THE BASE-CATALYZED CYCLIZATION OF ACYLMETHYL ETHERS OF 7-HYDROXYCOUMARINS

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Abstract: We have studied the base-catalyzed cyclization of acylmethyl ethers of 7-hydroxycoumarins which proceeds via lactone ring opening and yields psoralen derivatives. Corresponding cinnamic acid derivatives have been isolated. The cyclization is a highly regioselective reaction, producing only linear furocoumarins. According to MNDO calculations, the anionic σ-complex formed due to acylmethyl attack to the C-6 position of the coumarin turns out to be more stable than that to the C-8 position. A series of new psoralens with phenyl group in the lactone and (or) in the furan ring have been synthesized and characterized by NMR and mass spectra.

Introduction

Cyclization of the acylmethyl ethers of 7-hydroxycoumarins **1** in the presence of a base has been found to be one of the most convenient routes to psoralen derivatives **2** (4) which are important compounds because of their photo chemical and photo biological activity (1-3).

We used a base-catalyzed cyclization of **1** to synthesize psoralen derivatives **2**, which have a phenyl group as substituent in the lactone and (or) in the furan ring. These psoralen derivatives seem to be prospective substrates in search of new photochemotherapeutic agents.

We now report new results that deal with the mechanism of this reaction. Some intermediates of the reaction were isolated. Regioselectivity of the base-catalyzed cyclization of **1** was studied by the MNDO calculations of relative stability of the corresponding intermediate anionic σ-complexes.

Results and Discussion

Coumarins 1 were synthesized from corresponding 7-hydroxycoumarins and bromomethyl ketones. Psoralens 2 were prepared by base-catalyzed cyclization of coumarins 1(Scheme 1). Yields, melting points and spectral characteristics of ethers 1 and psoralens 2 are listed in **Experimental** section.

Scheme 1. Preparation of psoralens 2a-h.

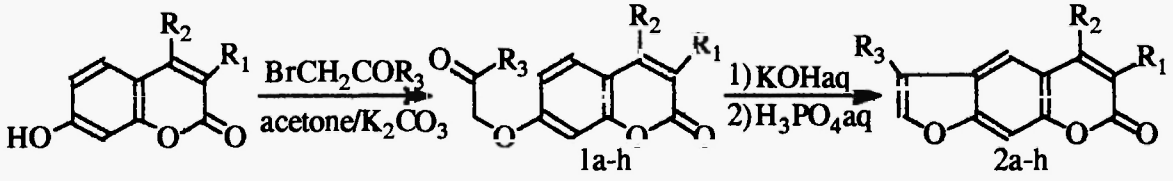
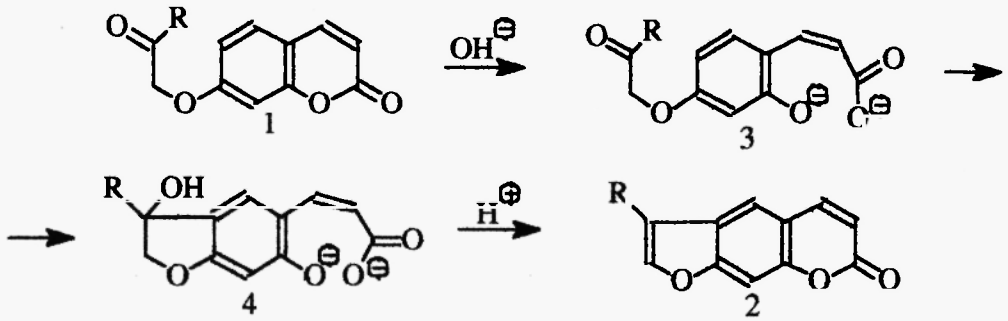


Table 1. Compounds 1a-h and 2a-h shown in Scheme 1.

Compound	R_1	R_2	R_3
1a and 2a	H	H	C_6H_5
1b and 2b	H	H	p-CH_3-C_6H_5
1c and 2c	H	CH_3	p-CH_3-C_6H_5
1d and 2d	H	C_6H_5	C_6H_5
1e and 2e	C_6H_5	H	C_6H_5
1f and 2f	C_6H_5	H	CH_3
1g and 2g	H	C_6H_5	CH_3
1h and 2h	H	H	CH_3

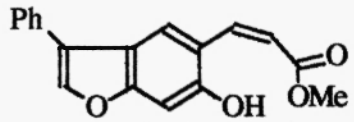
The mechanism of the base-catalyzed cyclization of 1 has not been previously studied (5), and none of the probable intermediates has been isolated. It has been suggested that the reaction starts with lactone ring opening of coumarin 1 which forms an intermediate 3. Then nucleophilic addition of the carbon atom of the benzene ring to the carbonyl function of the acylmethyl group forms an intermediate 4 which after acidification gives final product 2.(Scheme 2).

Scheme 2. The mechanism of the base- catalyzed cyclization.

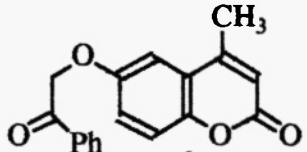


Nucleophilicity of the C-6 carbon atom of the benzene ring is increased to a large extent by the phenoxide oxygen atom that appears with lactone ring opening.

To prove the pyrone ring opening step we conducted cyclization of **1a** according to the standard procedure (**Experimental section**), but before the acidification dimethylsulfate was added to the reaction mixture, and **cis-5a** and **trans-5a** were isolated in ratio 9:1.



cis-5a



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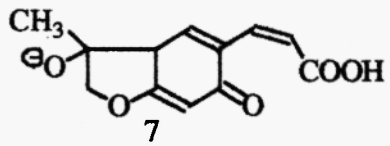
We tried to apply the base catalyzed cyclization for acylmethyl ethers of 6-hydroxycoumarin. Benzoylmethyl ether of 6-hydroxy-4-methylcoumarin **6** does not undergo the cyclization under standard conditions. This fact is in accordance with the proposed mechanism.

Cyclization of the acylmethyl ethers of 7-hydroxycoumarins **1** also occurs with potassium carbonate catalysis in alcohols under refluxing. The final reaction mixture is easier to separate, the reaction volume is 10-12 times lower than in the standard procedure, and only a small amount of potassium carbonate and phosphoric acid is required.

According to our results and the literature data (2, 5) the reaction yields only linear furocoumarins. But electrophilic attack of 7-hydroxycoumarins in the presence of the acidic catalysts usually give C-8 and C-6 substituted coumarins as major and as side products respectively. Halogenation, Friedel-Crafts acylation, and nitration reactions are such examples (6). By MNDO calculations of heats of formation ΔHf^{o} we have found that the intermediate σ-complex **7** corresponding to the linear cyclization is more stable than that of the angular cyclization **8**. These complexes and the MNDO calculated ΔHf^{o} values are shown below. Also the linear cyclization seems to be more preferable due to the steric factors.



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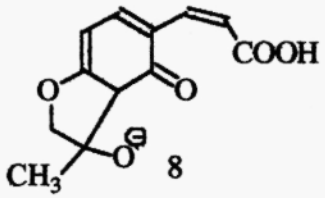
ΔHf^{o}=-174.4 kcal/mol



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ΔHf^{o}=-172.2 kcal/mol

Experimental

Spectral measurements

1H NMR Spectra were recorded on 200 MHz Bruker spectrometer; $CDCl_3$ was used as solvent and tetramethylsilane as internal standard; chemical shifts δ are given in ppm, splitting constants J are given in Hz. Mass spectra were scanned on a SSQ-710 (Finnigan MAT) spectrometer at the energy of ionizing electrons equals to 70 eV.

Preparation of acylmethyl ethers of 7-hydroxycoumarins 1a-h. General procedure.

A solution of the corresponding 7-hydroxycoumarin (3mmol) and bromomethyl ketone (3mmol) in a minimal amount of acetone (10-20 mL, depending on solubility of 3a-d) was refluxed for 1.5-6 hrs in the presence of potassium carbonate (3.5 mmol) with TLC tests (on Silufol UV-254 sheets) of the reaction. Reaction mixture was filtered, and the acetone was evaporated from the filtrate. The reaction product, ether 1a-h, was purified by recrystallization from aqueous ethanol or by column chromatography on silica gel with chloroform or chloroform-ethyl acetate mixture as eluent.

7-Benzoylmethoxycoumarin 1a, yield 98%, mp 168-169°C (lit. (2) 167-169°C)

7-(4'-Methylbenzoyl)methoxycoumarin 1b, yield 85%, mp 172-173°C; ^1H NMR: 2.45 (s, 3H, CH_3); 5.34 (s, 2H, CH_2); 6.26 (d, 1H, $J_{3,4}$=9.5, 3-H); 6.79 (d, 1H, $J_{8,6}$=2.5, 8-H); 6.92 (dd, 1H, $J_{6,5}$=8.5, $J_{6,8}$=2.5, 6- H); 7.32 (d, 2H, $J_{3'(5'),2'(6')}$=8.2, aryl-meta-H); 7.36 (d, 1H, $J_{5,6}$=8.5, 5-H); 7.63 (d, 1H, $J_{4,3}$=9.5, 4-H); 7.89 (d, 2H, $J_{2'(6'),3'(5')}$=8.2, aryl-ortho-H); MS: calcd for $C_{18}H_{14}O_4$-294, found-294

4-Methyl-7-[(4'-methylbenzoyl)methoxy]coumarin 1c, yield 89%, mp 147-148°C; ^1H NMR: 2.39 (d, 3H, $J_{CH3,3}$=1.2, 4-CH_3); 2.44 (s, 3H, 4'-CH_3); 5.34 (s, 2H, CH_2); 6.14 (q, 1H, $J_{3,CH3}$=1.2, 3-H); 6.80 (d, 1H, $J_{8,6}$=2.5, 8-H); 6.94 (dd, 1H, $J_{6,5}$=8.8, $J_{6,8}$=2.5, 6- H); 7.32 (d, 2H, $J_{3'(5'),2'(6')}$=8.3, aryl-meta-H); 7.51 (d, 1H, $J_{5,6}$=8.8, 5-H); 7.89 (d, 2H, $J_{2'(6'),3'(5')}$=8.3, aryl-ortho-H); MS: calcd for $C_{19}H_{16}O_4$-308, found-308

7-(Benzoylmethoxy)-4-phenylcoumarin 1d, yield 71%, mp 146-147°C; ^1H NMR: 5.40 (s, 2H, CH_2); 6.22 (s, 1H, 3-H); 6.85 (m, 2H, 6-H and 8-H); 7.42-7.85 (m, 9H, aryl-H and 5-H); 7.95-8.00 (m, 2H, aryl-H); MS: calcd for C23H16O4-356, found-356

7-(Benzoylmethoxy)-3-phenylcoumarin 1e, yield 83%, mp 173-174°C; ^1H NMR: 5.37 (s, 2H, CH_2); 6.81 (d, 1H, $J_{8,6}$=2.5, 8-H); 6.94 (dd, 1H, $J_{6,5}$=9.0, $J_{6,8}$=2.5, 6-H); 7.38-7.68 (m, 9H, aryl-H and 5-H); 7.73 (s, 1H, 4-H); 7.95-8.00 (m, 2H, aryl-H); MS: calcd for $C_{23}H_{16}O_4$-356, found-356

7-(Acetylmethoxy)-3-phenylcoumarin 1f, yield 80%; mp 159-160 °C, ^1H NMR: 2.31(s, 3H, CH_3); 4.64 (s, 2H, CH_2); 6.80 (d, 1H, $J_{8,6}$=2.5, 8-H); 6.89 (dd, 1H, $J_{6,5}$=8.7, $J_{6,8}$=2.5, 6-H); 7.41-7.49 (m, 4H, aryl-H and 5-H); 7.66-7.71 (m, 2H, aryl-H);7.76 (s, 1H, 4-H); MS: calcd for $C_{18}H_{14}O_4$-294, found-294

7-(Acetylmethoxy)-4-phenylcoumarin 1g, yield 78%; mp 144-145°C, ^{1}H NMR: 2.30 (s, 3H, CH_3); 4.65 (s, 2H, CH_2); 6.23 (s, 1H, 3-H); 6.80-6.85 (m, 2H, 6-H and 8-H); 7.40-7.45 (m, 4H, aryl-H and 5-H); 7.49-7.53 (m, 2H, aryl-H); MS: calcd for $C_{18}H_{14}O_4$-294, found-294

7-Acetylmethoxycoumarin 1h, yield 85%; mp 164-166°C, ^{1}H NMR: 2.29 (s, 3H, CH_3); 4.62 (s, 2H, CH_2); 6.27 (d, 1H, $J_{3,4}$=9.4, 3-H); 6.75 (d, 1H, $J_{8,6}$=2.5, 8-H); 6.85 (dd, 1H, $J_{6,8}$=2.5, $J_{6,5}$=9.0, 6-H); 7.40 (d, 1H, $J_{5,6}$=9.0, 5-H); 7.63 (d, 1H, $J_{4,3}$=9.4, 4-H); MS: calcd for $C_{12}H_{10}O_4$- 218, found- 218

Preparation of psoralens 2a-g. General procedure.

A solution of 1 (4 mmol) in a minimal amount of ethanol (30-40 mL) was mixed with 400 mL of aqueous 1M solution of NaOH and refluxed for 5 hrs under argon. The reaction mixture was acidified and kept cold over night. The precipitate that formed was filtered off and purified by recrystallization from aqueous ethanol or by column chromatography on silica gel with chloroform or chloroform-ethyl acetate mixture as eluent.

4'-Phenylpsoralen 2a, yield 70%, mp 127-128°C (lit. (2) mp 126-128°C)

4'-(p-Methylphenyl)psoralen 2b, yield 76%, mp 180-181°C; ^{1}H NMR: 2.42 (s, 3H, CH_3); 6.38 (d, 1H, $J_{3,4}$=9.8, 3-H); 7.31 (m, 2H, phenyl-H); 7.49 (s, 1H, 8-H); 7.51 (m, 2H, phenyl-H); 7.80 (d, 1H, $J_{4,3}$=9.8, 4-H); 7.83 (s, 1H, 5'-H); 7.86 (s, 1H, 5-H). MS: calcd for $C_{18}H_{12}O_3$-276, found-276

4-Methyl-4'-(p-methylphenyl)psoralen 2c, yield 80%, mp 173-174°C; ^{1}H NMR: 2.45 (s, 3H, phenyl-CH_3); 2.51 (d, 3H, $J_{CH3,3}$=1.2, 4-CH_3); 6.30 (q, 1H, $J_{3,CH3}$=1.2, 3-H); 7.34 (m, 2H, phenyl-H); 7.51 (s, 1H, 8-H); 7.53 (m, 2H, phenyl-H); 7.81 (s, 1H, 5'-H); 8.00 (s, 1H, 5-H). MS: calcd for $C_{19}H_{14}O_3$-290, found-290

4,4'-Diphenylpsoralen 2d, yield 72%, mp 189-190°C; ^{1}H NMR: 6.35 (s, 1H, 3-H); 7.34-7.55 (m, 10H, phenyl-H); 7.58 (s, 1H, 8-H); 7.81 (s, 1H, 5'-H); 7.88 (s, 1H, 5-H); MS: calcd for $C_{23}H_{14}O_3$ -338, found-338

3,4'-Diphenylpsoralen 2e, yield 45%, mp 69-70°C; ^{1}H NMR: 7.42-7.50 (m, 6H, phenyl-H); 7.55 (s, 1H, 8-H); 7.63-7.75 (m, 4H, phenyl-H); 7.86 (s, 1H, 4-H); 7.95 (s, 1H, 5'-H); 7.96 (s, 1H, 5-H); MS: calcd for $C_{23}H_{14}O_3$ -338, found-338

4'-Methyl-3-phenylpsoralen 2f, yield 40%, mp 216-217°C; ^{1}H NMR: 2.28 (d, 3H, $J_{CH3,5'}$=1.4, CH_3); 7.38-7.42 (m, 3H, phenyl-H); 7.43 (s, 1H, 8-H); 7.46 (q, 1H, $J_{5',CH3}$=1.4, 5'-H); 7.63 (s, 1H, 4-H); 7.70 (m, 2H, phenyl-H);7.92 (s, 1H, 5-H); MS: calcd for $C_{18}H_{12}O_3$ -276, found-276

4'-Methyl-4-phenylpsoralen 2g, yield 70%, mp 164-165°C; ^{1}H NMR: 2.16 (d, 3H, $J_{CH3,5'}$=1.4, CH_3); 6.31 (s, 1H, 3-H); 7.44 (q, 1H, $J_{5',CH3}$=1.4, 5'-H); 7.48 (s, 1H, 8-H); 7.48-7.58 (m, 5H, phenyl-H);7.53 (s, 1H, 5-H); MS: calcd for $C_{18}H_{12}O_3$ -276, found-276

4'-Methylpsoralen 2h, yield 0.21g (75%), mp 188-189°C (lit. (7) mp 189°C)

Cis- and trans-3-(6'-hydroxy-3'-phenylbenzo[d]fur-5'-yl)propenoic acid methyl ester, cis-5a and trans-5a.

A solution of 1a (0.32g, 1.14 mmol) in ethanol (10 mL) was added to the hot aqueous 1M NaOH solution (120 mL). The reaction mixture was refluxed for 5 hrs under argon, then cooled to 35°C and shook with 5 mL of dimethylsulfate for 2.5 hrs. Then the reaction mixture was acidified with 10% aqueous solution of H_3PO_4 and extracted with diethyl ether. The ether extract was dried and ether evaporated. The solid products were separated by column chromatography (silica gel 100/250, eluent - chloroform-ethyl acetate in ratio 10:1). The following compounds were obtained:

2a, yield 0.22g(70%), mp 127-128°C.

Cis-3-(6'-hydroxy-3'-phenylbenzo[d]fur-5'-yl)propenoic acid methyl ester, cis- 5a, yield 0.04g (12%), mp 72-73°C; ^{1}H NMR: 3.89 (s, 3H, OCH_3); 6.03 (d, 1H, $J_{2,3}$=12.5, 2-H); 7.02 (s, 1H, 7'-H); 7.26-7.56 (m, 5H, phenyl-H); 7.38 (d, 1H, $J_{3,2}$=12.5, 3-H); 7.68 (s, 1H, furyl-H); 8.21 (s, 1H, 4'-H); MS: calcd for $C_{18}H_{14}O_4$- 294, found- 294.

trans-5a, ^{1}H NMR: 3.95 (s, 3H, OCH_3); 6.55 (d, 1H, $J_{2,3}$=16.0, 2-H); 7.07 (s, 1H, 7'-H); 7.40-7.61 (m, 5H, phenyl-H); 7.71 (s, 1H, furyl-H); 7.96 (s, 1H, 4'-H); 8.20 (d, 1H, $J_{3,2}$=16.0, 3-H).

Conclusions

The base-catalyzed cyclization of the acylmethyl ethers of 7-hydroxycoumarins to psoralen occurs as a regioselective reaction via lactone ring opening.

Acknowledgments

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