The synthesis of α-benzotriazolyl ketones from acid halides

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Dedicated to Professor Mieczyslaw Makosza on his 70th anniversary

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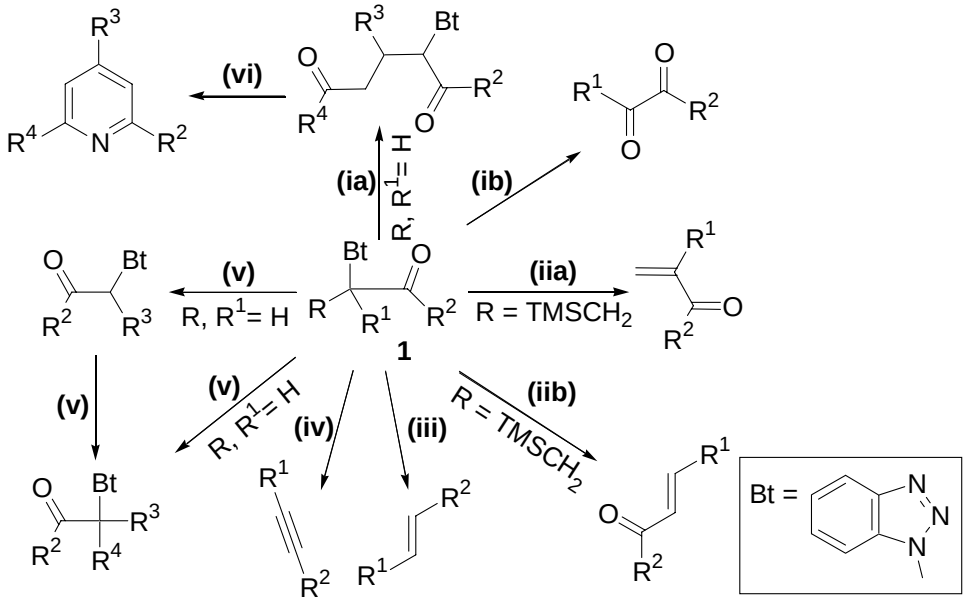
Abstract

Reactions of benzotriazolylacetic acid **7** dianion with electrophiles gave 2-benzotriazolylcarboxylic acids **9a–c**. Dianions of **9a–c** were transformed with acid halides to α-benzotriazolylketones **12a–i**.

Keywords: α-Benzotriazolyl ketones, acid halides, benzotriazolylacetic acid

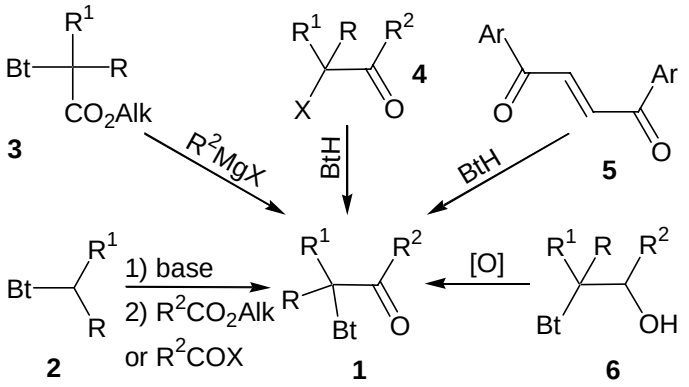
Introduction

Ketones carrying a benzotriazolyl substituent in the α-position to a carbonyl group, **1**, are versatile intermediates (Scheme 1) for the further synthesis of (i-a) α- and (i-b) δ- diketones;[1] (ii-a,b) α,β-unsaturated ketones;[2] (iii) olefins;[3] (iv) acetylenes;[4] (v) for the directed regioselective α-alkylation of ketones;[5] and (vi) in heterocycle ring synthesis.[1c]



Scheme 1

Available routes for the preparation of *α*-benzotriazolyl ketones **1** (Scheme 2) comprise (i) reactions of carbanions from *N*-alkylbenzotriazoles **2** with appropriate esters or acid chlorides;[1a–b,2,3,4,6] (ii) transformations of α-benzotriazolylalkylcarboxylic esters **3** with Grignard reagents;[4] (iii) from α-haloketones **4**;[7] (iv) addition of benzotriazole to but-2-ene-1,4-diones **5**;[8] and (v) oxidation of α-benzotriazolyl secondary alcohols **6**[9] (Scheme 2).



Scheme 2

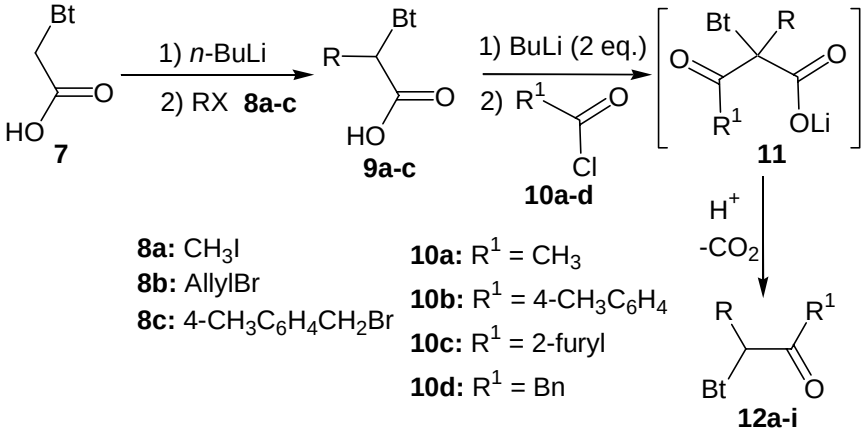
We have now established the capability of the benzotriazolyl group in 2-benzotriazolylacetic acid **7** to stabilize the dianions in successive subsequent reactions with alkyl halides **8a–c** and acid halides **10a–d** and then to induce decarboxylation to give α-benzotriazolyl ketones **12a–i** (Scheme 3). The new transformations now reported of acid halides with dianions of 2-benzotriazolylcarboxylic acids **9a–c**, derived from 2-benzotriazolylacetic acid **7**, provide a facile route to diverse α-benzotriazolyl ketones **12a–i** in good overall yields.

Results and Discussion

Benzotriazol-1-ylacetic acid **7** was easily prepared from chloroacetic acid and benzotriazole according to published procedure in 60% yield.[10] The treatment of benzotriazol-1-ylacetic acid **7** with *n*-butyllithium (2.2 eq.) in THF at –78 °C followed by the reaction with electrophiles **8a–c** (1.3–1.5 eq.) gave intermediates **9a–c** in 50–89% yields (Scheme 3, Table 1). The structures of compounds **9a–c** were supported by their ^{1}H NMR and ^{13}C NMR spectra.

The compounds **9a–c** were dilithiated with *n*-butyllithium (2.2 eq.) at –78 °C for 2 h (deep red color of reaction mixture) followed by addition of corresponding acid chlorides **10a–d** (1.0–1.1 eq.) at the same temperature to give intermediate lithium salts **11**. The decarboxylation of **11** upon acidification of the reaction mixture with mineral acid (hydrochloric or sulfuric) to pH=4–5 gave α-benzotriazolyl ketones **12a–i** in 60–84% overall yields. The attempted preparation of ketone **12a** using methyl 4-methylbenzoate, as an electrophile instead of 4-methylbenzoyl chloride **10b**, gave ketone **12a** in only 30% yield. The structures of ketones **12a–i** were supported by their ^{1}H NMR and ^{13}C NMR spectra. The ^{13}C NMR spectra of **12a–i** no longer show carbon signals in the 169.9–170.9 ppm range, which corresponds to the carboxyl group in

9a–c. For **12a–i**, new signals in 189.9–202.9 ppm range were assigned to the carbonyl group of α-benzotriazolyl ketones **12a–i**.



Scheme 3. For designation of R and R^1 in **9a–c**, **11**, and **12a–i** see Table 1.

Table 1. Synthesis of α-benzotriazolylcarboxylic acids **9a–c** and α-benzotriazolyl ketones **12a–i**

Compounds	R	R^1	Yields, %
9a	Me	-	50–65
9b	Allyl	-	65
9c	4-$CH_3C_6H_4CH_2$	-	89
12a[4,12]	H	4-$CH_3C_6H_4$	56 (30[a])
12b[12]	H	Bn	60
12c	Me	Me	61
12d[12]	Me	4-$CH_3C_6H_4$	80
12e	Me	2-Furyl	61
12f	Allyl	Me	60
12g	Allyl	4-$CH_3C_6H_4$	60
12h	4-$CH_3C_6H_4CH_2$	Me	84
12i	4-$CH_3C_6H_4CH_2$	4-$CH_3C_6H_4$	79

[a] Methyl 4-methylbenzoate was used instead of 4-methylbenzoyl chloride.

In summary, a novel and efficient procedure was developed for the preparation of α-benzotriazolyl ketones.

Experimental Section

General Procedures. All melting points were determined on a Mel-Temp II melting point apparatus and are uncorrected. NMR spectra were recorded on a Varian Gemini 300 spectrometer in chloroform-*d* and DMSO-d_6 with TMS as internal reference for ^{1}H (300 MHz) or a solvent as the internal reference for ^{13}C (75 MHz). The elemental analyses were performed on a Carlo Erba EA–1108 instrument. THF was dried over sodium / benzophenone and used freshly distilled. Column chromatography was conducted on silica gel 200–425 meshes. All of the chemicals were employed as supplied.

General procedure for the preparation of α-benzotriazolylalkylcarboxylic acids 9a–c
A solution of *n*-butyllithium (6.9 mL, 11.0 mmol, 1.6 M in hexane) was added dropwise to a stirred solution of benzotriazolylacetic acid **7** (0.89 g, 5 mmol) in THF (30 mL) at –78 °C. The reaction mixture was stirred at this temperature for 2 h and corresponding **8a–c** (7.5 mmol) in THF (10 mL) was added dropwise to the reaction mixture. The reaction mixture was stirred at –78 °C for 2 h and then for an additional 2 h at 20–25 °C. An aqueous sodium hydroxide solution (3%, 30 mL) was added to the reaction mixture and the mixture was washed with diethyl ether (3x30 mL). Diethyl ether remaining in the aqueous layer was removed in vacuum and the aqueous layer was acidified with concentrated hydrochloric acid to pH = 3–4. The precipitate was filtered off, washed with cold water (20-30 mL) and dried in vacuum to give pure **9a–c**.
2-(1*H*-1,2,3-Benzotriazol-1-yl)propionic acid (9a). White microcrystals from diethyl ether (50–65%), mp 181–182 °C (lit.[11] mp 179–181 °C). ^{1}H NMR (DMSO-d_6): δ = 8.09–8.06 (m, 1H), 7.86–7.83 (m, 1H), 7.58–7.53 (m, 1H), 7.44–7.39 (m, 1H), 5.98 (q, *J* = 7.2 Hz, 1H), 1.93 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (DMSO-d_6): δ = 170.9, 145.2, 133.0, 127.4, 124.0, 119.2, 110.9, 56.0, 16.5. Anal. Calcd. for $C_9H_9N_3O_2$ (191.19): C, 56.54; H, 4.74; N, 21.98. Found: C, 56.84; H, 4.80; N, 22.04.
2-(1*H*-1,2,3-Benzotriazol-1-yl)pent-4-enoic acid (9b). White microcrystals from diethyl ether (65%), mp 165–166 °C. ^{1}H NMR (DMSO-d_6): δ = 8.06 (d, *J* = 8.4 Hz, 1H), 7.87 (d, *J* = 8.2 Hz, 1H), 7.58–7.53 (m, 1H), 7.44–7.38 (m, 1H), 6.00 (dd, *J* = 9.6, 5.6 Hz, 1H), 5.74–5.60 (m, 1H), 4.94 (d, *J* = 17.2 Hz, 1H), 4.86 (d, *J* = 10.2 Hz, 1H), 3.20–3.14 (m, 2H). ^{13}C NMR (DMSO-d_6): δ 169.9, 145.2, 133.3, 133.1, 127.5, 124.0, 119.3, 118.5, 110.9, 60.1, 34.4. Anal. Calcd. for $C_{11}H_{11}N_3O_2$ (217.23): C, 60.82; H, 5.10; N, 19.34. Found: C, 61.13; H, 5.21; N, 19.31.
2-(1*H*-1,2,3-Benzotriazol-1-yl)-3-(4-methylphenyl)propionic acid (9c). White microcrystals from diethyl ether (89%), mp 208–209 °C. ^{1}H NMR (DMSO-d_6): δ = 7.99 (d, *J* = 8.3 Hz, 1H), 7.82 (d, *J* = 8.3 Hz, 1H), 7.51–7.46 (m, 1H), 7.35 (t, *J* = 7.5 Hz, 1H), 6.99 (d, *J* = 7.9 Hz, 2H), 6.90 (d, *J* = 7.9 Hz, 2H), 6.21 (dd, *J* = 9.0, 7.1 Hz, 1H), 3.72 (d, *J* = 8.6 Hz, 2H), 2.11 (s, 3H). ^{13}C NMR (DMSO-d_6): δ = 169.9, 145.0, 135.6, 133.4, 133.4, 128.8, 128.6, 127.4, 123.9, 119.1, 110.8, 61.8, 35.5, 20.5. Anal. Calcd. for $C_{16}H_{15}N_3O_2$ (281.32): C, 68.31; H, 5.37; N, 14.94. Found: C, 67.96; H, 5.32; N, 14.90.

General procedure for the preparation of α-benzotriazolyl ketones 12a–i
A solution of *n*-butyllithium (2.45 mL, 3.9 mmol, 1.6 M in hexane,) was added dropwise to a stirred solution of **7** or **9a–c** (1.8 mmol) in THF (30 mL) at –78 °C. The reaction mixture was

stirred at this temperature for 2 h and corresponding acid chloride **10a–d** (1.9 mmol) was added dropwise. The reaction mixture was stirred at –78 °C for 15–30 min and then for an additional 15 min at 20–25 °C. A diluted hydrochloric acid was added to the reaction mixture to adjust pH=5 and product was extracted with diethyl ether (2x50 mL). The extract was concentrated in vacuum and the product **12a–i** was purified by column chromatography or recrystallized.

2-(1*H*-1,2,3-Benzotriazol-1-yl)-1-(4-methylphenyl)ethanone (12a). White microcrystals from toluene (56%), mp 132–134 °C (lit.[4,12] mp 133–135 °C). ^{1}H NMR ($CDCl_3$): δ = 8.09 (d, *J* = 8.2 Hz, 1H), 7.96 (d, *J* = 8.2 Hz, 2H), 7.51–7.33 (m, 5H), 6.08 (s, 2H), 2.46 (s, 3H). ^{13}C NMR ($CDCl_3$): δ = 189.9, 146.1, 145.7, 133.8, 131.5, 129.8, 128.4, 127.8, 124.0, 120.1, 109.6, 53.8, 21.8.

1-(1*H*-1,2,3-Benzotriazol-1-yl)-3-phenyl-propan-2-one (12b). White microcrystals from diethyl ether (60%), mp 141–142 °C (lit.[12] mp 141–142 °C). ^{1}H NMR ($CDCl_3$): 8.03 (d, *J* = 8.2 Hz, 1H), 7.39–7.26 (m, 8H), 5.43 (s, 2H), 3.78 (s, 2H.). ^{13}C NMR ($CDCl_3$): δ = 199.7, 146.0, 133.5, 132.3, 129.4, 129.2, 127.9, 127.8, 124.2, 120.1, 109.2, 55.5, 47.4.

3-(1*H*-1,2,3-Benzotriazol-1-yl)butan-2-one (12c). Colorless oil (61%, column chromatography with ethyl acetate/hexanes 1:9). ^{1}H NMR ($CDCl_3$): δ = 8.09 (d, *J* = 8.2 Hz, 1H), 7.50 (d, *J* = 3.8 Hz, 2H), 7.42–7.37 (m, 1H), 5.67 (q, *J* = 7.3 Hz, 1H), 2.06 (s, 3H), 1.93 (d, *J* = 7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ = 202.9, 146.0, 132.5, 127.7, 124.2, 120.0, 109.5, 63.3, 26.1, 15.4. Anal. Calcd. for $C_{10}H_{11}N_3O$ (189.22): C, 63.48; H, 5.86; N, 22.21. Found: C, 63.68; H, 5.57; N, 22.18.

2-(1*H*-1,2,3-Benzotriazol-1-yl)-1-(4-methylphenyl)propan-1-one (12d). Colorless oil[12] (80%, column chromatography with ethyl acetate/hexanes 1:3). ^{1}H NMR ($CDCl_3$): δ = 8.01 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 8.1 Hz, 2H), 7.53 (d, *J* = 8.2 Hz, 1H), 7.42–7.37 (m, 1H), 7.31–7.26 (m, 1H), 7.16 (d, *J* = 8.1 Hz, 2H), 6.70 (q, *J* = 7.1 Hz, 1H), 2.29 (s, 3H), 1.95 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ = 193.2, 146.2, 144.9, 131.9, 131.4, 129.4, 128.6, 127.4, 123.8, 119.8, 110.2, 59.1, 21.4, 16.1.

2-(1*H*-1,2,3-Benzotriazol-1-yl)-1-(furan-2-yl)propan-1-one (12e). Colorless oil (61%, column chromatography with ethyl acetate/hexanes 1:9). ^{1}H NMR ($CDCl_3$): δ = 8.04 (d, *J* = 8.2 Hz, 1H), 7.61–7.57 (m, 2H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.37–7.32 (m, 1H), 7.26 (d, *J* = 3.7 Hz, 1H), 6.50–6.40 (m, 2H), 2.01 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ = 182.5, 150.2, 147.7, 146.5, 132.4, 127.7, 124.1, 120.1, 119.9, 112.9, 110.5, 59.7, 15.9. Anal. Calcd. for $C_{13}H_{11}N_3O_2$ (241.25): C, 64.72; H, 4.60; N, 17.42. Found: C, 64.51; H, 4.82; N, 16.78.

3-(1*H*-1,2,3-Benzotriazol-1-yl)hex-5-en-2-one (12f). Colorless oil (60%, column chromatography with ethyl acetate/hexanes 1:9). ^{1}H NMR ($CDCl_3$): δ = 8.10 (d, *J* = 8.3 Hz, 1H), 7.52 (d, *J* = 3.9 Hz, 1H), 7.44–7.39 (m, 2H), 5.70–5.53 (m, 2H), 5.05–4.93 (m, 2H), 3.22–3.10 (m, 2H), 2.06 (s, 3H). ^{13}C NMR ($CDCl_3$): δ = 202.2, 146.2, 132.9, 131.9, 128.0, 124.3, 120.3, 119.3, 109.6, 67.6, 33.8, 26.9. Anal. Calcd. for $C_{12}H_{13}N_3O$ (215.26): C, 66.96; H, 6.09; N, 19.52. Found: C, 66.69; H, 6.24; N, 19.63.

2-(1*H*-1,2,3-Benzotriazol-1-yl)-1-(4-methylphenyl)pent-4-en-1-one (12g). Colorless oil (60%, column chromatography with ethyl acetate/hexanes 1:9). ^{1}H NMR ($CDCl_3$): δ = 8.00 (d, *J* = 8.3 Hz, 1H), 7.92 (d, *J* = 8.2 Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.45–7.40 (m, 1H), 7.33–7.28 (m, 1H), 7.17 (d, *J* = 8.2 Hz, 2H), 6.65 (dd, *J* = 8.7, 6.4 Hz, 1H), 5.77–5.64 (m, 1H), 5.02–4.94 (m, 2H), 3.21–3.10 (m, 2H), 2.30 (s, 3H). ^{13}C NMR ($CDCl_3$): δ = 192.5, 146.6, 145.3, 132.2, 132.1,

132.0, 129.7, 129.0, 127.8, 124.1, 120.2, 119.3, 110.7, 63.2, 34.3, 21.7. Anal. Calcd. for $C_{18}H_{17}N_3O$ (291.36): C, 74.20; H, 5.88; N, 14.42. Found: C, 73.81; H, 5.92; N, 14.38.

3-(1*H*-1,2,3-Benzotriazol-1-yl)-4-(4-methylphenyl)butan-2-one (12h). Colorless oil (84%, column chromatography with ethyl acetate/hexanes 1:9). ^{1}H NMR ($CDCl_3$): δ = 8.03 (d, *J* = 8.1 Hz, 1H), 7.44–7.31 (m, 3H), 6.90 (d, *J* = 8.1 Hz, 2H), 6.85 (d, *J* = 8.1 Hz, 2H), 5.65 (dd, *J* = 10.0, 5.2 Hz, 1H), 3.72 (dd, *J* = 14.3, 5.2 Hz, 1H), 3.52 (dd, *J* = 14.3, 10.0 Hz, 1H), 2.16 (s, 3H), 2.02 (s, 3H). ^{13}C NMR ($CDCl_3$): δ = 202.2, 146.0, 136.6, 133.0, 132.8, 129.3, 128.6, 127.9, 124.2, 120.2, 109.5, 69.5, 35.4, 27.1, 20.9. Anal. Calcd. for $C_{17}H_{17}N_3O$ (279.34): C, 73.10; H, 6.13; N, 15.04. Found: C, 73.10; H, 6.29; N, 14.94.

2-(1*H*-1,2,3-Benzotriazol-1-yl)-1,3-bis(4-methylphenyl)propan-1-one (12i). White microcrystals from diethyl ether/hexanes (79%), mp 135–136 °C. ^{1}H NMR ($CDCl_3$): δ = 7.98 (d, *J* = 8.4 Hz, 1H), 7.89 (d, *J* = 8.2 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.46–7.41 (m, 1H), 7.34–7.29 (m, 1H), 7.15 (d, *J* = 8.1 Hz, 2H), 6.95 (d, *J* = 8.0 Hz, 2H), 6.87 (d, *J* = 8.0 Hz, 2H), 6.72 (dd, *J* = 9.0, 6.0 Hz, 1H), 3.74 (dd, *J* = 14.3, 6.0 Hz, 1H), 3.57 (dd, *J* = 14.3, 9.0 Hz, 1H), 2.31 (s, 3H), 2.22 (s, 3H). ^{13}C NMR ($CDCl_3$): δ = 192.6, 146.6, 145.4, 136.9, 133.1, 132.4, 132.2, 129.8, 129.5, 129.1, 129.0, 127.9, 124.2, 120.4, 110.8, 65.2, 35.9, 21.8, 21.1. Anal. Calcd. for $C_{23}H_{21}N_3O$ (355.44): C, 77.72; H, 5.96; N, 11.82. Found: C, 77.72; H, 6.08; N, 11.94.

References

1. (a) Katritzky, A. R.; Kuzmierkiewicz, W. *J. Chem. Soc., Perkin Trans. 1* **1987**, 819. (b) Katritzky, A. R.; Wang, Z.; Lang, H.; Feng, D. *J. Org. Chem.* **1997**, *62*, 4125. (c) Katritzky, A. R.; Abdel-Fattah, A. A. A.; Tymoshenko, D. O.; Essawy, S. A. *Synthesis* **1999**, 2114. (d) Faust, R.; Weber, C. US Pat. 6121442, 2000; Ger. Pat. DE 19626120, 1998; *Chem. Abstr.* **1998**, 128, 114783.
2. (a) Katritzky, A. R.; Voronkov, M. V.; Toader, D. *J. Chem. Soc., Perkin Trans. 2* **1998**, 2515. (b) Katritzky, A. R.; Toader, D.; Chassaing, C. *J. Org. Chem.* **1998**, *63*, 9983.
3. (a) Katritzky, A. R.; Fali, C. N.; Li, J. *J. Org. Chem.* **1997**, *62*, 4148. (b) Katritzky, A. R.; Cheng, D.; Li, J. *J. Org. Chem.* **1998**, *63*, 3438.
4. Katritzky, A. R.; Wang, J.; Karodia, N.; Li, J. *J. Org. Chem.* **1997**, *62*, 4142.
5. Katritzky, A. R.; Wang, Z.; Ji, Y.; Fang Y. *ARKIVOC* **2002**, *(iii)*, 46.
6. (a) Katritzky, A. R.; Lan, X.; Lam, J. N. *Chem. Ber.* **1991**, *124*, 1819. (b) Katritzky, A. R.; Lan, X.; Lam, J. N. *J. Org. Chem.* **1991**, *56*, 4397. (c) Katritzky, A. R.; Rachwal, S.; Hitchings, G. J. *Tetrahedron* **1991**, *47*, 2683. (d) Katritzky, A. R.; Yao, G.; Rachwal, S. *J. Heterocycl. Chem.* **1994**, *31*, 757. (e) Katritzky, A. R.; Zhang, G.; Jiang, J. *J. Org. Chem.* **1995**, *60*, 7605. (f) Katritzky, A. R.; Lang, H. *J. Org. Chem.* **1995**, *60*, 7612. (g) Katritzky, A. R.; Toader, D. *J. Am. Chem. Soc.* **1997**, *119*, 9321. (h) Katritzky, A. R.; Wang, J.; Henderson, S. A. *Heterocycles* **1998**, *48*, 1567.
7. (a) Katritzky, A. R.; Wu, J.; Wrobel, L.; Rachwal, S.; Steel, P. J. *Acta. Chem. Scand.* **1993**, *47*, 167. (b) Al-Omran, F.; Al-Awadl, N.; Yousef, O.; Elnagdi, M. H. *J. Heterocycl. Chem.* **2000**, *37*, 167.
8. Katritzky, A. R.; Rachwal, S.; Hughes, C. V.; Wang, Z. *Pol. J. Chem.* **1992**, *66*, 1633.

9. Faust, R.; Weber, C. *Liebigs Ann.* **1996**, 1235.
10. Krollpfeiffer, F.; Rosenberg, A.; Mühlhausen, C. *Liebigs Ann. Chem.* **1935**, *515*, 113.
11. Sparatore, F.; La Rotonda, M. I.; Caliendo, G.; Novellino, E.; Silipo, C.; Vittoria, A. *Farmaco, Ed. Sci.* **1988**, *43*, 29; *Chem. Abstr.* **1988**, *109*, 128916.
12. Katritzky, A. R.; Lam, J. N. *Heteroatom Chem.* **1990**, *1*, 21.