz, 2 H), 7.47 (d, *J* = 8.5 Hz, 2 H).

^{13}C NMR (75 MHz, DMSO): δ = 155.7, 135.0, 129.3, 128.4, 124.5.

MS (ESI): *m*/*z* = 181 [M + H].

HRMS (ESI): *m*/*z* [M + H] calcd for $C_7H_6ClN_4$: 181.0281; found: 181.0279.

5-(4-Nitrophenyl)-1*H*-tetrazole (2c)
Yellow solid; yield: 0.44 g (70%); mp 218–219 °C (Lit.[9o] 220 °C).

IR (KBr): 3443, 3106, 2924, 1604, 1514, 1452, 1347, 1292, 1102 cm^{-1}.

^1H NMR (300 MHz, DMSO): δ = 8.36 (d, *J* = 9.0 Hz, 2 H), 7.89 (d, *J* = 9.0 Hz, 2 H).

^{13}C NMR (75 MHz, DMSO): δ = 149.8, 146.6, 126.7, 115.1, 113.6.

MS (ESI): *m*/*z* = 192 [M + H].

HRMS (ESI): *m*/*z* [M + H] calcd for $C_7H_6N_5O_2$: 192.0521; found: 192.0524.

5-(3,4-Dimethoxyphenyl)-1*H*-tetrazole (2d)
Brown solid; yield: 0.50 g (80%); mp 198–200 °C.

IR (KBr): 3445, 3013, 2923, 2737, 1566, 1434, 1322, 1272, 1143, 1023 cm^{-1}.

^1H NMR (300 MHz, DMSO): δ = 7.69–7.67 (m, 2 H), 6.99 (d, *J* = 8.3 Hz, 1 H), 3.96–3.94 (6 H).

^{13}C NMR (75 MHz, DMSO): δ = 154.9, 150.6, 119.7, 116.2, 110.7, 109.5, 55.4, 55.3.

MS (ESI): *m*/*z* = 207 [M + H].

HRMS (ESI): *m*/*z* [M + H] calcd for $C_9H_{11}N_4O_2$: 207.2092; found: 207.2097.

5-[4-(Trifluoromethyl)phenyl]-1*H*-tetrazole (2e)
White solid; yield: 0.37 g (60%); mp 219–220 °C (Lit.[9e] 220–221 °C).

IR (KBr): 3422, 3021, 2965, 1597, 1450, 1386, 1296, 1125, 1098 cm^{-1}.

^1H NMR (300 MHz, DMSO): δ = 8.14 (d, *J* = 8.5 Hz, 2 H), 7.69 (d, *J* = 8.5 Hz, 2 H).

^{13}C NMR (75 MHz, DMSO): δ = 166.3, 133.8, 129.4, 126.9, 124.5.

MS (ESI): *m*/*z* = 215 [M + H].

HRMS (ESI): *m*/*z* [M + H] calcd for $C_8H_6F_3N_4$: 215.0545; found: 215.0549.

4-(1*H*-Tetrazol-5-yl)phenol (2f)
White solid; yield: 0.55 g (83%); mp 234–235 °C (Lit.[9o] 234–236 °C).

IR (KBr): 3442, 3397, 3227, 2983, 2839, 1544, 1459, 1322, 1232, 1141, 1028 cm^{-1}.

^1H NMR (300 MHz, DMSO): δ = 9.80 (s, 1 H), 7.72 (d, *J* = 8.6 Hz, 2 H), 6.92 (d, *J* = 8.6 Hz, 2 H).

^{13}C NMR (75 MHz, DMSO): δ = 162.2, 132.5, 130.7, 127.3, 114.6.

MS (ESI): *m*/*z* = 163 [M + H].

HRMS (ESI): *m*/*z* [M + H] calcd for $C_7H_7N_4O$: 163.0620; found: 163.0614.

(*E*)-5-Styryl-1*H*-tetrazole (2g)
White solid; yield: 0.51 g (79%); mp 154–156 °C (Lit.[9o] 155–156 °C).

IR (KBr): 3391, 3058, 2991, 1617, 1586, 1494, 1345, 1208, 1145 cm^{-1}.

^1H NMR (300 MHz, DMSO): δ = 7.71 (d, *J* = 16.6 Hz, 1 H), 7.59–7.57 (m, 2 H), 7.45–7.37 (m, 3 H), 7.16 (d, *J* = 16.6 Hz, 1 H).

^{13}C NMR (75 MHz, DMSO): δ = 136.1, 133.2, 127.7, 127.1, 125.5, 108.6.

MS (ESI): *m*/*z* = 173 [M + H].

HRMS (ESI): *m*/*z* [M + H] calcd for $C_9H_9N_4$: 173.0827; found: 173.0822.

5-(1-Phenylethyl)-1*H*-tetrazole (2h)
Yellow solid; yield: 0.49 g (76%); mp 120–121 °C.

IR (KBr): 3444, 2979, 1885, 1652, 1553, 1451, 1382, 1248, 1120, 1053 cm^{-1}.

^1H NMR (300 MHz, DMSO): δ = 7.33–7.23 (m, 5 H), 4.50–4.46 (q, *J* = 7.8 Hz, 6.8 Hz, 1 H), 1.77 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (75 MHz, DMSO): δ = 128.2, 127.7, 127.3, 126.8, 126.2, 34.4, 19.4.

MS (ESI): *m*/*z* = 175 [M + H].

HRMS (ESI): *m*/*z* [M + H] calcd for $C_9H_{11}N_4$: 175.0984; found: 175.0989.

5-(Bicyclo[2.2.1]hept-5-en-2-yl)-1*H*-tetrazole (2i)
Yellow solid: yield: 0.43 g (65%); mp 145–146 °C.

IR (KBr): 3451, 3065, 1861, 1633, 1571, 1452, 1338, 1260, 1133, 1024 cm^{-1}.

^1H NMR (300 MHz, DMSO): δ = 6.33–6.31 (m, 1 H), 6.19–6.15 (m, 1 H), 3.04–3.19 (m, 1 H), 2.86–2.82 (m, 1 H), 2.20–2.11 (m, 1 H), 1.57–1.49 (m, 2 H), 1.33–1.29 (m, 1 H), 1.21–1.19 (m, 1 H).

^{13}C NMR (75 MHz, DMSO): δ = 138.8, 137.2, 122.9, 47.7, 45.7, 42.3, 32.4, 27.02.

MS (ESI): *m*/*z* = 163 [M + H].

HRMS (ESI): *m*/*z* [M + H] calcd for $C_8H_{11}N_4$: 163.0984; found: 163.0988.

5-(Cyclohex-3-enyl)-1*H*-tetrazole (2j)
Yellow solid; yield: 0.54 g (79%); mp 127–128 °C.

IR (KBr): 3445, 3117, 3030, 1868, 1654, 1557, 1431, 1353, 1252, 1114 cm^{-1}.

^1H NMR (300 MHz, DMSO): δ = 5.85– 5.71 (m, 2 H), 3.32–3.20 (m, 1 H), 2.58–2.32 (m, 2 H), 2.21–2.12 (m, 3 H), 1.91–1.81 (m, 1 H).

^{13}C NMR (75 MHz, DMSO): δ = 159.0, 126.0, 124.0, 28.9, 28.7, 26.1, 23.5.

MS (ESI): *m*/*z* = 151 [M + H].

HRMS (ESI): *m*/*z* [M + H] calcd for $C_7H_{11}N_4$: 151.0984; found: 151.0979.

5-(Thiophen-2-yl)-1*H*-tetrazole (2k)
Pale yellow solid; yield: 0.58 g (86%); mp 204–205 °C (Lit.[9g] 205–206 °C).

IR (KBr): 3432, 3074, 2950, 1592, 1407, 1238, 1137, 1047 cm^{-1}.

^{1}H NMR (300 MHz, DMSO): δ = 8.45 (br s, 1 H), 7.81 (d, *J* = 3.7 Hz, 1 H), 7.55 (d, *J* = 5.3 Hz, 1 H), 7.17 (t, *J* = 3.7, 4.9 Hz, 1 H).

^{13}C NMR (75 MHz, DMSO): δ = 150.8, 127.9, 127.6, 127.0, 125.1.

MS (ESI): *m*/*z* = 153 [M + H].

HRMS (ESI): *m*/*z* [M + H] calcd for $C_5H_5N_4S$: 153.0235; found: 153.0231.

3-(1*H*-Tetrazol-5-yl)pyridine (2l)
White solid; yield: 0.58 g (84%); mp 242–244 °C (Lit.[9e] 241–242 °C).

IR (KBr): 3445, 3071, 2928, 1537, 1428, 1387, 1238, 1140, 1073, 1017 cm^{-1}.

^{1}H NMR (300 MHz, DMSO): δ = 9.32 (s, 1 H), 8.74–8.73 (m, 1 H), 8.44–8.42 (m, 1 H), 7.55–7.51 (m, 1 H).

^{13}C NMR (75 MHz, DMSO): δ = 155.7, 125.2, 120.4, 116.3.

MS (ESI): *m*/*z* = 148 [M + H].

HRMS (ESI): *m*/*z* [M + H] calcd for $C_6H_6N_5$: 148.0623; found: 148.0619.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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