Indian Journal of Chemistry
Vol. 36B, December 1997, pp.1175 - 1177

Note

A convenient synthesis of 5-amino-4-(2-benzothiazolyl)pyrazoles

Magda A Abdallah, Mosselhi A N Mosselhi, Sayed M Riyadh & Ahmad S Shawali*

Department of Chemistry, Faculty of Science, University of Cairo, Giza, Egypt

Received 4 November 1996; accepted (revised) 12 June 1997

Reaction of 2-cyanomethylbenzothiazole 1 with hydrazonoyl halides **2A-D** in ethanol in the presence of sodium ethoxide affords 5-amino-4-(2-benzothiazolyl)-pyrazoles 6.

Heterocycles bearing a benzothiazole ring residue are reported to show a broad spectrum of biological activities[1-3]. It is also reported that many pyrazole derivatives have found applications in both pharmaceutical and agrochemical fields[4]. In view of these observations we thought of interest to investigate the synthesis of novel 4-(2-benzothiazolyl)pyrazole derivatives which may be of pharmaceutical interest as the related 1-(2-benzothiazolyl)pyrazoles have significant anti-inflammatory activity[5]. The known method[6] adopted for synthesis of the latter compounds was not useful for the preparation of the title compounds. Therefore we developed a general synthetic route for the preparation of 5-amino-4-(2-benzothiazolyl)pyrazoles with various functionalities (Scheme I).

Results and Discussion

Reaction of 2-cyanomethylbenzothiazole **1** with each of the hydrazonoyl chlorides **2A-D** in ethanol in the presence of sodium ethoxide in a 1:1 molar ratio afforded, in each case, a single product as evidenced by TLC and ^{1}H NMR spectral analyses. The structures of the isolated products were established as **6A-D** by analytical and spectral data (IR, ^{1}H NMR and MS) (see Experimental). The assigned structures were further supported by their chemical reactions. Thus, each of the products **6Ba** and **6Db**, taken as representative examples of the series prepared, yielded the corresponding *N*-acetyl derivatives **7Ba** and **7Db**, respectively upon Treatment with acetic anhydride at reflux (Scheme I). In addition, diazotization of each **6AB** and **6Ba** followed by coupling with 2-naphthol in sodium hydroxide solution afforded the corresponding azo derivatives **9Ab** and **9Ba**, respectively (Scheme I). The structures of the latter products were consistent with their spectral data (IR and ^{1}H NMR) and analytical data (see Experimental).

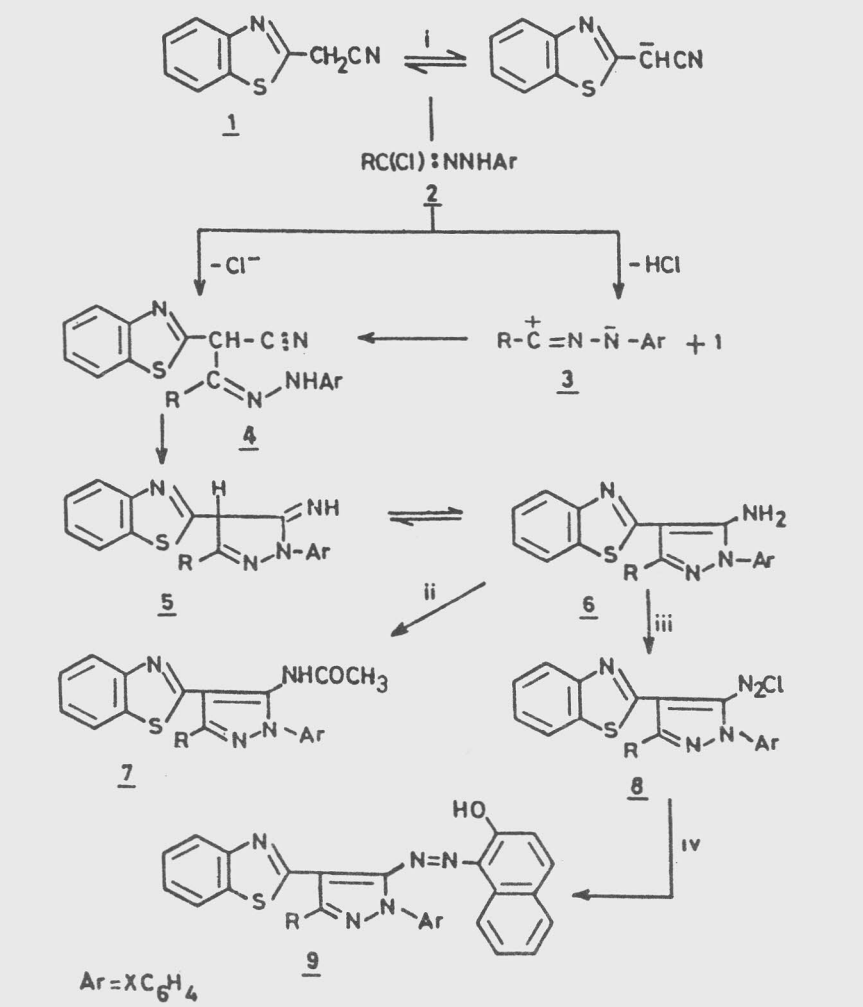
The formation of **6** from the reaction of **1** with **2** seems to follow the sequence outlined in Scheme 1. It is suggested that direct nucleophilic attack of the carbanion of **1** at the hydrazonoyl chloride **2** or 1,3-addition of **1** to the nitrile imide **3**, generated *in situ* from **2**, gives **4**. The latter undergoes intramolecular cyclization as soon as it is formed to give **5**. Aromatization of **5** via imine-enamine tautomerism leads to the end product **6**. The two steps **4⇒5⇒6** are analogous to those involved in the conversion of arylhydrazone derivatives of α-cyanoketones into 5-aminopyrazole derivatives[7].

Experimental Section

Mps. were measured on a Gallenkamp apparatus and are uncorrected. ^{1}H NMR spectra were recorded in [^{2}H]-chloroform on a Varian Gemini 200 spectrometer using TMS as internal reference and mass spectra on a GCMS-QP 100 EX spectrometer. Elemental analyses were carried out at the Microanalytical Laboratory at Cairo University, Giza, Egypt. The starting 2-cyanomethylbenzothiazole **1**[8] and the hydrazonoyl chlorides **2A-D**[9-11] were prepared as previously described.

Reaction of 1 with 2: General procedure. To a stirred ethanolic sodium ethoxide solution, prepared from sodium metal (0.23 g, 10 mg atom) and abs ethanol (20 ml), was added 2-cyanomethylbenzothiazole **1** (1.74 g, 10 mmol). After 10 min, the appropriate hydrazonoyl chloride **2** (10 mmol) was added to the resulting solution and the mixture was stirred at room temperature for 12 h, during which the chloride **2** dissolved and the crude reaction product **6** precipitated. The latter was filtered, washed with water, dried and finally crystallized from the proper solvent. The physical constants of the products **6A-D** are as follows.

6Aa (65%), m.p. 184-86°C (ethanol); IR (KBr):



	X
a	H
b	4-CH_3
c	4-Cl
d	4-Br

	R
A	CH_3CO
B	C_2H_5OCO
C	CH_3OCO
D	C_6H_5NHCO

	Reagent
i	EtONa / EtOH
ii	$(CH_3CO)_2O/CH_3COOH$
iii	$NaNO_2$/ HCl /CH_3COOH
iv	2-Naphthol / NaOH

Scheme I

3410-3240 (NH_2), 1676 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ 2.70 (3H, s), 6.5 (2H, s), 7.0-8.0 (9H, m); MS: m/z 334 (M^+) (Found : C, 64.5; H, 4.1; N, 16.4; S, 9.4. $C_{18}H_{14}N_4OS$ requires C, 64.67; H, 4.19; N, 16.76; S, 9.58%).

6Ab (60%), m.p. 150°C (methanol),IR (KBr): 3430-3244 (NH_2), 1686 cm^{-1} (CO); ^1H NMR ($CDCl_3$) δ2.45 (3H, s), 2.7 (3H, s), 6.5 (2H, s), 7.0-8.1 (8H, m); MS: m/z 348 (M^+) (Found: C, 65.1; H, 4.3; N, 15.8; S, 9.1. $C_{19}H_{16}N_4OS$ requires C, 65.51; H, 4.59; N, 16.09; S, 9.19%).

6Ac (60%), m.p. 190°C (ethanol), IR (KBr): 3423-3239 (NH_2), 1683 cm^{-1} (CO); ^1H NMR ($CDCl_3$) δ 2.6 (3H, s), 6.5 (2H, s), 7.1-8.0 (8H, m); MS: m/z 368 (M^+) (Found : C, 58.2; H, 3.3; N, 14.9; S, 8.4. $C_{18}H_{13}ClN_4OS$ requires C, 58.61; H, 3.52; N, 15.19; S, 8.68%).

6Ba (60%), m.p. 160°C (ethanol); IR (KBr): 3431-3260 (NH_2), 1708 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ 1.47 (3H, t), 4.50 (2H, q), 6.5 (2H, s), 7.0-8.0 (9H, m); m/z 364 (M^+) (Found: C, 62.3; H, 4.4; N, 14.9; S, 8.6. $C_{19}H_{16}N_4O_2S$ requires C, 62.63; H, 4.39; N, 15.38; S, 8.79%).

6Bb (65%), mp. 178°C (ethanol);IR (KBr): 3429-3271 (NH_2), 1729 cm^{-1} (CO); ^1H NMR ($CDCl_3$) δ 1.48 (3H, t), 2.4 (3H,s), 4.5 (2H, q), 6.4

(2H, s), 7.0-8.2 (8H, m); m/z 378 (M^+) (Found: C, 63.3; H, 4.5; N, 14.6; S, 8.5. $C_{20}H_{18}N_4O_2S$ requires C, 63.49; H, 4.76; N, 14.81; S, 8.46%).

6Bd (65%), m.p. 150°C (ethanol), IR (KBr): 3430-3243 (NH_2), 1712 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ 1.48 (3H, t), 4.5 (2H, q), 6.5 (2H, s), 7.0-8.2 (8H, m), m/z 443 (M^+) (Found: C, 51.7; H, 3.4; N, 12.8; S, 7.1. $C_{19}H_{15}BrN_4O_2S$ requires C, 51.46; H, 3.38; N, 12.64; S, 7.22%).

6Ca (65%), m.p.186-87°C (methanol), IR (KBr): 3405-3265 (NH_2), 1728 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ 4.15 (3H, s), 6.47 (2H, s), 7.26-7.95 (9H, m); m/z 350 (M^+) (Found: C, 61.9; H, 3.9; N, 15.8; S, 9.0; $C_{18}H_{14}N_4O_2S$ requires C, 61.71; H, 4.00; N, 16.00; S, 9.14%).

6Da (65%), m.p 186-87°C (methanol); IR (KBr): 3405-3265 (NH_2), 1658 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ 6.5 (2H, s), 7.2-8.1 (9H, m), 8.9 (1H, s); MS: m/z 411 (M^+) (Found : C, 67.0; H, 4.1; N, 16.9; S, 7.9. $C_{23}H_{17}N_5OS$ requires C, 67.15; H, 4.13; N, 17.03;S, 7.78%).

6Db (70%) mp. 186-88°C (dioxane-ethanol), IR (KBr): 3421-3298 (NH_2), 1681 cm^{-1} (CO); 1H NMR ($CDCl_3$): δ 2.4 (3H, s), 6.5 (2H, s), 7.0-8.2 (8H, m), 8.9 (1H, s); MS: m/z 425 (M^+) (Found : C, 67.5; H, 4.3; N, 16.5; S, 7.5. $C_{24}H_{19}N_5OS$ requires C, 67.76; H, 4.47; N, 16.47; S, 7.52%).

6Dc (70%) mp. 244-46°C (dioxane-ethanol); IR (KBr): 3422-3293 (NH_2), 1680 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ 6.6 (2H, s), 7.1-8.2 (8H, m), 8.9 (1H, s); m/z 445 (M^+) (Found: C, 61.8; H, 3.7; N, 15.8; S, 6.9. $C_{23}H_{16}ClN_5OS$ requires C, 61.95; H, 3.59; N, 15.71; S, 7.18%).

Acetylation of 6. To a solution of the appropriate **6** (0.005 mol) in acetic acid (5 mL) was added acetic anhydride (1 mL). The reaction mixture was refluxed for 3 h and then poured into ice-cold water. The crude solid that precipitated was filtered, dried and crystallized from ethanol to give the corresponding acetyl derivative **7**.

7Ba (60%), m.p. 180-81°C(ethanol), IR (KBr): 3260 (NH), 1718, 1704 cm^{-1} (CO); 1H NMR ($CDCl_3$): δ 1.45 (3H, t), 2.09 (3H, s), 4.54 (2H, q), 7.37-8.00 (9H, m), 10.25 (1H, s) (Found :C, 61.9; H, 4.3; N, 13.9; S, 7.7. $C_{21}H_{18}N_4O_3S$ requires C, 62.06; H, 4.43; N, 13.79; S, 7.88%).

7Db (63%), m.p. 244-45°C (acetic acid-ethanol), IR (KBr): 3354-3210 (NH), 1703, 1669 cm^{-1} (CO) (Found: C, 66.6; H, 4.5; N, 15.0; S, 6.8. $C_{26}H_{21}N_5O_2S$ requires C, 66.80; H, 4.49; N, 14.98; S, 6.85%).

Preparation of the azo derivatives 9. To a cold solution of **6Ab** (or **6Ba**) (5 mmol) in glacial acetic acid (3 mL) and conc. (3 mL) was added a solution of sodium nitrite (0.345 g, 5 mmol) in water (3 mL) gradually with stirring and cooling to 0°C. The resulting diazonium salt solution was added portionwise to a cold solution of 2-naphthol (0.72 g, 5 mmol) in NaOH (0.2 g, 5 mmol) in water (10 mL). The reaction mixture was stirred while being cooled for 2 h, during which red solid precipitated. The latter was filtered, washed with water, dried and crystallized from the proper solvent to give the corresponding azo derivative **9**.

9Ab (70%), m.p. 250-52°C (acetic acid-methanol); UV (methanol) (log ε) 490 nm (3.589); IR (KBr): 3350 (OH), 1685 (CO); ^1H NMR ($CDCl_3$): δ 2.5 (3H, s), 2.74 (3H, s), 6.4-8.49 (14H, m), 16.0 (1H, s) (Found : C, 68.9; H, 4.0; N, 13.7; S, 6.5. $C_{29}H_{21}N_5O_2S$ requires C, 69.18; H, 4.17; N, 13.91; S, 6.36%).

9Ba (75%), m.p. 278-80°C (acetic acid-water); UV (methanol) (log ε) 482 nm (3.519); IR (KBr): 3320 (OH), 1718 cm^{-1} (CO); ^1H NMR ($CDCl_3$): 1.4 (3H, t), 4.5 (2H, q), 6.5-8.5 (15H, m), 15.9 (1H, s) (Found : C, 67.0; H, 3.9; N, 13.1; S, 5.9. $C_{29}H_{21}N_5O_3S$ requires C, 67.05; H, 4.04; N, 13.48; S, 6.16%).

References

1 Knierzinger A & Wolfbeis O S, *J Heterocycl Chem*, 17, **1980,** 225.

2 Shigeta S, Hosoya M, Mochizuki S & Chiba T, *Yakugaku Zasshi*, 108, **1988**, 856; *Chem Abstr,* 110, **1989**, 306u.

3 Babichev F S, Patratii V K, Volovenko Yu M, Prodanchuk N G, SinchenkoV G & Nemazanyi A G, *Khim Farm Zh*, 22, **1988**, 1223; *Chem Abstr*, 111, **1989**, 7285r.

4 Elguero J, *Comprehensive heterocyclic Chemistry*, edited by A R Katritzky, (Pergamon Press, New York), , Vol. 5, **1984,** p. 291; Sugiura S, Ohno S, Ohtani O, Izumi K, Kitamikado T, Asai H, Kato K, Hori M & Fujimura H, *J Med Chem,* 20, **1977**, 80.

5 Singh S P & Vaid R K, *Indian J Chem*, 25B, **1986,** 288.

6 Mahesh V K, Chauhan V K, Prakash I & Prakash O, *J Indidn Chem Soc*, 60, **1983**, 269.

7 (a) Shawali A S, Hassaneen H M, Sami M &. Elfahham H M, *Heterocycl Chem* 13, **1976**, 1137; (b) Takamizawa A & Hamashima Y, *Yakugaku Zasshi*, 84, **1964**, 1113; *Chem Abstr*, 62, **1965**, 5276.

8 N. M. Fathy, F. M. Abdelmotti and G. E. H. Elgemeie, Arch. Pharm, 321,1988, 509.

9 A. S. Shawali and A. Osman, Tetrahedron, 27,1971, 2517.

10 A. S. Shawali, N. F. Eweiss, H. M. Hassaneen and M. Sami, Bull. Chem. Soc. Jpn., 48, 1975, 365 and the references there in.

11 A. S. Shawali, S. T. Ezmirly and H. M. Hassaneen, J. Chem. Engng. Data, 34, 1989, 259, and the references cited there in.