

**Reactions with Heterocyclic β -Enaminoesters:
A Novel Synthesis of
2-Amino-3-ethoxycarbonyl-(4*H*)-pyrans**

**Mohamed Rifaat Hamza Elmoghayer, Mohamed Ali Elsayed Khalifa,
Mohamed Kamal Ahmed Ibraheim, and Mohamed Hilmy Elnagdi***

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

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The reaction of ethyl cyanoacetate with α -cyanochalcone (**1**) leads to the formation of β -enaminoesters (**3**) via *Michael* addition. Compound **3** reacts with phenylmagnesium bromide to give the β -enaminoketone **5**. Acetylation of **3** gives the acetyl product **4**. Each of compounds **1** and **3** reacts with malononitrile to give β -enaminonitrile **6**. Phenylhydrazine reacts with **3** to give the hydrazone **7**. Similarly 3-phenyl-5-aminopyrazole reacts with **3** to give the *Schiff* base **8**.

(Keywords: Enaminopyrans; Michael addition; Pyrans, cleavage of)

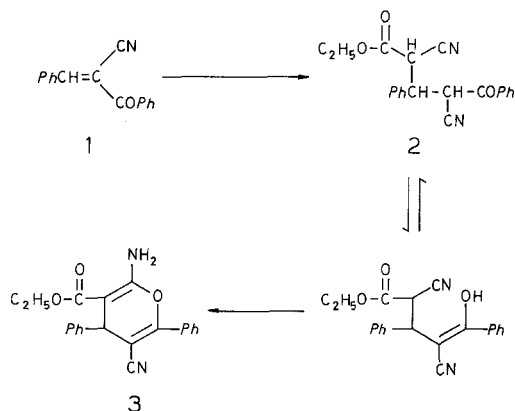
*Reaktionen mit heterocyclischen β -Enaminoestern:
Eine neue Synthese von 2-Amino-3-ethoxycarbonyl-(4*H*)-pyranen*

Die Reaktion von Ethylcyanoacetat mit α -Cyanochalcon **1** führt über eine *Michael*-Addition zum β -Enaminoester **3**. **3** gibt mit Phenylmagnesiumbromid das β -Enaminoketon **5**. Acetylierung von **3** gibt das Acetylderivat **4**. **1** und **3** reagieren mit Malodinitril zum β -Enaminonitril **6**. **3** gibt mit Phenylhydrazin das Hydrazon **7**; 3-Phenyl-5-aminopyrazol reagiert mit **3** zur *Schiff*-Base **8**.

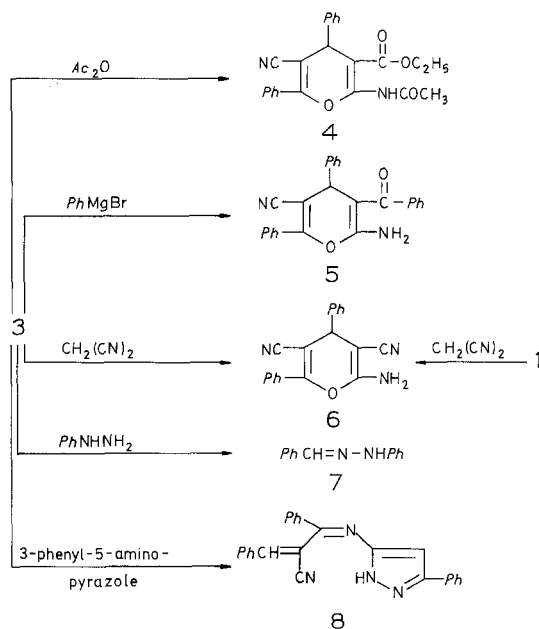
In continuation to our interest in the chemistry of heterocyclic β -enaminoesters¹⁻³ an attempt to synthesis 2-amino-3-ethoxycarbonyl-(4*H*)-pyrans was made. Cyclisation of the products obtained via *Michael* addition of ethyl cyanoacetate to α -Cyanochalcone (**1**) seemed to be a logical route⁴.

Thus **1** was treated with ethyl cyanoacetate in refluxing ethanol in presence of piperidine. The product obtained has a melting point

similar to that previously reported from our laboratories and also identical IR data. A one proton singlet at $\delta 5.0$ ppm and two proton singlets at $\delta 6.2$ ppm appeared in the ^1H -NMR spectrum in addition to the aromatic proton multiplet and the ethyl ester group protons. This



spectra clearly revealed that the reaction product is not in fact the acyclic derivative **2** as proposed in ⁴ and suggests that the correct structure for this product is that of the cyclic pyran **3**.



Compound **3** reacted with acetic anhydride to yield the acetyl derivative **4**, and with phenylmagnesium bromide to yield the enamino ketone **5**. Attempts to synthesise this compound by the action of benzoylacetonitrile on **1** were unsuccessful under a variety of conditions, **1** was recovered almost unaffected on excessive treatment with benzoylacetonitrile. When **3** was treated with malononitrile in refluxing ethanol the enamino nitrile derivative **6** was formed unexpectedly. Compound **6** could be directly obtained from the reaction of **1** with malononitrile.

Compound **3** reacted also with phenylhydrazine to yield benzaldehyde—phenylhydrazone **7** and with 3-phenyl-5-aminopyrazole to yield the aminopyrazole derivative **8**. The structure of the products was inferred from analytical and spectroscopical data and by identity with authentic specimens.

Experimental

All melting points are uncorrected. IR spectra were obtained (KBr; 1%) on a Perkin-Elmer 157G. $^1\text{H-NMR}$ spectra were obtained on Bruker WH-90 in *DMSO* using *TMS* as internal standard and chemical shifts are expressed as δ/ppm .

2-Amino-5-cyano-3-ethoxycarbonyl-4,6-diphenyl-4H-pyran (3)

A solution of **1** (0.1 mol) in absolute ethanol (100 ml) was treated with ethylcyanoacetate (0.1 mol) and 1 ml of piperidine. The reaction mixture was refluxed for 7 h, then evaporated to one half of its volume and left to stand at room temperature. The solid product, so formed, was collected by filtration and crystallised from ethanol. Compound **3** formed colourless crystals; m.p. 135°C yield 65%.

IR: 3400, 3300 (ν NH_2); 2200 (conjugated CN); 1675 (ester CO) and 1630 cm^{-1} (C=C).

$^1\text{H-NMR}$: 1.11 (t, 3 H, CH_3); 4.11 (q, 2 H, CH_2); 4.66 (s, 1 H, pyran CH); 6.2 (s, 2 H, NH_2) and 7.2–7.8 (m, 10 H, aromatic protons).

$\text{C}_{21}\text{H}_{18}\text{N}_2\text{O}_3$ (346). Found C 72.7, H 5.3, N 8.2.
Calcd. C 72.8, H 5.2, N 8.1.

2-Acetylamino-5-cyano-3-ethoxycarbonyl-4,6-diphenyl-4H-pyran (4)

A solution of **3** (2.0 g) in acetic anhydride (10 ml) was refluxed for 10 h. The reaction mixture was then poured onto water (50 ml) and the solid product formed on standing, was collected by filtration and crystallised from ethanol. Compound **4** formed colourless crystals, m.p. 207°C ; yield 50%.

IR: 3200, 3010 (NH); 2940, 2920 (CH_2 and CH); 2220 (conjugated CN); 1740 (acetyl CO); 1700 (ester CO); 1650 (C=C) and 1610 cm^{-1} (C=C).

$^1\text{H-NMR}$: 2.11 (s, 3 H, CH_3); 4.0 (q, 2 H, CH_2); 4.66 (s, 1 H, pyran H); 7.44–7.95 (m, 10 OH, 2 Ph) and 10.48 (s, 1 H, NH).

$\text{C}_{23}\text{H}_{20}\text{N}_2\text{O}_4$ (388). Found C 70.5, H 5.7, N 6.5.
Calcd. C 71.1, H 5.1, N 7.2.

2-Amino-3-benzoyl-5-cyano-4,6-diphenyl-4H-pyran 5

To a phenylmagnesium bromide solution (prepared from 2.0 g Mg and an equivalent of bromobenzene in 100 ml ether) 3.0 g of **3** were added. The reaction mixture was then refluxed for 4 h and then decomposed over saturated ammonium chloride solution. After complete decomposition the ether layer was separated, dried and evaporated. The remaining product was collected by filtration and crystallised from ethanol. Compound **5** formed colourless crystals; m.p. 110 °C; yield 40%.

IR: 3 200 (chelated NH); 2 220 (conjugated CN); 1 630 cm⁻¹ (conjugated CO).

C₂₅H₁₈N₂O₂ (378). Found C 79.3, H 4.7, N 7.2.
Calcd. C 79.3, H 4.7, N 7.4.

2-Amino-3,5-dicyano-4,6-diphenyl-4H-pyran 6

Method A: A solution of **3** (0.1 mol) in ethanol (100 ml) was treated with malononitrile (0.1 mol). The reaction mixture was refluxed for 10 h then evaporated in vacuo. The remaining product was triturated with ethanol and the resulting solid product was collected by filtration and crystallised from ethanol. Compound **6** formed colourless crystals; m.p. 167 °C; yield 60%.

IR: 3 400, 3 350 (NH₂); 2 230, 2 220 (two CN); 1 680 cm⁻¹ (C=C).

¹H-NMR: 4.66 (S, 1 H, pyran H-4); 6.2 (S, 2 H, NH₂) and 7.2 ~ 7.8 (m, 10 OH, aromatic protons).

C₁₉H₁₃N₃O (299). Found C 76.2, H 4.3, N 14.0.
Calcd. C 76.2, H 4.3, N 14.0.

Method B: A solution of **1** (0.1 mol) in ethanol (100 ml) was treated with malononitrile (0.1 mol) and few drops piperidine. The reaction mixture was refluxed for 7 h, then evaporated in vacuo. The remaining product was triturated with ethanol and the resulting solid product was collected by filtration and identified as **6** (m.p. and mixed m.p.).

*Reaction of 3 with**a) Phenylhydrazine*

A solution of **3** (0.1 mol) in ethanol (100 ml) was treated with phenylhydrazine (0.1 mol). The reaction mixture was refluxed for 7 h and then evaporated in vacuo. The remaining product was triturated with water and the excess phenylhydrazine was removed by acidification. The solid product, so formed, was collected by filtration and identified as benzaldehyde phenylhydrazone (m.p. and mixed m.p.).

b) 5-Amino-3-phenylpyrazole

A solution of **3** (0.1 mol) in ethanol was treated with 5-amino-3-phenylpyrazole (0.1 mol) and refluxed for 12 h. The reaction mixture was then evaporated and the remaining product was triturated with water. The solid product, so formed, was collected by filtration and purified by recrystallisation from water. Compound **8** formed colourless crystals; m.p. 271 °C; yield 40%.

IR: 3 200 ~ 2 600 (conjugately chelated NH); 2 200 cm⁻¹ (conjugated CN).

C₂₅H₁₈N₄ (374). Found C 79.2, H 4.9, N 14.9.
Calcd. C 80.2, H 4.8, N 14.9.

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