Synthesis of Ethyl α-Phenylthiocarbamylglyoxalate Arylhydrazones and their Reactions with Hydrazines

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Treatment of ethyl α-phenylthiocarbamylglyoxalate (1) with aromatic diazonium salts effects acetyl cleavage with the formation of ethyl α-phenylthiocarbamylglyoxalate arylhydrazones derivatives (2a-e) which afford the anilinopyrazolones (5) and (7) on treatment with hydrazine or phenylhydrazine. The pyrazolones 5a-e undergo aminolysisation with formaldehyde and piperidine to give the N-Mannich bases 7a-e, also obtained by treating the N-hydroxymethyl derivatives (9a-e) with piperidine.

The Japp-Klingemann reaction is a special case of the coupling of diazonium salts with a compound containing activated methinyl group distinguished by the fact that the coupling product ordinarily undergoes solvolysis as rapidly, or almost as rapidly as it is formed. A number of α-substituted derivatives of β-keto-esters\(^{±4}\) and β-diketones\(^{8}\) are reported to undergo acyl-group cleavage when treated with diazonium salts.

Alternatively, the arylazoderivatives of β-diketones\(^{6}\) and β-keto-esters\(^{7}\) have been shown to undergo aminomethylation accompanied by acyl-group cleavage upon treatment with formaldehyde and secondary amines. The study of the behaviour of ethyl α-phenylthiocarbamylglyoxalate (1) toward the action of diazonium salts has been undertaken.

Treatment of 1 with the appropriate aromatic diazonium salt in presence of sodium acetate also effected acetyl-group cleavage with the formation of the arylhydrazono derivatives 2a-e as inferred from their correct analytical data. The IR spectra of 2a-e show absorption at 1580 (C=N), 1660, 1675 (CO) and 3450 cm\(^{-1}\) (–NH). The low carbonyl absorption may be due to the possible hydrogen bonding (cf. structures 3 and 4).

No ethoxycarbonyl cleavage has been reported upon the coupling of diazonium salts with α-substituted β-keto-esters. Moreover, it is now evident that the acetyl group is cleaved in preferential to the thio carbamyl group. In contrast to the behaviour of arylazo derivatives of β-diketones\(^{6}\) and β-keto-esters\(^{7}\), compound 2a has been recovered unchanged upon treatment with formaldehyde and piperidine.

When the arylhydrazono derivatives (2a-e) were warmed with hydrazine hydrate, 3-anilino-4-arylhydrazono-2-pyrazolin-5-ones (5a-e) were formed. Compound 5a was found to be identical with the product obtained by WORREL et al.\(^{9}\) by the coupling of benzenediazonium chloride with 3-anilino-2-pyrazolin-5-one. The arylhydrazono derivatives (5a-e) were assigned the pyrazolone structure rather than the possible hydroxypyrazole structure (cf. 6) based on their infrared spectra which showed
absorption at 1670 (CO), 3400 (NH) and 1600 cm\(^{-1}\) (C=N) and revealed no OH absorption.

\[
\text{ArNNH}_2 + \text{C} = \text{O} \rightarrow \text{C}_6\text{H}_5\text{NH} + \text{C} = \text{O}
\]

The formation of 5a–e may have involved the condensation of the thio carbonyl thione group with hydrazine followed by the cyclisation of the intermediately formed hydrazone derivative with the loss of ethanol (cf. route a in Scheme 1). This is in analogy to the reported\(^{10}\) behaviour of thioamides of benzoylelactic acid towards the action of hydroxylamine and hydrazines. The possibility of an initial formation of ahydrazide intermediate followed by cyclisation with the thione group (cf. route b, scheme 1) leading to the same product 5 cannot be overlooked. However, in support of route a, we have found that treatment of 2a–e with phenylhydrazine afforded 3-anilino-4-arylhydrazono-1-phenyl-2-pyrazolin-5-ones (7a–e). The structure of 7a–e was based on the correct analytical data, the deep colour of the compounds and the infrared spectra which revealed absorption at 1590, 1610 (C=N), 1790 (CO) and 3500 cm\(^{-1}\) (NH). The carbonyl absorption at 1790 cm\(^{-1}\) is comparable with that reported by EVANS et al. for 1,3-dimethyl-2-pyrazoline-5-one\(^{11}\).

Treatment of the arylhydrazonopyrazolones (5a–e) with formaldehyde and piperidine in methanol afforded the corresponding N-Mannich bases (8a–e). This is in analogy with the behaviour of 3-alkyl-4-arylhydrazono-2-pyrazolin-5-one toward the same reagent\(^{12}\). Refluxing 5a–e with formalin solution resulted in the formation of the N-hydroxymethyl derivatives (9a–e), which when warmed with piperidine afforded the N-Mannich bases 8a–e.

\[
\text{ArNNN} + \text{C} = \text{O} \rightarrow \text{ArNNN} + \text{C} = \text{O}
\]

**Experimental**

All melting points are uncorrected. Infrared spectra were determined on KBr discs using a Unicam SP 1000 Infrared Spectrophotometer.

**Reaction of ethyl a-phenylthiocarbamylacetoacetate (1)** with diazonium salts

To a cold solution of 1\(^8\) (0.01 mole) in ethanol (40 ml). Sodium acetate (0.01 mole) was added and the mixture was stirred for few minutes. The appropriate freshly prepared aromatic diazonium salt (0.01 mole) was added gradually with continuous stirring. The solid product 2, that separated was filtered off and crystallised from ethanol.

2a formed lemon yellow crystals, m.p. 160 °C, yield 25%.

\[\text{C}_1\text{H}_1\text{N}_3\text{S}_2\]

Calcd C 62.38 H 5.19 N 12.84 S 9.78.

2b formed orange crystals, m.p. 123 °C, yield 40%.

\[\text{C}_1\text{H}_1\text{N}_3\text{S}_2\]

Found C 63.51 H 5.31 N 12.11.
Calcd C 63.34 H 5.57 N 12.31.

2c formed red crystals, m.p. 110 °C, yield 40%.

\[\text{C}_1\text{H}_1\text{N}_3\text{S}_2\]

Found C 63.12 H 5.71 N 12.21.
Calcd C 63.34 H 5.57 N 12.31.

2d formed orange crystals, m.p. 112 °C, yield 45%.

\[\text{C}_1\text{H}_1\text{N}_3\text{S}_2\]

Found C 60.71 H 5.92 N 11.46 S 8.65.
Calcd C 60.5 H 5.32 N 11.76 S 8.96.
2e formed red crystals, m.p. 117 °C, yield 40%.

\[ C_{18}H_{19}N_3SO_3 \]

Found C 60.61 H 5.12 N 11.46,
Calcd C 60.5 H 5.32 N 11.76.

2a was recovered almost unchanged after treating its methanolic solution with formaldehyde and piperidine, as described below.

**Action of hydrazine hydrate on 2a-e**

A mixture of each of 2a-e (0.01 mole), hydrazine hydrate (0.01 mole) and ethanol (50 ml) was refluxed for two hours and the solid product 5, that separated on cooling, was filtered off and crystallized from the appropriate solvent.

The pyrazolone derivative 5a, formed rosy crystals from toluene, m.p. 220 °C, not depressed when admixed with a sample prepared after worrall9.

The pyrazolone derivative 5b formed deep red crystals from toluene, m.p. 234 °C, yield 30%.

\[ C_{16}H_{16}N_5O \]

Found C 65.12 H 5.55 N 23.71,
Calcd C 65.3 H 5.44 N 23.88.

The pyrazolone derivative 5c formed reddish brown crystals from ethyl alcohol, m.p. 250 °C, yield 40%.

\[ C_{16}H_{16}N_5O_2 \]

Found C 65.41 H 5.33 N 23.61,
Calcd C 65.3 H 5.44 N 23.88.

The pyrazolone derivative 5d formed brown crystals from ethyl alcohol, m.p. 228 °C, yield 30%.

The pyrazolone derivative 5e formed deep brown crystals from ethanol, m.p. 231 °C, yield 40%.

\[ C_{16}H_{16}N_5O_2 \]

Found C 61.82 H 5.31 N 22.42,
Calcd C 61.93 H 5.16 N 22.58.

The pyrazolone derivative 5f formed red crystals, m.p. 180 °C, yield 20%.

\[ C_{26}H_{20}N_5O \]

Found C 71.72 H 5.41 N 18.71,
Calcd C 71.54 H 5.15 N 18.91.

The pyrazolone 7e, formed reddish brown crystals, m.p. 190 °C, yield 30%.

\[ C_{26}H_{20}N_5O_2 \]

Found C 68.72 H 5.11 N 17.92,
Calcd C 68.57 H 4.93 N 19.18.

The pyrazolone 7d, formed brown crystals, m.p. 195 °C, yield 35%.

\[ C_{22}H_{20}N_5O_2 \]

Found C 68.61 H 4.72 N 18.21,
Calcd C 68.57 H 4.93 N 18.18.

3-Anilino-4-arylhydrazono-1-phenyl-2-pyrazolin-5-ones (5a-e)

A mixture of each of 2a-e (0.01 mole) and phenylhydrazine (0.02 mole) was heated in an oil-bath at 260 °C for four hours. The oily residue was triturated with dilute alcohol and the resulting solid (7) was recrystallized from ethanol.

The Mannich base 8a formed bright red crystals, m.p. 145 °C, yield 60%.

\[ C_{21}H_{24}N_5O \]

Found C 66.71 H 6.42 N 22.12,
Calcd C 66.84 H 6.63 N 22.28.

The Mannich base 8b, formed brown crystal, m.p. 110 °C, yield 60%.

\[ C_{21}H_{24}N_5O \]

Found C 66.71 H 6.42 N 22.12,
Calcd C 66.84 H 6.63 N 22.28.

The Mannich base 8c, formed bright brown crystals, m.p. 231 °C, yield 40%.

\[ C_{21}H_{24}N_5O_2 \]

Found C 61.93 H 5.16 N 22.58.

The Mannich base 8d, formed brownish yellow crystals, m.p. 175 °C, yield 65%.

\[ C_{22}H_{27}N_5O \]

Found C 67.32 H 6.81 N 21.32,

The Mannich base 8e, formed bright brown crystals, m.p. 180 °C, yield 20%.

\[ C_{22}H_{27}N_5O_2 \]

Found C 67.61 H 6.71 N 21.61,

The Mannich base 8d, formed brownish yellow crystals, m.p. 130 °C, yield 60%.

\[ C_{22}H_{27}N_5O_2 \]

Found C 65.11 H 6.71 N 20.51,
Calcd C 64.86 H 6.63 N 20.69.

The Mannich base 8e, formed red crystals, m.p. 165 °C, yield 65%.
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C_{22}H_{21}N_2O_2

- Found C 64.91 H 6.51 N 20.42.
- Calcd C 64.86 H 6.63 N 20.63.

3-Anilino-4-arylhydrazono-1-hydroxymethyl-2-pyrazolin-5-ones (9a–e)

A suspension of each of 5a–e (0.5 g) and formalin (38%, 2 ml) in ethanol (30 ml) was refluxed for four hours. The solid product (9) that separated on cooling was filtered off and recrystallized from ethanol.

9a formed orange crystals, m.p. 130 °C, yield 60%.

C_{16}H_{16}N_3O_2

- Found C 62.12 H 5.32 N 22.71.
- Calcd C 61.93 H 5.16 N 22.58.

9b formed deep brown crystals, m.p. 126 °C, yield 60%.

C_{17}H_{18}N_3O_2

- Found C 63.12 H 5.71 N 21.82.

9c formed red crystals, m.p. 132 °C, yield 65%.

C_{17}H_{18}N_3O_2

- Found C 60.18 H 5.41 N 20.31.
- Calcd C 60.00 H 5.29 N 20.58.

9d formed brown crystals, m.p. 142 °C, yield 60%.

C_{17}H_{18}N_3O_2

- Found C 60.21 H 5.31 N 20.42.
- Calcd C 60.00 H 5.29 N 20.58.

Conversion of 4 into 8

A mixture of each of 9a–e (0.5 g) and piperidine (2 mol) was heated on a boiling water-bath for three hours. The oily residue was triturated with dilute alcohol and the solid product proved to be identical with the appropriate N-Mannich base 8a–e (m.p. and mixed m.p.).

9 D. E. Worral, J. Amer. Chem. Soc. 44, 1551 [1922].
12 W. P. Dunworth, Fr. Pat. 1,546,002 (1962); C. A. 72, 80330 [1970].