Commun. Fac. Sci. Univ. Ank. Series B
V. 41. pp. 87-94 (1995)

4-HYDROXYMETHYL-1-PHENYL-2-PYRAZOLIN -5- ONE IN THE SYNTHESIS OF NEW HETEROCYLES OF PHARMACEUTICAL INTEREST

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(Received Feb. 8, 1995; Revised June 1, 1995; Accepted June 15, 1995)

Condensation of the title compound (1) with malononitrile, ethyl cyanoacetate, ω-cyanoacetophenone, acetophenone, 1,3-diphenylacetone, ethyl acetoacetate and / or diethyl malonate resulted in the formation of derivatives (2a-c), (6a,b) and (8a,b.) The reaction of (2a) with hydrazine hydrate gave the diaminopyrazole (4.) On the other hand condensation of (6a, b) with hydrazine hydrate gave the 1,2-diazepines (7a,b.) Reaction of (1) with o-phenylenediamine afforded the 1,5- benzodiazepine (11). Treatment of (1) with $POCl_3$ afforded the 4-chloromethyl derivative (12) which underwent condensation with o-phenylenediamine to give (11).

Reaction of 12 with aromatic amines and hydrazines gave derivatives 13a,b and 15a,b. The structures of the unknown ring systems have been confirmed by analytical and spectral methods.

INTRODUCTION

In view of the well known importance$^{(1-8)}$ of 2- pyrazolin-5- ones as versatile intermediates for the synthesis of different types of heterocyclic moieties, which may by substituted, condensed or fused to other systems, 4- hydroxymethyl -1- phenyl -3- methyl -2- pyrazolin -5- one (1) represents an adaptable starting material for this work.

DISCUSSION

Malononitrile reacts with (1) in ethanol-piperidine to give the corresponding 4- (2,2- dicyanoethyl) derivative (2a) rather than the pyranopyrazole derivative (3).

Formulation of structure (2a) was based on elemental analysis, IR and^{1}H-NMR spectra. The IR spectrum shows the absorption bands at 2220, 1710 and 1600 cm^{-1} attributable to C≡N group and the pyrazolone moiety. The ^{1}H–NMR spectrum displayed signals at δ ppm 2.2

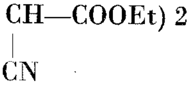
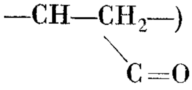
(s, 3H, CH_3), 2.5 (m, 1H, -CO-CH-CH_2-), 3.1 (m, 2H, -CH_2-) and 6.9-7.8 (m, 5H, ArH).

A search of the literature showed that phenylmalononitrile reacted with hydrazine hydrate to give the diaminopyrazole[9]. An attempt to obtain the corresponding diaminopyrazole (4) from (2) and hydrazine hydrate as inferred from the absorption due to CO pyrazolone and lacked the absorption due to C ≡ N. The mass spectrum of (4) gave a M^+ at 284 fitted exactly with the obtained molecular weight.

As a further extension for the reaction of (1) with active nitriles, it seemed of interest to react the 4- hydroxymethyl derivative (1) with ethyl cyanoacetate and / or ω -cyanoacetophenone.

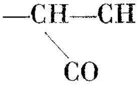
Thus, compound (1) was treated with ethyl cyanoacetate and / or ω-cyanoacetophenone to give derivatives (2b, c) rather than the pyranopyrazole derivative (3).

Structures (2b, c) were confirmed by their correct elemental analysis, IR and ^1H-NMR spectra, The IR spectrum of 2b showed absorption bands at 1600 (C=N), 1700 (CO pyrazolone), 1740 (CO ester) and 2225 (C=N), cm^{-1}.

The ^1H—NMR spectrum of (2b) displayed signals at δ ppm 1.3 (t, 3H, CH_3 ester), 1.6 (s, 1H,  $\underset{\mathrm{CN}}{\mathrm{CH}}\text{—COOEt}$) 2.1 (s, 3H, CH_3 pyrazolone). 2.8 (m, 1H,  $\text{—}\underset{\searrow \mathrm{C=O}}{\mathrm{CH}\text{—}\mathrm{CH_2}}\text{—}$) 3.2 (m, 2H, —CH—$CH_2$), 4.1 (q, 2H, CH_2 ester) and 7—7.8 (m, 5H, ArH). The IR and ^1H—NMR spectra of (2c) were in agreement with the proposed structure (cf experimental).

In connection with the above successful reactions, it was intended to examine the reactions of (1) with other active methylene components.

Thus, compound (1) was reacted with acetophenone, 1, 3- diphenylacetone, ethyl acetoacetate, and / or diethyl malonate to give derivatives (6a), (6b), (8a) and (8b) rather than (5), (10), (9a) and (9b) on the basis of their correct analytical and spectral data.

The IR spectrum of compound (6a) shows two absorption bands at 1690 and 1710 cm^{-1} characteristic for the two carbonyl groups, while the ^1H—NMR spectrum displayed signals at δ ppm 1.6 (S, 3H, CH_3), 2.15 (m, 2H, CH_2CO), 2.9 (m, 1H,  $—\underset{\diagdown CO}{CH}—CH_2$), 3.3 (m, 2H, $CH_2—CH_2—CO$) and 7—8.1 (m, 10 H, ArH) (see experimental).

The mass spectrum gave a $M^+ + 1$ at 307.

In the IR spectrum of compound (6b) a broad band extended from 1680 to 1720 cm^{-1} has been noticed (see experimental).

Futher confirmation for the structures (6a) and (6b) was gained upon treatment with hydrazine hydrate in ethanol to give the corresponding diazepines (7a) and (7b). Their structures were in accordance with the analytical and spectral data (see experimental).

Similar behaviour has been reported(10) by Yousif et al.

Structures (8a) and (8b) find support from their correct analytical and spectral data (cf. experimental).

As a further extension to the preparation of the diazepines (7a) and (7b) it was the intention to react (1) with o-phenylenediamine to obtain the benzodiazepine (11) as inferred from the absence of the absorption due to CO and the presence of one NH group in its IR spectrum.

The presence of absorption due to one NH group in its IR spectrum is in support of structure (11).

In the mass spectrum of (11) no molecular ion was observed, but the fragment m / z 273 corresponding to $C_{17}H_{13}N_4$ was obviously formed by loss of a proton from the parent ion.

In connection with the above successful reactions, it was intended to examine the reaction of 4-(hydroxymethyl)—2—pyrazolin—5—one (1) as a primary alcohol with phosphorous oxychloride. Treatment of (1) with phosphorous oxychlorid in equimolar amounts afforded the 4—chloromethyl —2— pyrazolin —5— one (12).

The IR spectrum lacked the band of the OH group and showed the absorption due to the (C=O, pyrazolone) at 1700 cm^{-1} confirming structure (12).

For more concerted evidence the mass spectrum of compound (12) was measured and the structure of the common ion produced under electron impact was assigned. Compound (12) gave a peak at m / z 174 (base peak) corresponding to $C_{10}H_{10}N_2O$, which was obviously formed due to a loss of CHCI from the parent ion.

This reaction is a further support for the importance of compound (12) as an intermediate, for the preparation of different 4— substituted 1— phenyl —3— methyl 2— pyrazolin —5— one.

Thus, when compound (12) was treated with hydrazine hydrate or phenylhydrazine we obtained only derivatives (13a, b) rather than (14). The structure of these compounds is based on the correct elemental analysis and the IR spectra which showed absorption bands at 1750—1710 (CO—pyrazolone) and 1595—1600 cm^{-1} due to (C=N).

Our interest, in the reactivity of compound (12), was focussed on the reaction with primary amines. Thus equimolar amounts of (12) and primary aromatic amines. namely p-toluidine and p-anisidine were fused to give the arylaminomethyl derivatives (15a, b). The structure (15) was established for the reaction products on the basis of their IR spectra which showed absorption nands at 1650—1670 and 1595—1600 cm^{-1}.

As a further extension on the reaction with amines, it was the intention to react (12) with o-phenylenediamine in dry acetone and anhydrous potassium carbonate to obtain the benzodiazepine derivative (11) in a good yield. The structure of compound (11) was based on the IR spectrum which lacked the absorption due to C=O and the identity of the product with that obtained from (1) and o-phenylenediamine (m.p. and mixed m.p.).

EXPERIMENTAL

Melting points (uncorrected) were determined on Fisher-Jones electric melting point apparatus. Microanalysis of C and H were determined at the Microanalytical lab., Faculty of Science (Mansoura and Cairo Universities). IR spectra in KBr or nujol were recorded on a Pye Unicam SP 1000 and 2000 and Beckman IR spectronphotometers.^{1} H—NMR spectra were determined on Varian XL 100 and Brucker 400 MHz in $CDCI_3$ or DMSO solvents. Mass spectra were measured using AET MS—9 mass spectrophotometer at 70 ev.

Condensation of 1 with active nitriles and active methylene components: Formation of (2a-c) and (6a,b): General Procedure:

To a solution of (1) (0.001 mol) and malononitrile, ethyl cyanoacetate, ω— cyanoacetophenone, acetophenone and 1,3—diphenylacetone (0.002 mol) in (100 ml) EtOH, few drops of piperidine was added. The reaction mixture was refluxed for 6 h. The solid product that separated was filtered off and crystallized from EtOH to give compounds (2a—c) and (6, a, b) (Table 1).

Table 1. Characterization data for Compounds 2a-c, 6a,b, 8a,b, 11, 12, 13a,b and 15a,b

Compound	Yield (%)	M.P. [°C]	Colour	Mol. Formula (Mol. Wt.)	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
2a	92	>290	deep-brown	$C_{14}H_{12}N_4O$ (252.27)	66.65	4.79	22.21	66.4	4.9	22.3
2b	77	127	” ”	$C_{16}H_{17}N_3O_3$ (299.32)	64.19	5.73	14.03	63.9	5.8	14.3
2c	63	144	red	$C_{20}H_{17}N_3O_2$ (331.36)	72.48	5.17	12.68	72.6	5.4	12.4
4	97	188	brown	$C_{14}H_{16}N_6O$ (284.32)	59.13	5.67	29.56	59.5	5.4	29.7
6a	90	133	deep-red	$C_{19}H_{19}N_2O_2$ (306.35)	74.48	5.92	9.14	74.6	5.8	9.3
6b	76	100	brown	$C_{26}H_{24}N_2O_2$ (396.47)	78.76	6.10	7.07	78.9	6.3	6.9
7a	83	96	red	$C_{19}H_{18}N_4$ (302.36)	75.47	6.00	18.53	75.6	5.9	18.4
7b	82	138	brown	$C_{26}H_{24}N_4$ (392.48)	79.56	6.16	14.27	79.7	4.2	14.1
8a	89	219	white	$C_{15}H_{14}N_2O_3$ (270.28)	66.65	5.22	10.36	66.7	5.2	10.4
8b	87	230	yellow	$C_{16}H_{16}N_2O_4$ (300.31)	63.98	5.37	9. 33	63.8	5.2	9.1
11	69	230	red	$C_{17}H_{14}N_4$ (274.31)	74.43	5.14	20.42	74.7	5.3	20.6
12	90	195–7	white	$C_{11}H_{11}N_2OCI$ (222.67)	59.32	4.98	12.58	59.4	4.8	12.7
13a	69	160	orange	$C_{11}H_{14}N_4O$ (218.25)	60.53	4.46	25.67	60.7	4.6	25.4
13b	71	240	red	$C_{17}H_{18}N_4O$ (294.34)	69.36	6.16	19.03	69.6	6.2	19.1
15a	95	188	pale-yellow	$C_{18}H_{19}N_3O$ (293.35)	73.69	6.52	14.32	73.8	6.6	14.4
15b	94	215	grey	$C_{18}H_{19}N_3O_2$ (309.35)	69.88	6.19	13.58	70.1	6.2	13.3

Condensation of (2a) with hydrazine hydrate: Formation of 4:

To a mixture of (2a) (2.52 g., 0.01 mol.) and hydrazine hydrate (1 ml., 0.02 mol) in (30 ml.) EtOH few drops of conc. HCL was added and the reaction mixture was refluxed for 5h. The solid product that separated was filtered off, dried and crystallized from ethanol to give compound 4 (Table 1).

Table. 1. Characterization data for Compounds 2a-c, 4, 6a, b, 8a, b, 11, 12, 13a,b and 15a,b contd.

Compound	IR (cm_{-1})	^{1}H NMR δ(ppm)	Mass spectra
2a	1600, 1700, 2220	s(DMSO), 2.2, 2.5, 3.1, 6.9–7.8	
2b	1600, 1700, 1740, 2225	s($CDCl_3$), 1.3, 1.6, 2.1, 2.8, 3.2,4.1. 7-7.8 J = 7Hz, 7, 14 Hz.	
2c	1600, 1690, 1705 2220.	—	
4	1600, 1705, 3100, 3160, 3220.	—	M / z M^+284.
6a	1690, 1710	s($CDCl_3$), 1.6, 2.15, 2.9, 3.3, 7–8.1	M / z, (M^++1) 307, 273, 223 (100), 205, 162, 102.
6b	1600, 1680, 1720	—	
7a	1595, 1610	—	
7b	1595, 1600, 1605	s(DMSO) 2.3, 2.5, 3.1, 6.7-7.7.	
8a	1600, 1680, 1720	—	
8b	1595, 1705-1735	—	
11	1595, 3350	s(DMSO), 2.3, 5.6, 7–7.9, 10.2.	m / z, (M^+–1) 273, 186, 174 132, 91, 77 (100)
12	1600, 1700	—	m / z, (M^+-CHCl), 174 (100), 145, 132, 119, 91.77
13a	1600, 1705, 3150, 3250 ;	—	
13b	1600, 1705, 3150, 3250 ;	—	
15a	1595, 1670, 3350	—	
15b	1600, 1650, 3350	—	

Condensation of (6a, b) with hydrazine hydrate: Formation of (7a, b):

A mixture of (6a, b) (0.01 mol) and hydrazine hydrate (0.02 mol) in EtOH (50 ml) was refluxed for 6 h. The solid product that separated was filtered off, dried and crystalized from pet. ether 60—80° (7a), EtOH (7b), (Table 1).

Condensation of (1) with ethyl acetoacetate and / or diethyl malonate: Formation of (8a, b):

To a mixture of (1) (0.02 mol), ethyl acetoacetate and / or diethyl malonate (0.02 mol), conc. H_2SO_4 (20 ml) was added. The temperature was kept between 0—5 °C. for 3 h. and left for two days at room temperature. The reaction mixture was poured onto ice-bath. The solid product that separated was filtered and washed with water and sodium bicarbonate solution, dried and crystallized from ethanol to give compjounds (8a, b) (Table 1).

Condensation of (1) with o-phenylenediamine: Formation of (11):

An equimolar ratio of (1) (0.01 mol) and o-phenylenediamine in EtOH (50 ml) and piperidine (4 drops) were refluxed for 6 h. The separated product was filtered and crystallized from EtOH to give compound (11) (Table 1).

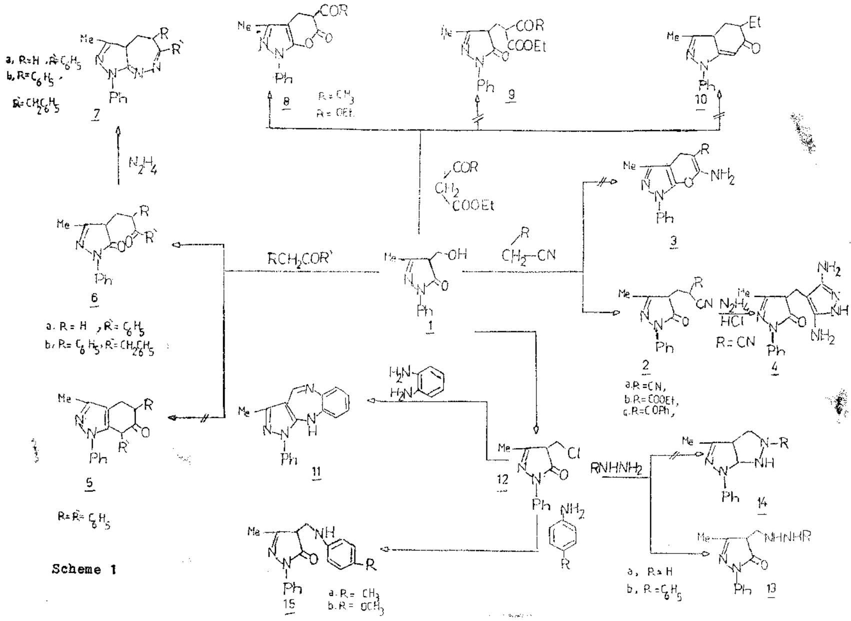
Reaction of (1) with phosphorous oxychloride: Formation of (12):

A mixture of 1 (0.05 mole) and $POCI_3$ (0.05 mole) was heated on a water-bath for 8—10 h. The reaction mixture was poured onto ice-water dropwise with stirring. The solid product that separated was filtered off, washed with water till the filtrate became neutral, crystallized from dil. EtOH to give white crystals of (12) (Table 1).

Condensation of (12) with hydrazine hydrate and / or phenylhydrazine: Formation of (13a, b).

To a well stirred solution of (12) (0.01 mole) and hydrazine hydrate or phenylhydrazine (0.02 mole) in EtOH (50 ml), $CHCI_3$ (3—4 drops) was added. After stirring for 3—4 h, the solution left to stand at room temperature for 72 h diluted with water. The solid product that separated was filtered off and crystallized from EtOH and / or pet. ether 60—80° to give compounds (1 a, b) (Table 1)

Reaction of (12) with p-toluidine and / or p-anisidine: Formation of (15a, b):



Scheme 1

A mixture of compound (12) (0.01 mole) and p-toluidine or p-anisidine was fused at 120—140° for 3—4 h The solid mass obtained was crystallized from EtOH to give compounds (15 a, b) (Table 1).

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