Studies on 3,5-Diamino Pyrazoles:
Chemical Behavior of 4-Phenylazo-3,5-diaminopyrazoles

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The behaviour of 3,5-diamino-4-phenylazopyrazole (1) toward isothiocyanates, acrylonitrile and ethyl ethoxymethylenecyanoacetate is investigated. An improved synthesis of 4-unsubstituted-3,5-diaminopyrazoles by an arylazo removal reaction is also reported.

In recent years emphasis has been placed on the synthesis and chemistry of aminopyrazoles because of their biological activity and their utility as intermediates for the synthesis of the biologically active pyrazolopyrimidines and pyrazolotriazines1-9. Although 3,5-diaminopyrazoles are interesting for both reasons, their chemistry and synthesis has received little attention6-9. In continuation to our work on the synthesis and chemistry of 3,5-diaminopyrazoles6-9, we report here some interesting chemical properties of 3,5-diamino-4-phenylazopyrazole (1). Thus, compound 1 adds to methyl- or benzyl-isothiocyanates to yield the corresponding adducts (cf. formulae 2,3). Although 5-amino pyrazoles were reported to react with isothiocyanates to yield compounds similar to 2 where addition would involve the primary amino nitrogen10-12, we obtained products that proved to be 3 rather than 2. Confirmatory evidence for the proposed structure was obtained from chemical and 1H NMR data. Whereas 5-pyrazolylthioureas have been reported to be stable to treatment under basic conditions10-11, thioacetylamidopyrazoles are readily decomposable under similar conditions12. When the adducts 3a,b were treated with methanolic sodium methoxide or with methanolic potassium hydroxide, compound 1 was reformed quantitatively. The observation that 1 reacted with isothiocyanates to yield products different than those to be expected by analogy to literature data shows that caution must be made in proposing structures by analogy to the behaviour of very similar systems.

In an attempt to affect rearrangement of 3a,b into the corresponding 2, compounds 3a,b were refluxed in acetic acid solution. Instead of the expected product 3,5-diacetamids-4-phenylazopyrazole (4) was the only isolated product. Compound 4 was also obtained when 1 was refluxed with acetic acid under the same conditions. The formation of 4 from 3a,b may be assumed to take place via dethiocarbamoylation and acylation. The ready acylation of 1 by action of acetic acid indicate a marked increment in basicity of the amino groups of 1 as compared with other amino pyrazoles. Such increment can be attributed to the opposition of the mesomeric effects of the two amino groups which increases the electron density at each nitrogen atom. Similar observation has been previously reported for aromatic p-diamines14.

It has been previously shown that 1 reacts with acrylonitrile in pyridine solution to afford ring N-1 alkylated product which could be cyclised into pyrazolo[1,5-a]pyrimidine derivative. The latter was obtained directly when 1 was treated with ethyl acrylate under the same conditions6. In the present paper an investigation of the behaviour of 1 toward acrylonitrile and ethyl acrylate in acetic acid media was undertaken. In this manners, when 1 was treated with acrylonitrile in refluxing acetic acid,
2,7-diamino-3-phenylazo-4,5-dihydropyrazolo[1,5-a]pyrimidine (5) was formed. Compound 5 could be readily converted into the corresponding keto derivative 6 by the action of acetic acid hydrochloric acid mixture. The latter derivative could be obtained directly from reaction of 1 with ethyl acrylate. The structure proposed for compounds 5 and 6 was based on elemental analysis and the non-identity of 6 with product of reaction of 1 with ethyl acrylate in pyridine solution. The dependence of the sequence of reaction of 1 with ethyl acrylate and with acrylonitrile on reaction conditions is similar to the previously reported behaviour of aminopyrazoles toward activated α,β-unsaturated double bond systems.

Compound 1 reacts with ethyl ethoxymethylene-cyanoacetate to yield the aminomethylene derivative (7). The structure of compound 7 was based on 1H NMR interpretation (cf. Experimental). Compound 7 could be converted into the corresponding pyrazolo[1,5-a]pyrimidine derivative (8) by long reflux in acetic acid. Since previous results indicate that ring N-1 is the most electrophilic center in the molecule, the formation of the aminomethylene derivative (7) might be assumed to proceed via intermediate formation of ring N-1 alkylated product. The latter then isomerises into 7. The ready isomerization of 1-β-cyanomethylene-5-aminopyrazoles into the corresponding 5-aminomethylene derivatives has been recently reported.

Unexpectedly, when 1, 3a, b or 4 were treated with acetic acid-sulphuric acid mixture a colourless product was obtained. The latter was identified as 3,5-diacetamidopyrazole based on its 1H NMR and the identity with the product obtained by the action of acetic acid on 3,5-diaminopyrazole (10). The easy removal of the phenylazo group under these conditions seems to be an interesting reaction which can be utilized for the synthesis of variety of aminoheterocyclic compounds that are reported to be difficult to access by other synthetic routes.

**Experimental**

Melting points were determined with a Thomas Hoover melting point apparatus and are uncorrected. Proton magnetic resonance spectra were obtained with a Varian A-60 spectrometer with TMS as internal standard and chemical shifts are expressed as δ parts per million with DMSO-D6 as solvent. The infrared spectra were determined utilizing pressed KBr disk, with a Beckman IR spectrometer. Elemental analysis were performed by M-H-W laboratories, garden city-Michigan and Analytical data unit in cairo University.

**Reaction of 1 with benzyl- or methyl-isothiocyanates**

**General procedure:** To a suspension of 1 (0.2 mol) in aceticone (100 ml) benzyl- or methyl-isothiocyanate (0.2 mol) were added. The reaction mixture was refluxed for 24 hours. The solvent was then removed in vacuo. The remaining product was triturated with methanol. The solid product, so formed, was collected by filtration and crystallised from methanol.

3,5-Diamino-1-benzylthiocarbanoyl-4-phenylazopyrazole (3a) formed yellow crystals, m.p. 123 to 125 °C, yield 80%. 1H NMR: 4.81 (d, = 5 Hz, 2 H becomes singlet after D2O exchange, benzyl CH2), 6.33 (S, 2 H, lost after D2O exchange, C-3 NH2), 7.3-7.8 (m, 1 OH, 2C6 H5); 9.0 (5, 2 H, lost after D2O exchange, C-5 NH2) and 9.80 (t, br, 1 H, lost after D2O exchange, NH).

C17H17N7S

([1,5-a]pyrimidine derivative (8)) by long reflux in acetic acid. Since previous results indicate that ring N-1 is the most electrophilic center in the molecule, the formation of the aminomethylene
Found C 58.07 H 4.92 N 28.03 S 9.16,
Caled C 58.11 H 4.84 N 27.92 S 9.11.

3,5-Diamino-1-methylthiocarbamoyl-4-phenylazopyrazole (3b), yellowish brown crystals, m.p. 132–133 °C (decompositions); yield 80%.

\[ \text{C}_9\text{H}_{13}\text{N}_7\text{S} \]

Found C 47.83 H 4.67 N 35.81 S 11.67,
Caled C 48.00 H 4.76 N 35.63 S 11.63.

**Reaction of 3a, b with:**

* a) Methanolic sodium methoxide: To a solution of each of 3a, b (0.5 g) in methanol (25 ml) sodium methoxide (0.2 g) was added. The reaction mixture was refluxed for 4 h. The solvent was then removed in vacuo and the remaining solid was dissolved in water and neutralised with acetic acid. The solid product, so formed, was collected by filtration and identified (m.p. and mixed m.p. and IR) as 1, yield 95%, in each case.

* b) Methanol and potassium hydroxide: To a solution of each of 3a, b (0.7 g) in methanol (45 ml) a solution of 0.2 g of potassium hydroxide in 5 ml of water was added. The reaction mixture was refluxed for 3 h and the solvent was then removed by vacuo. The remaining product was then treated as described above and the reaction product was identified (m.p. and mixed m.p. and IR) as 1.

3,5-Diacetamido-4-phenylazopyrazole (4): A solution of each of 1, 3a, b or 4 (2.0 g) in methanol (50 ml) was refluxed for 24 h. The solvent was then removed by vacuo and the remaining product was dissolved in water (15 ml) and neutralised by dilute ammonium hydroxide. The solid product, so formed, was collected by filtration and crystallised from methanol. Yields were 80% in each case.

4: m.p. 224 °C, \(^1\)H NMR: 1.35 (t, 3 H, ester CH\(_3\)), 4.44 (q, 2 H, CH\(_2\)), 7.01 (d, 1 H, pyrazole CH), 7.4–7.8 (m, 5 H, C\(_6\)H\(_5\)), 8.3 (s, 1 H, ring NH) and 12.7 (br, 1 H, ring NH).

\[ \text{C}_{13}\text{H}_{12}\text{O}_2\text{N}_2 \]

Found C 54.54 H 5.00 N 29.46,
Caled C 54.54 H 4.93 N 29.36.

2,7-Diamino-3-phenylazo-4,5-dihydropyrazolo[1,5-a]pyrimidine (5): A solution of 1 (2.0 g) in acetic acid (50 ml) was treated with acrylonitrile (0.5 ml) and the reaction mixture was then refluxed for 6 h. The solvent was then removed in vacuo and the remaining product was triturated with water and collected by filtration. The reaction product was purified by repeated crystallisation from ethanol.

5: Yellow crystals, m.p. 206 °C, yield 75%.

\[ \text{C}_{12}\text{H}_{12}\text{N}_7 \]

Found C 56.50 H 5.20 N 38.70,
Caled C 56.46 H 5.13 N 38.41.

2-Amino-7-azo-4,5,6,7-tetrahydropyrazolo[1,5-a]-pyrimidine (7)

* a) From 6 and acetic acid hydrochloric acid mixture: A suspension of compound 6 (2.0 g) in acetic acid (50 ml) was treated with concentrated hydrochloric acid (2 ml; 17.5%). The mixture was refluxed for 3 h and then evaporated in vacuo. The remaining product was triturated with water and the resulting solid was collected by filtration and crystallised from methanol.

7: m.p. 230 °C; yield 62%; IR: 1650 (\(\delta\)NH\(_2\)); 1700 cm\(^{-1}\) (ring CO) and 3250, 3340 cm\(^{-1}\) (\(\nu\)NH\(_2\)).

\[ \text{C}_{15}\text{H}_{12}\text{O}_2\text{N}_6 \]

Found C 56.35 H 4.90 N 32.50,
Caled C 56.24 H 4.72 N 32.80.

* b) From 1 and ethyl acrylate: Compound 6 was obtained in 85% yield when 1 was treated with ethyl acrylate utilising the same reaction conditions. Described above for reaction of 1 with acrylonitrile.

**Reaction of 1 with ethyl ethoxymethyleneacyanocate**

A suspension of 1 (2.0 g) in methanol (100 ml) was treated with ethyl ethoxymethyleneacyanocate (2.0 g) and the mixture was refluxed for two hours. The solid product, so formed, was collected by filtration. Yield 2.7 g of compound 7. Crystallization from ethanol afforded analytically pure sample.

3-Amino-5-(\(\beta\)-ethoxyacarbonyl-\(\beta\)-cyanomethyl)amino-4-phenylazopyrazole (7) formed yellow crystals from methanol, m.p. 281 °C, \(^1\)H NMR: 1.35 (t, 3 H, CH\(_3\)), 4.44 (q, 2 H, CH\(_2\)), 7.0 (d, J = 5 Hz, 1 H, CH\(_2\)), 7.3–8.2 (m, 5 H, \(\text{C}_6\text{H}_5\)), 9.65 (br, lost after D\(_2\)O exchange, amide NH), 11.76 (br, 1 H, ring NH) and 12.0 (d, 1 H, NH).

\[ \text{C}_{15}\text{H}_{12}\text{O}_2\text{N}_7 \]

Found C 55.49 H 4.70 N 30.20,
Caled C 55.38 H 4.62 N 30.15.

**Ethyl 2,7-diamino-3-phenylazo-2-phenylpyrazole[1,5-a]-pyrimidine-6-carboxylate (8)**

A suspension of 7 (2.0 g) in acetic acid (30 ml) was refluxed for 6 h. The clear solution, so obtained, was then left to cool and poured over ice cooled water. The crystals that separated (1.5 g), where collected by filtration and crystallised from acetic acid.

8: Afforded yellow crystals from acetic acid, m.p. 215 °C, \(^1\)H NMR: 1.3 (t, 3 H, H\(_2\)), 4.4 (q, 2 H, CH\(_2\)), 7.1 (s, 2 H, pyrazole NH\(_2\)), 7.4–8.7 (m, 5 H, \(\text{C}_6\text{H}_5\)), 8.33 (br, 2 H, lost after D\(_2\)O exchange, pyrimidine NH\(_2\)), 8.7 (s, 1 H, ring CH).

\[ \text{C}_{15}\text{H}_{12}\text{O}_2\text{N}_3 \]

Found C 55.50 H 4.80 N 30.40,
Caled C 55.38 H 4.62 N 30.15.

3,5-Diacetamido-4-phenylazopyrazole (9)

A solution of either of 1, 3a, b or 4 (2.0 g) acetic acid (50 ml) was treated with concentrated sulphuric acid (2.0 ml; 98%). The reaction mixture was refluxed for 3 h and the solvent was then removed in vacuo. The remaining product was then dissolved in little water cooled and neutralised by ammonium hydroxide. The solid product so formed was col-
lected by filtration and crystallized from ethanol (norit was used to eliminate coloured impurities). The yields obtained were 92% in each case.

9: Colourless crystals, m.p. 301 °C. *H NMR: 2.15 (s, 6 H, 2 CH₃), 6.30 (s, 1 H, ring CH), 10.4 (br, 2 H, lost after D₂O exchange amide NH) and 11.8 (br, s, 1 H, ring NH).

C₇H₁₀O₂N₄

Found C 46.06 H 5.60 N 31.28,
Caled C 46.15 H 5.60 N 30.76.

1 J. Haeufel and E. Breitmaier, Angew. Chem. 85, 939 [1973].