

## 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*

(Received November 15, 1988; revised February 4, 1989)

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, <sup>1</sup>H-NMR and mass spectral data.

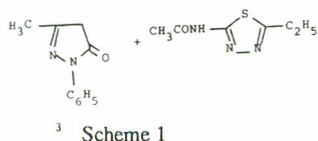
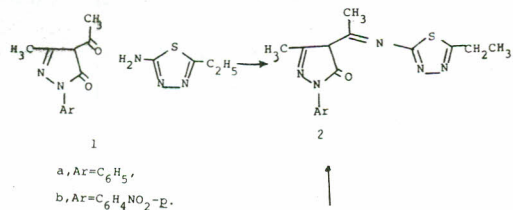
**Key words:** Condensation, Amino azoles, Heterocyclic synthesis.

### 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 mepyrzole [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 amino azoles.

4-Acetyl-1-aryl-3-methyl-2-pyrazolin-5-ones (1a-b), have now been found to condense with 2-amino-5-ethyl-1, 3, 4-thiadiazole to give (2). The IR and <sup>1</sup>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<sup>-1</sup>). The <sup>1</sup>H-NMR spectrum (400 MHz in CDCl<sub>3</sub>) displayed the signal of the methine proton of the pyrazolone at  $\sigma$  3.4 (s) (Table 2).

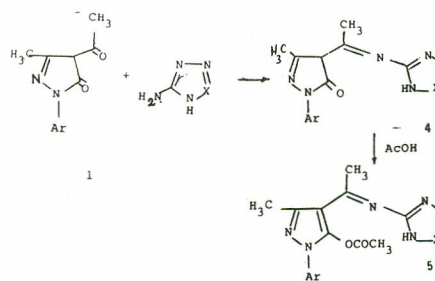


3 Scheme 1

Further evidence for the formation of 2a was gained from (a) its mass spectrum gave an M<sup>+</sup> 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).

It seemed of interest to us to react (1a) 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 <sup>1</sup>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 pyrazolo-pyrimidino-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 (1b) with 3-amino-1, 2, 4-triazole gave (4b).

Following the above condensations, when (1a-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<sub>6</sub>H<sub>5</sub>, X = CH; b, Ar = C<sub>6</sub>H<sub>4</sub>NO<sub>2</sub>-p, X = CH, X = N; d, Ar = C<sub>6</sub>H<sub>4</sub>NO<sub>2</sub>-p.

Scheme 2.

The usual procedure for the condensation of 2-amino-benzimidazole with the  $\beta$ -diketones gave the pyrazolopyrimidinobenzimidazolo derivatives [21]. 4-Acetylpyrazolinone (1a) 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

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

(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).

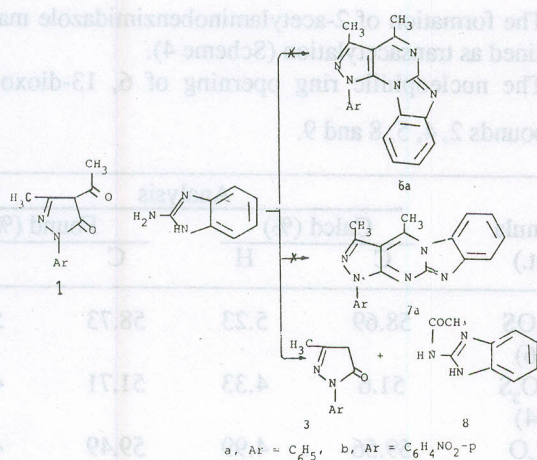
The nucleophilic ring opening of 6, 13-dioxo-6H,

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

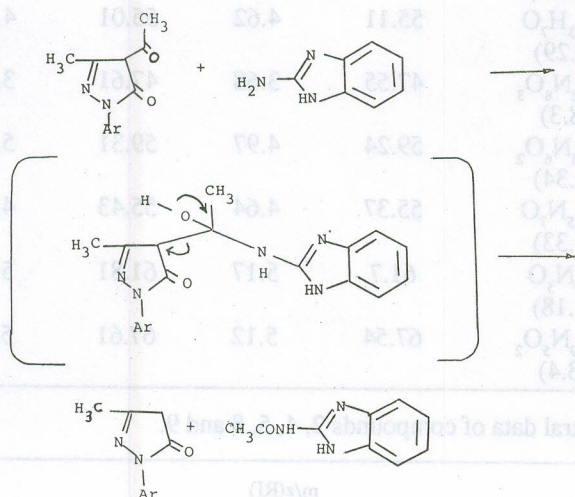
Compound No.	Colour	M.P. °C	Yield (%)	Mol. Formula (Mol. wt.)	Analysis			
					Calcd (%)		Found (%)	
					C	H	C	H
2a	Yellow	217	75	C <sub>16</sub> H <sub>17</sub> N <sub>5</sub> O <sub>3</sub> S (372.426)	58.69	5.23	58.73	5.18
b	Brown	>300	81	C <sub>16</sub> H <sub>16</sub> N <sub>6</sub> O <sub>3</sub> S (372.404)	51.6	4.33	51.71	4.22
4a	Colourless	266	70	C <sub>14</sub> H <sub>14</sub> N <sub>6</sub> O (282.30)	59.56	4.99	59.49	4.91
b	Yellow	>300	65	C <sub>14</sub> H <sub>13</sub> N <sub>7</sub> O <sub>3</sub> (327.297)	51.37	4.00	51.29	4.10
c	Colourless	265	70	C <sub>13</sub> H <sub>13</sub> H <sub>7</sub> O (283.29)	55.11	4.62	55.01	4.59
d	Brown	>300	68	C <sub>13</sub> H <sub>12</sub> N <sub>8</sub> O <sub>3</sub> (328.3)	47.55	3.68	47.61	3.71
5a	Colourless	285	85	C <sub>16</sub> H <sub>16</sub> N <sub>6</sub> O <sub>2</sub> (324.34)	59.24	4.97	59.31	5.02
c	Colourless	>300	90	C <sub>15</sub> H <sub>15</sub> N <sub>7</sub> O (325.33)	55.37	4.64	55.43	4.55
8.	Pale-yellow	>300	50	C <sub>9</sub> H <sub>9</sub> N <sub>3</sub> O (175.18)	61.7	5.17	61.81	5.11
9.	Golden-yellow	227	65	C <sub>21</sub> H <sub>19</sub> N <sub>5</sub> O <sub>2</sub> (373.4)	67.54	5.12	67.61	5.19

Table 2. IR, <sup>1</sup>H-NMR (400 MHz) and mass spectral data of compounds 2, 4, 5, 8 and 9.

Comp No.	IR (cm <sup>-1</sup> )	<sup>1</sup> H-NMR in CDCl <sub>3</sub> (400 MHz) δ-ppm	m/z(RI)
2a	1665, (C = O), 1595 (C = N)	2.48 and 2.89 (s, 2CH <sub>3</sub> ), 3.09 (q, 4H, CH <sub>2</sub> , J=7Hz), 1.45 (t, 3H, CH <sub>3</sub> , J = 7 Hz), 7.19 (dd) 7.41 (dd) and 7.95 (dd) (ArH) and 3.4(s, 1H, methine of pyrazolone).	M <sup>+</sup> 327 (100), 312 (M <sup>+</sup> -CH <sub>3</sub> ) (32), 272 (M <sup>+</sup> -C <sub>2</sub> H <sub>5</sub> CN) (24), 113 (312-C <sub>11</sub> H <sub>7</sub> N <sub>3</sub> O) (45), 154 (312-C <sub>10</sub> H <sub>6</sub> N <sub>3</sub> O)(6), 214 (M <sup>+</sup> -C <sub>2</sub> H <sub>5</sub> N <sub>2</sub> S (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 <sub>3</sub> ), 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 <sup>+</sup> (28.2) (100), 267 (M <sup>+</sup> -CH <sub>3</sub> ) (18), 68 (267-C <sub>11</sub> H <sub>7</sub> N <sub>3</sub> O) (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 (s, 2CH <sub>3</sub> ), 3.3 (s, 1H, methine pyrazole), 7.11, 7.21 and 7.62 (dd), J = 8Hz (ArH), 8.21 (s, 1H, NH).	M <sup>+</sup> 283(1), 268 (M <sup>+</sup> -CH <sub>3</sub> ) (2), 207 (2), 97 (4), 85 (M <sup>+</sup> -C <sub>12</sub> H <sub>10</sub> N <sub>2</sub> O) (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 <sub>3</sub> ), 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 <sup>+</sup> 175 (26), 133 (M COCH <sub>2</sub> ) (100), 76 (133-CH <sub>3</sub> N <sub>2</sub> ) (6), 57(6).
9	3440 (OH), 3340 and 3220 NH <sub>2</sub> , 1690 (C-O) and 1630 and 1600 (C = N).	2.28 and 2.39 (s, 2CH <sub>3</sub> ), 3.4 (s, 2H, NH <sub>2</sub> ), 7.26 dd and 7.67(m) (ArH) and 10.2 (s, 1H, OH).	m/z 175 (373-C <sub>2</sub> H <sub>10</sub> N <sub>2</sub> O) (25), 158 (175-NH <sub>2</sub> ) (7), 81 (41), 77(34)



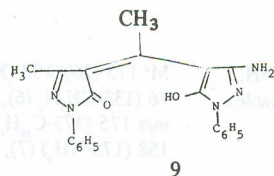
Scheme 3.



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 (1a) 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<sub>2</sub>), 1690 (C = O) and 1600 and 1630 (C = N). The <sup>1</sup>H-NMR spectrum does not show any absorption due to (-CH<sub>2</sub>-cyclic or olefinic protons). It thus appears that the condensation product has the structure (9) (Table 2).



## 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, <sup>1</sup>H-NMR spectra in CDCl<sub>3</sub> 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 (1a) or (1b) (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-1-phenyl-2-pyrazolin-5-one (3) (0.002 mole) and 2-acetylaminobenzimidazole (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 (1a-b) with 2-aminobenzimidazole: Formation of 2-acetylaminobenzimidazole and 3-methyl-1-phenyl (or p-nitrophenyl)-2-pyrazolin-5-ones. (8 and 3):**

A mixture of (1a) or (1b) (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 filtrate afforded an oily substance, which upon trituration with pet. ether (b.p. 40-60) and crystallization from ethanol gave 3-methyl-1-phenyl-2-pyrazolin-5-one (m.p. and mixed m.p. or 3-methyl-1-(p-nitrophenyl)-2-pyrazolin-5-one (m.p. and mixed m.p.).

**Condensation of (1a) with 3-amino-1-phenyl-2-pyrazolin-5-one. Formation of 9.** A mixture of (1a) (0.002 mole) and 3-amino-1-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).

## REFERENCES

1. L. Knorr, Chem. Ber., **17**, 546 (1984).
2. German Patent, **254**, 711 (1911), Chem. Abstr., **7**, 1403 (1913).
3. U.S. Patent, **2**, 562, 830 (1951), Chem. Abstr. **47**, 1191

- (1953).
4. T. Naito, T. Yoshikawa, S. Kitahara and N. Aoki, *Chem. Pharm. Bull.*, **17**, 1467 (1969).
  5. A.M. Ismaiel, M.Y. Yousif, M.A. Metwally and M.M. El-Kerdawy, *Indian J. Chem.*, **25B**, 1238 (1986).
  6. M.A. Metwally and F.A. Amer, *Pak. j. sci. ind. res.*, **24**, 135 (1981).
  7. M.A. Metwally and F.A. Amer, *Pharmazie*, **38**, 172 (1983).
  8. M.A. Metwally and E.M. Afsah, *Pak. j. sci. ind. res.*, **24**, 188 (1983).
  9. M.A. Metwally and F.A. Amer, *Indian J. Chem.*, **22B**, 316 (1983).
  10. O.M.O. Habib, T.M. Kassem, A.I. Eissa and M.A. Metwally, *Bull. N.R.C. Egypt*, **8**, 171 (1983).
  11. A.A. Fadda, M.A. Metwally and A.M. Khalil, *Indian J. Tex.*, **8**, 82 (1983).
  12. M.A. Metwally, M.Y. Yousif, A.M. Esmail and F.A. Amer, *Indian J. Chem. Soc.*, **62**, 54 (1985).
  13. M.A. Metwally, A.A. Fadda, H.M. Hassan and E. Afsah, *Org. Prep. Proced. Infr.*, **17**, 198 (1985).
  14. M.A. Metwally, M.L. Younes and S.A. Metwally, *Indian J. Chem.* **24B**, 970 (1985).
  15. M.A. Metwally, Y.M. Darwish and F.A. Amer, *J. Taiwan Pharm. Assoc.* (1987) in press.
  16. M.A. Metwally, M.M. Yousif, A.S. El-Ahl and F.A. Amer, *Mansoura Bull. Sci.* (1987) in press.
  17. *Ibid.*
  18. A.H. Harhash, F.A. Amer and M.A. Metwally, *Mansoura Bull. Sci.*, No. 4, 223 (1977).
  19. H.A. Etman, E.G. Sadek and M.A. Metwally, *J.f. Prakt. Chem.* (1988), Communicated.
  20. M.A. Metwally, M.Y. Yousif, A.M. Ismaiel and H.A. Etman, *Heterocycles*, **23**, 2251 (1985).
  21. E.M. Kandel and M.A. Metwally, *Pak. j. sci. ind. res.* **31**, 334 (1988).
  22. R. Rastogi, S. Sharma, R.N. Iyer, *Indian J. Chem. [B]*, **18**, 464 (1979).
  23. S.M. Fahmy, M.K.A. Ibrahim, K. Abouhadid and M.H. Elnagdi, *Arch. der. Pharm.*, **315**, H.9, 791 (1982).

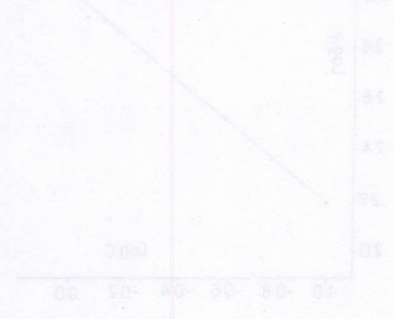


Fig. 1. Log V vs. log C.

The efficiency of the different halide ions can be arranged in the order:  $I > Br > Cl$ .

Chloride ion possesses the lowest inhibition efficiency and affords 11.6% protection to lead in 1.0 N HNO<sub>3</sub> at the highest concentration used (30 mM). Fluoride ion gives relatively low inhibition efficiency with respect to bromide and iodide ions but higher than that observed in presence of chloride ion.

Amongst the inhibitors used in 1.0 N nitric acid, iodide ion seems to be the best and affords nearly complete protection even at relatively low concentration (2 mM). Bromide ion is a satisfactory inhibitor for the dissolution of lead in 1.0 N HNO<sub>3</sub> at all concentrations used.

Table I shows the effect of concentration of sodium fluoride, sodium chloride, sodium bromide and Potassium iodide on the dissolution rate of lead in 1.0 N HNO<sub>3</sub>. From the results, it is interesting to note that all halide ions retard the dissolution of lead in 1.0 N nitric acid at all concentrations used. It may be generalized that the inhibition efficiency of all these compounds increases with increase in their concentrations.

Thus, the present investigation is on the effect of F, Cl, Br and I on the dissolution of lead in nitric acid solution because lead is one of the industrially important metals with valuable properties.

EXPERIMENTAL

The chemicals used were of analytical or reagent quality. All the solutions were prepared by dissolving the appropriate weights in distilled water. Lead sheets (99.99%) of size 1 x 1 cm were used in weight loss experiments. The surface was polished on 4/0 emery paper, cleaned thoroughly with distilled water and acetone. The dissolution rate of lead was carried out using weight loss technique [3]. The experiments were carried out in acetate solutions without stirring and the temperature was adjusted at 25° using an air thermostat. The inhibition efficiency (I) was evaluated using the equation:

$$I = \left( \frac{W_0 - W}{W_0} \right) \times 100$$

where W<sub>0</sub> is the weight loss in uninhibited solution and W is the weight loss in inhibited solution.

Galvanostatic technique was used for measuring potential vs. SCE using precision potentiometer.

RESULTS AND DISCUSSION

The dissolution rate of lead expressed in mg/cm<sup>2</sup> hr was found to depend on nitric acid concentration. The relation between V (corrosion rate) and C (acid concentration) is given by  $V = KC^n$ , where K is a constant (specific corrosion rate) and n is the order of the corrosion reaction which indicates the