Arch. Pharm. Res. 13(3), 261-264

Activated Nitriles in Heterocyclic Synthesis: Syntheses of Thiazole, Pyrazole and 4H-1,4-Benzothiazine Derivatives

Fathy Mohamed Abdel-Aziz El-Taweel[§] **, Mohamed Abdel-Hadi Mashaly and Abdel Ghani Ali Elagamey**

Department of Chemistry, Faculty of Science at Damietta, Mansoura University, Damietta, Egypt

(Received June 26, 1990)

Abstract□4-Arylazo-3-phenyl-5-aminopyrazoles (**5a,b**) and substituted hydroxythiazoles **8a,b** were synthesized from the reaction of **4a,b** with hydrazine hydrate and mercaptoacetic acid respectively. Compounds **5a,b** and **8a,b** were also obtained from coupling of **2a,b** with **6** and **7**, respectively. 4H-1,4-Benzothiazine **11** was prepared from **1** and **10**. The reaction of the diazonium salts **2a-c** with diethyl 3-amino-2-cyanopent-2-en-1,5-dicarboxylate **12** was also reported.

Keywords□Sulfonamides, thiazole, aminopyrazole, thiazine .

The first azo dyes containing the sulphonamide or sulphonamido moieties were synthesized in 1909 and were found to exhibit colour fastness[1]. This class of dyestuffs was subjected to many biomedical studies[2-7] and many compounds showed high antibacterial activities[3-5] and therapeutic significance[6,7].

This work was conducted as a part of our programme directed towards developing simple procedures for the synthesis of azoles[8,9], fused azoles[10] and azines[11] of promising biological activity[12,13].

In the first part of the work new thiazole and pyrazole derivatives containing sulphonamido moiety were prepared. Benzoylacetonitrile **1** was allowed to react with aryl diazonium chlorides containing p-sulphonamido substituent **2a-c** to afford the arylhydrazones **4a-c**. The IR spectra of **4a-c** revealed the presence of conjugated cyano function which was in a good agreement with the hydrazone structure **4** and not the anticipated tautomer **3**. The pyrazoles **5a,b** were obtained by the action of hydrazine hydrate on **4a,b**. The IR spectra of **5a,b** showed the absence of the cyano absorption band and the presence of the amino function. Structure **5a,b** were further established in an independent synthesis via coupling of **2a,b** with 3-phenyl-5-aminopyrazole[14] **6**.

The aryl diazonium salt **2a** was coupled with 3-phenacyl-4-hydroxythiazole[15] **7** to give a product of molecular formula $C_{19}H_{16}N_4O_5S_2$ for which the structure possibilities **8** and **9** had to be investigated. Structure **9** was readily ruled out based on the formation of **8a,b** from **4a,b** and mercaptoacetic acid. The same behaviour was also observed on reacting **2b** with **7**.

In this part of the work we report on the preparation of a new benzothiazine derivative. 4-Methyl-2-mercaptoaniline **10** was allowed to react with **1** to afford 4H-1,4-benzothiazine **11**. Formation of **11** from **1** and **10** is assumed to proceed via elimination of water and H_2. This type of reactions is in parallel to the recently reported reaction of forming benzothiazines from o-mercaptoanilines and 1,3-diketones[16].

We recently reported[17] on the formation of pyrazolo-[1,5-c] [1,2,4] triazine when the diazonium salt of 3-antipyrinyl-5-aminopyrazole was coupled with diethyl 3-amino-2-cyanopent-2-en-1,5-dicarboxylate **12**. However, in the present work, when the diazonium salts **2a-c** were coupled with **12** the open structures **13a-c** were obtained. ^{1}H-NMR spectra revealed the presence of two ester groups which agrees with the hydrazone structures **13a-c**. Trials to cyclize **13**into **14** by the action of acetic anhydride or acetic acid failed.

EXPERIMENTAL METHODS

All melting points are uncorrected. Recorded yields correspond to the pure products. IR (KBr) spectra were carried out using a Pye Unicam SP-1100 Spectrophotometer. ^{1}H-NMR spectra were measured on a Varian EM-360 Spectrometer (60 MHz), using tetramethylsilane as an internal standard and chemical shifts are expressed as δ values. The microanalysis was done at the Microanalytical Units at Cairo and

§To whom all correspondence should be addressed.

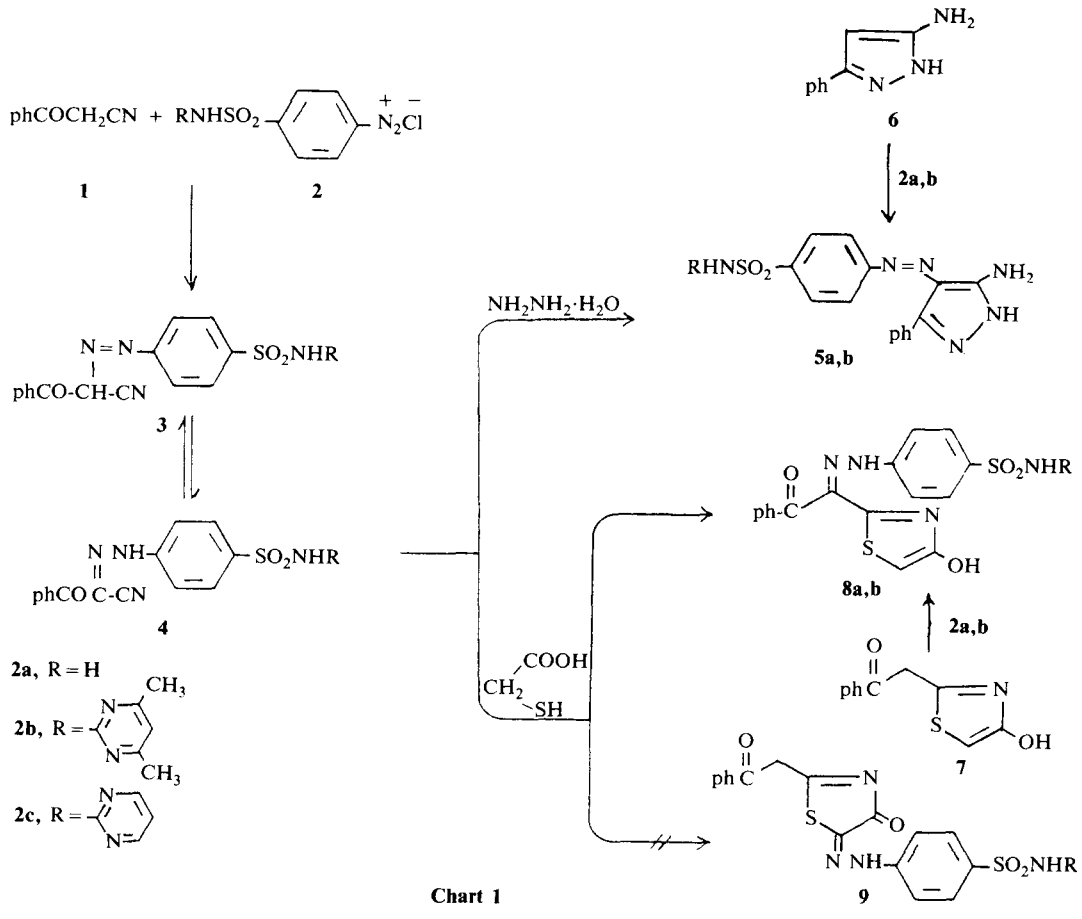

Chart 1

Mansoura Universities.

Coupling of benzoylacetonitrile 1 with the aryl diazonium salts 2a-c

Formation of the arylhydrazones 4a-c: A solution of benzoylacetonitrile (**1**) (0.01 mol) in ethanol: pyridine (1:1, 30 m*l*) was treated with a saturated sodium acetate solution (10 m*l*), then with **2a-c**. The mixture was left in the refrigerator for 24 h and the products so formed were collected by filtration, crystallized and identified as **4a-c**.

4a: mp. 233-235°C; from ethanol-DMF; yield 2.4g (75%); IR (cm^{-1}): 3370, 3280 (NH), 2220 (conjugated C≡N), 1680 (C=O), 1640 (C=N), 1600 (N=N). (Found: C, 54.83; H, 3.63; N, 17.03. $C_{15}H_{12}N_4O_3S$ (328.35) requires C, 54.87; H, 3.69; N, 17.06%).

4b: mp. 228-230; from ethanol-DMF, yield 3.0g (70%); IR (cm^{-1}): 3300-3100 (NH), 2220 (conjugated C≡N), 1685 (C=O), 1640 (C=N), 1605 (N=N). (Found: C, 58.07; H, 4.28; N, 19.36. $C_{21}H_{18}N_6O_3S$ (434.46) requires C, 58.05; H, 4.18; N, 19.35%).

4c: mp. 260-262°C; from ethanol-DMF; yield 3.25g (80%); IR (cm^{-1}): 3240, 3140 (NH); 2220 (conjugated C≡N), 1680 (C=O), 1620 (C=N), 1590 (N=N). (Found: C, 56.19; H, 3.41; N, 20.62. $C_{19}H_{14}N_6O_3S$ (406.42) requires C, 56.15; H, 3.47; N, 20.68%).

Formation of 3-phenyl-4-arylazo-5-aminopyrazole (5a,b)

(a) From 4a,b and hydrazine hydrate: Hydrazine hydrate (0.05 mole) (98%) was added to each of compounds **4a,b** (0.02 mole). The reaction mixture was heated on a water bath for 15 minutes. The product deposited after cooling was triturated with cold ethanol, then crystalized and identified as **5a,b**.

(b) Form 3-phenyl-5-aminopyrazole (6) and 2a,b: A cold solution of 3-phenyl-5-aminopyrazole (**6**) (0.01 mol in ethanol: H_2O (1:1, 50 m*l*) treated with a saturated sodium acetate solution (20 m*l*), then with **2a,b**. The reaction mixture was kept at room temper-

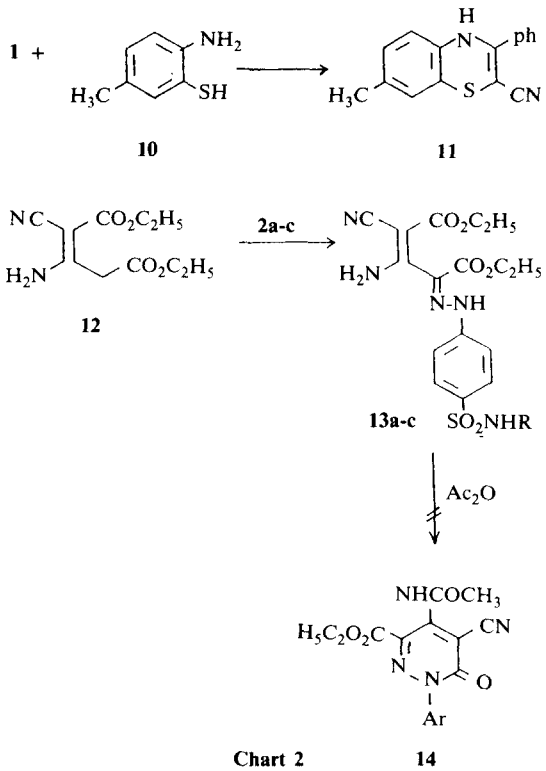

Chart 2

ature overnight. The solid product was collected by filtration, crystallized and identified as **5a,b**. Compounds **5a,b** formed by this method were identical (mp. 's, mixed mp. 's and IR) with those prepared by method (a).

5a: mp. >300°C, from ethanol-DMF, yield 2.0g (60%); IR (cm^{-1}): 3400-3200 (NH, NH_2), 1630 (C=N), 1610 (N=N). (Found: C, 52.59; H, 4.07; N, 24.49. C_{15} $H_{14}N_6O_2S$ (342.38) requires C, 52.62; H, 4.12; N, 24.55%).

5b: mp. 185-187°C; from ethanol-DMF, yield 2.9g (65%); IR (cm^{-1}): 3400-3100 (NH, NH_2), 1630 (C=N), 1600 (N=N). (Found: C, 56.22; H, 4.47; N, 25.01. C_{21} $H_{20}N_8O_2S$ (448.51) requires C, 56.23; H, 4.49; N, 24.98%).

Synthesis of 8a,b

(a) From 3-phenacyl-4-hydroxythiazol (7) and 2a,b: A cold solution of **7** (0.01 mol) in ethanol: H_2O) mixture (1:1, 100 m*l*) was treated with saturated sodium acetate solution (10 m*l*), then with either **2a** or **2b**. The reaction mixture was left overnight in the refrigerator and the solid product was collected by filtration, crystallized from the proper solvent and identified as **8a,b**.

(b) From 4a,b and mercaptoacetic acid: **4a,b** (0.01 mol) and mercaptoacetic acid (0.01 mol) in dry pyridine were refluxed for 6 h. The solvent was removed *i.vac.* and the remaining product was triturated for several times with pet. ether (40-60%). The solid product, so formed, was identified (mp.'s and mixed mp.'s) as **8a,b**.

8a: mp. 205-207°C; from ethanol, yield 2.7g (68%); IR (cm^{-1}): 3400, 3290, 3160 (OH, NH, NH_2), 1685 (exocyclic C=O), 1620 (C=N), 1590 (N=N). (Found: C, 5.68; H, 3.57; N, 13.96. $C_{17}H_{14}N_4O_4S_2$ (402.43) requires C, 50.73; H, 3.51; N, 13.92%).

8b: mp. 145-147°C, from ethanol, yield 3.2g (63%); IR (cm^{-1}): 3300-3200, 3100 (OH, NH), 1690 (C=O, exocyclic), 1620 (C=N), 1600 (N=N). (Found: C, 54.40; H, 4.01; N, 16.50. $C_{23}H_{20}N_6O_4S_2$ (508.58) requires C, 54.31; H, 3.96; N, 16.53%).

Synthesis of 4H-1,4-benzothiazine (11)

Benzoylacetonitrile (**1**) (0.01 mol), 4-methyl-2-mercaptoaniline (**10**) (0.01 mol) and dimethylsulphoxide (8 m*l*) were stirred together and heated at 140-145°C for 40 minutes. The product crystallized on cooling was filtered off and crystalized from ethanol to give **11**, mp. 187-189°C; yield 2.3g (87%); IR (cm^{-1}): 3310, 3080 (NH), 2200 (conjugated C=N); ^{1}H-NMR (ppm): 2.5 (s, 3H, CH_3); 6.6-7.45 (m, 8H, aromatic protons); 9.6 (s, 1H, NH). (Found C, 72.68; H, 4.48; N, 10.56. $C_{16}H_{12}N_2$ S (264.35) requires C, 72.69; H, 4.58; N, 10.60%).

Synthesis of 13a-c

To a stirred, cold solution of the active methylene compound **12** (0.01 mol) in ethanol: pyridine (5:1, 6 m*l*), the aryl diazonium salt **2a-c** (0.01 mol) was added in portionwise over a period of 30 minutes at <5°C. The reaction mixture was left overnight in the refirgerator. The product was filtered, crystallized from the proper solvent and identified as **13a-c**.

13a: mp. 210-212°C; from ethanol; yield 3.5g (85%); IR (cm^{-1}): 3400, 3320, 3100 (NH, NH_2), 2220 (conjugated C≡N); 1730, 1700 (two C=O, ester); 1630 (C=N), 1595 (N=N). (Found: C, 46.90; H, 4.72; N, 17.10. $C_{16}H_{19}N_5O_6S$ (409.41) requires C, 46.94; H, 4.68; N, 17.11%).

13b: mp. 135-137°C; from ethanol; yield 3.9g (76%); IR (cm^{-1}): 3500-3100 (NH, NH_2), 2210 (conjugated C≡N); 1720, 1710 (two C=O, ester), 1630 (C=N); 1600 (N=N). (Found: C, 51.30; H, 4.81; N, 18.97. $C_{22}H_{25}$-N_7O_6S (515.54) requires C, 51.25; H, 4.89; N, 19.02%).

13c: mp. 143-145°C; from ethanol, yield 3.9g (80%); IR (cm^{-1}): 3500-3240 (NH, NH_2), 2220 (conjugated

(C≡N), 1700, 1695 (two C=O, ester); 1630 (C=N), 1590 (N=N). (Found: C, 47.25; H, 4.31; N, 20.13. $C_{20}H_2N_7O_6S$ (487.49) requires C, 47.27; H, 4.34; N, 20.11%). ^{1}H-NMR (ppm): 1.1-1.45 (sixtet, 6H, two CH_3), 4.0-4.4 (octet, 8H, two CH_2), 6.85-8.5 (m, 7H, aromatic protons); 8.65-9.2 (brs, 2H, NH_2); 10.90-12.50 (s, 2H, two NH).

LITERATURE CITED

1. Godman, L.S. and Gilman, A.G.: *The Pharmacological Bases of Therapeutics.* Mcmillan Co., London 1177 (1970).
2. Bayer, A.: *Medicinal Chemistry,* 2nd ed, 1960, Interscience Publishers, Inc., New York.
3. Bentley and Driver's: *Textbook of Pharmaceutical Chemistry,* 8th ed, London Oxford University, Press, New York, Toronto, 688 (1969).
4. Tŕefouël, J., Tŕefouël, Mme. J., Nitti, F. and Bovet.: Action of p-aminophenylsulfamide in experimental streptococcus infections of mice and rabbits. *Compt. Rend. Soc. Biol.* **120,** 756 (1935).
5. Long, H.P. and Bliss, A.E.: p-Aminobenzenesulfonamide and its derivatives. Experimental and clinical observations on their use in the treatment of β-hemolytic streptococci infection. *J. Am. Med. Assoc.* **108,** 32 (1937).
6. Northey, E.H.: *The Sulphonamides and Allied Compounds.* Reinhold, New York (1948).
7. Burger, A.: *Medicinal Chemistry,* 3rd ed, part I, Wiley-Interscience, New York, London, Sydney, Toronto, 255 (1970).
8. Elnagdi, M.H., Hafez, E.A., El-Fahham, H.A. and Kandeel, E.M.: Reactions with heterocyclic amides (VIII): Synthesis of some new imidazo [1,2-b] pyrazole derivatives. *J. Heterocyclic Chem.* **17,** 73 (1980).
9. Elnagdi, M.H., Elmoghayar, M.R.H., Hafez, E.A.A. and Alnima, H.H.: Reaction of 2-arylhydrazono-3-oxonitriles with hydroxylamines: Synthesis of 3-amino-4-arylazoisoxazoles. *J. Org. Chem.* **40**(18), 2604 (1975).
10. Elgemeie, G.E.H., Elfahham, H.A., Hassan, E.S.M. and Elnagdi, M.H.: Activated nitriles in heterocyclic synthesis: The reaction of nitriles with mercapto acids. *Z. Naturforsch* **38b,** 781 (1983).
11. Elnagdi, M.H., Elfahham, H.A., Ghozlan, S.A.S. and Elgemeie, G.E.H.: Activated nitriles in heterocyclic synthesis: A new procedure for the synthesis of pyrimidine derivatives. *J. Chem. Soc. Perkin Trans.I,* 2667 (1982).
12. Shen, T.Y., Clark, R.L., Pessolano, A.A., Witzel, B.E. and Lanza, T.J. (Merck and Co., Inc.) *U.S.* 4,038,396 (Cl. 424-256; A61K31/44), 26 Jul. (1977), *Appl.* 574,173,02 May (1975).
13. Hayakawa, I., Tanaka, Y. and Nagata, Y.: Thiazolopyridine carboxylic acid derivatives (Daiichi Seiyaku Co., Ltd.) *Japan. Kokai* 7783,588 (Cl. C07D513/04), 12 Jul. (1977), *Appl.* 76/199, 01 Jan. (1976).
14. Behr, L.C., Fusco, R. and Jarbe, C.H.: The Chemistry of Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles and Condensed Rings In Chemistry of Heterocyclic Compounds. Weissberger, Ed. A., Interscience Publishers, New York (1967).
15. Elnagdi, M.H., Khalifa, M.A.E., Ibraheim, M.K.A. and Elmoghayar, M.R.H.: The reaction of nitriles with mercaptoacetic acid. A new synthesis of thiazole derivatives. *J. Heterocyclic Chem.,* **18,** 877 (1981).
16. Gupta, R.R. and Gautam, R.K.: Synthesis of 5-substituted 4H-1,4-benzothiazines. *Die Pharmazie,* **3**,40,203 (1985).
17. El-Agamey, A.A., El-Taweel, F.M.A. and Amer, F.A.: Synthesis of some new pyrazolo [1,5-a] pyrimidine and pyrazolo [1,5-c]-as-triazine derivatives. *Collection Czechoslovak Chem. Commun.* **2193,** 51 (1986).