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THE SYNTHESIS OF NEW 5-AMINOISOXAZOLES BY REACTION OF THIOCARBAMOYLCYANOACETATES WITH HYDROXYLAMINE

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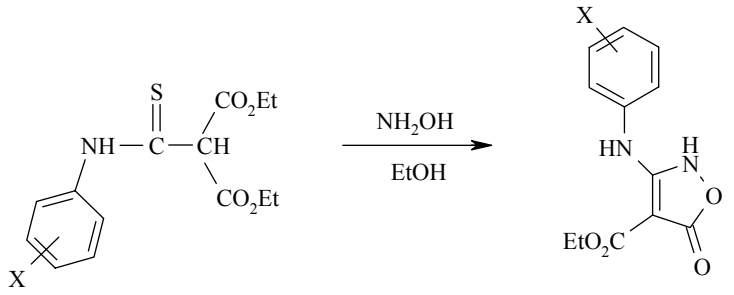
The reaction of thiocarbamoylcyanoacetates with hydroxylamine in ethanol under reflux conditions has provided a convenient method for the synthesis of 5-aminoisoxazoles.

Keywords: hydroxylamine, isothiocyanates, isoxazoles, thioxopropanoates.

Isoxazoles play an important role in biochemistry, organic chemistry, and bioorganic chemistry. The biological activity of substituted isoxazoles [1] has made them a focus of medicinal chemistry over the years. Isoxazoles are potent, selective agonists of human cloned dopamine D4 receptors [2] and exhibit $GABA_A$ antagonistic [3], analgesic [3], anti-inflammatory [4], ulcerogenic [4], antifungal [5], antimicrobial [5], COX-2 inhibitory [6, 7], antinociceptive [8], and anticancer [9] activities.

Many synthetic methods have been employed in the synthesis of isoxazoles [10], including the reactions of hydroxylamine with 1,3-dicarbonyl compounds [11], α,β-unsaturated carbonyl compounds [12], and α,β-unsaturated nitriles [13]. The reaction of oxime-derived dianion and ester [14] or amide [15, 16] also provides isoxazoles. [3+2] Cycloaddition reactions between alkynes and nitrile oxides have been also developed [17, 18]. However, these methods often require strong bases, strong mineral acids, and high temperatures, or provide poor regioselectivity.

We have reported that the reaction of *o*-, *m*-, and *p*-substituted diethyl phenylthiocarbamoylmalonates with hydroxylamine under reflux conditions gave *o*-, *m*-, and *p*-substituted 3-phenylaminoisoxazol-5(2H)-ones [19-21].



X = H, 2-Me, 2-MeO, 3-Br, 4-Br, 3-Me, 4-Me, 4-CO_2Et, 4-NO_2

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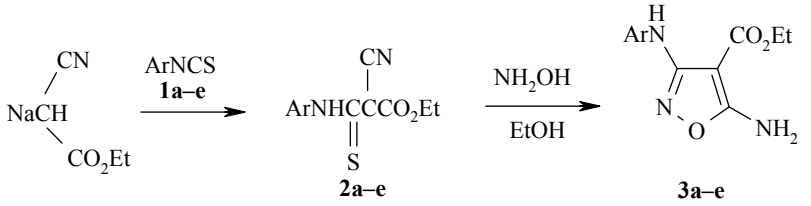
The reaction of diethyl (2-ethoxycarbonylphenyl)thiocarbamoylmalonate with hydroxylamine under reflux conditions gave ethyl 2,9-dioxo-4,9-dihydro-2H-isoxazolo[3,2-*b*]quinazoline-3-carboxylate by intramolecular condensation [16].

Herein, we report a new and direct method for the synthesis of 5-aminoisoxazoles by the reaction of thiocarbamoylcyanoacetates with hydroxylamine in ethanol under reflux conditions.

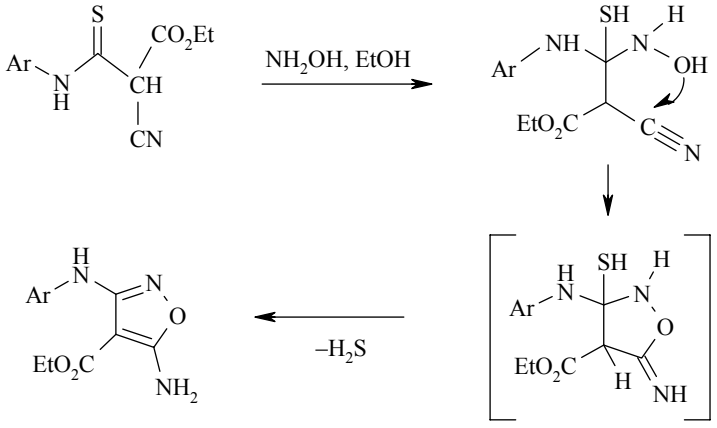
The reaction of aryl isothiocyanates **1a**–**e** with sodium ethylcyanoacetate in ethanol at room temperature gave the corresponding ethyl arylthiocarbamoyl- cyanoacetates **2a**–**e** in high yield.

The reaction of thiocarbamoylcyanoacetates **2a**–**e** with hydroxylamine by a modification of Worall [22] procedures in aqueous ethanol under reflux conditions afforded the corresponding 5-aminoisoxazoles **3a**–**e**.



a Ar =Ph, **b** Ar = 2-BrC_6H_4, **c** Ar = 3-BrC_6H_4, **d** Ar = 4-BrC_6H_4, **e** Ar = 1-naphthyl

The mechanism of the reaction is shown in the following Scheme:



We have reported [19–21] that the reaction of diethyl arylthiocarbamoylmalonate with hydroxylamine under reflux conditions gave 3-arylamino- isoxazol-5(2H)-ones, but the reaction of ethyl 3-arylamino-2-cyano-3-thioxopropanoates **2a**–**e** with hydroxylamine under reflux conditions gave the corresponding 5-amino-isoxazoles **3a**–**e** in good yields. The formation of isoxazoles instead of isoxazolones may be due to the higher electronegativity of cyano group, which in this case reacts with nucleophilic oximino group to form the corresponding aminoisoxazoles.

The above results showed that the reaction of thiocarbamoylcyanoacetates with hydroxylamine provides a synthetically useful method for obtaining 5-aminoisoxazoles in good yield.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded with a Bruker spectrometer (300 and 75 MHz, respectively). The spectra were measured in $CDCl_3$ (compounds **2a-e**) or DMSO-d_6 (compounds **3a–e**) using TMS as the

internal standard. IR spectra were recorded on a Thermonicolet (Nexus 670) FT-infrared spectrometer, using sodium chloride cells and measured as Nujol mulls or KBr disks. Mass spectra were recorded on a Finnigan TSQ-70 spectrometer at 70 eV. Microanalyses were performed on a Leco Analyzer 932. Melting points were determined on a Philip Harris C 4954718 apparatus and are uncorrected. All organic extracts were dried with anhydrous sodium sulfate.

Ethyl 2-cyano-3-(phenylamino)-3-thioxopropanoate (**2a**). In a one-liter round-bottomed flask, absolute ethanol (38 ml) was reacted with sodium (2.3 g, 0.1 mol) and after cooling to room temperature, ethylcyanoacetate (11.3 g, 0.1 mol) was added. The reaction mixture was stirred at room temperature for 15 min. Phenyl isothiocyanate (13.5 g, 0.1 mol) was added and the stirring was continued for a further 2 h, then water (50 ml) was added to the reaction mixture. The aqueous layer was extracted with chloroform (30 ml) and then acidified with diluted hydrochloric acid (10%) to maintain the pH at 3. The yellow precipitate was collected by vacuum filtration, and recrystallization from *n*-hexane gave the desired product (21.8 g, 87%) as cream needles; mp 120-121°C. FT-IR spectrum, ν, cm^{-1}: 3169 (N–H), 2981, 2201, 1658 (C=O), 1587, 1545, 1492, 1453, 1375, 1356, 1261, 1171, 778, 693. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.36 (3H, t, *J* = 7.2, CH_3); 4.30 (2H, q, *J* = 7.2, CH_2); 4.72 (1H, s, CH); 7.27–7.50 (5H, m, Ar); 11.75 (1H, br. s, exchanged by D_2O addition, NH). ^{13}C NMR spectrum, δ, ppm: 14.36, 61.06, 72.91, 126.12, 128.59, 129.76, 137.03, 167.78, 169.09. MS (EI), *m/z* (I_{rel}, %): 248 $[M]^+$ (3), 245 (100), 241 (45), 218 (19), 213 (26), 186 (29), 146 (13), 114 (17), 93 (12), 40 (10). Found, %: C 57.80; H 4.72; N 11.49. $C_{12}H_{12}N_2O_2S$. Calculated, %: C 58.05; H 4.87; N 11.28.

Ethyl 3-(2-bromophenylamino)-2-cyano-3-thioxopropanoate (**2b**) was prepared as described for the **2a** derivative, using 2-bromophenyl isothiocyanate (21.4 g, 0.1 mol) and stirring for a further 4 h after addition of 2-bromophenyl isothiocyanate to give ethyl 3-(2-bromophenylamino)-2-cyano-3-thioxopropanoate (29 g, 88%) as a yellow solid; mp 135-136°C. FT-IR spectrum, ν, cm^{-1}: 3159 (N–H), 3070, 2204, 1655 (C=O), 1474, 1307, 1378, 1256, 1033, 769. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.35 (3H, t, *J* = 7.2, CH_3); 3.46 (1H, s, CH); 4.27 (2H, q, *J* = 7.2, CH_2); 7.26-7.31 (2H, m, Ar); 7.41 (1H, dd, *J* = 7.2, *J* = 1.2, Ar); 7.71 (1H, dd, *J* = 8.1, *J* = 1.2, Ar); 11.73 (1H, s, exchanged by D_2O addition, NH). ^{13}C NMR spectrum, δ, ppm: 14.33, 61.23, 73.84, 118.81, 121.61, 128.43, 129.20, 130.10, 133.81, 137.15, 167.49, 169.11. Found, %: C 44.34; H 3.46; N 8.31. $C_{12}H_{11}BrN_2O_2S$. Calculated, %: C 44.05; H 3.39; N 8.56.

Ethyl 3-(3-bromophenylamino)-2-cyano-3-thioxopropanoate (**2c**) was prepared as described for the **2a** derivative, using 3-bromophenyl isothiocyanate (21.4 g, 0.1 mol) and stirring for a further 3 h after addition of 3-bromophenyl isothiocyanate to give the desired product (30 g, 91%) as yellow needles; mp 120-121°C. FT-IR spectrum, ν, cm^{-1}: 3150 (N–H), 3062, 2203, 1673 (C=O), 1474, 1376, 1259, 769, 695. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.36 (3H, t, *J* = 7.2, CH_3); 3.51 (1H, s, CH); 4.27 (2H, q, *J* = 7.2, CH_2); 7.23–7.63 (4H, m, Ar); 11.75 (1H, s, exchanged by D_2O addition, NH). ^{13}C NMR spectrum, δ, ppm: 14.31, 61.31, 63.07, 113.22, 123.04, 124.65, 129.06, 130.91, 131.56, 138.26, 165.68, 167.62. Found, %: C 44.29; H 3.54; N 8.32. $C_{12}H_{11}BrN_2O_2S$. Calculated, %: C 44.05; H 3.39; N 8.56.

Ethyl 3-(4-bromophenylamino)-2-cyano-3-thioxopropanoate (**2d**) was prepared as described for the **2a** derivative, using 4-bromophenyl isothiocyanate (21.4 g, 0.1 mol) and stirring for a further 2 h after addition of 4-bromophenyl isothiocyanate to give ethyl 3-(4-bromophenylamino)-2-cyano-3-thioxopropanoate (27 g, 83%) as yellow needles; mp 145-146°C. FT-IR spectrum, ν, cm^{-1}: 3182 (N–H), 3069, 2973, 2200, 1671 (C=O), 1656, 1486, 1402, 1372, 1257, 1161, 1048, 768. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.39 (3H, t, *J* = 7.2, CH_3); 4.30 (2H, q, *J* = 7.2, CH_2); 4.76 (1H, s, CH); 7.15 (2H, d, *J* = 7.5, Ar); 7.57 (2H, d, *J* = 7.5, Ar); 11.70 (1H, s, exchanged by D_2O addition, NH). ^{13}C NMR spectrum, δ, ppm: 14.33, 61.23, 73.55, 118.83, 122.34, 127.64, 132.93, 136.03, 167.67, 168.78. MS (EI), *m/z* (I_{rel}, %): 328 $[M+2]^+$ (2), 326 $[M]^+$, (2), 296 (96), 294 (100), 250 (59), 248 (59), 223 (31), 221 (32), 182 (28), 184 (28), 142 (41), 115 (18), 76 (15), 52 (10). Found, %: C 44.44; H 3.48; N 8.69. $C_{12}H_{11}BrN_2O_2S$. Calculated, %: C 44.05; H 3.39; N 8.56.

Ethyl 2-cyano-3-(naphth-1-ylamino)-3-thioxopropanoate (**2e**) was prepared as described for the **2a** derivative, using 1-naphthyl isothiocyanate (18.5 g, 0.1 mol) and stirring for a further 5 h after addition of 1-naphthyl isothiocyanate to give the desired product (22.6 g, 79%) as yellow needles; mp 131-132°C. FT-IR spectrum, ν, cm^{-1}: 3400 (N–H), 2991, 2203, 1651 (C=O), 1570, 1375, 1277, 777. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.41 (3H, t, *J* = 7.2, CH_3); 4.34 (2H, q, *J* = 7.2, CH_2); 4.62 (1H, s, CH); 7.45-7.66 (4H, m, Ar); 7.89–7.96 (3H, m, Ar); 11.98 (1H, br. s, exchanged by D_2O addition, NH). ^{13}C NMR spectrum, δ, ppm: 14.42, 61.14, 73.01, 119.04, 121.98, 125.07, 125.23, 127.25, 127.80, 128.60, 129.51, 129.58, 133.22, 134.36, 168.03, 170.64. MS (EI), *m/z* (I_{rel}, %): 298 $[M]^+$, (14), 295 (100), 292 (64), 281 (24), 263 (29), 236 (16), 196 (13), 164 (19). Found, %: C 64.30; H 4.83; N 9.10. $C_{16}H_{14}N_2O_2S$. Calculated, %: C 64.41; H 4.73; N 9.39.

Ethyl 5-amino-3-(phenylamino)isoxazole-4-carboxylate (**3a**). Potassium hydroxide (6 g, 0.1 mol) was slowly added to a solution of hydroxylamine hydrochloride (7.08 g, 0.1 mol) in water (30 ml). Ethanol (80 ml) was added and the resulting potassium chloride was filtered off. Propanoate **2a** (2.47 g, 0.01 mol) was added to the filtrate and the mixture was refluxed for 24 h, water (80 ml) was added to the reaction mixture and the white precipitate was collected by vacuum filtration. The white solid was recrystallized from ethanol to give the desired product (2.42 g, 97%) as white needles; mp 167-168°C. FT-IR spectrum, ν, cm^{-1}: 3481 (N–H), 3268 (NH_2), 1667 (C=O), 1654, 1606, 1559, 1120, 779, 746. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.29 (3H, t, *J* = 7.2, CH_3); 4.24 (2H, q, *J* = 7.2, CH_2); 6.94 (1H, t, *J* = 7.2, Ar); 7.30 (2H, t, *J* = 7.5, Ar); 7.44 (2H, d, *J* = 7.2, Ar); 7.79 (2H, br. s, exchanged by D_2O addition, NH_2); 8.10 (1H, s, exchanged by D_2O addition, NH). ^{13}C NMR spectrum, δ, ppm: 14.87, 60.01, 77.09, 117.83, 121.47, 129.41, 140.33, 159.41, 163.52, 169.75 (C=O). Mass spectrum (EI), *m/z* (I_{rel}, %): 247 $[M]^+$ (58), 246 (100), 201 (14), 200 (20), 159 (43), 157 (95), 131 (36), 129 (73), 102 (57), 90 (73), 78 (27), 77 (27), 65 (58). Found, %: C 58.11; H 5.67; N 16.70. $C_{12}H_{13}N_3O_3$. Calculated, %: C 58.29; H 5.30; N 16.99.

Ethyl 5-amino-3-(2-bromophenylamino)isoxazole-4-carboxylate (**3b**) was prepared as described for compound **3a**, using ethyl propanoate **2b** (3.27 g, 0.01 mol) and refluxing for 48 h, to give the desired product (2.63 g, 80%) as white needles; mp 155-156°C. FT-IR spectrum, ν, cm^{-1}: 3480 (N–H), 3281 (NH_2), 1654 (C=O), 1599, 1584, 1555, 1458, 1442, 1129, 1022, 782, 742. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.31 (3H, t, *J* = 7.2, CH_3); 4.29 (2H, q, *J* = 7.2, CH_2); 6.90 (1H, td, *J* = 7.2, *J* = 1.5, Ar); 7.38 (1H, td, *J* = 8.1, *J* = 1.2, Ar); 7.63 (1H, dd, *J* = 7.8, *J* = 1.2, Ar); 7.90 (2H, br. s, exchanged by D_2O addition, NH_2), 8.06 (1H, dd, *J* = 8.6, *J* = 1.5, Ar), 8.69 (1H, br. s, exchanged by D_2O addition, NH). ^{13}C NMR spectrum, δ, ppm: 14.86, 60.62, 77.21, 119.25, 122.32, 126.56, 128. 58, 132.29, 138.82, 157.75, 163.22, 172.34 (C=O). Found, %: C 44.43; H 3.67; N 12.76. $C_{12}H_{12}BrN_3O_3$. Calculated, %: C 44.19; H 3.71; N 12.88.

Ethyl 5-amino-3-(3-bromophenylamino)isoxazole-4-carboxylate (**3c**) was prepared as described for compound **3a**, using compound **2c** (3.27 g, 0.01 mol) and refluxing for 48 h, to give the desired product (2.9 g, 88%) as white needles; mp 160-161°C. FT-IR spectrum, ν, cm^{-1}: 3481 (N–H), 3269 (NH_2), 1650 (C=O), 1604, 1578, 1552, 1467, 1120, 773. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.30 (3H, t, *J* = 7.2, CH_3); 4.26 (2H, q, *J* = 7.2, CH_2); 7.10 (1H, br. d, *J* = 7.8, Ar); 7.24 (1H, t, *J* = 8.1, Ar); 7.41 (1H, d, *J* = 7.5, Ar); 7.80 (1H, s, Ar); 7.85 (2H, s, exchanged by D_2O addition, NH_2); 8.23 (1H, s, exchanged by D_2O addition, NH). ^{13}C NMR spectrum, δ, ppm: 14.88, 60.07, 77.21, 117.05, 120.27, 122.29, 124.05, 131.22, 141.92, 159.17, 163.30, 169.86. Mass spectrum (EI), *m/z* (I_{rel}, %): 327 $[M+2]^+$ (50), 325 $[M+2]^+$ (50), 281 (10), 279 (10), 200 (16), 173 (20), 171 (21), 157 (100), 118 (14), 92 (27), 90 (88), 64 (39), 62 (40). Found, %: C 44.40; H 3.56; N 12.65. $C_{12}H_{12}BrN_3O_3$. Calculated, %: C 44.19; H 3.71; N 12.88.

Ethyl 5-amino-3-(4-bromophenylamino)isoxazole-4-carboxylate (**3d**) was prepared as described for compound **3a**, using compound **2d** (3.27 g, 0.01 mol) and refluxing for 48 h to give the desired product (2.6 g, 79%) as white needles; mp 160-161°C. FT-IR spectrum, ν, cm^{-1}: 3469 (N–H), 3275 (NH_2), 1667 (C=O), 1652, 1600, 1556, 1476, 1112, 781. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.30 (3H, t, *J* = 7.2, CH_3); 4.28 (2H, q, *J* = 7.2, CH_2); 7.25–7.56 (4H, m, Ar); 7.82 (2H, br. s, exchanged by D_2O addition, NH_2); 8.19 (1H, s, exchanged by D_2O addition, NH). ^{13}C NMR spectrum, δ, ppm: 14.88, 60.04, 77.18, 112.91, 120.06, 132.02, 139.77, 159.24,

161.54, 169.85 (C=O). MS (EI), *m/z* (I_{rel}, %): 327 $[M+2]^+$ (6), 325 $[M]^+$ (6), 199 (84), 198 (84), 197 (100), 169 (16), 118 (10), 98 (18), 90 (58), 44 (22). Found, %: C 44.31; H 3.63; N 12.50. $C_{12}H_{12}BrN_3O_3$. Calculated, %: C 44.19; H 3.71; N 12.88.

Ethyl 5-amino-3-(naphth-1-ylamino)isoxazole-4-carboxylate (**3e**) was prepared as described for compound **3a**, using propanoate **2e** (2.86 g, 0.01 mol) and refluxing for 48 h to give the desired product (1.78 g, 60%) as white needles; mp 138-139°C. FT-IR spectrum, ν, cm^{-1}: 3310 (N–H), 3274 (NH_2), 1651 (C=O), 1628, 1595, 1512, 1465, 1441, 1127, 786, 767. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.50 (3H, t, *J* = 7.1, CH_3); 4.52 (2H, q, *J* = 7.1, CH_2); 7.19 (2H, s, exchanged by D_2O addition, NH_2); 7.52–7.71 (3H, m, Ar); 7.77 (1H, t, *J* = 8.4, Ar); 7.86–7.97 (2H, m, Ar); 8.03 (1H, t, *J* = 8.4, Ar); 9.00 (1H, br. s, exchanged by D_2O addition, NH). ^{13}C NMR spectrum, δ, ppm: 14.43, 61.07, 112.98, 119.231, 122.30, 124.42, 127.65, 128.59, 132.29, 169.06 (C=O). MS (EI), *m/z* (I_{rel}, %): 297 $[M]^+$ (3), 269 (7), 199 (56), 185 (100), 158 (27), 114 (19), 79 (13), 40 (18). Found, %: C 64.83; H 5.18; N 14.01. $C_{16}H_{15}N_3O_3$. Calculated, %: C 64.64; H 5.09; N 14.13.

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REFERENCES

1. For a brief Review see: L. Carlsen, D. Dopp, H. Dopp, F. Duus, H. Hartmann, S. Lang-Fugmann, B. Schulze, R. K. Smalley, and B. J. Wakefield, in: E. Schaumann (editor), *Houben-Weyl*, *Methods in Organic Chemistry*; Georg Thieme Verlag, Stuttgart, Germany, 1992, Vol. E 8a, p. 45.
2. M. Rowley, H. B. Broughton, I. Collins, R. Baker, F. Emms, R. Marwood, S. Patel, and C. I. Ragan, *J. Med. Chem.*, **39**, 1943 (1996).
3. B. Frolund, A. T. Jorgensen, L. Tagmose, T. B. Stensbol, H. T. Vestergaard, C. Engblom, U. Kristiansen, C. Sanchez, P. Krogsgaard-Larsen, and T. Liljefors, *J. Med. Chem.*, **45**, 2454 (2002).
4. G. Daidone, D. Raffa, B. Maggio, F. Plescia, V. M. C. Cutuli, N. G. Mangano, and A. Caruso, *Arch. Pharm. Med. Chem.*, **332**, 50 (1999).
5. K. Tomita, Y. Takahi, R. Ishizuka, S. Kamamura, M. Nakagawa, M. Ando, T. Nakanishi, and T. Nakamura, H. Udaira, *Ann. Sankyo Res. Lab.*, **1**, 25 (1973); *Chem. Abstr.*, **80**, 120808 (1974).
6. J. J. Talley, *Prog. Med. Chem.*, **13**, 201 (1999).
7. J. J. Talley, D. L. Brown, J. S. Carter, M. J. Graneto, C. M. Koboldt, J. L. Masferrer, W. E. Perkins, R. S. Rogers, A. F. Shaffer, Y. Y. Zhang, B. S. Zweifel, and K. Seibert, *J. Med. Chem.*, **43**, 775 (2000).
8. M. P. Giovannoni, C. Vergelli, C. Ghelardini, N. Galeotti, A. Bartolini, and V. Kal Piaz, *J. Med. Chem.*, **46**, 1055 (2003).
9. W. T. Li, D. R. Hwang, C. P. Chen, C. W. Shen, C. L. Huang, T. W. Chen, C. H. Lin, Y. L. Chang, Y. Y. Chang, Y. K. Lo, H. Y. Tseng, C. C. Lin, J. S. Song, H. C. Chen, S. J. Chen, S. H. Wu, C. T. Chen, *J. Med. Chem.*, **46**, 1706 (2003).
10. For a recent Review, see: B. J. Wakefield, in: E. Shaumann (editor), *Science of Synthesis*: *Houben-Weyl Methods of Molecular Transformations,* Georg Thieme Verlag, Stuttgart, 2001, vol. 11, p. 229.
11. T. Bandiera, T, P. Grunanger, and F. M. Albini, *J. Heterocycl. Chem.*, **29**, 1423 (1992).
12. P. Cuadrado, A. M. Gonzalez-Nogal, and R. Valero, *Tetrahedron*, **58**, 4975 (2002).
13. C. B. Vicentini, A. C. Verones, T. Poli, M. Guarneri, P. Giori, and V. Ferretti, *J. Heterocycl. Chem.*, **27**, 1481 (1990).
14. Y. He and N. H. Lin, *Synthesis*, **9**, 989 (1994).
15. G. N. Barber and R. A. Olofson, *J. Org. Chem.*, **43**, 3015 (1978).
16. T. J. Nitz, D. L. Volkots, D. J. Aldous, and R. C. Oglesby, *J. Org. Chem.*, **59**, 5828 (1994).
17. S. E. Denmark and J. M. Kallemeyn, *J. Org. Chem.*, **70**, 2839 (2005).

18. V. Jaeger and P. A. Colinas, in: A. Padwa and W. H. Pearson (editors), *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles Natural Products*, Chemistry of Heterocyclic Compounds, Wiley, Hoboken, 2002, vol. 59, p. 361.
19. J. Khalafy, A. R. Molla Ebrahimlo, R. Eisavi, and K. Akbari Dilmaghani, *ARKIVOC*, xiv, 59 (2005).
20. J. Khalafy, A. Poursattar Marjani, and A. R. Molla Ebrahimlo, *J. Braz. Chem. Soc.*, **17**, 570 (2006).
21. M. M. Baradarani, J. Khalafy, S. Khadivi, and A. Poursattar Marjani, *ХГС*, 751 (2008). [*Chem. Heterocycl. Comp.*, **44** (2008)].
22. D. E. Worrall, *J. Am. Chem. Soc*., **45**, 3092 (1923).