Cyanoacetic Acid Hydrazide in Heterocyclic Synthesis: A New Route for the Synthesis of Several Annelated Pyran Derivatives

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Cyanoacetic acid hydrazide reacted with some 2-pyrazolin-5-one, isoxazol-5-one and 2-thiazolin-4-one and their ylidene derivatives to yield several new annelated pyran heterocycles. Structures were established on the basis of elementary analyses and spectral data studies in addition to synthesis via other routes.

Key words: 2-Pyrazolin-5-ones, 2-Thiazolin-4-ones, Isoxazolin-5-ones, Pyrano[2,3-c]pyrazoles, Pyrano[2,3-c]isoxazooles, Pyrano[2,3-d]thiazoles

INTRODUCTION

Pyran and its annelated azole and thiazole derivatives were reported to have diverse biological activities (Townsend *et al.*, 1963; Hori *et al.*, 1964; Cremlyn, 1978). They are long known to exhibit bactericidal, bacteriostatic and fungicidal properties (Anrep *et al.*, 1949; Rich, 1960). Thiazoles and thiazolines are of great importance as potent drugs (Makie *et al.*, 1954; Mostafa *et al.*, 1960; Mitzger, 1979). The above findings stimulated our interest for the synthesis of several derivatives of these ring systems.

The readily available cyanoacetic acid hydrazide (**1**) seemed to be a suitable starting material for the synthesis of these heterocycles. Different pyrazolones, isoxazolones and thiazolinones reacted with **1** to give several, otherwise abtainable with difficultyy, annelated pyran heterocycles bearing latent functional substituents which make them highly promising for biological activity studies as well as for further chemical transformations.

MATERIALS AND METHODS

All melting points are uncorrected. IR spectra were recorded on a Pye-Unicam SP-1100 spectrophotometers in KBr discs. ^{1}H-NMR spectra were recorded on Geminai-200 and Varian EM 390 90 MHz spectrometers in DMSO-d_6 using TSM as an internal standard and chemical shifts are expressed as δppm units. Elementary analses were performed at the Microanalytical Center of Cairo University using the Perkin-Elmer 2400 CHN Elemental Analyzet. Compound **17** was prepared following literature procedure (Elnagdi *et al.*, 1989).

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Reactions of 1 with each of 3a-d, 7a, b, 11a, b and 17: Reactions of 2a, b with each of 6a, b 10 and 14a, b: General Procedure:

A solution of equimolecular amounts of each of the reactants (0.01 mole; 0.02 mole in case of their reacion with **14**a, b and 0.02 mole of **1** in case of its reaction with **17**) in absolute ethanol (30 ml) and triethylamine (0.5 ml) was heated under reflux for 4-5 hrs. The solid products thus obtained either on hot or after cooling were filtered off and crystallised from ethanol to give the respective reaction product in each case (cf. Tables I and II).

Cyclisation of 4a-d; 8a, b and 12a, b: General Procedure

A solution of each of **4**a, b; **8**a, b or **12**a, b (0.01 mole) in ethanol (30 ml) was treated with conc. HCl (5 ml) and the reaction mixture was heated under reflux for 3 hrs. The reaction mixture was then poured onto cold water and the product thus obtained was filtered off, washed with water then crystallised from ethanol to give **5**a-d; **9**a, b and **13**a, b respectively (cf. Tables I and II).

RESULTS AND DISCUSSION

It has been found that **1** reacted with 4-benzyylidene-3-methyl-2-pyrazolin-5-one (**3a**) to give a product of molecular formula $C_{14}H_{15}N_5O_2$ corresponding to the

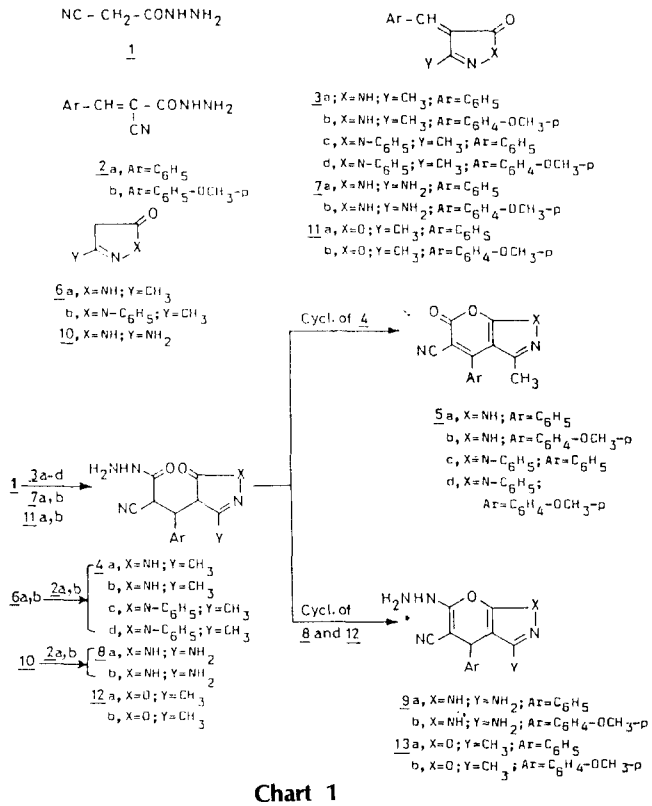

Chart 1

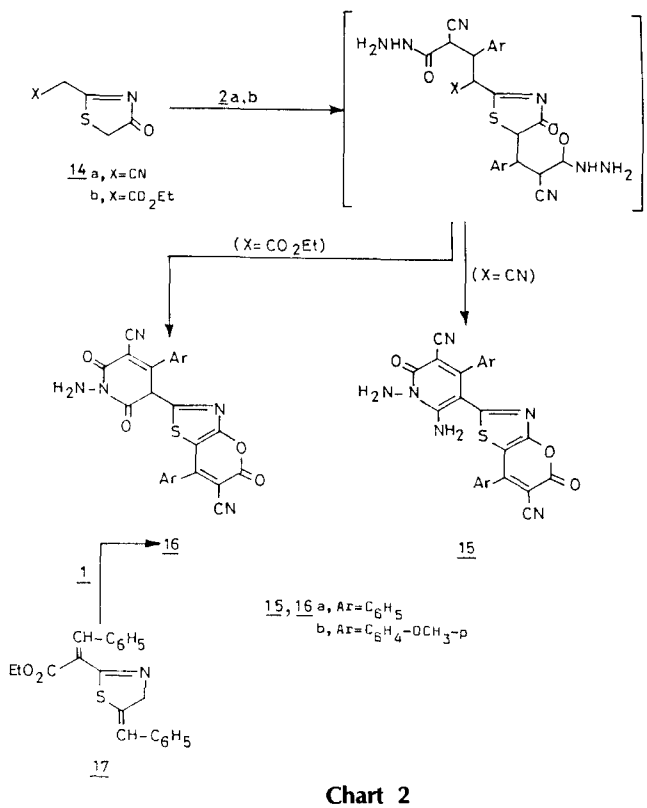

Chart 2

addition of one molecule of **1** to one molecule of **3a**. The reaction product could, however, be formulated as the pyrazole derivative **4a** depending on elemental analysis and spectral data. The IR spectrum of **4a** showed absorption bands (cm $^{-1}$) of NH_2(3400, 3350), NH(3300), CN(2220) and two CO(1700, 1680) in addition to the saturated CH(3000) groups. Moreover, the ^{1}H-NMR spectrum of **4a** revealed signals of two saturated CH, pyrazoline H-4, aromatic protons (5H), two NH and NH_2 groups (cf. Experimental Part). The structure of **4a** was also elucidated via its cyclization into the corresponding pyrano[2,3-c]pyrazole derivative **5a** on boiling its ethanolic solution with conc. HCl. The structure of **5a** was, in turn, established on the basis of elemental analysis and spectral data. The IR spectrum of **5a** was entirely free from the bands of NH_2 and side chain CO groups. On the other hand, its ^{1}H-NMR spectrum revealed signalls of CH_3, aromatic and NH protons only indicating that the reaction product suffered autoxidation under the applied reaction conditions.

An additional and solid evidence for the structure of both **4a** and **5a** was achieved via their synthesis through another route. Thus, the benzylidene derivative of cyanooacetic acid hydrazide **2a** reacted, base catalysed, with 3-methyl-2-pyrazolin-5-one (**6a**) to afford **4a** with the same characterization data as the product of reaction of **1** with **3a**. This could also be cyclised into the corresponding **5a** by boiling its ethanolic solution with conc. HCl.

Similarly, **1** reacted with the ylidene derivatives **3b-d** to yield the Michael adducts **4b-d** respectively which were, in turn, cyclised into the corresponding pyrano[2,3-c]pyrazole derivatives **5b-d** respectively by the action of conc. HCl. Each of **4b-d** and **5b-d** gave correct elemental analysis and the expected IR and ^{1}H-NMR spectral data.

The structure of both **4b-d** and **5b-d** was further elucidated by synthesis through other routes. Thus, the 2-pyrazolin-5-one derivatives **6a**, b reacted with the ylidenes **2a**, b to give the Michael adducts **4b-d** rspectively which could, in turn, be cyclised into **5b-d** respectively by the action of conc. HCl.

Similar to the behaviour of **3a-d**, the ylidene derivatives of 3-amino-2-pyrazolin-5-one **7a**, b reacted with **1** inder the same experimental conditions to afford the Michael adducts **8a**, b respectively whose structure was established by correct elemental analysis and spectral data which gave patterns that can only be intelligibly interpretted in terms of the assigned structure.

In contrast to the behaviour of **4a-d**, compounds **8a**, b could be cyclised via loss of water into the corresponding hydrazinopyrano[2,3-c]pyrazole derivatives **9a**, b respectively whose structure was established via correct elemental analysis and spectral data. The IR spectra of **9a**, b were free from the absorption bands of the CO groups proving that they were involved in the cyclisation step. Moreover, the ^{1}H-NMR spectra

Table I. Characterization data of the newly synthesised heterocyclic derivatives

Comp.	Colour	M.P. (°C)	Yield (%)	Mol. Formula	% Analysis Calcd./Found C	H	N	S
4a	Buff	210-12	80	$C_{14}H_{15}N_5O_2$	58.94	5.6	24.56	–
					58.8	5.4	24.7	–
4b	Yellow	175	76	$C_{15}H_{17}N_5O_3$	57.14	5.39	22.22	–
					57.3	5.6	22.1	–
4c	Buff	160	68	$C_{20}H_{19}N_5O_2$	66.48	5.26	19.39	–
					66.6	5.4	19.5	–
4d	White	205-6	81	$C_{21}H_{21}N_5O_3$	64.45	5.37	17.90	–
					64.7	5.6	17.6	–
5a	Yellow	240-2	78	$C_{14}H_9N_3O_2$	66.93	3.58	16.72	–
					66.6	3.3	16.9	–
5b	Yellow	202	72	$C_{15}H_{11}N_3O_3$	64.05	3.91	14.94	–
					64.2	4.2	15.2	–
5c	Yellow	204-1	81	$C_{20}H_{13}N_3O_2$	73.39	3.97	12.84	–
					73.6	4.1	13.1	–
5d	Yellow	210-11	84	$C_{21}H_{15}N_3O_3$	70.58	4.20	11.76	–
					70.8	4.5	11.5	–
8a	White	165	71	$C_{13}H_{14}N_6O_2$	54.54	4.89	29.37	–
					54.7	4.6	29.6	–
8b	Orange	175	86	$C_{14}H_{16}N_6O_3$	53.16	5.06	26.58	–
					53.4	5.2	26.8	–
9a	Yellow	195-6	84	$C_{13}H_{12}N_6O$	58.20	4.47	31.34	–
					58.4	4.7	31.7	–
9b	White	203-4	81	$C_{14}H_{14}N_6O_2$	56.37	4.69	28.18	–
					56.6	4.9	28.4	–
12a	Buff	146	86	$C_{14}H_{14}N_4O_3$	58.74	4.89	19.58	–
					58.6	5.1	19.8	–
12b	Yellow	152	82	$C_{15}H_{16}N_4O_4$	56.96	5.06	17.72	–
					56.7	5.3	17.9	–
13a	White	189	80	$C_{14}H_{12}N_4O_2$	62.68	4.47	29.89	–
					62.4	4.6	20.6	–
13b	Yellow	206-7	76	$C_{15}H_{14}N_4SO_3$	60.40	4.69	18.79	–
					60.3	4.9	19.0	–
15a	Yellow	176	86	$C_{25}H_{14}N_6SO_3$	62.76	2.92	17.57	6.69
					62.9	3.1	17.8	6.8
15b	Yellow	202-3	91	$C_{27}H_{18}N_6SO_5$	60.22	3.34	15.61	5.94
					60.4	3.1	15.4	6.1
16a	Pink	176	84	$C_{25}H_{13}N_5SO_4$	62.63	2.71	14.61	6.68
					62.5	2.9	14.8	6.9
16b	Buff	151	86	$C_{27}H_{17}N_5SO_6$	60.11	3.15	12.98	5.93
					60.4	3.4	13.2	6.1

of **9**a, b revealed among their signals those of the pyran H-4 at 4.8 δppm. Compounds **8**a, b could also be synthesised via another route by the reaction of 3-amino-2-pyrazolin-5-one (**10**) with **2**a, b. Compounds **8**a, b prepared via this route could also be cyclized into the corresponding **9**a, b respectively.

Similar to its behaviour towards **7**a, b, compound **1** reacted with the 4-arylidene-3-methyl-2-isoxazolin-5-one derivatives **11**a, b to yield the corresponding isolable Michel adducts **12**a, b respectively that could also be converted to the corresponding pyrano[2,3-c] isoxazole derivatives **13**a, b respectively via loss of water by the action of conc. HCl. The IR spectra of **13**a, b were found free from the absorption bands of CO groups indicating that these were involved in the cyclisation step while their ^{1}H-NMR spectra revealed the signals of pyran H-4 at 4.9.

The study was also extended to investigate the behaviour of **2**a, b towards the action of the 2-thiazolin-4-one derivatives **14**a, b. It has been found that **2**a, b racted with 2-cyanomethyl-2-thiazolin-4-one (**14**a) to afford products resulting from the addition of two molecules of **14**a to one molecule of each of **2**a, b and the loss of one molecule of hydrazine and four hydrogen atoms. These products were formulated as the pyrano[2,3-d]isoxazole derivatives **15**a, b respectively. Trials to obtain the mono-adducts were unsccessful under a variety of reaction conditions. Signals of pyran, thiazole or pyridine were not detected in the ^{1}H-NMR spectra of **15**a, b indicating autoxidatio under the app-

Table II. IR and ^{1}H-NMR spectral data

Comp.	IR (cm^{-1})	^{1}H-NMR (δ)
4a	3400, 3350, 3300 (NH_2 and NH); 3000 (sat. CH); 2220 (CN); 1700, 1680 (two CO) and 1640 (C=N)	2.6 (dd, 1H, CH); 2.7 (d, 1H, CH); 2.9 (s, 3H, CH_3); 3.3 (d, 1H, pyrazoline H-4); 7.1-8.4 (m, 5H, Ar); 8.9 (s, br, 2H, two NH) and 10.1 (s, br, 2H, NH_2)
4b	3450, 3400, 3350 (NH_2 and NH); 3000 (sat. CH); 2220 (CN); 1710, 1680 (two CO) and 1630 (C=N)	2.6 (dd, 1H; CH); 2.7 (d, 1H, CH); 2.9 (s, 3H, CH_3); 3.3 (d, 1H, pyrazoline H-4); 3.8 s, 3H, OCH_3); 7.0-8.5 (m, 4H, Ar); 9.1 (s, br, 2H, two NH) and 9.9 (s, br, 2H, NH_2)
4c	3450, 3400, 3380 NH_2 and NH); 2980 (sat. CH); 2220 (CN); 1710, 1670 (two CO) and 1640 (C=N)	2.6 (dd, 1H; CH); 2.8 (d. 1H, CH); 2.9 (s, 3H, CH_3); 3.4 (d, 1H, pyrazoline H-4); 7.0-8.6 (m, 0H, Ar); 8.9 (s, br, 1H, NH) and 9.9 (s, br, 2H, NH_2)
5a	3340 (NH); 2220 (CN); 1670 (ring CO) and 1640 (C=N)	s.8 (s, 3H, CH_3); 6.9-7.9 (m, 5H, Ar) and 9.1 9s, br, 1H, NH)
5b	3400 (NH); 2220 (CN); 1680 (ring CO) and 1640 (C=N)	2.9 (s, 3H, CH_3); 3.8 (s, 3H, OCH_3); 7.1-8.0 (m, 4H, Ar) and 8.9 (s, br, 1h, NH)
5c	2220 (CN); 1670 (ring CO) and 1630 (C=N)	2.8 (s, 3H, CH_3) and 7.1-8.3 (m, 10H, Ar)
5d	2220 (CN); 1670 (ring CO) and 1640 (C=N)	2.9 (s, 3H, CH_3); 3.7 (s, 3H, OCH_3) and 7.2-8.3 (m, 9H, Ar)
8a	3450, 3400, 3380, 3340 (NH and NH_2); 2980 (sat. CH); 2220 (CN); 1700, 1670 (two CO) and 1640 (C=N)	2.6 (dd, 1H, CH); 2.7 (d, 1H, CH); 3.3 (d, 1H, pyrazoline H-4); 7.1-7.9 (m, 5H, Ar) and 8.9 (s, br, 6H, two NH and two NH_2)
8b	3420, 3400, 3370, 3340 (NH and NH_2); 2980 (sat. CH); 2220 (CN); 1700, 1660 (two CO) and 1640 (C=N)	2.7 (dd, 1H; CH); 2.9 (d, 1H, CH); 3.3 (d, 1H, pyrazoline H-4); 3.8 (s, 3H, OCH_3); 7.1-8.4 (m, 4H, Ar); and 9.1 (s, br, 6H, two NH and two NH_2)
9a	3460, 3420, 3380, 3350 (NH and NH_2); 2980 (sat. CH); 2220 (CN) and 1630 (C=N)	4.8 (s, 1H, pyran H-4); 7.3-8.2 (m, 5H, Ar); 9.9 (s, br, 6H, two NH and two NH_2)
9b	3460, 3420, 3380, 3350 (NH and NH_2); 2980 (sat. CH); 2220 (CN) and 1620 (C=N)	3.8 (s, 3H, OCH_3); 4.8 (s, 1H, pyran H-4); 7.3-8.3 (m, 4H, Ar) and 9.8 (s, br, 6H, two NH and two NH_2
12a	3400, 3350, 3300 (NH and NH_2); 2980 (sat. CH); 2220 (CN); 1700, 1680 (two CO) and 1630 (C=N)	2.5 (dd, 1H, CH); 2.7 (d, 1H, pyran H-4); 7.3-8.3 (m, 4H, Ar): 9.5 (s, br, 1H, NH) and 10.1 (s, br, 2H, NH_2)
12b	3400, 3350, 3300 (NH and NH_2); 2990 (sat. CH); 2200 (CN); 1700, 1680 (two CO) and 1640 (C=N)	2.6 (dd, 1H, CH); 2.7 (d, 1H, CH); 2.9 (s, 3H, CH_3); 3.5 (d, 1H, isoxazole H-4); 3.8 (s, 3H, OCH_3); 7.2-8.5 (m, 4H, Ar); 9.4 (s, br, 1HH, NH) and 10.2 (s, br, 2H, NH_2)
13a	3400, 3350, 3320 (NH and NH_2); 3000 (sat. CH); 2220 (CN) and 1640 (C=N)	2.8 (s, 3H, CH_3); 4.9 (s, 1H, pyran H-4); 6.9-7.9 (m, 5H, Ar); 8.8 (s, br, 1H, NH) and 9.6 (s, br, 2H, NH_2)

lied reaction conditions.

Analogously, **14**b reacted with **2**a, b to give the pyrano[2,3-d]-thiazoles **16**a, b respectively. Their ^{1}H-NMR spectra revealed signals of pyridine H-3 indicating partial autoxidation of these products. On the other hand, **16**a could be synthesised also by the reaction of the bis-ylidene derivative **17** (Elnagdi *et al.*, 1988) with two molecules of **1** in absolute ethanol in the presence of triethylamine.

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