Nitriles in Organic Synthesis

A Route to Polyfunctionally Substituted Azabiaryls

Nitrile als Synthesebausteine: Polyfunktionalisierte Azabiaryle

Nadia S. Ibrahim, Mona H. Mohamed, and Mohamed H. Elnagdi

Department of Chemistry, Faculty of Science, Cairo University, Giza, Egypt.

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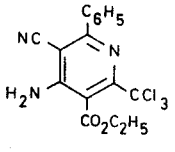
In previous work we have shown that the reaction of trichloroacetonitrile with bifunctional nitriles leads to aminoheterocycles having a trichloromethyl substituent[1]. The trichloromethyl function in these heteroaromatic amines can be readily replaced by nucleophilic reagents[1]. Recent interest in utility of this synthetic approach for preparation of aromatic aminoheterocycles[2-4] as well as reported abnormal reactivity of the trichloromethyl function in π-deficient heterocycles[5] prompt us to report our further results in this area. This work was undertaken in connection with a biological chemistry project in our laboratories when samples of different derivatives of azabiaryls were required.

Inspection of literature revealed that **2** has not been synthesized. Reacting the iminoester **3** with benzoylacetonitrile **(4a)** led to **2**. Structure **2** was established instead of **5** for the reaction product based on IR- and ^{1}H-NMR-evidence as well as on the formation of the arylhydrazones **6a,b** on coupling with aryldiazonium salts. **2** reacted with trichloroacetonitrile catalyzed with sodium acetate to yield **1**. The alternative pyrimidine **7** was ruled out on basis of the ^{1}H-NMR spectrum which revealed no signal for CH_2 protons. The formation of the pyridine **1** is thus assumed to take place by addition of the active methylene moiety in **2** to the nitrile followed by cyclization with water elimination.



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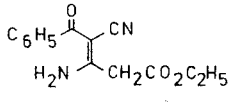

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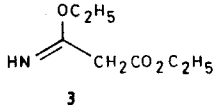

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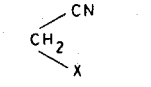
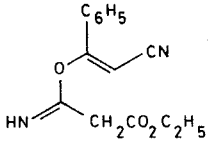


4a, X = COC_6H_5
b, X = CN
c, X = $CO_2C_2H_5$



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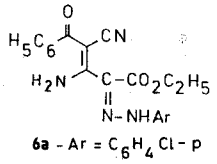
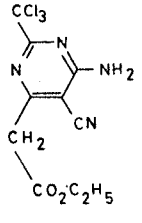


6a - Ar = C_6H_4Cl-p
b - Ar = C_6H_4Cl-o



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Compound **1** reacted with hydrazine hydrate to yield the pyrido[2,3-c]pyrazole **8**. Although intermediates for formation of **8** could not be isolated, it is assumed that **9** rather than **10** is the intermediate. This belief finds support from isolation of **11** on reacting **1** with phenylhydrazine.

Compound **1** reacted with **4b, c** and Na° in dioxane to yield the disubstituted alkylpyridine derivatives **12a, b**. Substitution of the trichloromethyl function in trichloromethyl pyridines by carbanions has been observed[1]. **12a** reacted with hydrazine hydrate to yield **13a**. Compound **13a** is assumed to be formed via the intermediacy of **14a** which could not be isolated. In contrast, **12b** afforded **14b** on reaction with hydrazine in ethanol. Compound **14b** could not cyclized into **13b** even on long reflux in ehtanol.

Experimental Part

I. R. spectra: KBr discs, Pye-Unicam SP-1100 spectrophotometer. – ^{1}H-NMR spectra: Varian A-60 spectrometer, TMS as internal standard. – Analytical Data: microanalytical center at Cairo University. – Melting points: uncorrected.

Ethyl 3-Amino-4-cyano-5-oxo-5-phenylpent-3-enoate **(2)**

Diethyl iminomalonate (0.2 mole) was refluxed with benzoylacetonitrile (0.2 mole) in 200 ml chloroform in presence of triethylamine (20.2 mol) for 1 h. The reaction mixture was washed several times with water. The chloroform layer was separated and evaporated in vacuo. The solid product, so formed, was separated and crystallized from ethanol as yellow crystals, m.p. 92 °C, yield 43.8 g (85 %). – IR: 3400, 330 (NH_2); 2200 (CN); 1710, 1690 (CO). – ^{1}H-NMR (DMSO): δ = 1.3 (t, 3H, CH_3); 3.8 (s, 2H, NH_2); 4.2 (m, 4H, 2 CH_2); 7.4–7.8 (m, 5H, aromat.). – $C_{14}H_{14}N_2O_3$ (258.3) Calcd. C 65.1 H 5.4 N 10.9 Found C 65.0 H 5.2 N 10.9.

Ethyl 3-amino-2-arylhydrazono-4-cyano-5-oxo-5-phenylpent-3-enoate **(6a, b)**

A solution of **2** (0.01 mole) in ethanol (50 ml) containing sodium acetate (5 g) was cooled to 0 °C, stirred and treated gradually with a cooled solution of the appropriate aryldiazonium salt. The solid product formed on standing was collected and crystallized from the proper solvent.

6a: yellow crystals from ethanol; m.p. 186 °C; yield 3.3 g (85 %). – IR: 3400, 3300 (NH_2 and NH); 2200 (CN); 1710, 1690 (CO). – $C_{20}H_{17}N_4O_3Cl$ (396.8) Calcd. C 60.6 H 4.3 N 14.1 Found C 60.6 H 4.5 N 14.3.

6b: yellow crystals from ethanol; m.p. 141 °C; yield 2.9 g (75 %). – IR: 3480, 3380 (NH_2 and NH); 2200 (CN); 1710, 1690 (CO). – $C_{20}H_{13}N_4O_3Cl$ (396.8) Calcd. C 60.5 H 4.3 N 14.1 Found C 60.5 H 4.2 N 14.0.

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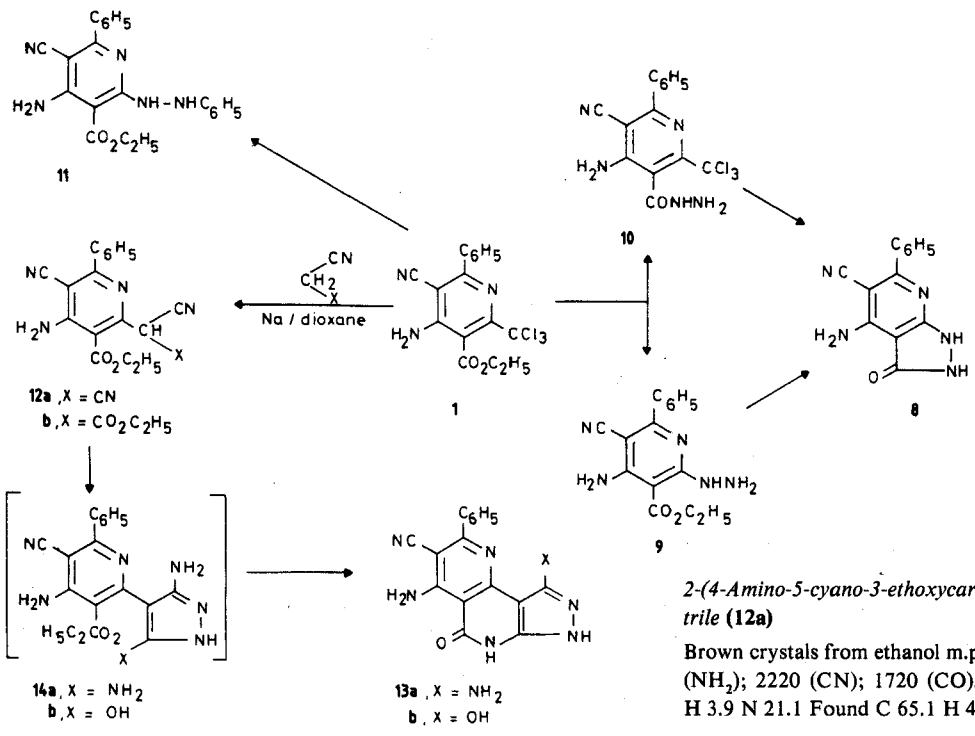

Ethyl 4-amino-5-cyano-6-phenyl-2-trichloromethyl-3-pyridinecarboxylate **(1)**

Equimolecular amounts of **2** (0.01 mole) and trichloroacetonitrile (0.01 mole) were left overnight in an ethanolic solution (30 ml) catalyzed with sodium acetate (3 g). The reaction mixture was poured into water and the solid product was separated and crystallized from ethanol as colourless needles; m.p. 136 °C; yield 2.8 g (75 %). – IR: 3500, 3390 (NH_2); 2220 (CN); 1725 (CO). – ^{1}H-NMR (DMSO): δ = 1.3 (t, 3H, CH_3); 4.4 (q, 2H, CH_2); 7.1 (s, 2H, NH_2); 7.5–8.0 (m, 5H, aromat.). – $C_{16}H_{12}N_3O_2Cl_3$ (384.6) Calcd. C 50.0 H 3.1 N 11.0 Found C 50.0 H 3.2 N 10.9.

4-Amino-5-oxo-2-phenylpyrido[2,3-c]pyrazole-3-carbonitrile **(8)**

0.01 mole of **1** were heated with hydrazine hydrate (0.01 mole) at 160 °C (bath temp.) for 1 h. The formed solid product was crystallized from DMF/H_2O as yellow crystals, m.p. > 300 °C, yield 1.7 g (70 %). – IR: 3480, 3380 (NH_2 and NH); 2220 (CN); 1720 (CO). – ^{1}H-NMR (DMSO): δ = 6.9 (s, 2H, NH_2); 7.3–7.9 (m, 7H, aromatic and 2 NH protons). – $C_{13}H_9N_5O$ (251.3) Calcd. C 62.1 H 3.6 N 27.9 Found C 62.2 H 3.6 N 27.6.

(Ethyl 4-amino-5-cyano-6-phenyl-3-pyridinecarboxylate-2-yl)phenylhydrazine **(11)**

0.01 mole of 1 were heated with phenylhydrazine (0.01 mole) at 160 °C (bath temp.) for 1 h. The formed product was crystallized from ethanol as brown crystals; m.p. > 300 °C; yield 2.2 g (60 %). – IR: 3450, 3350 (NH_2 and NH); 2210 (CN); 1720 (CO). – $C_{21}H_{19}N_5O_2$ (373.5) Calcd. C 67.5 H 5.1 N 18.7 Found C 67.6 H 5.1 N 18.5.

General procedure for the preparation of **12a, b**

To a suspension of sodium metal (0.01 mole) in dioxane (30 ml), either malononitrile (0.01 mole) or ethyl cyanoacetate (0.01 mole) was added. The mixture was refluxed for 10 min, then 0.01 mole of 1 was added. The solution was refluxed for 5 h and then left to cool. The mixture was poured into ice water, then neutralized with conc. HCl till pH 7. The solid products formed were collected by filtration and crystallized from the proper solvent.

2-(4-Amino-5-cyano-3-ethoxycarbonyl-6-phenylpyridine-2-yl)malononitrile **(12a)**

Brown crystals from ethanol m.p. 254 °C; yield 2.6 g (80 %). – IR: 3400 (NH_2); 2220 (CN); 1720 (CO). – $C_{18}N_{13}N_5O_2$ (331.4) Calcd. C 65.2 H 3.9 N 21.1 Found C 65.1 H 4.0 N 21.3.

Ethyl 2-(4-amino-5-cyano-3-ethoxycarbonyl-6-phenylpyridine-2-yl)-cyanoacetate **(12b)**

Yellow crystals from ethanol m.p. > 300 °C; yield 2.6 g (70 %). – IR: 3400 (NH_2); 2200 (CN); 1720, 1690 (CO). – $C_{20}H_{18}N_4O_4$ (378.4). Calcd. C 63.5 H 4.8 N 14.8 Found C 63.3 H 4.6 N 14.6.

Ethyl 4-amino-2-(5-amino-3-hydroxypyrazol-4-yl)-5-cyano-6-phenyl-3-pyridinecarboxylate **(14b)**

To a solution of **12b** (0.01 mole) in ethanol (20 ml), hydrazine hydrate (0.01 mole) was added. The mixture was refluxed for 2 h then evaporated in vacuo. The remaining product was triturated with water containing a few drops of HCl. The solid product was collected by filtration and crystallized from ethanol as brown crystals; m.p. > 300 °C; yield 2.3 g (65 %) – IR: 3530 (OH); 3450, 3350 (NH_2 and NH); 2200 (CN); 1710 (CO). – $C_{18}H_{16}N_6O_3$ (364.4) Calcd. C 59.3 H 4.4 N 23.1 Found C 59.2 H 4.4 N 23.1.

3,7-Diamino-8,9-dihydro-8-oxo-5-phenyl-1H-pyrazolo[3,4:2',3']pyrido[3,2-c]pyridin-6-ylcarbonitrile **(13a)**

Equimolar amounts of **12a** (0.01 mole) and hydrazine hydrate (0.01 mole) were refluxed in ethanol (20 ml) catalyzed with 1 ml piperidine for 3 h. The reaction mixture was poured into water. The formed solid product was collected and crystallized from ethanol as brown crystals; m.p. > 300 °C; yield 2.3 g (75 %) – IR: 3530–3350 (NH_2 and NH); 2220 (CN); 1690 (CO). – $C_{16}H_{11}N_7O$ (317.3) Calcd. C 60.6 H 3.5 N 30.9 Found C 60.3 H 3.5 N 31.1.

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