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Activated Nitriles in Heterocyclic Synthesis: Synthesis of Several New Coumarin Derivatives

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Several new benzopyran and benzopyranopyridine derivatives were synthesized via condensation of 2-amino-1,1,3-tricyanopropene (**1**) and diethyl 2-amino-1-cyanopropene-1,3-dicarboxylate (**2**) with salicylaldehyde and treatment of the resulted products with active methylene reagents. The spectroscopic data of the synthesized compounds are reported and discussed.

(Keywords: Benzopyrano[2,3—c]pyridines; Enamino nitriles; Iminocoumarins)

Aktivierte Nitrile in der Heterocyclen-Synthese: Darstellung einiger neuer Cumarinderivate

Einige neue Benzopyran- und Benzopyranopyridin-derivate wurden durch Kondensation von 2-Amino-1,1,3-tricyanopropen (**1**) und 2-Amino-1-cyanopropen-1,3-dicarbonsäuredimethylester (**2**) mit Salicylaldehyd und Behandlung der Reaktionsprodukte mit aktiven Methylenreagenzien dargestellt. Die spektroskopischen Daten der neuen Verbindungen werden diskutiert.

Introduction

As a part of our program directed to the development of new procedures for the synthesis of heterocyclic derivatives from readily accessible activated nitrile derivatives[1–3] we have investigated the reaction of salicylaldehyde with 2-amino-1,1,3-tricyano-propene (**1**)[4] and diethyl 2-amino-1-cyanopropene-1,3-dicarboxylate (**2**)[5].

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Results and Discussion

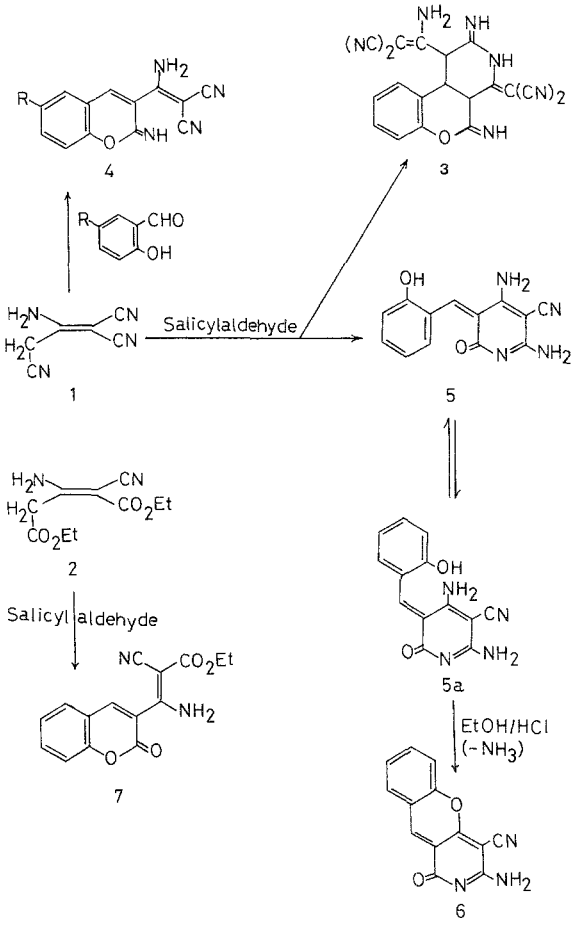
Junek[6] has reported that salicylaldehyde reacts with **1** to yield the benzopyrano[3,4—c]pyridine derivative **3**. Substituted salicylaldehyde have been reported[6] to afford the iminocoumarin derivatives **4**. In our laboratory, however, salicylaldehyde reacted with **1** to yield a product of the molecular formula $C_{13}H_{10}O_2N_4$. The IR spectrum of this product revealed absorption peaks for NH_2, CN and CO groups. The presence of phenolic OH was indicated by the development of a deep green colour on adding $FeCl_3$ to a suspension of the reaction product in ethanol. Structure **5** was thus suggested for the reaction product. The formation of **5** in this reaction is assumed to proceed *via* the sequence demonstrated in Scheme 1. Two possible geometrical isomers for **5** were considered. The reaction product was considered to exist mainly in the **5a** form based on its ready conversion into the benzopyrano[2,3—c]pyridine derivative **6**, via loss of ammonia, on treatment with ethanolic hydrochloric acid.

In contrast to the behaviour of **1**, compound **2** reacted with salicylaldehyde to yield the coumarin derivative **7**. Although geometrical isomers are possible for **7**, structure **7** was established for this product based on ^1H NMR which revealed the coumarin H-4 proton at δ 6.22 ppm—upfield shifted by δ 2 ppm with regard to its expected position. This upfield shift can only be rationalized in terms of shielding by the anisotropy of the cyano group. Compound **7** could be readily converted into several—otherwise difficultly accessible—coumarin derivatives (Scheme 2). Thus, **7** reacted readily with hydrazine hydrate and with phenylhydrazine to yield the 3-coumarinyl aminomethylene-pyrazolone derivatives **8a, b**. The formation of **8a, b** from **7** is assumed to proceed *via* the addition of the reagent to the cyano group and cyclization *via* elimination of ethanol. This is in contrast to the reported addition of hydrazines to the double bond in enamino esters and enamino nitriles under similar conditions[7]. The inactivity of the double bond in **7** toward hydrazines is rationalized by the decrement of its reactivity by conjugation with the coumarin ring.

Compound **7** readily reacted with active methylene heterocyclic derivatives to yield 1:1 adducts. Thus, with the 2-pyrazolin-5-one derivatives **9a, b** and with the 2-isooxazolin-5-one derivativative **9c**, the 4-azolyl-substituted dihydrocoumarins **10a–c** were formed in good yields. The reactivity of the double bond in **7** in *Michael* reactions is analogous to the activity of the double bond in coumarins and in benzopyrans in similar reactions[8,9].

7 condensed with malononitrile to yield a product of the molecular formula $C_{16}H_8O_3N_4$. The IR spectrum of this product revealed ab-

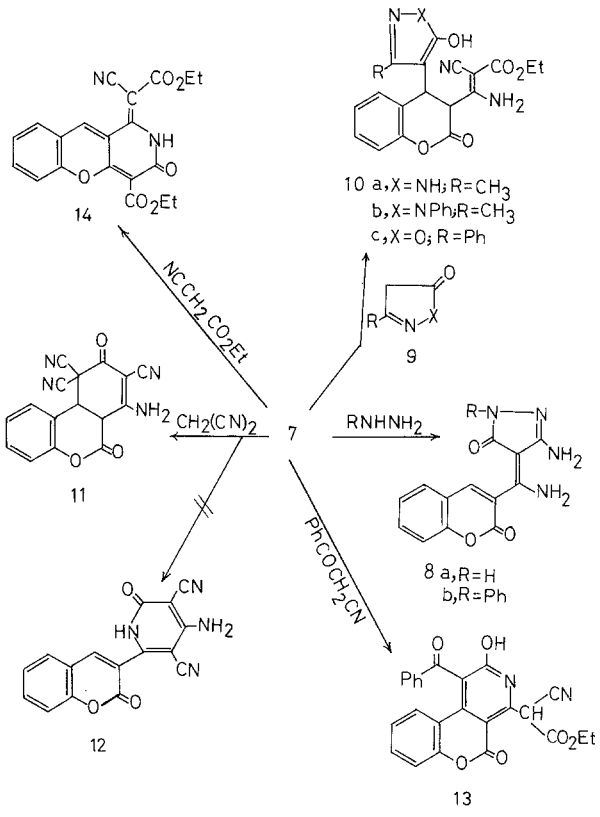
Scheme 1



sorption peaks at 3400, 1720, and 2220, 2210 cm^{-1} for amino, CO and two CN groups. Structure **11** and **12** were considered for the reaction product and a mechanism could be suggested to account for the formation of both products. Structure **11** was established for the reaction product based on ^1H NMR which revealed a multiplet for two nonaromatic protons at δ 4 ppm.

Similarly, **7** reacted with benzoylacetonitrile to yield the pyridinyl-coumarin derivative **13** (or possible tautomers). The formation of **13** is assumed to proceed *via* initial addition to the double bond. In contrast, ethyl cyanoacetate reacted with **7** to yield the pyridine derivative **14** (cf. Scheme 2).

Scheme 2



The behaviour of **1** and **2** towards the action of other aldehydes is now being investigated. The work offers a new route for the synthesis of pyridine derivatives and will be the subject of a subsequent communication.

Experimental

Melting points are uncorrected. IR spectra were recorded (KBr) on a Pye Unicam SP-1000. ^{1}H NMR spectra were obtained on an EM-360 MHz spectrometer in *DMSO* using *TMS* as internal standard and chemical shifts are expressed as δ ppm. Analytical data were performed by the microanalytical unit, Cairo University.

Reactions of **1** *and* **2** *with Salicylaldehyde*

To a solution of each of **1** and **2** (0.01 mol) in ethanol (30 ml), salicylaldehyde (0.01 mol) and one drop of piperidine were added. The reaction mixture was

Table 1. *Synthetic data for compounds* **5a**, **6**, **7**, **8a**, **b**, **10a–c**, **11**, **13** *and* **14**

Comp.	colour	m.p. °C	Yield %	Mol. Formula*
5a	canary yellow	>300	96	$C_{13}H_{10}O_2N_4$
6	yellow	277	70	$C_{13}H_7O_2N_3$
7	yellow	235	85	$C_{15}H_{12}O_4N_2$
8a	orange	>280	65	$C_{13}H_{10}O_3N_4$
8b	brown	205	60	$C_{19}H_{14}O_3N_4$
10a	pale yellow	268	65	$C_{19}H_{16}O_5N_4$
10b	orange	278	60	$C_{25}H_{20}O_5N_4$
10c	red	240	70	$C_{24}H_{17}O_6N_3$
11	pale yellow	>300	85	$C_{16}H_8O_3N_4$
13	canary yellow	246	50	$C_{24}H_{18}O_6N_2$
14	orange	217	70	$C_{20}H_{16}O_6N_2$

* All compounds gave satisfactory elemental analyses (C, H, N).

refluxed for 5 min in case of **1** and for 30 min in case of **2**. The solid product so formed was collected by filtration and crystallized from *DMF*/H_2O (cf. Tables 1 and 2 for data of **5a** and **7**).

Reaction of **5a** *with Ethanolic Hydrochloric Acid*

A mixture of **5a** (1 g), conc. HCl (10 ml) and ethanol (30 ml) was boiled under reflux for 2 h. The reaction mixture was then cooled and neutralized with sodium carbonate solution. The solid thus formed was filtered off and washed with water. Crystallization from *DMF*/H_2O gave **6** (cf. Tables 1 and 2).

Reactions of **7** *with Hydrazines*

A solution of **7** (0.01 mol) in *DMF* (20 ml) was treated with hydrazine hydrate or phenylhydrazine (0.01 mol). The reaction mixture was boiled under reflux for 2 h, then evaporated in vacuo. The remaining product was triturated with ethanol, collected by filtration and crystallized from *DMF*/H_2O to give **8a** or **b** (cf. Tables 1 and 2).

Reactions of **7** *with Active Methylene Heterocyclic Derivatives*

A solution of **7** (0.01 mol) and each of the active methylene heterocyclic derivatives **9a–c** (0.01 mol) in *DMF* (30 ml) was boiled under reflux for 3 h. The solvent was then evaporated in vacuo and the residue triturated with ethanol. Crystallization of the residue from *DMF*/H_2O gave **10a–c** (Tables 1 and 2).

Table 2. IR *and* ^{1}H NMR *data*

Comp.	IR; cm^{-1}; selected bands	^{1}H NMR; δ ppm
5a*	3490 (OH); 3390, 3370, 3250 and 3100 (NH_2 groups); 2290 (CH); 2210 (conjugated CN); 1635 (ring CO) and 1605 (C=N)	
6	3430 ~ 3300 (chelated NH_2); 2210 (CN); 1660 ~ 1630 (ring CO and NH_2 deformation)	5.6 (br, 2H, NH_2) and 7.0 ~ 8.0 (m, 5H, aromatic protons)
7	3420, 3300 (NH_2); 3050 (aromatic CH); 2980 ~ 2960 (CH_2 and CH_3); 2210 (CN); 1710 (conjugated ester CO); 1685 (ring CO) and 1630 (NH_2 deformation)	1.16 (t, 3H, CH_3); 6.22 (s, 1H, benzopyran H-4); 4.06 (q, 2H, CH_2); 7.2 ~ 7.85 (m, 4H, aromatic protons) and 8.8 ~ 9.0 (m, br, 2H, NH_2)
8a*	3400 ~ 2400 (chelated NH) and 1680 ~ 1630 (chelated CO groups)	
8b*	3480 ~ 2300 (chelated NH) and 1670 ~ 1630 (ring CO)	
10a*	3400 ~ 2300 (chelated NH); 2220 (conjugated CN); 1750 ~ 1730 (ring and ester CO) and 1630 (C=C)	
10b*	3500 ~ 3200 (NH); 2220 (CN); 1740 (ester CO); 1680 (ring CO) and 1620 (C=C)	
10c	3500, 3200 (NH_2); 2210 (CN); 1740 (ester CO); 1670 (ring CO) and 1620 (C=C)	1.16 (t, 3H, CH_3); 3.26 (m, 2H, benzopyran H-3 and H-4); 4.16 (q, 2H, CH_2) and 7.25 ~ 9.10 (m, 12H, aromatic, NH_2 and OH protons)
11	3480, 3380, 3270 (NH_2); 2225, 2205 (CN bands); 1710, 1670 (ring CO groups); 1645 (NH_2 deformation) and 1610 (C=C)	4.0 (m, 2H, benzopyran H-3 and H-4); 7.2-8.16 (m, 6H, aromatic and NH_2 protons)
13	3320 ~ 3300 (chelated OH); 2240 (CN) and 1730, 1720, 1710 (CO groups)	1.16 (t, 3H, CH_3); 3.2 (s, 1H, CH); 4.05 (q, 2H, CH_2); 5.4 (d, 1H, benzopyran H-4); 6.8 ~ 7.9 (m, 4H, aromatic and pyridine H-3) and 10.0 (s, br, 1H, OH)
14*	3440, 3300 (NH group); 2220 (CN); 1715, 1690 (CO groups) and 1640 ~ 1610 (C=C)	

* Compound is insoluble in most known ^{1}H NMR solvents.

Reactions of **7** *with Activated Nitriles*

A solution of **7** (0.0 mol) and each of malononitrile, benzoylacetonitrile or ethyl cyanoacetate (0.01 mol) in *DMF* (20 ml) was treated with piperidine (1 ml) and the whole heated to boiling for 2 h. The solvent was evaporated in vacuo and the residue triturated with ethanol then crystallized from *DMF*/H_2O to give compounds **11**, **13** and **14** respectively (cf. Tables 1 and 2).

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