JOC*Note*

A General Route to 5-Aminotetrazoles

Alan R. Katritzky,* Boris V. Rogovoy, and Katherine V. Kovalenko

Center for Heterocyclic Compounds, Department of Chemistry, University of Florida, Gainesville, Florida 32611-7200

katritzky@chem.ufl.edu

Received November 4, 2002

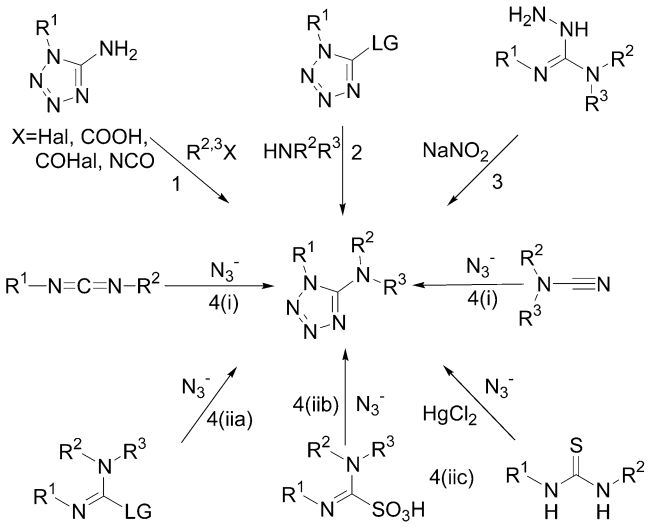
Abstract: Various di- and trisubstituted (benzotriazolyl)-carboximidamides were used for the preparation of *N*,*N*-di- and 1,*N*,*N*-trisubstituted 5-aminotetrazoles **3a**−**e** and **6a**−**d** under mild conditions in good to excellent yields.

Tetrazoles exhibit a wide scope of biological activity.[1] In particular, 5-aminotetrazoles show anti-allergic and anti-asthmatic,[2] antiviral and anti-inflammatory,[3] anti-neoplastic,[4] and cognition disorder activities.[5a] Activity as CCK antagonists[5b] and antibiotics against a range of bacteria[6] has been observed.

Syntheses of substituted 5-aminotetrazole derivatives fall into four main types (Scheme 1): (1) amino group or ring functionalization of 5-aminotetrazole,[2d,7a,b] which often results in mixtures of isomers;[6,7c] (2) the substitution of a leaving group in the tetrazole 5-position with amines;[8] (3) reactions of aminoguanidine derivatives with sodium nitrite;[9] and (4) various azide-mediated tetrazole ring constructions.

Formations of 5-aminotetrazole rings using azide anion include the following: (i) addition of NaN_3 to carbodiimides[9c,10a] or cyanamides;[11] and (ii) nucleophilic substitution by N_3^- of (a) chlorine in α-chloroformamidines,[12a] which can be obtained from nitriles and alkyl halides,[12b−d] (b) the sulfite anion in aminoiminomethanesulfonic acids,[12e] and (c) sulfur from thioureas in the presence of mercury[12f] or lead salts[9a] (Scheme 1).

SCHEME 1



We now report an efficient preparation of substituted 5-aminotetrazoles by a variation of route 4(ii) starting from 1-(benzotriazolyl)carboximidamides. 1-(Benzotriazolyl)carboximidamides and their acyl derivatives were previously demonstrated to be efficient reagents for the preparation of polysubstituted guanidines,[13] 1,2,4-triazoles,[14] 1,3,5-triazin-2-ones and 1,3,5-triazine-2-thiones,[15] and 2-amino-1,3-quinazoline-4-thiones.[16]

N,*N*-Disubstituted (benzotriazolyl)carboximidamides and their acyl derivatives were obtained by a known procedure[13,14] starting from di(benzotriazolyl)methanimine **1** in reactions with an appropriate secondary amine (Scheme 2). *N*,*N*′-Di- and *N*,*N*,*N*′-trisubstituted 1-(benzotriazolyl)carboximidamides were obtained from the respective (benzotriazolyl)carboximidoyl chlorides.[16] *N*,*N*-Disubstituted (benzotriazolyl)carboximidamides were treated with sodium azide in chloroform in the presence

(1) (a) Wittenberger, S. J. *Org. Prep. Proced. Int.* **1994**, *26*, 499. (b) Butler, R. N. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 4, p 674.

(2) (a) Yoshinaga, J.; Shogaki, T.; Kakita, T.; Ozeki, H.; Sugimoto, N.; Kato, Y. Eur. Patent EP 262873, 1988; *Chem. Abstr.* **1988**, *109*, 54782. (b) Cetenko, W. A.; Connor, D. T.; Mullican, M. D.; Sorenson, R. J. Eur. Patent EP 249236, 1987; *Chem. Abstr.* **1988**, *108*, 150482. (c) Connor, D. T.; Unangst, P. C.; Weikert, R. J. Eur. Patent EP 279466, 1988; *Chem. Abstr.* **1988**, *109*, 231035. (d) Ford, R. E.; Knowles, P.; Lunt, E.; Marshall, S. M.; Penrose, A. J.; Ramsden, C. A.; Summers, A. J. H.; Walker, J. L.; Wright, D. E. *J. Med. Chem.* **1986**, *29*, 538. (e) Peet, N. P.; Baugh, L. E.; Sundler, S.; Lewis, J. E.; Matthews, E. H.; Olberding, E. L.; Shah, D. N. *J. Med. Chem.* **1986**, *29*, 2403.

(3) Girijavallabhan, V. M.; Pinto, P. A.; Ganguly, A. K.; Versace, R. W. Eur. Patent EP 274867, 1988; *Chem. Abstr.* **1989**, *110*, 23890.

(4) (a) Akimoto, H.; Ootsu, K.; Itoh, F. Eur. Patent EP 530537, 1993; *Chem. Abstr.* **1993**, *119*, 226417. (b) Taveras, A. G.; Mallams, A. K.; Afonso, A. Int. Patent WO 9811093, 1998; *Chem. Abstr.* **1998**, *128*, 230253.

(5) (a) Mitch, C. H.; Quimby, S. J. Int. Patent WO 9851312, 1998; *Chem. Abstr.* **1998**, *130*, 13997. (b) Castro Pineiro, J. L.; Chambers, M. S.; Hobbs, S. C.; Matassa, V. G. Int. Patent WO 9319052, 1993; *Chem. Abstr.* **1994**, *120*, 134543.

(6) Andrus, A.; Partridge, B.; Heck, J. V.; Christensen, B. G. *Tetrahedron Lett.* **1984**, *25*, 911.

(7) (a) Peet, N. P. *J. Heterocycl. Chem.* **1987**, *24*, 223. (b) Kato, T.; Chiba, T.; Daneshtalab, M. *Chem. Pharm. Bull.* **1976**, *24*, 2549. (c) Butler, R. N.; Scott, F. L. *J. Org. Chem.* **1966**, *31*, 3182.

(8) (a) Klich, M.; Teutsch, G. *Tetrahedron* **1986**, *42*, 2677. (b) Barlin, G. B. *J. Chem. Soc. B* **1967**, 641.

(9) (a) Finnegan, W. G.; Henry, R. A.; Lieber, E. *J. Org. Chem.* **1953**, *18*, 779. (b) Jensen, K. A.; Holm, A.; Rachlin, S. *Acta Chem. Scand.* **1966**, *20*, 2795. (c) Percival, D. F.; Herbst, R. M. *J. Org. Chem.* **1957**, *22*, 925.

(10) Ding, Y.-X.; Weber, W. P. *Synthesis* **1987**, 823.

(11) (a) Moderhack, D.; Goos, K.-H.; Preu, L. *Chem. Ber.* **1990**, *123*, 1575. (b) Garbrecht, W. L.; Herbst, R. M. *J. Org. Chem.* **1953**, *18*, 1014. (c) Herbst, R. M.; Roberts, C. W.; Harvill, E. J. *J. Org. Chem.* **1951**, *16*, 139. (d) Marchalin, M.; Martvon, A. *Collect. Czech. Chem. Commun.* **1980**, *45*, 2329.

(12) (a) Ried, W.; Erle, H.-E. *Liebigs Ann. Chem.* **1982**, 201. (b) Ried, W.; Dietschmann, H.; Erle, H.-E. *Synthesis* **1980**, 619. (c) Kühle, E.; Anders, B.; Klauke, E.; Tarnow, H.; Zumach, G. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 20. (d) Kühle, E.; Anders, B.; Zumach, G. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 649. (e) Miller, A. E.; Feenay, D. J.; Ma, Y.; Zarcone, L.; Aziz, M. A.; Magnuson, E. *Synth. Commun.* **1990**, *20*, 217. (f) Batey, R. A.; Powell, D. A. *Org. Lett.* **2000**, *2*, 3237.

(13) Katritzky, A. R.; Rogovoy, B. V.; Chassaing, C.; Vvedensky, V. *J. Org. Chem.* **2000**, *65*, 8080.

(14) Katritzky, A. R.; Rogovoy, B. V.; Vvedensky, V. Y.; Kovalenko, K.; Steel, P. J.; Markov, V. I.; Forood, B. *Synthesis* **2001**, 897.

(15) Katritzky, A. R.; Rogovoy, B. V.; Vvedensky, V. Y.; Hebert, N.; Forood, B. *J. Org. Chem.* **2001**, *66*, 6797.

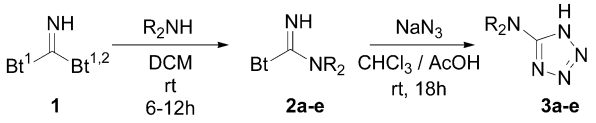
(16) Katritzky, A. R.; Rogovoy, B.; Klein, C.; Insuasty, H.; Vvedensky, V.; Insuasty, B. *J. Org. Chem.* **2001**, *66*, 2854.

10.1021/jo0266543 CCC: $25.00
Published on Web 05/09/2003

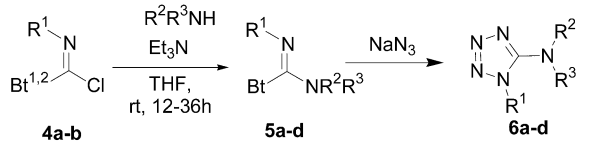
TABLE 1. Synthesis of 5-Aminotetrazoles 3a−e and 6a−d

entry	compd	R^1	HNR_2	yield, %	mp [lit. mp] (°C)
1	**3a**	H	morpholine	80	168.0−169.0 [180.5−181.0[18]]
2	**3b**	H	*N*-methylpiperazine	27	270.0 dec [−]
3	**3c**	H	pyrrolidine	60	227.0 dec [231 dec[18]]
4	**3d**	H	piperidine	73	195.0 dec [199.0−199.5[18]]
5	**3e**	H	diethylamine	61	121.5−122.5 [124.0−125.0[18]]
6	**6a**	$TsCH_2$	morpholine	89	148.0−150.0 [−]
7	**6b**	$TsCH_2$	pyrrolidine	71	160.0−161.0 [−]
8	**6c**	4-$NO_2C_6H_4$	morpholine	41	201.0 dec [−]
9	**6d**	$TsCH_2$	diethylamine	62	77.0−79.0 [−]

SCHEME 2



SCHEME 3



of acetic acid to give the desired *N*,*N*-disubstituted 5-aminotetrazoles **3a**−**e** in moderate to high yields (Scheme 2). Reactions were performed at room temperature and stirred overnight. Signals ranging from 156 to 159 ppm (depending on the nature of the substituents in the amino functionality) in the ^{13}C spectra were assigned to the tetrazole carbon atoms.

According to the ^1H NMR spectra, the amount of compound **3b** in the crude reaction mixture was about 70%. However, due to its low solubility and high polarity, only 27% of the desired compound **3b** was isolated after gradient column chromatography (Table 1).

Di- and trisubstituted (benzotriazolyl)carboximidamides **5a**,**b**, obtained from (benzotriazolyl)carboximidoyl chlorides **4a**,**b**,[16] provide access to 1,*N*,*N*-trisubstituted 5-aminotetrazoles **6a**−**d** (Scheme 3). The versatility of intermediates **4a**,**b** is demonstrated by the variety of substituents (alkyl, aryl, heteroaryl) that can be introduced at all three possible sites of the molecule. Reactions were performed at room temperature, and the desired compounds **6a**−**d** were obtained in 41−90% yield.

In conclusion, in this work we have developed an efficient procedure for the preparation of substituted 5-aminotetrazoles. Unlike previously described methods, which frequently require unstable and/or moisture-sensitive starting materials, such as isocyanide dichlorides,[12c,d] chloroformamidines,[12c] or aminoiminomethanesulfonic acids,[12b] our method uses (benzotriazolyl)carboximidamides as starting compounds, which are relatively stable and can be prepared in high yields. The reaction conditions for the formation of the final 5-aminotetrazoles are mild and purification is simple. Benzotriazole is a good leaving group that is easily introduced to form intermediates that are typically stable and nonvolatile. Benzotriazole formed during the substitution step of the reaction sequence is environmentally safe and can be recycled.[17]

Experimental Section

General Methods. Melting points were determined using a capillary melting point apparatus equipped with a digital thermometer and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a 300 MHz NMR spectrometer (300 and 75 MHz, respectively) using $CDCl_3$ or DMSO-d_6 as a solvent with tetramethylsilane as an internal standard. Column chromatography was conducted with silica gel 230−400 mesh. All other reagents were of reagent grade and were used without purification.

Di(1*H*-benzotriazol-1-yl)methanimine (1) and 1*H*-Benzotriazol-1-yl(2*H*-benzotriazol-2-yl)methanimine (1′) (utilized as a 2:1 mixture of isomers) were prepared and characterized according to the previously published procedure.[13]

(1-Benzotriazolyl)carboximidamides 2a−**e** were prepared according to a previously published procedure[13] and were used as crude products without purification as follows: To a suspension of di(1*H*-benzotriazol-1-yl)methanimine **1** (1.67 g, 0.006 mol) in dichloromethane (30 mL) was added dropwise the appropriate amine (0.006 mol, 1 equiv) under vigorous stirring. Completion of the reaction was monitored by TLC. Upon completion, the reaction mixture was washed twice with a 10% solution of Na_2CO_3, dried over $MgSO_4$, and filtered. The solvent was evaporated under reduced pressure to afford compounds **2a**−**e** in analytical purity.

General Procedure for the Preparation of 5-Aminotetrazoles 3a−**e.** To a solution of starting (1-benzotriazolyl)-carboximidamide **2** (1 equiv) in chloroform were added subsequentially sodium azide (1 equiv) and acetic acid (1 equiv). The mixture obtained was allowed to react overnight at room temperature with stirring. Upon completion (TLC monitoring), the solvent was evaporated under reduced pressure and the desired aminotetrazole **3** was isolated by gradient column chromatography with a mixture of ethyl acetate with hexanes as eluent (from 5% to 50% of ethyl acetate, step 5%).

5-(4-Morpholinyl)-1*H*-1,2,3,4-tetrazole (3a): white prisms; ^1H NMR δ 3.34−3.37 (m, 4H), 3.70−3.73 (m, 4H); ^{13}C NMR δ 46.9, 65.2, 159.7. Anal. Calcd for $C_5H_9N_5O$: N, 45.14. Found: N, 44.77.

5-(4-Methylpiperazine)-1*H*-1,2,3,4-tetrazole (3b): white microcrystals; ^1H NMR δ 2.17 (s, 3H), 2.34−2.37 (m, 4H), 3.18 (s, 4H); ^{13}C NMR δ 46.1, 48.3, 54.5, 168.2; HRMS (EI) calcd for $C_6H_{12}N_6$ (M) 168.1123, found 168.1113.

5-(1-Pyrrolidinyl)-1*H*-1,2,3,4-tetrazole (3c): white prisms; ^1H NMR δ 1.92 (s, 4H), 3.33 (s, 4H); ^{13}C NMR δ 25.1, 48.2, 156.8. Anal. Calcd for $C_5H_9N_5$: C, 43.16; H, 6.52; N, 50.33. Found: C, 43.44; H, 6.60; N, 50.02.

5-(1-Piperidinyl)-1*H*-1,2,3,4-tetrazole (3d): white microcrystals; ^1H NMR δ 1.55 (s, 6H), 3.35 (s, 4H); ^{13}C NMR δ 23.4, 24.3, 47.7, 159.4. Anal. Calcd for $C_6H_{11}N_5$: N, 45.72. Found: N, 45.82.

***N*,*N*-Diethyl-1*H*-1,2,3,4-tetrazol-5-amine (3e):** white flakes; ^1H NMR δ 1.23 (t, 6H, J = 7.1 Hz), 3.58 (q, 4H, J = 7.1 Hz); ^{13}C NMR δ 12.8, 44.4, 157.7.

Preparation of Compounds 6a−**d.** Compounds **4a**,**b** and **5a**−**d** were prepared according to a previously reported proce-

(17) Katritzky, A. R.; Lan, X.; Yang, J. Z.; Denisko, O. V. *Chem. Rev.* **1998**, *98*, 409.

(18) Garbrecht, W. L.; Herbst, R. M. *J. Org. Chem.* **1953**, *18*, 1003.

dure[16] and were used without isolation and purification for the preparation of 1,*N*,*N*-trisubstituted-1*H*-tetrazoles.

To a solution of (benzotriazolyl)carboximidoyl chloride **4** (0.0026 mol) in chloroform (20 mL) was added the amine (0.0026 mol) followed by the addition of triethylamine (0.0026 mol) at room temperature with vigorous stirring. The reaction was monitored by TLC. Upon completion, the reaction mixture was washed twice with water, dried over $MgSO_4$, and filtered. The solvent was partially removed under reduced pressure.

To a solution of obtained (benzotriazolyl)carboximidamide **5** in chloroform (20 mL) was added sodium azide (0.0031 mol) followed by the addition of acetic acid (0.0031 mol). During the reaction, the formation of a cloudy white precipitate was observed. Upon completion (TLC monitoring), the reaction mixture was washed twice with 10% Na_2CO_3. The organic layer was separated, dried over $MgSO_4$, and concentrated. The final 1,*N*,*N*-trisubstituted 5-aminotetrazoles **6a**−**d** were isolated by gradient column chromatography (eluent: EtOAc/hexanes).

5-(Morpholin-4-yl)-1-(toluene-4-sulfonylmethyl)-1*H*-tetrazole (6a): white microcrystals; ^{1}H NMR δ 2.48 (s, 3H), 3.44−3.47 (m, 4H), 3.83−3.86 (m, 4H), 5.45 (s, 2H), 7.39 (d, 2H, J = 8.1 Hz), 7.65 (d, 2H, J = 8.2 Hz); ^{13}C NMR δ 21.8, 50.1, 65.2, 66.0, 129.1, 130.3, 132.7, 146.8, 158.9. Anal. Calcd for $C_{13}H_{17}N_5O_3S$: C, 48.28; H, 5.30. Found: C, 48.57; H, 5.62.

5-(Pyrrolidin-1-yl)-1-(toluene-4-sulfonylmethyl)-1*H*-tetrazole (6b): white microcrystals; ^{1}H NMR δ 2.04−2.08 (m, 4H), 2.46 (s, 3H), 3.68−3.72 (m, 4H), 5.55 (s, 2H), 7.35 (d, 2H, J = 8.1 Hz), 7.58 (d, 2H, J = 8.1 Hz); ^{13}C NMR δ 21.8, 25.7, 49.4, 65.5, 129.0, 130.2, 132.7, 146.5, 155.0. Anal. Calcd for $C_{13}H_{17}N_5O_2S$: C, 50.80; H, 5.57; N, 22.78. Found: C, 50.58; H, 5.88; N, 22.72.

5-(Morpholin-4-yl)-1-(4-nitrophenyl)-1*H*-tetrazole (6c): white prisms; ^{1}H NMR δ 3.16−3.19 (m, 4H), 3.66−3.69 (m, 4H), 8.02 (d, 2H, J = 8.8 Hz), 8.48 (d, 2H, J = 8.9 Hz); ^{13}C NMR δ 48.7, 65.1, 125.1, 125.4, 139.2, 147.5, 157.4. Anal. Calcd for $C_{11}H_{12}N_6O_3$: C, 47.83; H, 4.38; N, 30.42. Found: C, 47.89; H, 4.30; N, 30.54.

5-(*N*,*N*-Diethylamino)-1-(toluene-4-sulfonylmethyl)-1*H*-tetrazole (6d): white microcrystals; ^{1}H NMR δ 1.22 (t, 6H, J = 7.1 Hz), 2.46 (s, 3H), 3.52 (q, 4H, J = 7.1 Hz), 5.45 (s, 2H), 7.36 (d, 2H, J = 8.2 Hz), 7.61 (d, 2H, J = 8.4 Hz); ^{13}C NMR δ 13.0, 21.7, 45.7, 65.7, 128.9, 130.2, 132.8, 146.5, 157.3. Anal. Calcd for $C_{13}H_{19}N_5O_2S$: C, 50.47; H, 6.19; N, 22.64. Found: C, 50.77; H, 6.34; N, 22.95.

JO0266543