Pyrimidine Derivatives and Related Compounds, IX
Preparation of 5-Aminopyrazolo[1,5-a]pyrimidines
and of Oxazino[4,5 : 5,6]pyrazolo[1,5-a]pyrimidines, a New Ring System

MOHAMED HILMY ELMAGDI*, SHERIF MAHMOUD FAHMY,
MOHAMED RIFFAAT HAMZA ELMOHAYAR, and ABDALLA MOHAMED NEGM
Department of Chemistry, Faculty of Science, Cairo University, Giza, A. R. Egypt
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Pyrimidine Derivatives

Whereas the 5-aminopyrazole derivatives (1a, b) react with ethyl β-amino-β-trichloromethylenecyanoacetate (2) in basic media to yield the corresponding 5-aminopyrazolo[1,5-a]pyrimidine derivatives (3a, b), the reaction of 1a, b with 2 in refluxing acetic acid has afforded oxazino[4,5 : 5,6]pyrazolo[1,5-a]pyrimidine derivatives.

5-Amino-3-phenyl-4-phenylazopyrazole (12) reacted with 2 in refluxing pyridine to yield the 5-amino-2-phenyl-3-phenylazopyrazolo[1,5-a]pyrimidine derivative (13). On the other hand, the reaction of 12 and 2 in refluxing acetic acid has afforded a mixture of the oxazino[4,5 : 5,6]pyrazolo[1,5-a]pyrimidine derivatives (14) and the pyrazolo[3,4-d]-astatriazine derivatives (15). The mechanism of the formation of reaction products is discussed.

Pyrazolo[1,5-a]pyrimidines have become of recent importance due to their biological activities1-5. In previous work from this laboratory we have described a variety of new procedures for the synthesis of differently substituted pyrazolo[1,5-a]pyrimidines6-11. Now for a continuing investigation of the described a variety of new procedures for the synthesis of differently substituted pyrazolo[1,5-a]pyrimidines. Thus, 5-amino-3-phenylpyrazole (1a) reacted with ethyl β-amino-β-trichloromethylenecyanoacetate (2) in basic media to yield the 5-amino-4-cyano-3-cyanomethylpyrazole (1, R = CN) with 2 under the same conditions was unsuccessful. That (1b) was inactive toward (2). However when the reaction of (1b) and 2 was conducted in ethanolic sodium ethoxide, the 5-amino-3-phenylpyrazolo[1,5-a]pyrimidine derivative (3b) was formed in 80% yield. Attempted condensation of 5-amino-4-cyano-3-cyanomethylpyrazole (1, R = CH2CN, R = CN) with 2 under a variety of experimental conditions were unsuccessful. That 1a condensed readily with 2 whereas more drastic conditions were needed to effect condensation of 1b with the same reagent and 1, R = CH2CN, R = CN was inactive toward 2 is understandable in terms of the decrease in the reactivity of the amino group in the latter two aminopyrazole derivatives resulting from inductive and mesomeric effects of the cyano group adjacent to the amino group.

Attempted condensation of (1a) with 2 in refluxing acetic acid has resulted in the formation of a mixture of two products of melting points 130 and 215 °C.
These were formed in the respective ratio 1:4. The low melting product was identified as 5,7-diamino-6-ethoxycarbonyl-2-phenylpyrazole based on its IR and pmr data. The higher melting product revealed a molecular formula of C_{15}H_{11}O_{2}N_{5}. Four structures seemed possible for this product (cf. structures 6-9 in Chart I). The angular structures 6 and 7 were readily eliminated based on the presence of a pyrimidine ring signal in the pmr of the reaction product which cannot be accounted for in terms of such structures. Structure 8 was also eliminated since its formation would proceed either via acylation of initially formed 3a or by acylation of 2 prior to condensation with 1a. Both 3a and 2 proved highly stable toward sever treatment with acetic acid. Thus, structure 9 was assumed for the reaction product of 1a and 2. Similar to the behaviour of 1a, compound 1b reacted with 2 in refluxing acetic acid to yield compound 9b as the only isolable product. The methyl group signal of 9b is deshielded by 1.15 ppm as compared to the methyl group resonance of 9a. This deshielding may be attributed to the long range diamagnetic anisotropy of the cyano group.

The reaction of 1a, b with 2 might be assumed to proceed via a mechanism similar to that established for its reaction with amines and hydrazines. Thus, initial condensation of 1a, b with 2 via elimination of chloroform might be suggested. Such condensation reaction may involve either the pyrazole ring NH or the exocyclic amino group. Inspite of our inability to isolate or identify acyclic reaction intermediates, structure 10 (resulting from condensation of 2 with the pyrazole amino group) can be assumed for this intermediate since the cyclisation of possible isomeric 11 (resulting from condensation of 2 with the pyrazole ring NH) in basic media would lead to the formation of product 4 rather than the isolated 3a, b (cf. Scheme I). Although an enamine group might appeal a better leaving group as compared with a trichloromethyl one, the high yield obtained from reaction products (90% in case of 3a) might lead to a conclusion that the reaction of 1a, b with 2 proceeds almost exclusively via chloroform elimination. However the preferential elimination of chloroform on reaction of 2 with nucleophilic reagents is in contrast to the reported elimination of ammonia on reaction of β-amino-β-trifluoromethylenemalononitrile with hydrazine. An investigation of the exact mechanism of these reactions aiming to find an explanation of these facts is being now undertaken.

5-Amino-3-phenyl-4-phenylazopyrazole (12) reacted with 2 in refluxing pyridine to yield the expected 5-aminopyrazolo[1,5-a]pyrimidine derivative (13). On the other hand, from reaction of 12 with 2 in acetic acid media a mixture of two products of m.p. 218 and 230 °C was isolated. The product m.p. 218 °C was identified as 14 on the basis of its elemental, and spectral data and by analogy to the behaviour of 1a, b in similar reaction. The methyl group signal of 9b is deshielded by 1.15 ppm as compared to the methyl group resonance of 9a. This deshielding may be attributed to the long range diamagnetic anisotropy of the cyano group.

The formation of 15 from reaction of 12 and 2 in acetic acid is assumed to proceed via formation of acyclic intermediate similar to that previously suggested to account for the reaction of 1a, b and 2. The latter then cyclises into the intermediate 16 via elimination of ammonia. The intermediate 16 then decomposes into the final product. The ready cleavage of the double bond in 16 finds parallelism to the reported ylidenicity of the double bond in similar systems.
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Experimental

All melting points are uncorrected. IR spectra were obtained on a Perkin-Elmer model 337 spectrometer. PMR spectra were obtained on a Varian A-60 spectrometer in DMSO using TMS as internal standard. Chemical shifts are expressed as δ ppm.

5-Amino-6-cyano-6,7-dihydro-7-oxo-2-phenylpyrazolo[1,5-a]pyrimidine (3a)

A solution of 1a (1.6 g) in pyridine (100 ml) was treated with 2 (2.6 g). The reaction mixture was refluxed for four hours and the solvent was then removed in vacuo. The remaining product was triturated with water and the resulting solid product was collected by filtration. The crude product was purified by extraction with hot ethanol and filtration.

Compound 3a, light brown powder, m.p. 300 °C, yield 2.7 g. IR: 1630 cm⁻¹ (δNH₂), 1700 cm⁻¹ (ring CO), 2230-2230 cm⁻¹ (CN bands) and 3050, 3310 and 3400 cm⁻¹ (νNH₂). PMR: 6.98 (s, 1H, pyrazole CH), 7.4-7.6 (m, 5H, C₆H₅), 8.33 (s, 1H, pyrimidine ring CH) and 9.33 (s, 2H, lost after D₂O exchange, NH₂).

C₁₃H₁₅N₅O₅

Found C 61.27 H 3.75 N 23.70,
Calcd C 61.17 H 3.75 N 23.70.

5-Amino-3,6-dicyano-6,7-dihydro-7-oxopyrazolo[1,5-a]pyrimidine (3b)

A suspension of 1b (1.08 g) in methanol (100 ml) was treated with 2 (2.6 g) and sodium methoxide (1.5 g). The reaction mixture was refluxed for three hours. The solvent was then distilled off and heating was then continued in oil bath at 160 °C (bath temperature) for other three hours. The reaction mixture was then left to cool to room temperature, dissolved in little water and neutralised by addition of ammonium hydroxide. The solid product, so formed, was collected by filtration and crystallised from DMF-H₂O mixture.

Compound 3b, colourless crystals, m.p. 340 °C, yield 90%. IR: 1650 cm⁻¹ (δNH₂), 1700 cm⁻¹ (ring CO), 2200 and 2220 cm⁻¹ (CN bands) and 3050, 3310 and 3400 cm⁻¹ (νNH₂). PMR: 8.50 (s, 1H, pyrazole CH), 8.73 (s, 1H, pyrimidine CH and 9.33 (s, 2H, lost after D₂O exchange, NH₂).

C₉H₁₄ON₂

Found C 60.59 H 5.09 N 23.56,
Calcd C 60.59 H 5.09 N 23.56.

10-Hydroxy-9-imino-3-methyl-6-phenyloxazino[4,5:5':6']pyrazolo[1,5-a]pyrimidine (9)

Compound 1b was treated with 2 using the experimental procedure described for the synthesis of 9a from 1a and 2. A period of eight hours was required for complete reaction. The reaction product was crystallised from ethanol.

Compound 9b, colourless crystals, m.p. 230 °C, yield 80%. IR: 1630 cm⁻¹ (δNH₂), 1690 (δ lactone
CO), 2220 cm$^{-1}$ (conjugated CN) and 3050–3350 (NH vibrations). PMR: 3.28 (s, 3H, CH$_3$), 8.56 (s, br, 1H, pyrazole (CH)), 8.76 (s, 1H, pyrimidine ring (CH)) and 9.28 (s, br, 1H, lost after D$_2$O exchange, NH).

C$_{18}$H$_{19}$O$_2$N$_6$

Found C 49.59 H 2.30 N 35.00,
Calcd C 49.59 H 2.30 N 35.00.

5-Amino-6-cyano-6,7-dihydro-7-oxo-2-phenyl-3-phenylazopyrazolo[1,5-a]pyrimidine (13)

Compound 12 was treated with 2 using the experimental conditions described for the preparation of 3a from 1a and 2. The reaction product was crystallised from ethanol.

Compound 13, yellow crystals, m.p. 230 °C, yield 80%. IR: 1640 cm$^{-1}$ (δNH$_2$), 1700 cm$^{-1}$ (ring CO), 2200 cm$^{-1}$ (CN) and 3200–3350 cm$^{-1}$ (2NH$_2$).

C$_{19}$H$_{19}$O$_2$N$_7$

Found C 63.95 H 3.40 N 27.41,
Calcd C 64.22 H 3.66 N 27.60.

reaction of 12 with 2 in refluxing acetic acid

A suspension of 12 (2.6 g) in acetic acid (100 ml) was treated with 2 (2.6 g) and the reaction mixture was refluxed for eight hours. The solvent was then removed in vacuo and the remaining solid product was extracted with hot ethanol. The insoluble part (1.5 g) was collected by filtration, crystallised from acetic acid and identified (m.p. and mixed m.p.) as 15.

Concentration of the ethanol extract afforded yellow crystals (1.0 g) which were recrystallised from ethanol-water mixture to yield pure sample of 14. m.p. 218 °C. IR: 1635 cm$^{-1}$ (δNH$_2$) and 3250–3350 cm$^{-1}$ (NH vibrations).

C$_{21}$H$_{19}$O$_2$N$_7$

Found C 62.83 H 4.77 N 24.00,
Calcd C 62.58 H 4.50 N 24.00.

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