Activated Nitriles in Heterocyclic Synthesis: Novel Syntheses of Pyrano[2,3-*b*]pyridines and Pyrano[2,3-*d*]pyrimidines

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Reactions of β-(2-furanyl)- and β-(2-thienyl)-acrylonitrile with ethyl acetoacetate are reported. They lead to new polyfunctional derivatives of pyrano[2,3-*b*]pyridine and pyrano[2,3-*d*]-pyrimidine. The structures of these products and the mechanisms of their formation are reported.

Aktivierte Nitrile in der Heterocyclen-Synthese: Neue Synthese von Pyrano[2,3-b]pyridinen and Pyrano[2,3-b]-pyrimidinen

Es wird über die Reaktionen von β-(2-Furanyl)- and β-(2-Thienyl)-acrylonitril mit Ethylacetoacetat berichtet. Einige neue Pyrano[2,3-b]pyridine und Pyrano[2,3-d]-pyrimidine wurden synthetisiert. Über die Strukturen und die Bildungsmechanismen wird berichtet.

In the last decade we have been involved in a program aiming to explore the synthetic potential, scope and limitations of α, β-unsaturated nitriles in heterocyclic synthesis[1]. Several new approaches to five- and six-membered and fused heterocyclic derivatives could be achieved during this work[2].

As a part of a medicinal chemistry program[3,4], in our laboratories the synthesis of several substituted pyrans was required. Several new, otherwise difficultly accessible, pyrans have been prepared. Moreover, the results offer a new and efficient route for the synthesis of pyranopyridines and pyranopyrimidines.

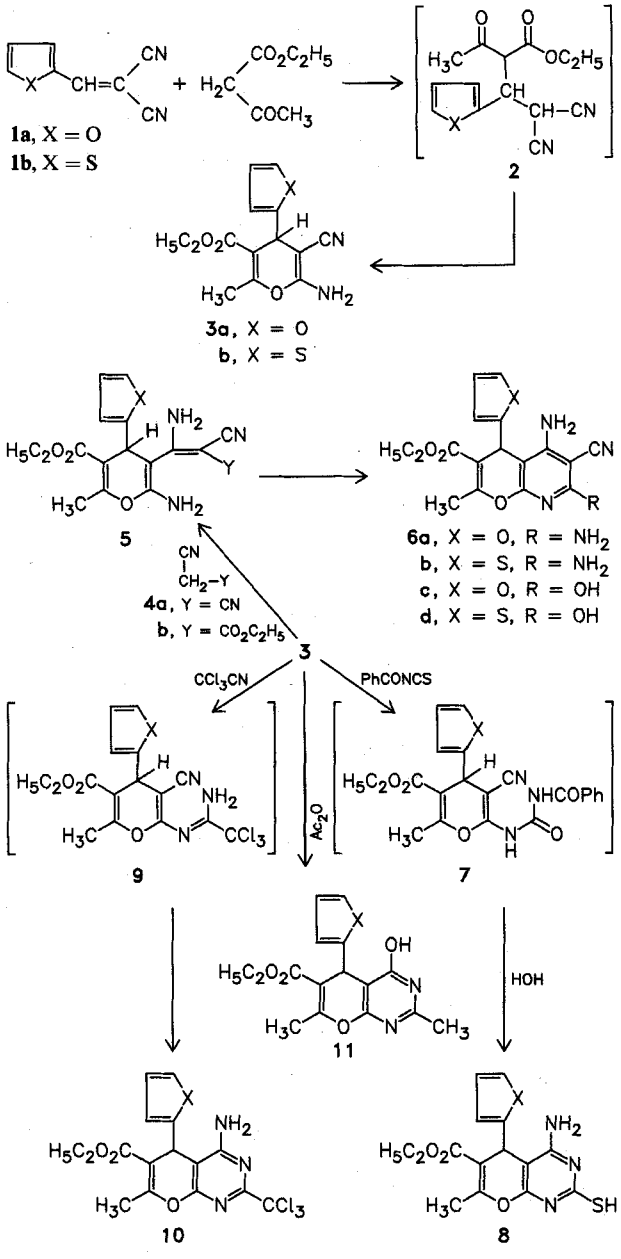
α-Cyanofuran-2-yl-acrylonitril (**1a**) and α-cyanothiophen-2-yl-acrylonitrile (**1b**) reacts with ethyl acetoacetate to yield 1:1 adducts. ^{1}H-NMR- and IR-spectra establish the pyran structure **3** for these products. Thus, it revealed for **3a** the ethyl ester protons, the methyl singlet at δ = 3.3 ppm, the pyran 4-H at δ = 4.4 ppm, two amino protons at δ = 6.8 ppm and furan protons at δ = 6.9–7.5 ppm (m).

The reactivity of compound **3** towards some cyano methylene reagents was investigated. Thus, **3** reacted with malononitrile **(4a)** and ethyl cyanoacetate **(4b)** in ethanol in the presence of triethylamine to yield the pyrano[2,3-b]-pyridines **6a–d**. The formation of **6a, b** from **3** with **4a** is assumed to proceed via addition of the methylene group in **4a** to the cyano group in **3** to yield **5** followed by cyclization. The formation of **6c, d** from **3** with **4b** is assumed to proceed via addition followed by ethanol elimination.

Compound **3** also reacted with the highly activated cyano group of trichloroacetonitrile to give the pyranopyrimidine derivatives **10**. Compounds **10** are assumed to be formed via the intermediacy of **9**.

Compound **3a** reacted with benzoylisothiocyanate to yield a product $C_{15}H_{15}N_3O_4S$. Structure **8a** was established for this compound based on its ^{1}H-NMR spectrum which revealed a NH_2 singlet at δ = 8.0 ppm. The formation of **8a** might be assumed to proceed via addition of benzoylisothiocyanate to yield the intermediate **7a**, which cyclises under the reaction condition and then hydrolyses into the finally isolated product **8a**.

Compound **3** reacted with acetic anhydride to afford the pyranopyrimidines **11**. These results indicate that the reac-



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tion of **3** with suitable active functionally substituted nitriles and isothiocyanates can be utilised as an effective route for the synthesis of several, otherwise difficultly accessible heterocyclic derivatives.

Experimental

Melting points uncorrected. – IR spectra: (KBr) Pye Unicam sp-1000 spectrophotmeter. – ^{1}H-NMR spectra: Varian EM-390 90 MHz spectrometer, DMSO as solvent, TMS as int. reference. Chemical shifts in δ units (ppm). – Mass spectra: MS 30 (AEI), 70 ev. – Analytical data: Microanalytical Centre, Cairo University.

Reaction of **1** *with ethyl acetoacetate*

To a suspension of each of **1a, b** (0.01 mole) in ethanol (30 ml) and ethyl acetoacetate (0.01 mole) 1 ml of piperidine was added. The mixture was refluxed for 6 h then cooled and poured into water. The solid product was collected and crystallised from the proper solvent.

Ethyl 6-amino-5-cyano-4-furanyl(2)-2-methyl-4H-pyran 3-carboxylate **(3a)**

Violet crystals from ethanol; 85 %; m.p. 208 °C. – IR: 3430, 3360 (NH_2), 2220 (CN), 1710 (CO) cm^{-1}. – ^{1}H-NMR: 1.1 (t, 3H, CH_3), 3.3 (s, 3H, CH_3), 4.1 (q, 2H, CH_2), 4.4 (s, 1H, pyran H-4), 6.8 (s, br, 2H, NH_2), 6.9 (dd, 1H, furan H-4), 7.3 (dd, 1H, furan H-3), 7.5 (m, 1H, furan H-5). – ^{13}C-NMR: 166.2 (CO), 155.6 (pyran C-2), 154.8 (C-6), 146.2 (C-5), 142–138.2 (furan carbons), 118.1 (CN), 104.2 (C-3), 58.2 (CH_2 ester), 16.8 (CH_3), 12.8 (CH_3 ester). – $C_{14}H_{14}N_2O_4$ (274) Calcd. C 61.3 H 5.1 N 10.2 Found C 61.0 H 4.8 N 9.9.

Ethyl 6-amino-5-cyano-2-methyl-4-thienyl(2)-4H-pyran 3-carboxylate **(3b)**

Yellow crystals from ethanol; 80 %; m.p. 196 °C. – IR: 3450, 3380 (NH_2), 2210 (CN), 1720 (CO) cm^{-1}. – ^{1}H-NMR: 1.2 (t, 3H, CH_3), 3.1 (s, 3H, CH_3), 4.2 (q, 2H, CH_2), 4.6 (s, 1H, pyran H-4), 6.4 (s, br, 2H, NH_2), 6.8 (dd, 1H, thiophene H-4), 7.5 (m, 1H, thiophene H-3), 7.8 (dd, 1H, thiophene H-5). -M.S: m/z = 290 ($M^{+\cdot}$). – $C_{14}H_{14}N_2O_3S$ (290) Calcd. C 57.9 H 4.8 N 9.3 Found C 58.0 H 4.5 N 9.1.

Reaction of **3** *with* **4a, b**

A solution of **3** (0.01 mole) in ethanol (30 ml), malononitrile or ethyl cyanoacetate (0.01 mole) and 1 ml of triethylamine was refluxed for 5 h, then cooled and poured into water. The solid product was collected and crystallised from the proper solvent.

Ethyl 6-cyano-5,7-diamino-4-furanyl(2)-2-methyl-4H-pyrano[2,3-b]-pyridine-3-carboxylate **(6a)**

Yellow crystals from dioxane; 65 %; m. p. 242-4 °C. – IR: 3450, 3360 (NH_2); 2220 (CN); 1710 (CO) cm^{-1}. – ^{1}H-NMR: 1.1 (t, 3H, CH_3); 3.2 (s, 3H, CH_3); 3.6 (s, br, 2H, NH_2); 4.2 (q, 2H, CH_2); 4.6 (s, 1H, pyran H-4); 5.6 (s, br, 2H, NH_2); 6.8–7.9 (m, 3H, furan H-3,4,5). – $C_{17}H_{14}N_4O_4$ (338) Calcd. C 60.0 H 4.7 N 16.5 Found C 59.8 H 4.6 N 16.2.

Ethyl 6-cyano-5,7-diamino-2-methyl(4)-thienyl-2-4-H-pyrano[2,3-b]pyridine-3-carboxylate **(6b)**

Buff crystals from dioxane; 60 %; m.p. 236 °C. – IR: 3400, 3360 (NH_2), 2210 (CN), 1700 (CO) cm^{-1}–^{1}HNMR: 1.3 (t, 3H, CH_3); 2.6 (s, 3H, CH_3); 3.5 (s, br, 2H, NH_2); 4.1 (q, 2H, CH_2); 4.8 (s, 1H, pyran H-4); 5.5 (s, br, 2H, NH_2); 6.6 (dd, 1H, thiophene H-4); 7.0 (m, 1H, thiophene H-3); 7.7 (m, 1H, thiophene H-5). – $C_{17}H_{16}N_4O_3S$ (356) Calcd. C 57.3 H 4.5 N 15.7Found C 56.8 H 4.2 N 15.5.

Ethyl 5-amino-6-cyano-7,8-dihydro-4-furanyl-2-methyl-7-oxo-4H-pyrano[2,3-b]pyridine-3-carboxylate **(6c)**

Yellow crystals from dioxane; 66 %; m.p. 222–4 °C. – IR: 3450–3320 (OH); 2220 (CN); 1695 (CO) cm^{-1}. – $C_{17}H_{15}N_3O_5$ (341) Calcd. C 59.8 H 4.4 N 12.3 Found C 39.6 H 4.2 N 12.0.

Ethyl 5-amino-6-cyano-7,8-dihydro-2-methyl-7-oxo-4-thienyl-4H-pyrano[2,3-b]pyridine-3-carboxylate **(6c)**

Yellow crystals from ethanol; 55 %; m.p. 228–30 °C. – IR: 3420–3200 (OH); 2210 (CN); 1700 (CO) cm^{-1}. – $C_{17}H_{15}N_3O_4S$ (357) Calcd. C 57.1 H 4.2 N 11.8 Found C 56.8 H 4.0 N 11.6.

Reaction of **3** *with trichloroacetonitrile*

3 (0.01 mole) and trichloroacetonitrile (0.01 mole) were refluxed in dry benzene (30 ml) with a catalytic amount of triethylamine for 8 h. The solid product was collected and crystallised from the proper solvent.

Ethyl 4-amino-5-furanyl(2)-7-methyl-2-trichloromethyl-4H-pyrano-[2,3-d]pyrimidine-6-carboxylate **(10a)**

Buff crystals from benzene; 68 %; m.p. 247–9 °C – IR: 3480, 3360 (NH_2); 1700 (CO) cm^{-1}. – ^{1}H-NMR: 1.1 (t, 3H, CH_3); 2.6 (s, 3H, CH_3); 4.1 (q, 2H, CH_2); 4.8 (s, 1H, pyran H-4); 6.2 (s, br, 2H, NH_2); 6.8 (m, 1H, furan H-4); 7.3 (m, 1H, furan H-3); 7.6 (m, 1H, furan H-5). – $C_{16}H_{14}N_3O_4Cl_3$ (417) Calcd. C 46.0 H 3.4 N 10.1 Found C 45.8 H 3.0 N 9.8.

Ethyl 4-amino-7-methyl-5-thienyl(2)-2-trichloromethyl-4H-pyrano-[2,3-d]pyrimidine-6-carboxylate **(10b)**

Brown crystals from dioxane; 70 %; m.p. 244–5 °C. – IR: 3400, 3360, (NH_2); 1695 (CO) cm^{-1}. – ^{1}H-NMR: 1.2 (t, 3H, CH_3); 2.8 (s, 3H, CH_3); 4.2 (q, 2H, CH_2); 4.6 (s, 1H, pyran H-4); 6.4 (s, br, 2H, NH_2); 6.7–7.5 (m, 3H, thiophene H-3, 4, 5). – $C_{16}H_{14}N_3O_3SCl_3$ (433) Calcd. C 44.3 H 3.2 N 9.7 Found C 44.0 H 3.0 N 9.6.

Reaction of **3** *with benzoyl isothiocyanate*

A solution of **3** (0.01 mol) in dry dioxan (30 ml) and the appropriate amount of benzoyl isothiocyanate was refluxed for 5 h. The reaction mixture was cooled and poured onto water. The oily product, so formed was left over night, the precipitated solid was collected and crystallised from the proper solvent.

Ethyl 4-amino-1,2-dihydro-4-furanyl(2)-7-methyl-2-thioxo-5H-pyrano-[2,3-d]pyrimidine-6-carboxylate **(8a)**

Orange crystals from methanol; 75 %, m.p. 196 °C. – IR: 3480–3680 (NH_2), 1710 (CO) cm^{-1}. ^{1}H-NMR: 1.2 (t, 3H, CH_3); 2.6 (s, 3H, CH_3); 4.1 (q, 2H, CH_2); 5.2 (s, 1H, pyran H-4); 6.7–7.8 (m, 3H, furan H-3,4,5); 8.0 (s, br,2H, NH_2). – $C_{15}H_{15}N_3O_4S$ (333) Calcd. C 54.1 H 4.5 N 12.6 Found C 53.8 H 4.2 N 12.4.

Ethyl 4-amino-1,2-dihydro-7-methyl-4-thienyl(2)-2-thioxo-5H-pyrano-[2,3-d]pyrimidine-6-carboxylate **(8b)**

Yellow crystals from ethanol; 70 %; m.p. 191 °C. – IR: 3450, 3400, 3750 (NH_2); 1705 (CO) cm^{-1}.–^{1}H NMR: 1.1 (t, 3H, CH_3); 2.4 (s, 3H, CH_3); 4.2 (q, 2H, CH_2); 5.4 (s, 1H, pyran H-4); 6.8–7.9 (m, 3H, thiophene H-3,4,5); 8.2 (s, br, 2H, NH_2). –$C_{15}H_{15}N_3O_3S_2$ (349) Calcd. C 51.6 H 4.3 N 12.0 Found C 51.8 H 4.2 N 11.7.

Reaction of **3** *with acetic anhydride*

A solution of **3** (0.01 mol) in acetic anhydride (30 ml) was refluxed for 4 h, the solvent was then evaporated under vacuum to about 25 % of its original volume and left to cool, the solid product, so formed, was collected and crystallised from the proper solvent.

Ethyl 3,4-dihydro-4-furanyl-2-2,7-dimethyl-4-oxo-5H-pyrano[2,3-d]-pyrimidine-6-carboxylate **(11a)**

Colourless crystals from ethanol, 82 %; m.p. 279–80 °C. – IR: 3200–2850 (OH), 1685 (CO) cm^{-1}.–^{1}H-NMR: 1.1 (t, 3H, CH_3); 2.1 (s, 3H, CH_3); 2.6 (s, 3H, CH_3); 4.1 (q, 2H, CH_2); 4.6 (s, 1H, pryan H-4), 6.8–7.8 (m, 3H, furan H-3,4,5), 12.6 (s, br, 1H, NH). – $C_{16}H_{16}N_2O_5$ (316) Calcd. 60.8 H 5.1 N 8.9 Found C 60.6 H 4.8 N 8.8.

Ethyl 3,4-dihydro-2,7-dimethyl-4-oxo-4-thienyl-5H-pyrano-[2,3-d]pyrimidine-6-carboxylate **(11b)**

Yellow crystals from methanol, 60 %; m.p. 272–4 °C. – IR: 3350–3200 (OH), 1680 (CO) cm^{-1}.–^{1}H-NMR: 1.2 (t, 3H, CH_3); 2.2 (s, 3H, CH_3); 2.8 (s, 3H, CH_3); 4.2 (q, 2H, CH_2); 4.8 (s, 1H, pyran H-4); 6.7–7.9 (m, 3H, thiophene H-3,4,5); 12.9 (s, br. 1H, NH). – $C_{16}H_{16}N_2O_4S$ (332) Calcd. C 57.8 H 4.8 N 8.4 Found C 57.6 H 4.6 N 8.0.

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