Pyrimidine Derivatives and Related Compounds, VII
Synthesis of Some New Pyrazolo[1,5-a]-S-triazines, Pyrazolo[3,4-c]-as-triazines, Pyrazolo[1,5-a]pyrimidines and Pyrazolo[3,4-b]pyrones

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Pyrimidine Derivatives, Pyrazolylthiourea Derivatives

3-Amino-4-phenylhydrazono-2-pyrazolin-5-one (1) reacts with isothiocyanate to yield the corresponding pyrazolylthiourea derivatives (2a–c). Whereas 2a reacted with hydrazines to yield the pyrazolylamino-1,2,4-triazoles (3a, b), it cyclised into the pyrazolo-[3,4-e]-as-triazine derivative (4) upon treatment with concentrated sulphuric acid. On the other hand, the pyrazolo[1,5-c]-8-triazine derivative (5) was formed from reaction of 2a with ethanolic sodium ethoxide.

3-Amino-2-pyrazolin-5-one (8) reacted with ethyl acrylate to yield a mixture of the 4-diarylated derivative (9) and the pyrazolo[3,4-b]pyrone (11). Compound 11 could be converted into the corresponding pyrazolo[3,4-b]pyrones (12) and (13) by the action of acetic acid hydrochloric acid mixture and of concentrated sulphuric acid, respectively.

The chemistry of fused pyrazoles has received considerable recent attention1–5. Many fused pyrazole derivatives proved to be active antiinflammatory and antitumur agents6–8. In previous work we have reported a variety of new routes for the synthesis of fused pyrazole derivatives9–14, from readily obtainable 5-aminopyrazoles. In continuation of this work we report here the results of our investigations directed for the development of new synthetic procedures for the synthesis of fused pyrazole derivatives.

Synthesis of Pyrazolo[1,5-a]-S-triazines and Pyrazolo[1,5-c]-e-triazines

Recently15 it has been shown that 5-amino-4-aryl-hydrazono-3-substituted-pyrazoles react with benzoylisothiocyanate to yield the corresponding pyrazolylthioureas which could be readily cyclized into the corresponding pyrazolo[3,4-e]-as-triazine derivatives.

Requests for reprints should be sent to Dr. M. H. ELNAGDI, Chemistry Department, Faculty of Science, Cairo University, Giza, A. R. Egypt.

We have been particularly interested to see if reactions of this type might be extended to include more general synthesis of other substituted pyrazolo[3,4-c]-as-triazines. It has been found that 4-phenylhydrazones-3-amino-2-pyrazolin-5-one (1) react with benzoyl isothiocyanate, ethoxy carbonyl isothiocyanate and with phenyl isothiocyanate to afford the corresponding pyrazolylthiourea derivatives (2a, c). That the reaction of 1 with isothiocyanates has involved the exocyclic aminonitrogen rather than pyrazole ring NH groups was assumed on the basis of analogy to the well established behaviour of 3(5)-aminopyrazoles toward the same reagents. However, this is in contrast to the recently reported formation of 1-thiocarbamoylpyrazoles on treatment of 3,5-diamino-4-arylazopyrazoles with isothiocyanates16.

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Compound 2a could be cyclised under different conditions to form different polycyclic compounds. Thus, when 2a was treated with hydrazine hydrate or with phenylhydrazine it was converted into the corresponding 2-(pyrazol-5-yl)amino-1,2,4-triazole derivatives (3a,b). On the other hand the pyrazolo[3,4-c]-as-triazine derivative (4) was formed upon treatment of 2a with concentrated sulphuric acid. However, when 2a was treated with ethanolic sodium ethoxide the pyrazolo[1,5-c]-S-triazine derivative (5) was formed. The structures proposed for compounds 3-5 were based on analytical and IR data.

In contrast to the behaviour of 2a, attempted cyclization of 2b under the same experimental conditions has resulted in its decomposition quantitatively into 1. On the other hand, attempted cyclization of 3e by the action of ethanolic sodium ethoxide has resulted in the formation of the pyrazolylurea derivative (2d). Compound 2d was also obtained by the action of phenyl isocyanate on 1.

**Synthesis of 3-Phenyldiazonino-2-oxo-2,3-dihydropyrazolo[1,5-a]pyrimidines**

For continuing investigation of the biological activity of 3-arylhydrazinopyrazolo-1,5-a-pyrimidine derivatives samples of some 3-phenylhydrazono-2-oxo-2,3-dihydropyrazolo-1,5-a-pyrimidine derivatives were required. The reaction of 1 with a variety of b-bifunctional reagents was performed. Thus, 1 reacted with acetyl acetone to yield the 5,6-dimethylpyrazolo[1,5-a]pyrimidine derivative (6). Similarly, treatment of 1 with ethyl acetoacetate has afforded the 2,7-dioxopyrazolo[1,5-a]pyrimidine derivative (7). Structure 7 was established for this product on basis of elemental data and analogy to the well established behaviour of 3-amino-4-arylazopyrazoles toward the same reagent.

**Synthesis of Pyrazolo[3,4-b]pyrones**

In previous work the behaviour of 1 toward activated double bond systems has been reported. Also the reaction of 3-amino-1-phenyl-2-pyrazolin-5-ones toward the same reagents was investigated. In the present work the behaviour of 3-amino-2-pyrazolin-5-one (8) toward acrylonitrile and ethyl acrylate was investigated. We have found that the reaction of 8 with acrylonitrile under a variety of experimental conditions results in the formation of an oily mixture of several products. These could not be isolated in pure state. On the other hand, from the reaction of 8 with ethyl acrylate two products of m.p. 168 and 300 °C were formed and separated by fractional crystallisation. The molecular formula of the former was found to be C_{12}H_{16}O_{3}N_{3} via its analytical and molecular weight determination. This formula corresponds to an adduct formed from two molecules of ethyl acrylate and one molecule of 8. Structure 9 was assumed for this adduct based on analogy to the well established behaviour of 3-amino-1-phenyl-2-pyrazolin-5-one toward the same reagent and on the fact that the IR spectra of this product revealed the presence of a free NH_{2} band.

Molecular weight determinations and analytical data for the latter (m.p. 300 °C) indicated a molecular formula of C_{12}H_{14}O_{3}N_{4}. Two structures seemed probable for this compound (cf. formulae 10 and 11). NMR of this product revealed a complicated pattern and it seemed difficult to utilise it for the discrimination between both structures. The IR spectra of this compound showed the presence of δ lactone CO group at 1730 cm\(^{-1}\), amide CO band at 1680 cm\(^{-1}\) and revealed absence of absorption for NH_{2} group. The absence of NH_{2} absorption in the IR spectrum of this product might eliminate the possible structure 10. Thus, it seems most likely that this product have structure 11.

When compound 11 was refluxed in acetic acid-hydrochloric acid mixture, the carboxylic acid (12) was formed. On the other hand, when 11 was treated with concentrated sulphuric acid it was converted into the pyrazolo[3,4-b]pyrone derivative (13). 13 was also obtained when 12 was treated with concentrated sulphuric acid. Structures 12 and 13...
were inferred from analytical and IR data. The readily elimination of acrylic acid from \( \text{II} \) to yield \( \text{III} \) is similar to the reported ready dealkylation N-cyanoethylated and N-β-carboxyethylamines.

\[
\begin{align*}
\text{II} & \rightarrow \text{III} \\
\text{NH}_2 \text{C}_5\text{H}_5\text{O}_2\text{C} \text{CH}_2\text{CH}_2 \text{N} & \text{H}_2 \\
\end{align*}
\]

**Experimental**

All melting points are uncorrected. The IR spectra were recorded with a Hitachi Grating IR spectrophotometer Model EPI-G3.

**4-Phenylazo-5-oxo-2-pyrazolin-5-ylthiourea (2a, b)**

To a solution of benzoyl isothiocyanate or of ethoxycarbonyl isothiocyanate (prepared from 0.12 mole of \( \text{NH}_4\text{SCN} \) and the appropriate quantity of \( \text{BCl}_2 \) or \( \text{CICO}_2\text{H}_5 \) as has been described by DOUGLASS and DAINS\(^{18}\)) 0.1 mole of \( \text{I} \) in 50 ml of acetone was added. The reaction mixture was refluxed for 6 h, left to cool to room temperature and then poured over water. The resulting solid product was collected by filtration and crystallised. 2a formed from crystals from acetic acid m.p. 204–205 °C; yield 80%.

\[
\begin{align*}
\text{C}_{17}\text{H}_{18}\text{O}_2\text{N}_6\text{S} \\
\text{Found C 55.00 H 5.00 N 22.40 S 9.50,} \\
\text{Caled C 55.13 H 4.90 N 22.69 S 9.64.}
\end{align*}
\]

2b formed from crystals from ethanol m.p. 168 °C; yield 80%.

\[
\begin{align*}
\text{C}_{13}\text{H}_{14}\text{O}_3\text{N}_6\text{S} \\
\text{Found C 56.76 H 4.21 N 32.66,} \\
\text{Caled C 56.80 H 4.04 N 32.79.}
\end{align*}
\]

**N-(4-Phenylazo-5-oxo-2-pyrazolin-5-yl)-N'-phenylthiourea (2c)**

A suspension of \( \text{I} \) (2.0 g) in pyridine (50 ml) was treated with phenyl isothiocyanate (10 ml). The reaction mixture was refluxed for 2 h and then evaporated in vacuo. The resulting product was then triturated with ethanol and the resulting solid product was collected by filtration and crystallised from acetic acid.

\[
\begin{align*}
\text{2c} & \text{ orange crystals; m.p. 250 °C; yield 90%}. \\
\text{C}_{16}\text{H}_{14}\text{ON}_8 \text{S} \\
\text{Found C 56.76 H 4.21 N 32.66,} \\
\text{Caled C 56.80 H 4.04 N 32.79.}
\end{align*}
\]

**3-(4-Phenylazo-5-oxo-2-pyrazolin-5-yl)-amino-5-phenyl-1,2,4-triazoles (3a, b)**

A mixture of \( \text{2a} \) (2.0 g) and hydrazine hydrate (2.0 ml; 98%) or phenylhydrazine (2.0 ml) was heated on a boiling water bath for three hours. The reaction mixture was then dissolved in ethanol, diluted with water and acidified with hydrochloric acid. The resulting solid product was collected by filtration and crystallised.

\[
\begin{align*}
\text{3a} & \text{ red crystals from acetic acid m.p. 286 °C; yield 70%}. \\
\text{C}_{17}\text{H}_{14}\text{ON}_8 \text{S} \\
\text{Found C 58.50 H 4.32 N 32.66,} \\
\text{Caled C 58.98 H 4.04 N 32.37.}
\end{align*}
\]

3b: yellow crystals from ethanol; m.p. 241 °C; yield 75%.

\[
\begin{align*}
\text{C}_{23}\text{H}_{18}\text{ON}_8 \text{S} \\
\text{Found C 65.70 H 4.00 N 26.35,} \\
\text{Caled C 65.40 H 4.26 N 26.54.}
\end{align*}
\]

**6,7-Dihydro-4-phenyl-8-phenylhydrazono-7-oxo-2-thioxopyrazolo[1,5-a]-1,3,5-triazine (4)**

To a sodium ethoxide solution prepared from 1 g of sodium metal and 100 ml of ethanol was added 2.0 g of \( \text{2a} \). The reaction mixture was refluxed for three hours and then evaporated in vacuo. The remaining product was dissolved in water and neutralised with hydrochloric acid. The solid product, so formed, was collected by filtration and crystallised from ethanol.

4: yellow crystals from m.p. 208 °C; yield 70%.

\[
\begin{align*}
\text{C}_{17}\text{H}_{15}\text{ON}_8 \text{S} \\
\text{Found C 58.26 H 3.21 N 23.91 S 9.00,} \\
\text{Caled C 58.62 H 3.47 N 23.83 S 9.18.}
\end{align*}
\]

**N-(4-Phenylazo-5-oxo-2-pyrazolin-3-yl)-N'-phenylurea (2d)**

\[ a \] From \( \text{2c} \) and ethanolic sodium ethoxide: Compound 2c was treated with ethanolic sodium ethoxide using experimental conditions described above for cyclization of \( \text{2a, b} \).

2d: orange crystals from acetic acid; m.p. 236 °C; yield 78%.

\[
\begin{align*}
\text{C}_{16}\text{H}_{14}\text{ON}_8 \text{S} \\
\text{Found C 59.39 H 4.50 N 25.85,} \\
\text{Caled C 59.62 H 4.38 N 25.67.}
\end{align*}
\]

\[ b \] From \( \text{I} \) and phenyl isocyanate: A mixture of \( \text{I} \) (0.1 mole) and phenyl isocyanate (0.12 mol) in pyridine (100 ml) was refluxed for six hours and then evaporated in vacuo. The remaining product
was triturated with water and acidified with acetic acid. The solid product, so formed was collected by filtration, crystallised from acetic acid and identified (m.p. and mixed m.p.) as \(2d\).

**2,3-Dihydro-5,7-dimethyl-2-oxo-3-phenylazopyrazolo-[1,5-a]-pyrimidine (6)**

A mixture of 1 (2.0 g) and acetylacetone (1.0 ml) was treated with acetic acid (30 ml). The reaction mixture was refluxed for 12 hours then evaporated in vacuo. The remaining product was then triturated with water, neutralised with ammonia and the resulting solid product was collected by filtration and crystallised from acetic acid.

6: orange crystals; m.p. 216 °C; yield 2.5 g.

\[\text{C}_{12}\text{H}_{13}\text{ON}_5\]

Found C 63.00 H 5.00 N 26.00,

**2,3,6,7-Tetrahydro-5-methyl-2,7-dioxo-3-phenylhydrazono-pyrazolo-1,5-a-pyrimidine (7)**

7 was obtained in 80% yield by treatment of 1 with ethyl acetoacetate under the experimental conditions described above for the preparation of 6 from 1 and acetylacetone.

7: orange crystals from ethanol; m.p. > 300 °C.

\[\text{C}_{12}\text{H}_{11}\text{O}_2\text{N}_5\]

Found C 58.10 H 4.40 N 26.30,
Caled C 57.98 H 4.12 N 26.01.

**Reaction of 11 with ethyl acrylate**

A suspension of 9 (10.0 g) in ethanol (250 ml) and water (150 ml) was treated with ethyl acrylate (25 ml) and few drops of a concentrated potassium hydroxide solution. The reaction mixture was refluxed for six hours and the so formed solid product was collected while the solution is still hot to yield 10 g of 14, m.p. 300 °C; IR: 1610 (C=N) bands (chelated NH).

13 formed colourless crystals from water m.p. 258 °C; yield 40% IR.

\[\text{C}_{13}\text{H}_7\text{O}_2\text{N}_3\]

Found C 48.01 H 4.95 N 18.83,
Caled C 48.00 H 4.92 N 18.66.

**b) Concentrated sulphuric acid:** A mixture of 13 (2.0 g) and concentrated sulphuric acid (12.0 ml) was heated at 140 °C (bath-temperature) for 30 minutes then left overnight at room temperature. The resulting reaction mixture was then diluted with water and neutralised by ammonium hydroxide. The solid product form on standing was purified by filtration and crystallised from water.

14: colourless crystals; m.p. 310 °C; yield 1.0 g.

\[\text{C}_{13}\text{H}_{14}\text{N}_3\text{O}_8\]

Found C 49.93 H 5.07 N 23.66,
Caled C 60.00 H 4.48 N 23.23.

Concentration of the filtrate of the above reaction mixture afforded 8 g of 10; which was purified by crystallization from ethanol.

10: m.p. 158 °C; IR: 1610 (C=N); 1640 (ΔNH); 1695 (ring CO); 1710, 1700 (ester CO) and 3200, 3370 (NH bands).

**Reaction of 12**

a) With acetic acid-hydrochloric acid mixture: A solution of 12 (2.0 g) in acetic acid (30 ml) was treated with hydrochloric acid (5 ml; 22%) the reaction mixture was refluxed for three hours and then evaporated in vacuo. The remaining product was triturated with water and the remaining product was collected by filtration.

13 formed colourless crystals from water m.p. 258 °C; yield 40% IR.

\[\text{C}_{13}\text{H}_7\text{O}_2\text{N}_3\]

Found C 48.01 H 4.95 N 18.83,
Caled C 48.00 H 4.92 N 18.66.

b) Concentrated sulphuric acid: A mixture of 13 (2.0 g) and concentrated sulphuric acid (12.0 ml) was heated at 140 °C (bath-temperature) for 30 minutes then left overnight at room temperature. The resulting reaction mixture was then diluted with water and neutralised by ammonium hydroxide. The solid product form on standing was collected by filtration and crystallised from water. 14: colourless crystals; m.p. 310 °C; yield 1.0 g.

\[\text{C}_{13}\text{H}_{14}\text{N}_3\text{O}_8\]

Found C 49.93 H 5.07 N 23.66,
Caled C 60.00 H 4.48 N 23.23.

Concentration of the filtrate of the above reaction mixture afforded 8 g of 10; which was purified by crystallization from ethanol.

10: m.p. 158 °C; IR: 1610 (C=N); 1640 (ΔNH); 1695 (ring CO); 1710, 1700 (ester CO) and 3200, 3370 (NH bands).