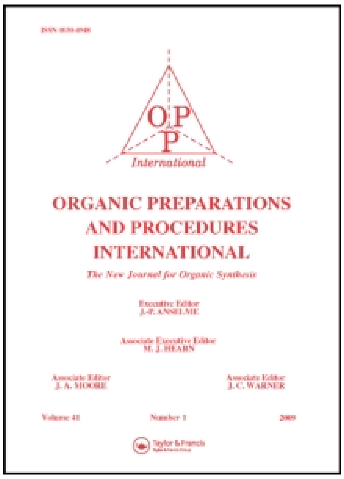

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N. M. Abed[a]; N. S. Ibrahim[a]; S. M. Fahmy[a]; M. H. Elnagdi[a]
[a] Chemistry Department, Faculty of Science, Cairo University, Giza, EGYPT

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ACTIVATED NITRILES IN HETEROCYCLIC SYNTHESIS. NOVEL SYNTHESES OF PYRIMIDINES AND PYRIDINES

N. M. Abed, N. S. Ibrahim, S. M. Fahmy and M. H. Elnagdi*

Chemistry Department, Faculty of Science,
Cairo University, Giza, EGYPT

The enamino nitrile derivatives 1a and 1b, readily obtained *via* dimerization of ethyl cyanoacetate[1] and of malononitrile,[2] are versatile reagents and have been extensively utilized as intermediates in heterocyclic synthesis.[3-6] As a part of our program directed to the development of some new procedures for synthesis of azoles,[7] azines[8] and azoloazines[9-11] from readily available materials, we have used 1a and 1b to synthesize difficulty accessible pyridines, pyridazines and pyrazoles.

Thus it has been found that 1a and 1b couple with aromatic diazonium chlorides to yield the corresponding hydrazone derivatives 2a-2d respectively, which are readily cyclized into the pyridazine derivatives 3a-3d upon boiling in weak alkaline solutions. When 2a was refluxed with acetic anhydride it was converted into the acetamidopyridazin-6-one derivative 4. Attempts to convert 3a into 4 by the action of acetic anhydride were unsuccessful. The amino group of 3a proved also highly stable toward nucleophilic reagents; the inertness of 4-aminopyridazines toward nucleophilic reagents has been previously noted and suggests that 3a exists mainly as zwitterion 5. As previously observed[3] for 1a, 1b reacted with benzylidenemalononitrile to yield the pyridine derivative 6.

Compound 1a also coupled with diazotized 5-amino-3-phenylpyrazole (7) to yield the corresponding arylhydrazone derivative 8. Attempted cyclization of 8 by the action of acetic acid afforded a product of molecular formula $C_{15}H_{10}N_6O_5$. Two isomeric structures (9 and 10) seemed possible for this product. Although we are not in a position to exclude structure

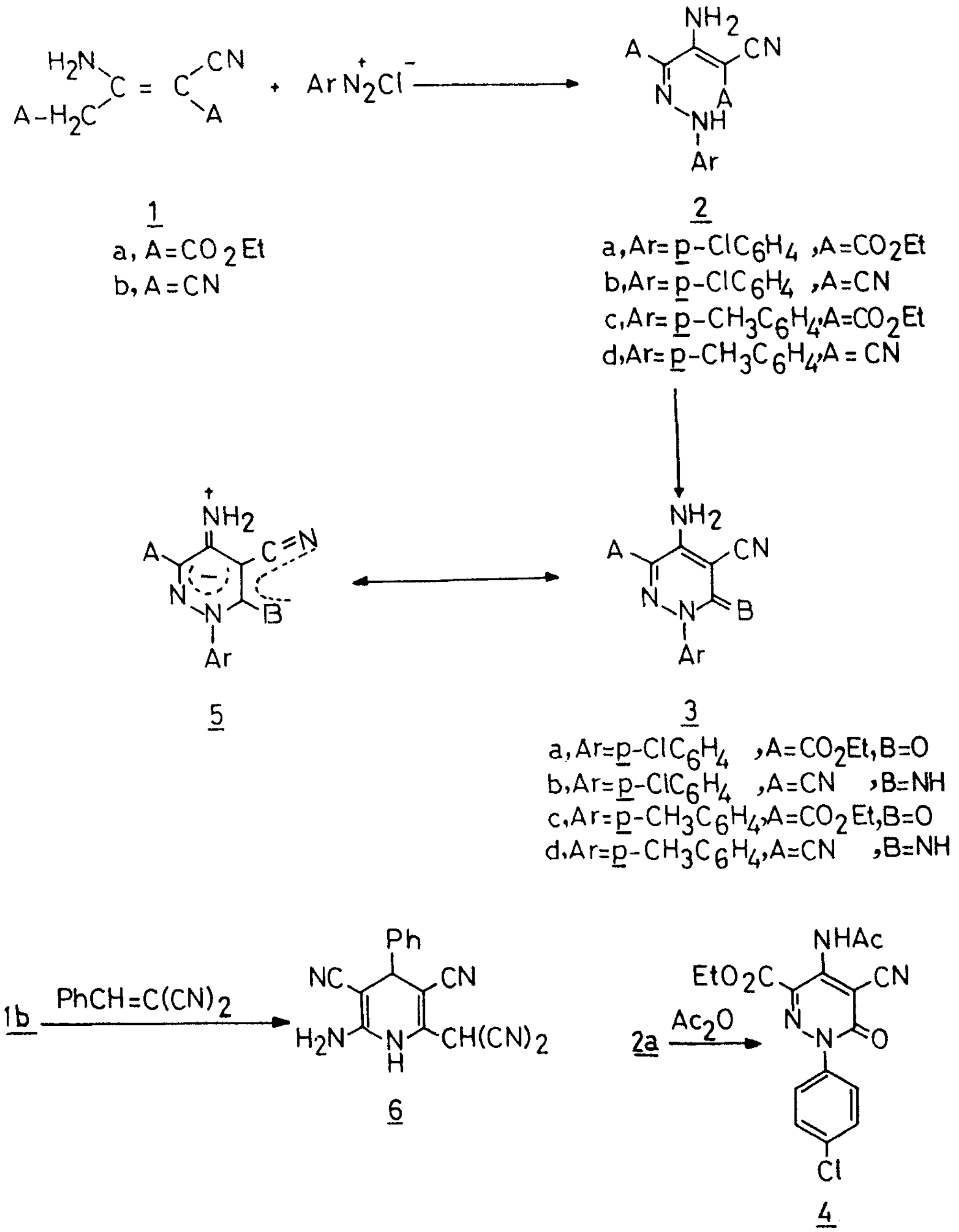

Chart 1

10 completely, structure 9 seems most likely as there is no convincing mechanism to rationalize the evidently facile hydrolysis of one of the ester groups final product, shown to contain a free carboxylic group by titration against sodium carbonate. Indeed the ester group of compound 3c, related to the putative pyridazin-6-one 10, proved stable under even more

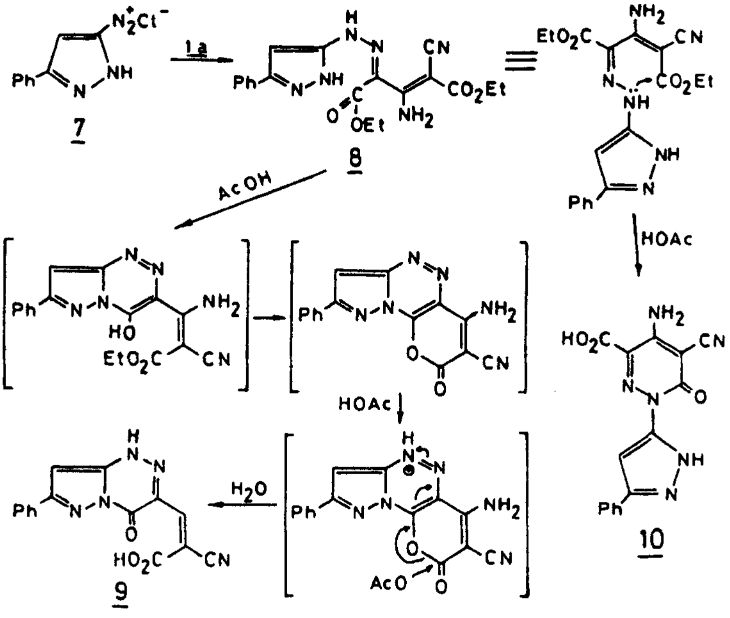

Chart 2

drastic conditions and the reaction product proved stable under conditions reported to effect rearrangement of pyridazinones.[12] On the other hand, the formation of acid 9 can be understood in terms of cyclization into a pyrazolo[1,5-c]-as-triazine followed by further cyclization under the reaction conditions into pyrano[2,3:6',7']pyrazolo[1,5-c]-as-triazine. The latter is unstable and readily opened during treatment of the reaction mixture to yield 9 as shown in Chart 2. Although pyrones are known to be stable on treatment in weakly acidic solutions, the opening of the pyrone ring may be attributed to protonation of the triazine ring nitrogen which enhances pyrone ring opening under reaction conditions (Chart 2).

Acknowledgement.- The authors are grateful to Mr. R. M. Mohareb for his help with large scale preparation of some of the products described.

EXPERIMENTAL SECTION

Melting points are uncorrected. IR spectra were obtained on a Pyre Unicam SP-1100 spectrophotometer (KBr). Analytical data were performed by the Microanalytical Centre, Cairo University. Compounds 1a and 1b were prepared following literature procedures.[1,2]

Coupling of 1a and 1b with Aromatic Diazonium Chloride.- A solution of the aromatic diazonium chloride (prepared from 0.01 mol of aromatic amine and the appropriate quantity of HCl and $NaNO_2$) was added to a well-stirred solution of each of 1a or 1b (0.01 mol) containing 5 g of anhydrous sodium acetate. The reaction mixture was left at room temperature for 15 min. The resulting solid product was collected by filtration and crystallized from ethanol.

Compound 2a, orange crystals (92%), mp. 135°.

IR: 3420, 3350, 3300 (NH_2 and NH); 2200 (CN); 1740, 1720 (two ester C=O) and 1650 (C=N) cm^{-1}.

Anal. Calcd for $C_{16}H_{17}ClN_4O_4$: C, 52.62; H, 4.67; N, 15.38

Found: C, 52.60; H, 4.60; N, 15.30

Compound 2b, yellow crystals (70%), mp. 278°.

IR: 3410, 3310, 3300 (NH_2 and NH); 2220, 2210, 2190 (three CN); 1650 (δ NH) and 1640 (C=N)cm^{-1}.

Anal. Calcd for $C_{12}H_7ClN_6$: C, 53.13; H, 2.90; N, 30.90; Cl, 13.20

Found: C, 53.20; H, 3.20; N, 31.00; Cl, 13.00

Compound 2c, pale yellow crystals (90%), mp. 130°.

IR: 3410, 3330, 3300 (NH_2 and NH); 2220 (CN); 1730, 1700 (two ester C=O) and 1640 (C=N) cm^{-1}.

Anal. Calcd for $C_{15}H_{14}N_4O_3$: C, 60.30; H, 4.73; N, 18.78

Found: C, 60.00; H, 4.90; N, 18.60

Compound 2d, orange crystals (60%), mp. 140°.

IR: 3410, 3320, 3300 (NH_2 and NH); 2220, 2200, 2190 (three CN); 1650 (δ NH) and 1630 (C=N) cm^{-1}.

Anal. Calcd for $C_{13}H_{10}N_6$: C, 61.89; H, 4.79; N, 33.60

Found: C, 61.80; H, 5.00; N, 33.80

Cyclization of 2a-2d.- A solution of each of 2a-2d (0.01 mol) in ethanolic sodium hydroxide (prepared from 0.01 mol of sodium hydroxide in 30 ml of ethanol) was heated to boiling for 30 minutes. The solvent was evaporated in vacuo and the product was collected, washed with water and crystallized from ethanol.

Compound 3a, yellow crystals (70%), mp. 250°.

IR: 3400, 3350 (NH_2), 2220 (CN); 1730 (ester CO); 1690 (ring C=O) and 1650 (C=N) cm^{-1}.

Anal. Calcd for $C_{14}H_{11}ClN_4O_3$: C, 52.82; H, 3.53; N, 17.58

Found: C, 52.80; H, 3.80; N, 17.40

Compound 3b, brown crystals (80%), mp. > 300°.

IR: 3400, 3350, 3310 (NH_2 and NH); 2220, 2210 (two CN) and 1660 (C=N) cm^{-1}.

Anal. Calcd for $C_{12}H_7N_6Cl$: C, 53.13; H, 2.90; N, 30.90; Cl, 13.20

Found: C, 53.20; H, 3.20; N, 31.20; Cl, 13.50

Compound 3c, pale yellow crystals (80%), mp. 270°.

IR: 3400, 3340 (NH_2); 2200 (CN); 1720 (ester C=O); 1670 (ring C=O) and 1650 (C=N) cm^{-1}.

Anal. Calcd for $C_{15}H_{14}N_4O_3$: C, 60.39; H, 4.73; N, 18.79

Found: C, 60.00; H, 4.40; N, 18.70

Compound 3d, orange crystals (85%), mp. > 300°.

IR: 3390, 3330, 3300 (NH_2 and NH); 2210, 2200 (two CN) and 1640 (C=N) cm^{-1}.

Anal. Calcd for $C_{13}H_{12}N_6$: C, 61.89; H, 4.79; N, 33.33

Found: C, 62.10; H, 4.50; N, 33.40

Reaction of **2a** with Acetic Anhydride.- A solution of 2a (5g) in acetic anhydride (20 ml) was boiled under reflux for 10 hrs, evaporated *in vacuo* and then poured into water. The solid product thus obtained was collected by filtration and crystallized from ethanol.

Compound **4**, brown crystals (80%), mp. 235°.

IR: 3300 (NH); 2220 (CN); 1740 (ester C=O); 1720 (acetyl C=O); 1680 (ring C=O) and 1640 (C=N) cm^{-1}.

Anal. Calcd for $C_{16}H_{13}ClN_4O_4$: C, 53.25; H, 3.69; N, 15.53

Found: C, 53.00; H, 3.50; N, 15.30

Reaction of **1b** with Benzylidenemalononitrile.- A solution of **1b** (0.01 mol) in ethanol (20 ml) was treated with benzylidenemalononitrile (0.01 mol) and one ml of triethylamine. The reaction mixture was refluxed for 3 hrs then evaporated. The remaining product was triturated with ethanol and then neutralized by the addition of acetic acid. The solid product so formed was collected by filtration and crystallized from ethanol.

Compound **6** colorless crystals (40%), mp. 195°.

IR: 3400, 3350, 3300 (NH_2 and NH)); 2240, 2230, 2220 (CN) and 1640 (δ NH) cm^{-1}.

Anal. Calcd for $C_{16}H_{10}N_6$: C, 67.13; H, 3.53

Found: C, 67.10; H, 3.50

Coupling of **1a** with Diazotized 5-Amino-3-phenylpyrazole.- An ice cold solution of diazotized aminopyrazole (prepared from 0.05 mol of 5-amino-3-phenylpyrazole and the appropriate quantities of HCl and $NaNO_2$) was gradually added to an ethanolic solution of **1a** (0.05 mol). The solid product so formed was collected by filtration and crystallized from ethanol.

Compound 8, yellow crystals (70%), mp. 55°.

IR: 3420, 3350, 3300 (NH_2 and NH); 2220 (CN); 1740, 1720 (two ester C=O); 1660 (C=N) and 1640 (C=C) cm^{-1}.

Anal. Calcd for $C_{19}H_{20}N_6O_4$: C, 57.12; H, 5.00; N, 21.22

Found: C, 57.10; H, 4.70; N, 21.30

Cyclization of 8.- A solution of 8 (0.01 mol) in acetic acid (20 ml) was boiled under refluxed for 1 hr. The reaction mixture was diluted with water and the solid product so formed was collected by filtration and crystallized from ethanol-acetic acid mixture.

Compound 9, yellow crystals (49%), mp. > 300°.

IR: 3430, 3390, 3350 (NH_2 and NH); 2210 (CN); 1730 (acid C=O); 1690 (ring C=O); 1660 (C=N) and 1640 (C=C) cm^{-1}.

Anal. Calcd for $C_{15}H_{10}N_6O_3$: C, 55.92; H, 3.10; N, 26.08

Found: C, 55.90; H, 3.30; N, 26.10

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