UNUSUAL ONE-POT "SUBSTITUTION" OF 3- ACETYL AND 3- ETHOXYCARBONYL FUNCTIONS FOR CYANO GROUP IN COUMARINS

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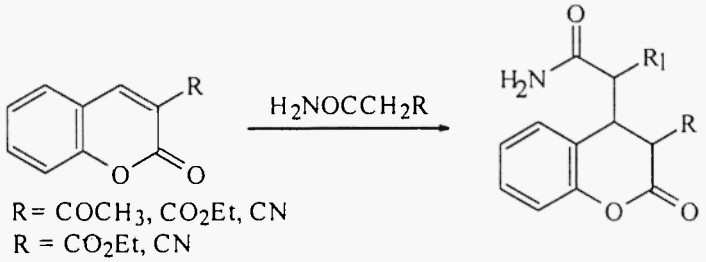
Abstract: Interaction of 3-ethoxycarbonyl and 3-acetylcoumarins with cyanoacetylhydrazide or its N-acetyl and N-ethoxycarbonyl derivatives in the Michael reaction conditions results in corresponding 3-cyanocoumarins. Apparently the reaction undergoes through pyrone ring opening and recyclization steps. Possible mechanism of the "substitution" is discussed.

Introduction

Some base- catalyzed coumarin reactions go through pyrone ring opening and recyclization steps (1-3). Coumarins which contain electron acceptor groups like acetyl, benzoyl, cyano, ethoxycarbonyl functions at position 3 react with different C-nucleophiles to produce 4-substituted 3,4-dihydrocoumarins or their transformation products. Thus 3-acetyl, 3-ethoxycarbonyl and 3-cyanocoumarins yield Michael reaction products (Scheme 1) when react with cyanoacetamide or malonic ester monoamide (4,5).

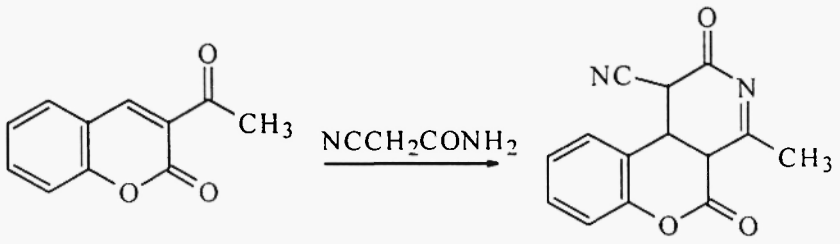
Scheme 1



R= $COCH_3$, CO_2Et, CN
R = CO_2Et, CN

3-Acetylcoumarin reacts also with malonic acid derivatives (6) to produce angular condensed coumarins (**Scheme 2**).

Scheme 2

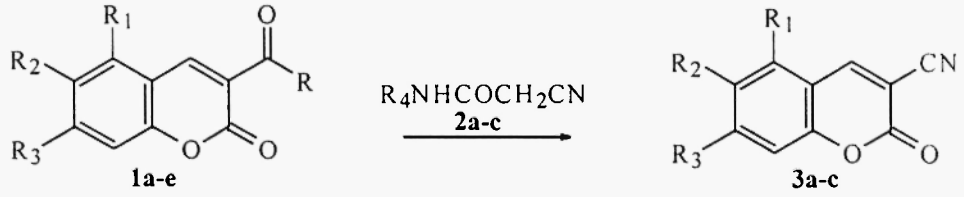


Looking for new ways to hetarenocoumarins (7,8) we have found one-pot "substitution" of 3-acetyl(3-ethoxycarbonyl) functions for cyano group, when 3-acetyl and 3-ethoxycoumarins react with cyanoacetylhydrazides in the Michael reaction. This unexpected reaction seems to start with Michael addition of cyanoacetylhydrazide carbanion at position 4 of the coumarin, followed by lactone ring opening and recyclization steps.

Results and discussion

We found that 3-ethoxycarbonyl and 3-acetylcoumarins react with cyanoacetohydrazide in ethanol in the presence of piperidine as catalyst to produce 3-cyanocoumarin instead of 4-substituted 3,4-dihydrocoumarin. Formally the reaction looks like "substitution" of acetyl or ester functions for cyano group at position 3 of coumarin. This reaction undergoes also with different 3-acetyl and 3-ethoxycarbonylcoumarins which have substituents at positions 5,6,7 and with their benzoanalogs. Starting compounds, products and their yields are shown in Scheme 3 and Table 1.

Scheme 3



1a-e **3a-c**

1a, R=OC_2H_5, $R_1=R_2=R_3=H$
1b, R=CH_3, $R_1=R_2=R_3=H$
1c, R=OC_2H_5, $R_1=R_2=H$, $R_3=OCH_3$
1d, R=CH_3, $R_1=R_2=H$, $R_3=OCH_3$
1e, R=OC_2H_5, R_1-R_2= o-C_6H_4, $R_3=H$
1f, R=CH_3, R_1-R_2= o-C_6H_4, $R_3=H$

2a, $R_4=NH_2$
2b, $R_4=NHCOCH_3$
2c, $R_4=NC(CH_3)_2$

3a, $R_1=R_2=R_3=H$
3b, R_1-R_2=o-C_6H_4, $R_3=H$
3c, $R_1=R_2=H$, $R_3=OCH_3$

Table 1. Yields of 3-cyanocoumarins, 3a-c

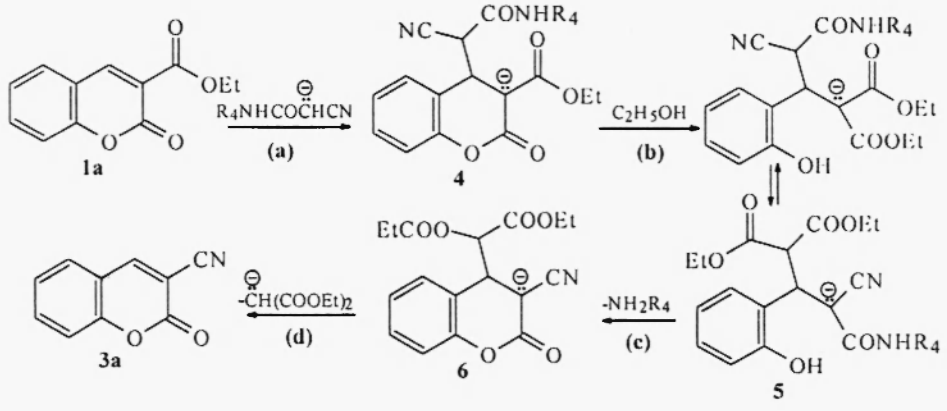
Coumarins	Hydrazides		
	2a	2b	2c
3-cyanocoumarins , yield, %			
1a	3a, 32	3a, 43	3a, 63
1b	3a, 38	3a, 44	3a, 55
1c	3b, 32	3b, 81	3b, 78
1d	3b, 42	3b, 40	3b, 43
1e	3c, 43	3c, 72	3c, 72
1f	3c, 45	3c, 74	3c, 76

Melting points and spectral characteristics of cyanocoumarins **3a-c** are in accordance to (9,10,11).

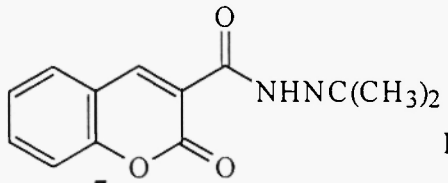
According to Table 1, the best yields are achieved when 3-ethoxycarbonylcoumarins **1a**, **1c**, **1e** and hydrazide **2c** have been used.

The possible mechanism of the "substitution"includes a number of sequent transformations which result in 3-cyanocoumarins (Scheme 4). We suppose that the reaction starts with the Michael addition of cyanoacetohydrazide **2** to the C-4 position of the coumarin to form intermediate **4** (step a). Then pyrone ring opening takes place (step b), followed by relactonization (step c) to form intermediates **5** and **6** respectively. Finally, intermediate **6** eluminates 1,3-dicarbonyl derivative to yield 3-cyanocoumarin.

Scheme 4



To confirm the proposed mechanism we analyzed by-products of interaction of coumarin **1a** and cyanoacetylhydrazide **2c**. After separation of 3-cyanocoumarin, filtrate was evaporated and mass-spectra of solid residue have been recorded. We found molecular ion peaks m/z=403, 357, 244, 186, 72 and their fragmentation ions which correspond to nonionized **5**, **4** and **7**, **8**, **9** respectively. Thus peak m/z=357 (structure **4**) and 403 (structure **5**) corresponds to the Michael addition (step a) and pyrone ring opening (step b) respectively. Peaks m/z=244 (structure 7) and 72 (structure **9**) are in accordance with the relactonization (step c) which is accompanied by elimination of hydrazide derivative. Peak m/z= 186 (structure **8**) confirms elimination of 1,3-dicarbonyl derivative (step d).



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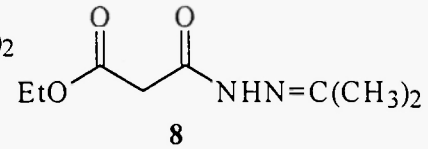

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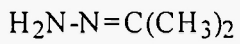

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Conclusions

We have found that 3-ethoxycarbonyl and 3-acetylcoumarins **1a-d** as well as benzoanalogs (**1e-f**) react with cyanoacetylhydrazides **2a-c** in the presence of piperidine as catalyst to produce 3-cyanocoumarins **3a-c**.

Experimental

Mass-spectra

All mass- spectra were scanned on a SSQ-710 (Finnigan MAT) spectrometer at the energy of ionizing electrons equal to 70 eV. The temperature of ionizing source was equal to 150°C.

Synthesis of starting compounds

3-Ethoxycarbonyl and 3-acetylcoumarins **1a-e** have been synthesized according to (12,13). Syntheses of cyanoacetylhydrazides **2a-c** have been performed by (14).

Preparation of 3- cyanocoumarins **3a-c**

A solution of coumarin **1a-e** (0.01 mole) and cyanoacetylhydrazide **2a-c** (0.01 mole) in 20 ml of ethanol in the presence of piperidine (3 drops) has been stirred for 60 min.(**3a,b**) or 24 hours (**3c**) at room temperature untill precipitate is formed. Then precipitate was filtered off, washed with 5 ml of cold ethanol, dried and recrystallized from ethanol (for **3a,b**) or DMF (for **3c**). Yields are listed in **Table1**.

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