Arch. Pharm. Res. 13(3), 274-277

Reactions with Activated Nitriles : A new route for the synthesis of new pyridine and pyrazolopyridine derivatives

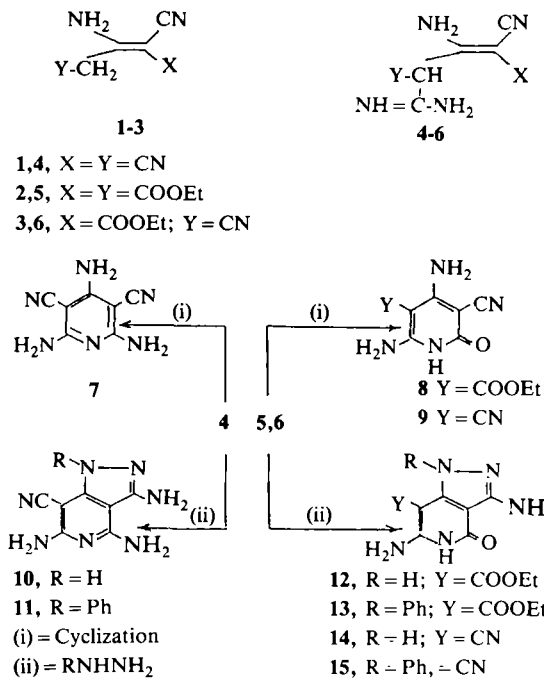
Fawzy A. Attaby and Sanaa M. Eldin
Department of Chemistry, Faculty of Science, Cairo University, Giza, and National Research Center, Dokki, Giza, A.R. Egypt
(Received August 10, 1990)

Abstract□It has been found that α, β -unsaturated nitrile derivatives **1-3** reacted with S-methylisothiourea to give the propene derivatives **4-6** respectively. Cyclisation of **4-6** using ethanolic hydrochloric acid afforded the pyridine derivatives **7-9** in good yields. On the other hand, the reactions of hydrazine hydrate and of phenylhydrazine with each of **7-9** gave the corresponding pyrazolopyridine derivatives **10-15**. The structures of the newly synthesised derivatives were assigned on the basis of elemental analyses, IR and ^{1}H-NMR spectral data studies.

Keywords□ α, β-Unsaturated nitriles, pyridines, pyrazolopyridine, S-methylisothiourea.

Several diverse biological activities have been reported for pyridine and fused pyridine heterocycles. Among these activities may be mentioned their use as herbicides[1-3], antibacterial[4], hypoglycemic agents[5, 6] hyperglycemic agents[6, 7], antihypertensive agenst[9]. In addition several biological activities have also been reported for pyrazole derivatives[10-12]. The above findings prompted our interest for the synthesis of derivatives containing both of the two systems. The reaction of α, β -unsaturated nitriles **1-3** with S-methylisothiourea seemed to be a logic and easy route for the synthesis of these derivatives.

Thus, it has been found that 2-amino-1,1,3-tricyanopropene (**1**) reacted with S-methylisothiourea to give a product which was unexpectedly found to contain no sulphur. This reaction product was found to be corresponding to the addition of one molecule of **1** to one molecule of the thiourea derivative followed by the loss of methylmercaptan. The reaction product could, however, be formulated as the propene derivative **4** based on elemental analysis and spectral data. The IR spectrum of 4 showed bands related to the presence of three CN, NH and NH_2 groups. The ^{1}H-NMR spectrum of **4** revealed a pattern a which is completely intelligibly interpreted in terms of the assigned structure only (cf, Experimental Part). Similar to the behaviour of **1** towards S-methylisothiourea, the propene derivatives **2** and **3** reacted with the same reagent to afford the condensation products **5** and **6** respectively. Again the assigned structures for **5** and **6** were based on both elemental analysis and spectral data studies (cf. Experimental Part).



Structures **4-6** were further confirmed via their cyclisation using ethanolic-hydrochloric acid to afford the fully substituted pyridine derivatives **7-9** respectively. Structures of the cyclisation products 7-9 were assigned on the basis of elemental analyses and spectral data. Thus, the IR spectrum of **7** showed bonds

related to the presence of three amino and two cyano groups in addition to the C=N group. The IR spectra of **8** and **9** revealed bands related to the presence of NH, NH_2, CN and CO groups only. The ^{1}H-NMR spectrum of **7** revealed signals at 5.6 and 9.3 ppm which are attributible to the presence of three NH_2 groups. The ^{1}H-NMR spectra of **8** and **9** were in a good agreement with the assigned structures (cf. Experimental Part). The synthetic potential of **7-9** was demonstrated via their reactions with hydrazine hydrate and with phenylhydrazine. Thus, it has been found that the pyridine derivative **7** reacted with hydrazine hydrate to afford a product corresponding to the addition of one molecule of **7** to one molecule of hydrazine followed by the loss of one molecule of ammonia. The reaction product was assigned to the pyrazolo[4,5-c] pyridine structure **10** on the basis of elemental analysis and spectral data. The IR spectrum of **10** showed bands related to the presence of NH_2, NH and CN groups only. The ^{1}H-NMR spectrum of **10** revealed signals due to the presence of NH_2 and NH groups only (cf. Experimental Part). Compound **7** reacted similarly with phenylhydrazine to give also the pyrazolo pyridine derivative **11** whose structure was based on both elemental analysis and spectral data. The IR spectrum of **11** showed bands related to the presence of NH_2 and CN groups only while its ^{1}H-NMR spectrum revealed signals due to the presence of NH_2 groups and aromatic protons only (cf. Experimental Part). Similar to the behaviour of **7** towards hydrazine hydrate and phenylhydrazine, the pyridinone derivatives **8** and **9** reacted with hydrazine hydrate and with phenylhydrazine to afford the pyrazolo pyridine derivatives **12,14** and **13,15** reactively. The structures assigned for **12-15** were established on the basis of elemental analyses and spectral data (cf. Experimental Part).

Table I. Characterisation data of the newly synthesised derivatives

Comp.	Mp. (°C)	Cryst. Solv.	Yield (%)	Mol. formula	% Analysis C	H	N	Calcd. Found
4	>300	Acetic acid	65	$C_7H_6N_6$	48.27	3.47	48.25	
					48.20	3.45	47.95	
5	200-1	Acetic acid	68	$C_{11}H_{16}N_4O_4$	47.13	6.75	19.98	
					47.18	5.70	19.95	
6	>300	Acetic acid	70	$C_9H_{11}N_5O_2$	48.86	5.00	31.65	
					48.80	5.06	31.60	
7	>300	Acetic acid	72	$C_7H_6N_6$	48.27	3.47	48.25	
					48.30	3.50	48.10	
8	280	Acetic acid	70	$C_9H_{10}N_4O_3$	48.64	4.53	25.21	
					48.70	4.53	25.25	
9	>300	Acetic acid	75	$C_7H_5N_5O$	48.00	2.87	39.98	
					48.06	2.86	39.99	
10	185-6	EtOH	80	$C_7H_7N_7$	44.44	3.72	51.82	
					44.39	3.74	51.80	
11	197	EtOH	75	$C_{13}H_{11}N_7$	58.86	4.17	36.95	
					58.90	4.20	36.80	
12	212-3	EtOH	80	$C_9H_{11}N_5O_3$	45.56	4.67	29.52	
					45.50	4.65	29.50	
13	242-3	EtOH	80	$C_{15}H_{15}N_5O_3$	57.50	4.82	22.35	
					57.48	4.80	22.33	
14	207	EtOH	82	$C_7H_6N_6O$	44.20	3.17	44.19	
					44.22	3.20	44.13	
15	238-9	EtOH	75	$C_{13}H_{10}N_6O$	58.64	3.78	31.56	
					58.66	3.75	31.55	

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded on a Pye-Unicam SP-1100 spectrophotometer using KBr discs. ^{1}H-NMR spectra were recorded on a Varian EM-390 90 MHz spectrometer using DMSO-d_6 as a solvent and TMS as an internal standard. Chemical shifts are expressed as δ (ppm) units. The microanalysis were performed by the microanalytical center at Cairo University.

Reaction of 1-3 wiht S-methylisothiourea

A solution of each of **1-3** (0.01 mol) and S-methylisothiourea sulphate (0.01 mol) in absolute ethanol (50 m*l*) containing triethylamine (2 m*l*) was heated under reflux for 3 hours. The reaction mixture was then allowed to cool and the product so formed was collected by filtration, washed with water, and then crystallised from the proper solvent (cf. Table I and II).

Cyclisation of 4-6 into 7-9

A solution of each of **4-6** (1g) in ethanol (20 m*l*) containing conc. HCl (5 m*l*) was heated under reflux for 2 hours. The reaction mixture was then poured onto ice-cold water and the solid thus formed was filtered off, washed with water then crystallished from the proper solvent to afford the pyridine derivatives **7-9** respectively (cf. Tabels I and II).

Action of hydrazines on 7-9

A solution of each of **7-9** (0.01 mol) and each of

Table II. IR and $_1$H NMR spectral data

Comp.	IR (cm^{-1})	^{1}H-NMR (δ ppm)
4	3450, 3370, 3270, 3180 (NH, NH_2 groups) and 2270, 2220, 2200 (CN groups).	1.5 (s, 1H, CH), 6.5 (s, br., 4H, $2NH_2$) and 8.2 (s, br., 1H, NH).
5	3450, 3370, 3280 (NH, NH_2 groups), 2220 (CN) and 1730 (CO)	1.1 (t, 3H, CH_2CH_3), 1.3 (t, 3H, CH_2CH_3), 2.7 (s, 1H, CH), 4.1 (q, 2H, CH_2CH_3), 4.3 (q, 2H, CH_2CH_3), 5.6 (s, br., 4H, $2NH_2$) and 8.3 (s, br., 1H, NH).
6	3450, 3370, 3280 (NH, NH_2 groups); 2240, 2220 (CN groups) and 1715 (CO).	1.1 (t, 3H, CH_2CH_3); 2.7 (s, 1H, CH), 4.2 (q, 2H, CH_2CH_3); 5.8 (s, br., 1H, NH).
7	3450, 3380, 3290, 3150 (NH_2 groups) and 2240 (CN groups).	6.6 (s, br., NH_2 protons).
8	3420, 3310, 3260 (NH and NH_2 groups), 1730 (CO ester) and 1690 (CO amido)	1.3 (t, CH_2CH_3), 4.2 (q, 2H, CH_2CH_3), 6.6 (s, br., 4H, $2NH_2$) and 8.2 (s, br., 1H, NH).
9	3420, 3350, 3270 (NH and NH_2 groups), 2250, 2220 (CN groups) and 1690 (CO).	6.6 (s, br., 4H, $2NH_2$) and 8.1 (s, br., 1H, NH).
10	3450, 3380, 3290, 3180 (NH and NH_2 groups) and 2220 (CN).	8.1-8.5 (s, br., NH and NH_2 groups).
11	3420, 3370, 3280, (NH_2 groups) and 2220 (CN).	6.4-6.8 (s, br., 6H, $3NH_2$) and 7.1-7.5 (m, 5H, ArH's).
12	3450, 3380, 3270 (NH, NH_2 groups), 1730 (CO ester) and 1680 (CO).	1.3 (t, 3H, CH_2CH_3), 4.2 (q, 2H, CH_2CH_3), 5.6 (s, br., 4H, $2NH_2$) and 8.2 (s, br., 2H, 2NH).
13	3450, 3370, 3280 (NH, NH_2 groups), 1730 (CO ester) and 1680 (CO).	1.1 (t, 3H, CH_2CH_3), 4.2 (q, 2H, CH_2CH_3), 6.2 (s, br., 4H, $2NH_2$), 7.1-7.3 (m, 5H, ArH's) and 8.2 (s, br., 1H, NH).
14	3430, 3380, 3290, 3170 (NH, NH_2 groups), 2220 (CN) and 1680 (CO).	6.4 (s, br, 4H, $2NH_2$); 8.1 (s, br., 1H, NH) and 8.7 (s, br., 1H, NH).
15	3450, 3380, 3290, 3170 (NH, NH_2 groups) 2220 (CN) and 1680 (CO)	6.2-6.4 (s, br., 4H, $2NH_2$); 7.1-7.5 (m, 5H, ArH's) and 8.2 (s, br., 1H, NH).

hydrazine hydrate or phenylhydrazine (0.01 mol) in ethanol (30 m*l*) was heated under reflux for 3 hours. Cooling of the reaction mixture afforded products which could be filtered off and crystallised from the proper solvent to give the pyrazolopyridine derivatives **10, 12, 14** and **11, 13, 15** respectively (cf. Tables I and II).

LITERATURE CITED

1. Ashton, F.M. and Crafts, A.S.: Mode of action of herbicides, Wiley, New York (1973).
2. Corbett, J.R.: The biochemical mode of action of pesticides, Academic Press, London and New York (1974).
3. Pesticide Manual (Eds. Martin, H. and Worthing, C.R.), 4th ed. British Crop Protection Council (1974).
4. Shaw, E., Bernstein, J., Losee, K. and Lott, W.A.: *J. Am. Chem. Soc.* **72,** 4362 (1950).
5. Blank, B., DiTullio, N.W., Owings, F.F., Devineg, L. Miao, C.K. and Saunders, H.L.: *J. Med. Chem.,* **20,** 572 (1977).
6. Blank, B., DiTullio, N.W., M, Miao, C.K., Owings, F.F., Gleason, J.G. Ross, S.T., Berkoff, C.E. Saunders, W.L., Delarge, J. and Lapiere, C.L.: *J. Med. Chem.* **17,** 1065 (1974).
7. Berkoff, C.E., DiTullio, N.W. and Weisbach, J.A.: Smith Kline and French Laboratories, *German Patent,* 2216576; *Chem. Abstr.* **78,** 16044 (1973).
8. Finch, N., Compbell, T.R., Gemenden, C.W., Antonaccio, M.J. and Powlask, H.J.: *J. Med. Chem.* **21,** 1269 (1978).
9. Colbry, N.L., Elslager, E.F. and Werbel, L.M.: *J. Heterocyclic Chem.* **21,** 1521 (1984).
10. Hori, H., Ito, E., Jakta, T., Kayama, G. and Umezawa, H.: *J. Antibit.* **17A,** 96 (1964).
11. Koyama, G. and Umezawa, H.: *J. Antibiot.,* **18A,** 175 (1965).
12. Robins, P.K., Townsend, L.B., Cassidy, F.C., Gerster, J.F. Lewis, A.F. and Miller, R.L.: *J. Heterocyclic Chem.* **3,** 110 (1966).