NEW WAYS OF LACTONE RING SHORTENING AND CYCLOPROPANATION IN COUMARIN DERIVATIVES

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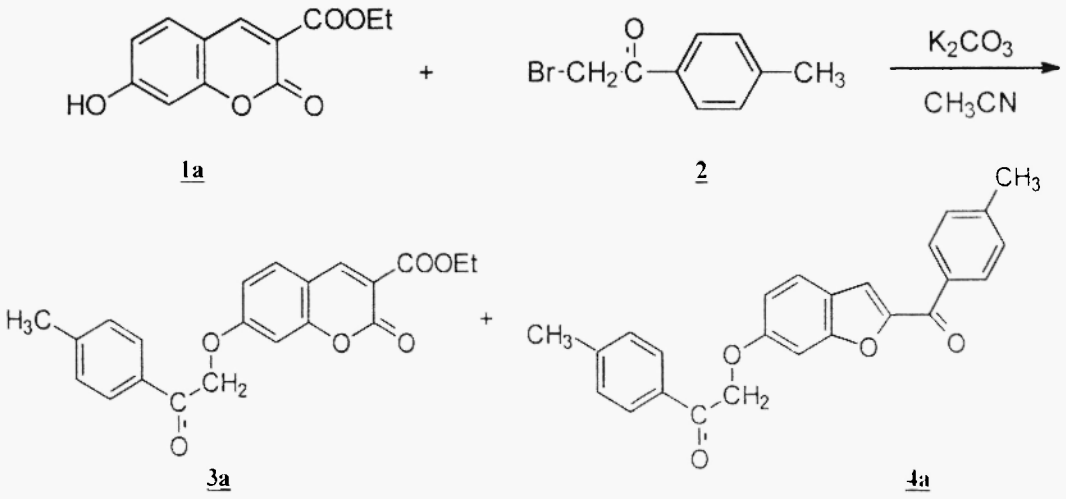
Abstract: Depending on their structures, substituted 3-carboethoxycoumarins react with 4-methylphenacylbromide in presence of potassium carbonate (solvent - acetonitrile) via lactone ring shortening (with formation of corresponding benzofuran derivatives) or via lactone ring cyclopropanation (with formation of condensed cyclopropane derivatives of coumarin).

Introduction

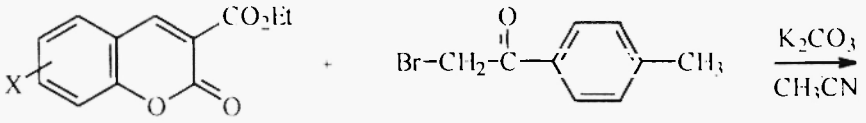
While studying of synthetic paths of new furocoumarins preparation (1,2), we have found an unexpected result. Interaction of 3-carboethoxy-7-hydroxycoumarin **1a** with 4-methylphenacylbromide **2** in presence of potassium carbonate in acetonitrile provides benzofuran derivative **4a** as a main product instead of 3-carboethoxy-7-(p-methylphenacyloxy)coumarin **3a**. Structures of initial compounds and final products are shown in scheme 1.

Scheme 1.



We have found that a way of lactone ring transformation in 3-carboethoxycoumarins in the used conditions depends predominantly on the substituent in benzene ring of coumarin derivative. The results of this study are shown in scheme 2.

Scheme 2



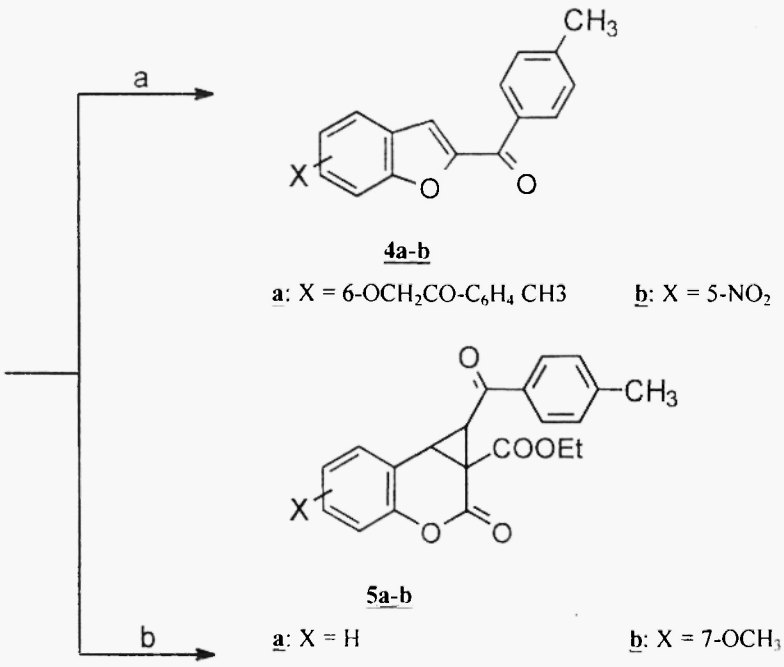
1a-d **2**

a: X=7-OH

b: X=6-NO_2

c: X=H

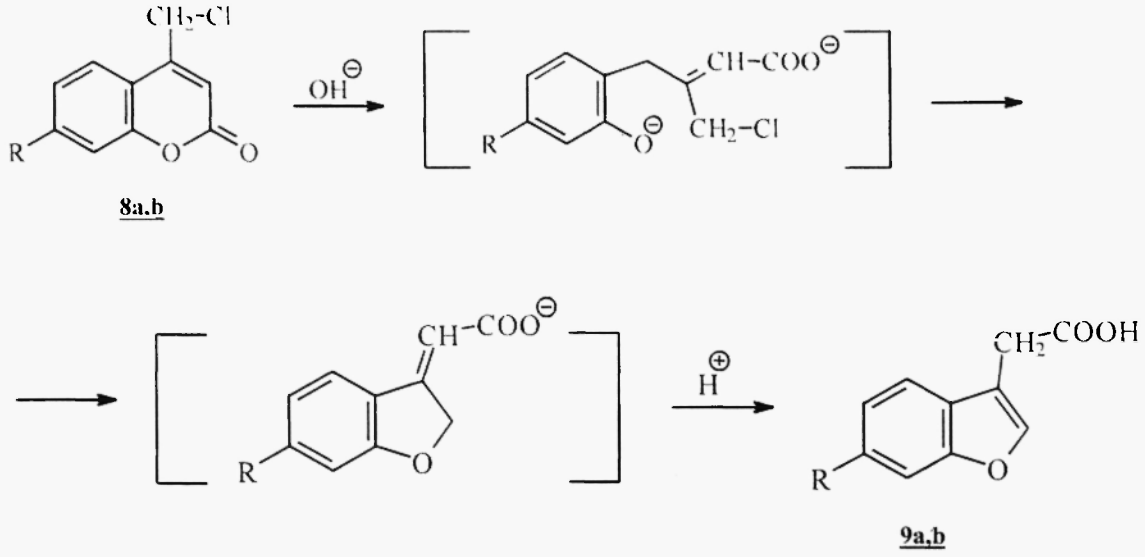
d: X=7-OCH_3



Several examples of transformation of lactone ring into furan ring have already been reported along studies in coumarin chemistry. For example, treatment of 3-halogenocoumarins **6** with potassium hydroxide aqueous solution leads to benzofuran-2-carboxylic acid **7** (3,4). At the same time, interaction of 4-chloromethylcoumarin **8** with sodium hydroxide aqueous solution provides (3-benzofuryl)acetic acid **9** (5,6). However, certain difference should be noted when results shown in schemes 1 and 2 are compared with those reported earlier. The previous examples

of lactone ring shortening have been only detected in presence of strong bases (3-6). The reaction in these conditions starts with lactone ring opening due to addition of hydroxide ion to carbon atom of carbonyl function as it is shown in scheme 3.

Scheme 3



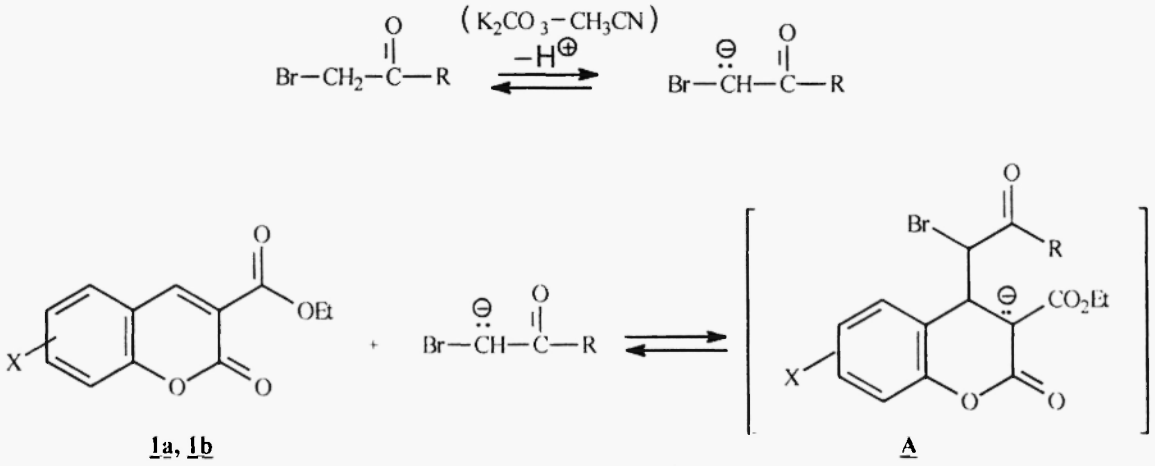
8a,b

9a,b

a: R = OH; **b**: R = OCH_3

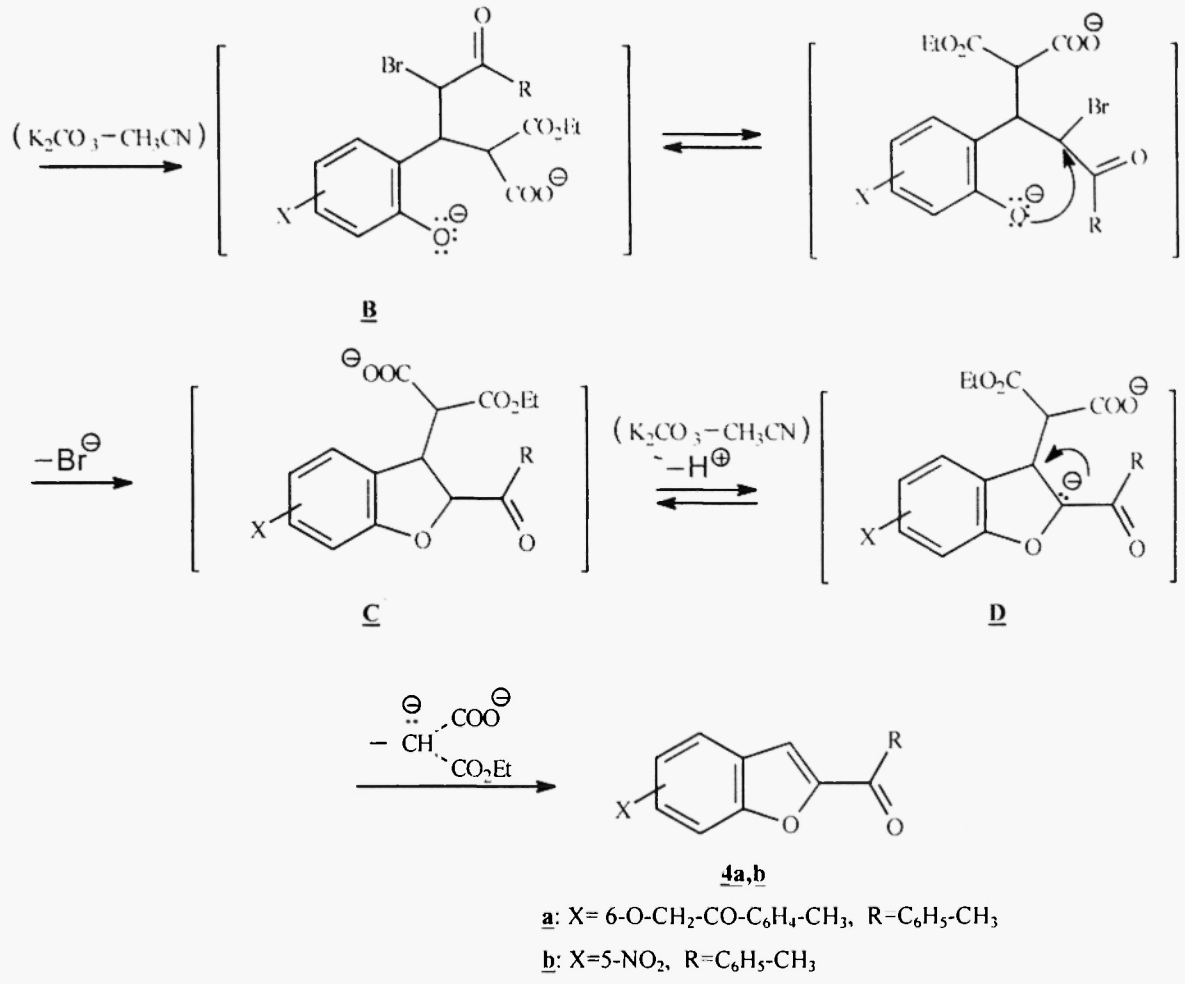
In opposite, neither coumarin nor 3-carboethoxycoumarin do not open lactone ring in presence of potassium carbonate in acetonitrile. In these conditions reaction seems to start as nucleophilic addition at the position 4 of lactone ring with formation of adduct **A**. Carbanion formed from 4-methylphenacylbromide **2** acts as a nucleophile in this interaction. The proposed sequence of the following steps is shown in scheme 4.

Scheme 4



1a, 1b

A



B

C

D

4a,b

a: X= 6-O-CH_2-CO-C_6H_4-CH_3, R=C_6H_5-CH_3

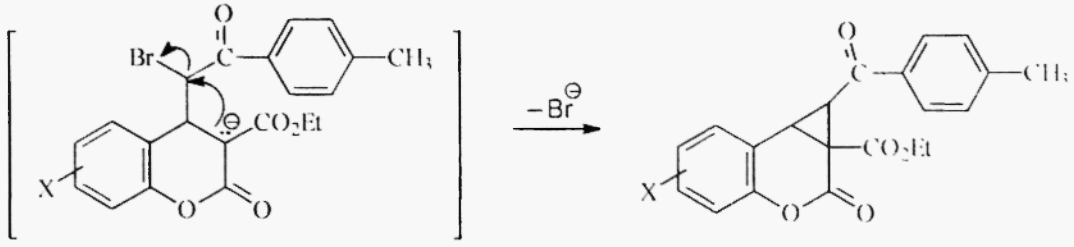
b: X=5-NO_2, R=C_6H_5-CH_3

Appearance of negative charge at C-3 atom in adduct **A** leads to opening of lactone ring and intermediate **B** formation. This step is then followed by substitution of bromide ion by phenoxide group with closure of dihydrofuran cycle (intermediate **C**). Intermediate **C** is ionized in presence of base with aromatization as a final step.

The earlier reported examples of the Michael addition agree with the proposed sequence of steps. Coumarins with electronowithdrawing substituents in position 3 react with nucleophiles at position 4 (7-9).

Scheme 4 is also in a good accordance with cyclopropanation of the lactone ring which we have also detected along our studies. The adduct **A** seems to participate in competitive transformation as it is shown below in scheme 5.

Scheme 5



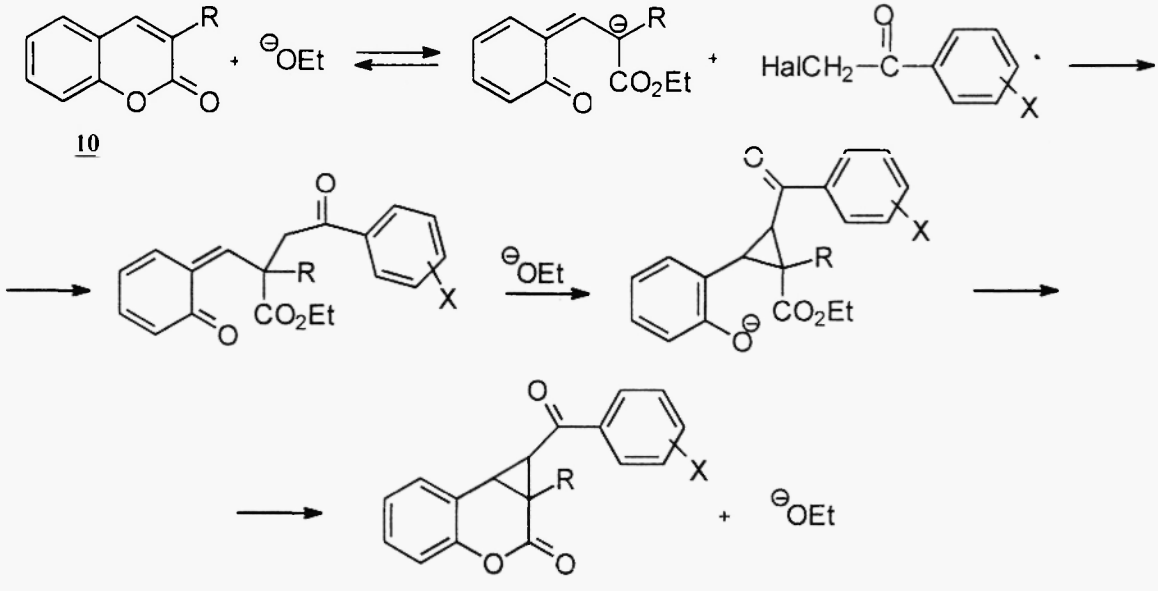
A **5a,b**

a: X=H

b. X=7-OCH_3

Formation of cyclopropane-fused derivatives of coumarin has been previously reported in presence of strong bases (10-13). This reaction has been presumably started with opening of the lactone ring as it is shown in scheme 6 (13).

Scheme 6



10

11

R=$COCH_3$, COPh, COOEt, CN, COEt, $COOCH_3$

X=H, OCH_3, NO_2

Hal=Br, Cl

Effects of the substituents in coumarin benzene ring agree also with the proposed scheme 4. The following consideration seems to explain the found experimental results. Strong electronowithdrawing substituent (like nitro group) in benzene ring accelerates lactone ring opening due to stabilization of phenoxide ion **B**. 7-(4'-Methylphenacyloxy) group operates also as

a weak electronowithdrawing substituent when it is located at meta position to phenoxide oxygen atom in the intermediate B (scheme 4).

When benzene ring contains even a weaker electronoaceeptor (like methoxy group or hydrogen atom) lactone ring opening does not take place at all in presence of relatively weak base such as carbonate ion. Formation of cyclopropane-fused .coumarin derivative undergoes in these conditions. The carbanion **A** transforms via intramolecular nucleophilic substitution reaction (like in the Widman reaction) with formation of 3-carboethoxy-7-R-9-(p-tolylmethyl)-3,4-dihydro-3,4-methano-2H-benzo(b)pyran-2-ones **5a,b** (yields 30% and 70% respectively).

Experimental

General procedure

To boiling solution of 3-carboethoxycoumarin **1a-d** and potassium carbonate (6 mmol, 0.83 g) in acetonitrile solution of 4-methylphenacylbromide **2** (2 mmol, 0.43 g) was added under intensive stirring Then the reaction mixture was refluxed, with stirring, for 5-7 h. After end of the reaction (TLC-control) the solvent was distilled off. The residue was treated by water (75 ccm) and diluted HCl to pH 3. The precipitate was washed with water. Then it was purified by a silica gel column chromatography (chloroform as a solvent).

^{1}H NMR and Mass spectra

^{1}H-NMR spectra were recorded on a WP 200 (Bruker) spectrometer at 200 MHz in $CDCl_3$ solutions using TMS as an internal standard. Chemical shifts are given in ppm.

Mass spectra were scanned on a SSQ-710 (Finnigan MAT) spectrometer at the energy of ionizing electrons equal to 70 ev.

2-(p-Methylbenzoyl)-6-(p-methylphenacyloxy)benzofuran 4a: yield 12%; m.p. 138-139 ^{0}C (EtOH); ^{1}H NMR ($CDCl_3$, J/Hz), 2.404 (s, 3H, 4-MePh), 2.416 (s, 3H, 4-MePh), 5.313 (s, 2H, OCH_2), 7.408 (s, 1H, 3-H), 7.556 (d, J=8.4, 1H, 4-H), 7.883 (d, J=8,44,H, H-ortho Ph), 7.279 (d, J=8.0,4H, H-meta Ph), 7.038 (d, J=1.61,H, 7-H), 7.015 (dd, J=1.6, J=8.4, 1H, 5-H). MS: m/z(%) 384(60)$[M]^+$,119 (100) $[MePhCO]^+$ $C_{25}H_{20}O_4$.

2-(p-Methylbenzoyl)-5-nitrobenzofuran 4b: yield 15%; m.p. 206-207 ^{0}C (EtOH); ^{1}H NMR ($CDCl_3$, J/Hz) 2.485 (s, 311, 4-MePh), 7.279 (d, J=8.0, 211, H-meta Ph), 7.630 (s, 111, 3-H), 7.748

(d, J=9.12, 1H, 7-H), 7.987 (d, J=8.2, 2H, H-ortho Ph), 8.407 (dd, J=9.14,J=2.36, 1H, 6-H), 8.687 (d, J=2.32, 1H, 4-H). MS: m/z(%) 281(70) $[M]^+$. $C_{16}H_{11}NO_4$.

3-Carboethoxy-7-(p-methylphenacyloxy)coumarin 3a: yield 6%; m.p. 176-177 ^{0}C (EtOH); ^{1}H NMR ($CDCl_3$, J/Hz) 1.40 (t, J=7.08, 3H, OEt), 2.46 (s, 3H, 4-MePh), 4.40 (q, J=7.06, 2H, OEt), 5.40 (s, 2H, OCH_2), 6.76 (d, J=2.52, 1H, 8-H), 6.98 (dd, J=8.84, J=2.54, 1H, 6-H), 7.34 (d, J=8.22, 2H, H-meta Ph), 7.53 (d, J=8.86, 1H, 5-H), 7.88 (d, J=8.20, 2H, H-ortho Ph), 8.50 (s, 1H, 4-H). MS: m/z(%) 366(65)$[M]^+$ $C_{21}H_{18}O_6$.

3-Carboethoxy-9-(p-toluyl)-3,4-dihydro-3,4-methano-2H-benzo(b)pyran-2-one 5a, yield 30%; m.p. 161-162 ^{0}C (EtOH); ^{1}H NMR ($CDCl_3$, J/Hz) 1.343 (t, J=7.08, 3H, OEt), 3.381 (d, J=9.66, 1H, 4-H), 4.141 (d, J=9.68, 1H, H_a), 4.308 (q, J=7.06, 2H, OEt), 7.29–7.0078 (m, 6H, 2H-meta Ph, H_5, H_6, H_7, H_8), 7.814 (d, J=8.26,J=2.36, 2H, H-ortho, Ph); MS: m/z(%) 350(60)$[M]^+$ $C_{21}H_{18}O_5$.

3-Carboethoxy-7-methoxy-9-(p-toluyl)-3,4-dihydro-3,4-methano-2H-benzo(b)pyran-2-one 5b, yield 70%; m.p. 150-151 ^{0}C (EtOH); ^{1}H NMR ($CDCl_3$, J/Hz) 1.37 (t, J=7.08, 3H, OEt), 2.384 (s, 3H, 4-MePh), 3.348 (d, J=9.5, 1H, 4-H,), 3.750 (s, 3H, OMe), 4.10 (d, J=9.48, 1H, H_a), 4.295 (q, J=7.06, 2H, OEt), 6.638 (d, J=2.38, 1H, 8-H), 6.567 (dd, J=8.44, J=2.52, 1H, 6-H), 7.136 (d, J=8.42, 1H, 5-H), 7.224 (d, J=7.88, 2H, H-meta Ph), 7.810 (d, J=8.16, 2H, H-orhto Ph); MS: m/z(%) 380(65) $[M]^+$ $C_{22}H_{20}O_6$.

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