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CONDENSATION OF 4-ACETYL-1-ARYL-3-METHYL-2-PYRAZOLIN-5-ONES WITH AMINO AZOLES*

Mamdouh A. Sofan, Hassan A. Etman and M.A. Metwally

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

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Condensation of the 4-acetyl-2-pyrazolin-5-ones (1) with 2-amino-5-ethyl-1, 1, 3, 4-thiadiazole, 3-amino-1, 2, 4-triazole, 5-aminotetrazole, 2-aminobenzimidazole and/or 3-amino-1-phenyl-2-pyrazolin-5 one was investigated. The structures of the products were confirmed by IR, ^{1}H-NMR and mass spectral data.

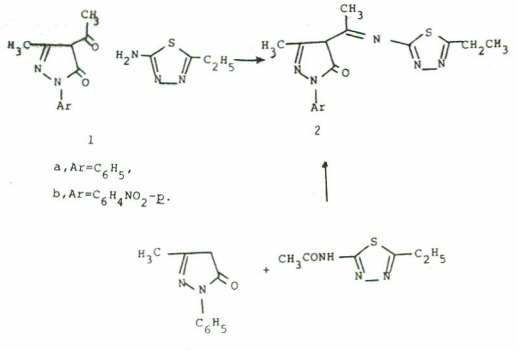
Key words: Condensation, Amino azoles, Heterocyclic synthesis.

INTRODUCTION

Derivatives of a pyrazole ring linked to an aromatic ring or a heteroaromatic ring have been found to contain antirheumatic and antipyretic properties. The compounds such as antipyrine [1], dipyron [2], phenylbutazone [3], and mepyrazole [4] are well known drugs.

In continuation of our previous studies in the pyrazolone series [5-19], this work describes the reactions of 4-acetyl-1-aryl-3-methyl-2-pyrazolin-5-ones (1) with aminoazoles.

4-Acetyl-1-aryl-3-methyl-2-pyrazolin-5-ones (la-b), have now been found to condense with 2-amino-5-ethyl-1, 3, 4-thiadiazole to give (2). The IR and ^{1}H-NMR spectra favours structure (2) rather than its enol or the NH structure. The IR spectrum of (e.g. 2a, showed the carbonyl of pyrazolone at 1665 and the C = N at 1595 cm^{-1}). The ^{1}H-NMR spectrum (400 MHz in $CDCl_3$) displayed the signal of the methine proton of the pyrazolone at σ 3.4 (s) (Table 2).



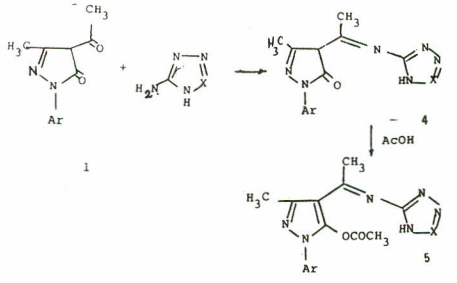
Scheme 1

Further evidence for the formation of 2a was gained from (a) its mass spectrum gave an M$^+$ at 327 (100) and (b) independent synthesis through the reaction of 2-acetamido-5-ethyl-1, 3, 4-thiadiazole with 1-phenyl-3-methyl-2-pyrazolin-5-one (3).

*Part XV in the series of "Pyrazolone Derivativ es", for Part XIV, see Ref. 19.

It seemed of interest to us to react (la) with 3-amino-1, 2, 4-triazole to obtain compound (4a). The IR spectrum of this product shows a carbonyl and NH absorptions. The formation of (4a) finds support from the ^{1}H-NMR spectrum (400 MHz) which displayed NH signal at 8.1, methine triazole at 3.7 and the methine pyrazolone at 3.2 as singlets (Table 1). Attempts to cyclise (4a) to the possible pyrazolopyrimidino-triazole by heating with acetic acid, effected acetylation to give the O-acetyl compound (5a) as inferred from the analytical data (Table 1). Similar treatment of (lb) with 3-amino-1, 2, 4-triazole gave (4b).

Following the above condensations, when (la-b) were treated with 5-aminotetrazole compounds (4c-d) were obtained. Compound (4c) underwent acetylation with glacial acetic acid to give (5c) (Table 2).



a, Ar = C_6H_5, X = CH; b, Ar = $C_6H_4NO_2$-*p* X = CH, X = N; d Ar = $C_6H_4NO_2$-*p*.

Scheme 2.

The usual procedure for the condensation of 2-aminobenzimidazole with the β-diketones gave the pyrazolopyrimidinobenzimidazolo derivatives [21]. 4-Acetylpyrazolinone (la) was reacted with 2-aminobenzimidazole in dry xylene to give two products, which were separated by virtue of their different solubility in ethanol. The soluble product was identified as 3-methyl-1-phenyl-2-pyrazolin-5-one (3) (m.p. and mixed m.p.) and IR and mass spectral data for the less soluble product were in agreement with the structure 2-acetylaminobenzimidazole (8). Compounds (6a) and

(7a) could not be detected in the reaction mixture. The mass spectrum of compound (8) gave an m/z at 175 (100) (see experimental) (Scheme 3).

The formation of 2-acetylaminobenzimidazole may be explained as transacetylation (Scheme 4).

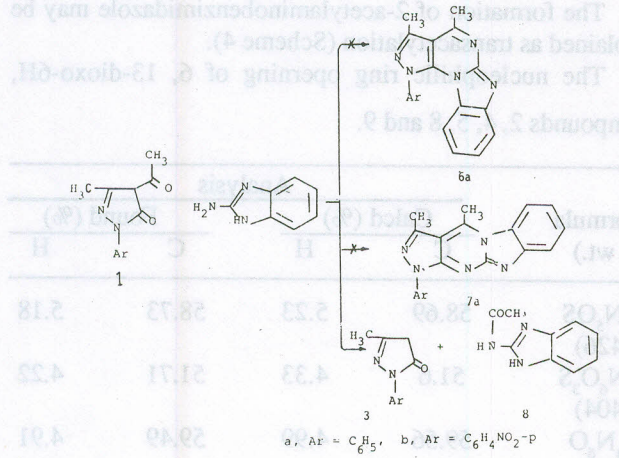
The nucleophilic ring operning of 6, 13-dioxo-6H,

Table 1. Characterization data of compounds 2, 4, 5, 8 and 9.

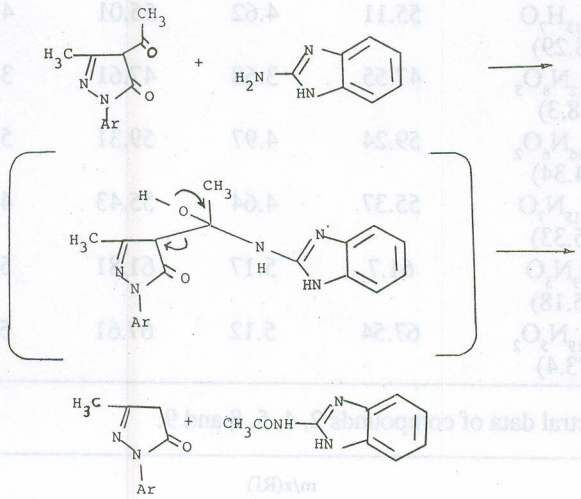
Compound No.	Colour	M.P. °C	Yield (%)	Mol. Formula (Mol. wt.)	Analysis Calcd (%) C	Calcd (%) H	Found (%) C	Found (%) H
2a	Yellow	217	75	$C_{16}H_{17}N_5OS$ (372.426)	58.69	5.23	58.73	5.18
b	Brown	>300	81	$C_{16}H_{16}N_6O_3S$ (372.404)	51.6	4.33	51.71	4.22
4a	Colourless	266	70	$C_{14}H_{14}N_6O$ (282.30)	59.56	4.99	59.49	4.91
b	Yellow	>300	65	$C_{14}H_{13}N_7O_3$ (327.297)	51.37	4.00	51.29	4.10
c	Colourless	265	70	$C_{13}H_{13}H_7O$ (283.29)	55.11	4.62	55.01	4.59
d	Brown	>300	68	$C_{13}H_{12}N_8O_3$ (328.3)	47.55	3.68	47.61	3.71
5a	Colourless	285	85	$C_{16}H_{16}N_6O_2$ (324.34)	59.24	4.97	59.31	5.02
c	Colourless	>300	90	$C_{15}H_{15}N_7O$ (325.33)	55.37	4.64	55.43	4.55
8.	Pale-yellow	>300	50	$C_9H_9N_3O$ (175.18)	61.7	5.17	61.81	5.11
9.	Golden-yellow	227	65	$C_{21}H_{19}N_5O_2$ (373.4)	67.54	5.12	67.61	5.19

Table 2. 1R, ^{1}H-NMR (400 MHz) and mass spectral data of compounds 2, 4, 5, 8 and 9.

Comp No.	1R (cm^{-1})	^{1}H-NMR in $CDCl_3$ (400 MHz) δ-ppm	m/z(RI)
2a	1665, (C = O), 1595 (C = N)	2.48 and 2.89 (s, $2CH_3$), 3.09 (q, 4H, CH_2, J=7Hz), 1.45 (t, 3H, CH_3, J = 7 Hz), 7.19 (dd) 7.41 (dd) and 7.95 (dd) (ArH) and 3.4(s, 1H, methine of pyrazolone).	M^+ 327 (100), 312 (M^+-CH_3) (32) 272 (M^+-C_2H_3CN) (24), 113 (312-$C_{11}H_9N_3O$) (45), 154 (312-$C_9H_6N_2O$)(6), 214 (M^+-$C_4H_5N_2S$ (11), 77 (26), 57 (12).
2b	1670 (C = O), 1600 (C = N)		
4a	3220 (NH), 1665 (C = O), 1995 (C = N).	2.28 and 2.47 (s, $2CH_3$), 3.7 (s, 1H, olefinic triazole, 3.2 (s, 1H, methine pyrazolone), 7.1 (dd), 7.32 dd, J = 8Hz) and 7.79 dd, J = 8 Hz) (ArH) and 8.1 (s, 1H, NH).	M^+ (28.2) (100), 267 (M^+-CH_3) (18) 68 (267-$C_{11}H_9N_3O$) (48), 109 (32), 77 (2) 57 (82).
4b	3225 (NH), 1670 (C = O) 1600 (C = N)		
4c	3250 (NH), 1675 (C = O) 1620 (C = N)	2.26 and 2.32 (5,$2CH_3$), 3.3 (s, 1H, methine pyrazole), 7.11, 7.21 and 7.62 (dd), J = 8Hz (ArH), 8.21 (s, 1H, NH).	M^+ 283(1), 268 (M^+-CH_3) (2), 207 (2), 97 (4), 85 (M^+-$C_{12}H_{10}N_2O$) (100), 57 (26).
4d	3230 (NH), 1670 (C = O), 1610 (C = N)		
5a	3280 (NH), 1695 (CO), 1620 (C = N)		
5c	3220 (NH), 1700 (CO), 1615 (C = N)		
8	3120 and 3300 (NH), 1660 (CO-)	2.18 (s, 3H, $NHCOCH_3$), 7.09-7.14 and 7.33-7.39 (m, 4H, (ArH), 8.1 (s, 1H, NHCO) and 12.3 (s, 1H, NH, imidazole).	M^+ 175 (26), 133 (M $COCH_2$) (100), 76 (133-CH_3N_3 (6), 57(6).
9	3440 (OH), 3340 and 3220 NH_2), 1690 (C-O) and 1630 and 1600 (C = N).	2.28 and 2.39 (s, $2CH_3$), 3.4 (s, 2H, NH_2), 7.26 dd and 7.67(m) (ArH) and 10.2 (s, 1H, OH).	m/z 175 (373-$C_{12}H_{10}N_2O$) (25), 158 (175-NH_3) (7), 81 (41), 77(34)



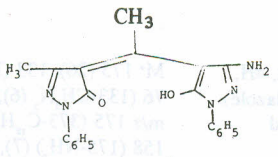
Scheme 3.



Scheme 4.

13H-pyrazino [1, 2-a: 4, 5-a] bisbenzimidazoles with 2-aminobenzimidazole has been reported [22]. The formation of 2-acetylaminobenzimidazole was also reported as a secondary product during the reaction of 2-aminobenzimidazole with benzoyl isothiocyanate [23].

Condensation of (la) with 3-amino-1-phenyl-2-pyrazolin-5-one gave a product m.p. 227°. The IR spectrum of this product shows the following absorption bands: 3440 (OH), 3340 and 3220 (NH_2), 1690 (C = O) and 1600 and 1630 (C = N). The ^{1}H-NMR spectrum does not show any absorption due to (-CH_2-cyclic or olefinic protons). It thus appears that the condensation product has the structure (9) (Table 2).



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EXPERIMENTAL

Melting points (uncorrected) were determined on Fisher-Johns electric melting point apparatus. IR spectra were recorded using KBr disc technique on a Pye SP 1000 Unicam spectrophotometer, ^{1}H-NMR spectra in $CDCl_3$ on a Bruker 400 MHz and mass spectra on a Varian Mat 711 instrument using direct inlet system at 70 eV.

Procedure

Condensation of 4-acetyl-1-aryl-3-methyl-2-pyrazolin-5-ones (1) with 2-amino-5-ethyl-1, 3, 4-thiadiazole, 3-amino-1, 2, 4-triazole, 5-aminotetrazole monohydrate: Formation of (2a and b) and (4a-d). A mixture of (la) or (lb) (0.002 mole) and the appropriate amino azole (0.002 mole) was refluxed in 30 ml. dry xylene for 7 hrs. After cooling, the solid products that separated were filtered off and recrystallized from ethanol (Table 1).

Independent synthesis of (2a). A mixture of 3-methyl-l-phenyl-2-pyrazolin-5-one (3) (0.002 mole) and 2-acetylamino-5-ethyl 1, 3, 4-thiadiazole (0.002 mole) in 30 ml. of ethanol were refluxed for 4 hrs. and left to cool. The product that separated was collected and crystallized from ethanol to give compound (2a) (m.p. and mixed m.p. 217°).

Heating (4a and c) with glacial acetic acid: Formation of (5a and c). Compounds (4a and c) (0.5g) were refluxed in 30 ml glacial acetic acid. After concentration and cooling, the solid products separated were filtered off and recrystallized from acetic acid to give compounds (5a and c) (Table 1).

Condensation of (la-b) with 2-aminobenzimidazole: Formation of 2-acetylaminobenzimidazole and 3-methyl-l-phenyl (or p-nitrophenyl)-2-pyrazolin-5-ones. (8 and 3):

A mixture of (la) or (lb) (0.002 mole) and 2-aminobenzimidazole (0.002 mole) in 30 ml. dry xylene was refluxed for 10 hrs. The solid product that separated after cooling, was filtered off and crystallized from ethanol/DMF to give 2-acetylaminobenzimidazole (8) (cf. Table 1 and 2). Evaporation of the filterate afforded on oily substance, which upon trituration with pet. ether (b.p. 40-60) and crystallization from ethanol gave 3-methyl-l-phenyl-2-pyrazolin-5-one (m.p. and mixed m.p. or 3-methyl-l-(p-nitrophenyl)-2-pyrazolin-5-one (m.p. and mixed m.p.).

Condensation of (la) with 3-amino-l-phenyl-2-pyrazolin-5-one. Formation of 9. A mixture of (la) (0.002 mole) and 3-amino-l-phenyl-2-pyrazolin-5-one (0.002 mole) was refluxed in 30 ml. dry xylene for 7 hrs. After cooling, the solid product that separated was filtered off and recrystallized from ethanol (Table 1).

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