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Heterocyclic Enaminonitriles, Trichloroacetonitrile, Pyrano[2,3-c]pyrazole,
Ring-Chain Tautomerism in Pyrans

A variety of novel pyrano[2,3,d]pyrimidines could be obtained via reaction of ethyl 2-amino-3-cyano-6-methylpyran-4-carboxylate with a variety of reagents. Evidence for the existence of this pyran derivative as a ring chain tautomer is presented.

Although 2-amino-3-cyanopyrans became recently readily obtainable via Soto's pyran synthesis [1], utility of these enaminonitriles in heterocyclic synthesis has received only limited interest compared with enaminofurans [2]. In conjunction of our effort directed toward exploring the synthetic potential of enaminonitriles [3–5], we report here a synthesis of a new enaminopyran derivative and the chemistry of this enaminonitrile.

Benzyldenemalononitrile 1 reacted with ethyl acetoacetate in refluxing ethanoic triethylamine to yield a 1:1 adduct. This could be proved to be the pyran derivative 2 and not the possible intermediate Michael adduct 3 based on ^1H NMR of the reaction product. Thus, ^1H NMR revealed the absence of signals for protons in the region 3–6, other than the methylene quartet and pyran H-4 singlet at δ 4.8 ppm. If the reaction product was the acyclic 3, a multiplet should have appeared at δ 3–6 ppm.

In contrast to the observed ready reaction of 2-amino-3-cyano-4,5-dihydrofurans with ethyl cyanoacetate [6], compound 2 was recovered unreacted when treated with ethyl cyanoacetate under the same reaction conditions. However, when 2 was heated at 160 °C (bath T) a product of molecular formula C_{11}H_{17}N_{2}O_{4} was obtained. Two isomeric structures were considered (cf. structures 4 and 5). Structure 4 was eliminated based on IR spectrum which revealed only one CN signal and a highly chelated NH and OH bands extending from 3500 to 2700 cm⁻¹. Moreover, the reaction product failed to couple with benzenediazonium chloride under conditions reported [7] to effect ready coupling of aryldiazonium salts with cyanoacetamide derivatives. In contrast to ethyl cyanoacetate, malononitrile reacted with 2 in refluxing ethanoic triethylamine to yield an adduct which was formulated as 6 and not 7, 8 or 9 based on IR spectrum which revealed two CN signals. Although ^1H NMR of the reaction product points to structure 6 it can be also interpreted for 7 or 8. Thus, other evidence to support form 6 was needed. Since the reaction product failed to couple with benzenediazonium chloride, structure 6 was considered most likely, as 7 or 8 is expected to couple readily with aryldiazonium salts [7]. Compound 6 could be converted into 9 on long reflux in dioxane. Compound 9 was also obtained from fusion of 2 with malononitrile at 160 °C for 2 h.

Compound 2 reacted with trichloroacetonitrile to yield the pyranopyrimidine derivative 10. The formation of 10 from reaction of 2 with trichloroacetonitrile is a further example of the usefulness of the newly reported synthesis of pyrimidine from enaminonitriles [8, 9]. However, the limitations of this reaction recently reported by Gewald and Hain should be considered [10].

Compound 2 also reacted with ethyl 3-amino-2-cyano-4-trichlorocrotonate to yield pyrano[2,3-d]-pyrimidine derivative 11.

Compound 2 reacted with benzylosiathiocyanate to yield the pyranopyrimidine derivative 12, formed most likely via intermediacy of the thiourea derivative 13. In contrast, ethoxycarbonylsiathiocyanate reacted with 2 to yield the ethoxycarbonylamino pyran 14. Ethoxycarbonylation of aminoheterocycles by this reagent has been previously reported [8, 11].

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and rationalised by assuming involvement of heteroatom in formation of the reaction product. However in the present work, involvement of ring oxygen seems least likely. Consequently it is assumed that the reaction occurs via attack of the isothiocyanate on pyran C-3. This assumption seems logical as \(^{13}\)C NMR [12] of 2 revealed that C-3 is highly shielded and thus points to participation of resonance form 2a in the structure of this pyran. Similar assumptions are also made by Wamhoff [2] to account for spectra and chemistry of enaminofurans.

Compound 2 reacted with hydrazine hydrate to yield a product of molecular formula C\(_{14}\)H\(_{12}\)N\(_4\)O. This product was believed thus to be 15. The structure of the reaction product could be established via its synthesis from reaction of 1 with 3-methyl-2-pyrazolin-5-one 16 as has been recently described [13]. The formation of 15 indicates that 2 exhibits ring chain tautomerism and that the Michael adduct 15 suggested on the reaction pathway is in equilibrium with its constituents. In presence of hydrazine, rapid reaction of ethylacetoacetate with hydrazine would afford in situ 3-methyl-2-pyrazolin-5-one 16. This latter compound reacts with 1 to yield 15. Similar assumption was previously made to account for the conversion of 17 into 18 [14].

![Diagram](chart1.png)
Ethyl-5-amino-6-cyano-7,8-dihydro-2-methyl-7-oxo-4H-pyran[2,3-b]pyridine-3-carboxylate (5)

Compound 2 (0.01 mol) was fused with ethyl cyanoacetate (0.01 mol) in presence of few drops of piperidine at 160 °C (bath T) for 2 h. The solid product, so formed, was crystallized from acetic acid as brown powder 5, yield 65%, m.p. 210 °C. IR: 3400, 3200 (NH₂); 2220 (CN); 1720, 1680 (CO).

C₁₉H₁₇N₃O₄ (351)
Calcd C 64.9  H 4.8  N 11.9,
Found C 64.8  H 4.6  N 11.8.

Reaction of 2 with malononitrile

(a) Compound 2 (0.01 mol) was refluxed with malononitrile (0.01 mol) in ethanol (20 ml) with catalytic amount of triethylamine for 4 h. The solid product, so formed on cooling, was collected by filtration and crystallized from ethanol as yellow crystals 6, yield (75%), m.p. 235 °C. IR: 3410, 3310, 3200 (NH₂); 2220, 2190, (CN); 1700 (CO). ¹H NMR: 1.2 (t, 3H, CH₃); 2.4 (s, 3H, CH₃); 3.4 (s, 2H, NH₂); 4.2 (q, 2H, CH₂); 4.8 (s, 1H, H₄); 5.9 (s, 2H, NH₂); 7.2—7.6 (m, 5H, aromatic protons).

(b) Compound 2 (0.01 mol) was heated with malononitrile (0.01 mol) in presence of few drops of piperidine at 160 °C (bath T) for 2 h. The solid product, so formed, was crystallized from acetic acid as brown powder 9, yield (70%), m.p. 290 °C. IR: 3400, 3260 (NH₂); 2210 (CN); 1720 (CO).

(c) Compound 6 (0.01 mol) was refluxed in dioxane (30 ml) for 10 h. The solid product, so formed on standing, was collected by filtration, crystallized from acetic acid and identified as compound 9 (m.p. and mixed m.p.).

C₁₉H₁₈N₄O₃ (350)
Calcd C 65.1  H 5.1  N 16.0,
Found C 65.3  H 5.2  N 16.3.

Ethyl-4-amino-7-methyl-5-phenyl-2-trichloromethyl-4H-pyran[2,3-d]pyrimidine-6-carboxylate (10)

Equimolecular amounts of compound 2 (0.01 mol) and trichloroacetonitrile (0.01 mol) were refluxed in dry toluene (30 ml) with catalytic amount of piperidine for 6 h. The product, so formed, was collected by filtration and crystallized from toluene as brown crystals 10 yield (70%), m.p. 235°C. IR: 3400, 3200 (NH₂); 1710 (CO). ¹H NMR: 1.3 (t, 3H, CH₃); 2.2 (s, 3H, CH₃); 4.2 (q, 2H, CH₂); 4.6 (s, 1H, H-4); 6.8 (s, 2H, NH₂); 7.2—7.8 (m, 5H, aromatic protons).

C₁₉H₁₆N₃O₃Cl₃ (428.5)
Calcd C 50.4  H 3.7  Cl 24.8,
Found C 50.6  H 3.5  Cl 24.6.

In support of this view, 2 reacted with 16 to yield also 15.

Experimental

All melting points are uncorrected. IR spectra were recorded on a Beckman spectrophotometer. ¹H NMR on a Varian EM-390-90 MHz spectrometer using TMS as internal indicator and chemical shifts are expressed as ppm. The microanalysis were performed by the microanalytical unit at Cairo University.
Studies on Heterocyclic Enamines

Reaction of compound 2 with ethyl-3-amino-2-cyano-4-trichlorocrotonate

Equimolecular amounts of compound 2 (0.01 mol) and ethyl-3-amino-2-cyano-4-trichlorocrotonate (0.01 mol) were refluxed in 20 ml pyridine for 3 h. The reaction mixture was cooled and poured onto water. The oil, so formed, was collected by extraction with ether and crystallized from acetic acid as brown crystals 11; yield (80%), m.p. >300 °C. IR: 3380 (NH₂); 2220 (CN); 1720 (CO).

\[ C_{22}H_{21}N_4O_5 \text{ (421)} \]
Calcd C 62.7 H 4.9 N 13.3,
Found C 62.9 H 4.9 N 13.2.

Reaction of compound 2 with isothiocyanates

Equimolecular amounts (0.01 mol) of 2 and the appropriate isothiocyanate were refluxed in dry dioxane (50 ml) for 4 h. The reaction mixture was cooled and poured onto water. The oil, so formed, was extracted with ether and crystallized from ethanol.

Compound 12, orange crystals; yield 80%; m.p. 110 °C. IR: 3200 (NH); 1720, 1690 (CO). \[^1\text{H NMR: 1.3 (t, 3H, CH}_3\text{); 2.4 (s, 3H, CH}_3\text{); 3.4 (s, 1H, NH); 4.2 (q, 2H, CH}_2\text{); 5.0 (s, 1H, H-4); 7.2-7.7 (m, 10H, aromatic protons); 8.2 (s, br, 1H, NH).} \]

\[ C_{24}H_{21}N_3O_4S \text{ (447)} \]
Calcd C 64.4 H 4.6 N 9.3 S 7.1,
Found C 64.2 H 4.5 N 9.3 S 7.2.

7-Amino-6-cyano-3-methyl-4-phenyl-4H-pyrano[2,3-c]pyrazole (15)

(a) Compound 2 (0.01 mol) was refluxed with hydrazine hydrate (0.01 mol) in 20 ml ethanol for 1/2 h. The solid product was collected by filtration and crystallized from DMF/H₂O as colourless crystals 15; yield (70%), and the reaction product was identified (m.p. and mixed m.p.) as 15 [13].

(b) Compound 15 was also prepared via reaction of 2 (0.01 mol) with 16 (0.01 mol) in refluxed pyridine (20 ml) for 1 h. The solid product, so formed, was collected by filtration, crystallized from DMF/H₂O and identified as compound 15 (m.p. and mixed m.p. 250 °C). IR: 3400, 3320, 3200 (NH₂); 2200 (CN). \[^1\text{H NMR: 1.9 (s, 3H, CH}_3\text{); 4.5 (s, 1H, H-4); 6.8 (s, 2H, NH); 7.2-7.7 (m, 5H, aromatic protons); 10.1 (s, br, 1H, NH).} \]

\[ C_{14}H_{12}N_4O_5 \text{ (252)} \]
Calcd C 66.6 H 4.7 N 22.2,
Found C 66.6 H 4.6 N 22.1.

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