

Pyrimidine Derivatives and Related Compounds VI. A Novel Synthesis of 3,5-Diacetamidopyrazole and of 2-Aminopyrazolo[1,5-*a*]pyrimidines

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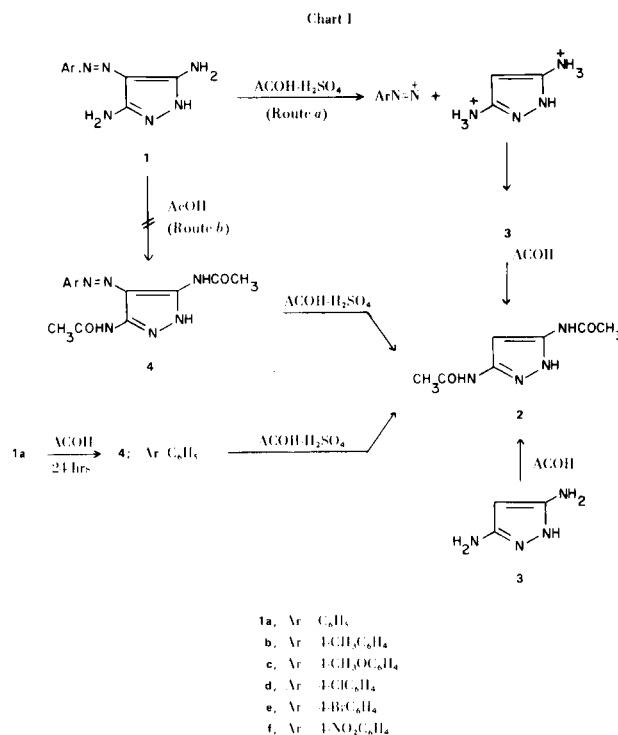
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3,5-Diacetamidopyrazole (**2**) could be prepared *via* arylazo group decoupling from 3,5-diamino-4-arylazopyrazoles (**1a-c**) by the action of acetic acid-sulfuric acid mixture. Arylazo group removal could also be effected when 2-amino-5-methyl-7-oxo-6,7-dihydro-3-phenylazopyrazolo[1,5-*a*]pyrimidine (**5**) was similarly treated. The 2-aminopyrazolo[1,5-*a*]pyrimidine derivative was obtained in this case. On the other hand, under the same experimental conditions compounds **7a-c** and **8** were recovered almost unaffected. The mechanism of the reaction is discussed.

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Recently we have reported a convenient synthesis of 3,5-diamino-4-arylazopyrazoles and their conversion into 2-amino-3-arylazopyrazolo[1,5-*a*]pyrimidines (**1-3**). Now, for a continuing investigation of the biological activity of 3,5-diaminopyrazoles as well as that of 2-aminopyrazolo[1,5-*a*]pyrimidine (**4**) derivatives of both ring systems without the arylazo substituent were needed. Inspection of the literature data indicated that these derivatives are only obtainable *via* a multistage inefficient synthesis and, in most cases, from starting materials unavailable in the laboratory (5-7). For these reasons we have considered a possible preparation of such derivatives *via* arylazo group removal from the corresponding, readily available, arylazo derivatives. A mixture of acetic acid and sulfuric acid was chosen to effect arylazo removal to avoid possible hydrolysis or cleavage (**8**) of the azoline ring by the action of acetic acid-hydrochloric acid mixture previously used by us to effect arylazo group removal from some 3-arylazopyrazolo[1,5-*a*]pyrimidines (9,10). The reaction proceeded under the new conditions more readily and afforded much higher yields of the required products. Thus, when 4-phenylazo-3,5-diaminopyrazole (**1**) was treated with an acetic acid-sulfuric acid mixture, 3,5-diacetamidopyrazole (**2**) was obtained in 92% yield. Compound **2** could be prepared by the action of acetic acid on 3,5-diaminopyrazole (**3**). It seems most probable that the reaction proceeds *via* a mechanism which is a reversal for the azo coupling (*cf.* Chart 1). In support of this view is the observed facilitating effect of electron releasing groups in the arylazo moiety on the overall reaction rate and the



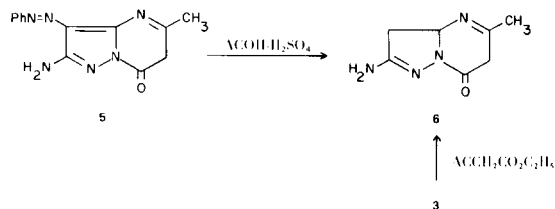
reverse effect induced by electron attracting substituents. Approximate reaction times needed for the completion of the reaction with compounds **1a-f** as observed by tlc is compiled in Table I. The formation of **2** from **1a-e** may proceed *via* route *a* or *b* (*cf.* Chart 1). Preliminary results suggest that route *a* is more probable. This was indicated from the fact that **3** was readily converted into **2** by the

Table I

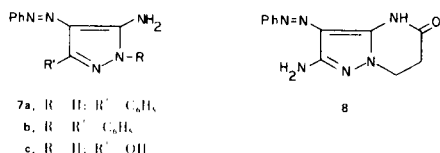
Compound	Time required for completion of reaction in minutes	Yield
1		
a	90	95
b	30	95
c	20	quantitative
d	240	82
e	240	82
f	no reaction	

action of acetic acid, whereas compounds **1a-e** were recovered unreacted when similarly treated. Moreover, conversion of 3,5-diacetamido-4-phenylazopyrazole (**4**), prepared by refluxing **1a** in acetic acid for 24 hours, into **2** by acetic acid-sulfuric acid mixture required a longer reaction period than that needed for the conversion of **1a** into **2** by the same reagent. Kinetic investigations on this matter are now being carried out in order to obtain a definitive answer to the problem.

Phenylazo group decoupling could be effected when the pyrazolo[1,5-*a*]pyrimidine derivative **5** was treated similarly and 2-amino-5-methyl-7-oxo-6,7-dihydropyrazolo[1,5-*a*]pyrimidine (**6**) was formed in good yield. Compound **6** could be also obtained by the action of ethyl acetoacetate on **3**.



In order to define the scope and limitation for the utility of the acetic acid-sulfuric acid mixture as a reagent for arylazo group decoupling the 4-aryloxy-5-aminopyrazole derivatives **7a-c** and the pyrazolo[1,5-*a*]pyrimidine



derivative **8** were treated with the same reagent. All these compounds were recovered almost unreacted after being refluxed with the reagent for more than 72 hours. These results suggest that the presence of two sufficiently basic nitrogen atoms adjacent to the arylazo group is necessary for the arylazo decoupling reaction to take place.

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 the internal standard and chemical shifts are expressed as δ parts per million with DMSO-*d*₆ as the solvent. Elemental analysis were performed by M. H. W. Laboratories, Garden City, Michigan, USA, and by the analytical data unit at Cairo University.

3,5-Diacetamidopyrazole (**2**).

a) From **1a-e**, **4** and Acetic Acid-Sulfuric Acid Mixture.

A solution of **1a-e** and **4** (2.0 g.) in acetic acid (50 ml.) was treated with concentrated sulfuric acid (2.0 ml., 98%). The reaction mixture was refluxed until complete reaction (as indicated by spot tests on tlc) and the solvent was then removed *in vacuo*. The remaining product was then dissolved in a little water, cooled and neutralized by ammonium hydroxide. The solid product, so formed, was collected by filtration and crystallized from ethanol (Norite was used to eliminate coloured impurities).

Compound **2** formed colourless crystals, m.p. 301°; pmr: 2.15 (s, 6H, 2CH₃), 6.30 (s, 1H, ring CH), 10.4 (br, 2H, lost after deuterium oxide exchange; amide NH) and 11.8 (br, s, 1H, ring NH).

Anal. Calcd. for C₇H₁₀N₄O₂: C, 46.15; H, 5.60; N, 30.76. Found: C, 46.06; H, 5.60; N, 31.28.

b) From **3** and Acetic Acid.

A solution of **3** (1.0 g.) in acetic acid (20 ml.) was refluxed for 20 minutes. The solvent was removed *in vacuo*. The remaining product was triturated with water. The resulting solid product was collected by filtration, crystallized from ethanol and identified as **2** (by m.p., mixed m.p. and ir). The yield was 1.2 g.

3,5-Diacetamido-4-phenylazopyrazole (**4**; Ar = C₆H₅).

A solution of **1a** (2.0 g.) in acetic acid (50 ml.) was refluxed for 24 hours. The solvent was then removed *in vacuo* and the remaining product was dissolved in water (15 ml.) and neutralized by dilute ammonium hydroxide. The solid product, so formed, was collected by filtration and crystallized from methanol, yield 2.2 g., m.p. 224°; pmr: 2.17 (s, 6H, 2CH₃), 7.43-7.90 (m, 5H, C₆H₅) and 10.33 (s, br, 2H, lost after deuterium oxide exchange, amide NH) and 12.7 (br, 1H, ring NH).

Anal. Calcd. for C₁₃H₁₄N₆O₂: C, 54.54; H, 4.93; N, 29.36. Found: C, 54.54; H, 5.00; N, 29.46.

2-Amino-5-methyl-7-oxo-6,7-dihydropyrazolo[1,5-*a*]pyrimidine (**6**).

a) From **5** and Acetic Acid-Sulfuric Acid.

A solution of **5** (1.0 g.) in acetic acid (30 ml.) was treated with sulfuric acid (1.5 ml.), the reaction mixture was refluxed for 8 hours and the solvent was then removed *in vacuo*. The remaining product was triturated with water and neutralized with ammonium hydroxide. The solid product, so formed, was collected by filtration and crystallized from I. P. L., m.p. > 360°, yield 0.75 g.; pmr: 2.10 (s, 3H, CH₃), 2.30 (s, 2H, CH₂), 5.60 (br, s, 2H, NH₂, lost after deuterium oxide exchange) and 6.43 (s, 1H, CH).

Anal. Calcd. for C₇H₈N₄O: C, 51.27; H, 4.91; N, 34.13. Found: C, 51.27; H, 4.89; N, 34.13.

b) From **3** and Ethyl Acetoacetate.

A mixture of **3** (1.0 g.) and ethyl acetoacetate (1.5 ml.) was heated on a water bath for 3 hours. The reaction mixture was

then triturated with water. The resulting solid was collected by filtration and identified (by ir and pmr) as **6**, yield 1.2 g.

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