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SYNTHESIS OF CHOLESTERYL ESTERS OF HETEROCYCLIC ANALOGS OF CINNAMIC ACID AND HETAROYLOXYCINNAMIC ACIDS BY THE WITTIG REACTION

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The reaction of cholesteryl triphenylphosphonioacetate chloride with heterocyclic aldehydes and hetaroyloxyarenecarbaldehydes in the presence of base gave the corresponding cholesteryl esters of substituted propenoic acids possessing liquid crystal properties.

Keywords: heterocyclic aldehydes, liquid crystals, cinnamic acid, α,β-unsaturated acids, triethylamine, phosphonium salts, phosphorylides, cholesteryl esters, acylation, Wittig reaction.

Cholesteryl esters of cinnamic, *p*-nitrocinnamic, and several other α,β-unsaturated acids are manufactured for use as liquid crystals. Interest in these compounds is based on their thermodynamically stable high-temperature mesophase [1]. The presence of double bonds, especially, conjugated bonds, favors the formation of the cholesteric mesophase [2]. Various workers have sought new and effective compounds in this class [3-6].

In previous work [7], we showed that cholesteryl triphenylphosphonioacetate chloride (**1**) is a suitable synthone for the preparation of cholesteryl esters of α,β-unsaturated acids and may be readily converted to alkylidenephosphorane **2**. In the present work, this salt was used for the preparation of cholesteryl esters of heterocyclic analogs of cinnamic acid and heteroaroyloxycinnamic acids from the corresponding heterocarbaldehydes **3a-g** and hetaroyloxyarenecarbaldehydes **4a-c**. The synthesis of **4a-c** will be given below. The Wittig reaction between alkylidenephosphorane **2** formed from salt **1** by the action of triethylamine and aldehydes **3** and **4** is carried out under mild conditions at room temperature. Heating is required in only a few cases to dissolve aldehydes with low solubility.

Lower alcohols – ethanol and 2-propanol are convenient solvents for this reaction. The starting phosphonium salt is readily soluble in these alcohols, while the resultant cholesteryl esters **5a-g** and **6a-c** form a precipitate (see Table 1). The crystallization of these esters usually begins 1-5 min after adding triethylamine to the solution of salt **1** and aldehyde.

Triethylamine proved a sufficiently strong base for the conversion of triphenylphosphonium salt **1** into alkylidenephosphorane **2**, which then reacts with aldehydes. The reaction proceeds less rapidly when a weaker base – pyridine is used. The reversible equilibrium **1** $\rightleftarrows$ **2** is obviously considerably shifted toward the phosphonium salt by the action of pyridine. However, the reaction may be accomplished also in the presence of pyridine in the case of sufficiently active aldehydes such as, for example, 5-nitro-2-thiophenecarbaldehyde **3b**. The reactivity of **3b** relative even to stable alkylidenephosphoranes is so high that it was recommended for the

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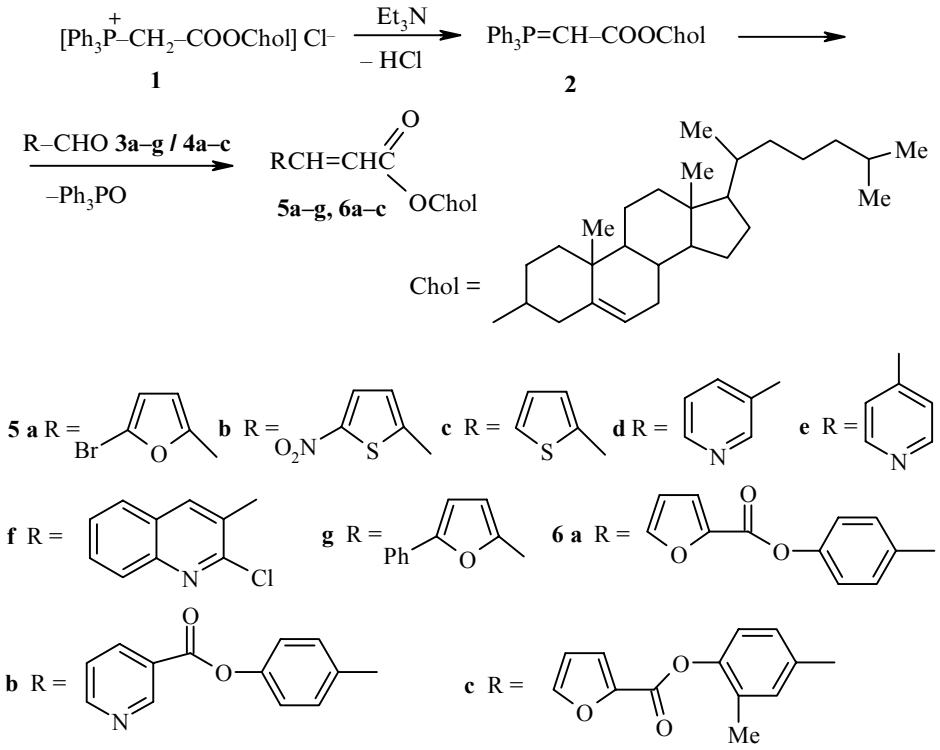
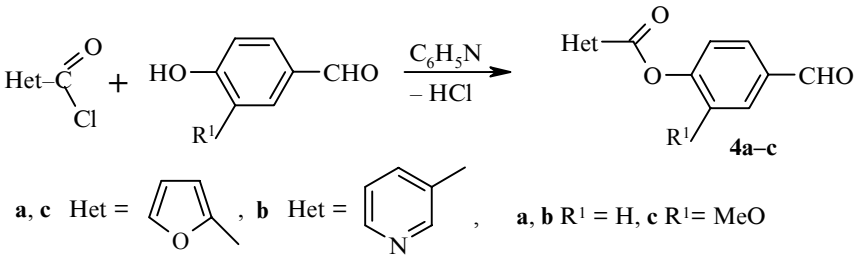
qualitative determination of this class of compounds [8, 9]. The reaction of aldehyde **3b** with salt **1** in the presence of pyridine is complete after several hours and product **5b** separates out as a greenish yellow precipitate.



Aldehydes **4a-c** required for the synthesis of esters of hetaroyloxycinnamic acids **6a-c** were obtained by the reaction of furancarboxylic or nicotinic acid chlorides with *p*-hydroxybenzaldehyde or vanillin in the presence of triethylamine (**4a,b**) or pyridine (**4c**).



Esters **5a-g** and **6a-c** are obtained predominantly as the *trans* isomers, sometimes with a slight admixture of the *cis* isomer. The products are purified to remove the *cis* isomer by single crystallization. These esters form a high-temperature mesophase at 140-200°C, while esters **5c** and **5d** form blue phase.

EXPERIMENTAL

The ^{1}H NMR spectra were obtained on a Varian VXR-300 spectrometer with TMS as the internal standard. The characteristics of **5a-g** and **6a-c** are given in Table 1.

TABLE 1. Characteristics of Cholesteryl Esters Synthesized

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	Hal (S)		
5a	$C_{34}H_{49}BrO_3$			13.92 / 13.64	179-180	74
5b	$C_{34}H_{49}NO_4S$			(5.43) / (5.65)	144-145	82
5c	$C_{34}H_{50}O_2S$			(5.87) / (6.13)	180-181	67
5d	$C_{35}H_{51}NO_2$	81.50 / 81.19	9.81 / 9.93		155-156	70
5e	$C_{35}H_{51}NO_2$	80.18 / 81.19	9.68 / 9.93		141-142	83
5f	$C_{39}H_{52}ClNO_2$			6.09 / 5.90	205-206	75
5g	$C_{40}H_{54}O_3$	82.97 / 82.43	9.22 / 9.34		137-139	50
6a	$C_{41}H_{54}O_5$	79.04 / 78.55	8.89 / 8.68		190-191	70
6b	$C_{42}H_{55}NO_4$	78.75 / 79.08	8.61 / 8.69		160-161	66
6c	$C_{42}H_{56}O_6$	76.35 / 76.78	8.43 / 8.59		150-151	71

Cholesteryl Esters of 3-Hetarylpropenoic Acids (5a-g) (General Method). Hetarylcarbaldehyde **3a-g** (3 mmol) was added to solution of salt **1** (2.2 g, 3 mmol) in 2-propanol or ethanol (20-30 ml). The mixture was sometimes slightly heated and an additional amount of solvent was added to improve the solubility of carbaldehyde. After complete dissolution of aldehyde, triethylamine (0.5 ml, 3.5 mmol) was added and crystallization of ester **5a-g** began after 2-5 min. The reaction mixture was maintained for 2-3 h. The precipitate was filtered off, washed with solvent, dried, and crystallized (in most cases, from heptane).

4-(2-Furoyloxy)benzaldehyde (4a). 2-Furoyl chloride (13.3 g, 0.102 mol), a strong lacrimator, was added to solution of 4-hydroxybenzaldehyde (12.2 g, 0.1 mol) in dry dioxane (60 ml). Triethylamine (14.2 ml, 0.103 mol) was added to the stirred solution dropwise with ice water cooling over 45 min. Anhydrous pyridine may also be used. Triethylammonium chloride separates out as a precipitate. The reaction mixture was stirred for an additional 15 min and left in a sealed flask at room temperature for several hours. Then, cold water (50 ml) was added in portions with shaking. Ammonium salt gradually dissolved and product **4a** began to precipitate out. The reaction mixture was maintained for several hours for complete crystallization of the product, which was then filtered and washed with 1:1 aqueous dioxane and a small amount of ethanol. Yield of compound **4a** 18-19.5 g (85-90%). When the starting reagents were sufficiently pure, aldehyde **4a** was obtained as a pure product. When necessary, the crude product was crystallized from ethanol; mp 95°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 9.88 (1H, s, CHO); 8.02 (2H, m, 2-, 6-H in C_6H_4); 7.43 (1H, m, 5-H_{Fur}); 7.13 (2H, m, 3-, 5-H in C_6H_4); 6.90 (1H, m, 3-H_{Fur}); 6.40 (1H, m, 4-H_{Fur}). Found, %: C 67.02; H 3.87. $C_{12}H_8O_4$. Calculated, %: C 66.66; H 3.73.

4-Nicotinoyloxybenzaldehyde (4-Formylphenyl-3-pyridinecarboxylate) (4b) was obtained in 68% yield from 4-hydroxybenzaldehyde and nicotinic acid chloride analogously to aldehyde **4a**; mp 93-94°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 10.04 (1H, s, CHO); 9.28 (1H, s, H_{Het}); 8.92 (1H, m, H_{Het}); 8.47 (1H, m, H_{Het}); 8.03 (2H, m, C_6H_4); 7.65 (1H, m, H_{Het}); 7.60 (2H, m, C_6H_4). Found, %: N 6.30. $C_{13}H_9NO_3$. Calculated, %: N 6.16.

4-(2-Furoyloxy)-3-methoxybenzaldehyde (4c). 2-Furoyl chloride (10 ml) in dry ether (20 ml) was added dropwise over 1 h to stirred solution of vanillin (15.2 g, 0.1 mol) in dry ether (300 ml) and pyridine (10 ml) cooled with ice water. The reaction mixture was stirred for an additional hour at room temperature and then maintained at this temperature for several hours. The precipitate consisting of pyridinium chloride and

most of product **4c** was filtered off and washed consecutively with ether and several water portions with good stirring. Pyridinium salt was washed out and virtually pure product **4c** remained. After distilling of most of ether (to a volume of 20-30 ml), an additional small amount of pure product **4c** precipitated out of the ethereal filtrate. When necessary, crude product **4c** was crystallized from 2-propanol. Yield of aldehyde **4c** 80%; mp 103-104°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 9.87 (1H, s, CHO); 7.64 (1H, m, C_6H_3); 7.61 (1H, m, C_6H_3); 7.44 (1H, m, H_{Fur}); 6.97 (1H, m, C_6H_3); 6.88 (1H, m, H_{Fur}); 6.40 (1H, m, H_{Fur}); 3.82 (3H, s, CH_3). Found, %: C 62.93; H 4.22. $C_{13}H_{10}O_5$. Calculated, %: C 63.42; H 4.09.

Cholesteryl Ester of 4-(2-Furoyloxy)cinnamic Acid (6a). Triethylamine (0.5 ml, 3 mmol) was added to solution of salt **1** (2.2 g, 3 mmol) and aldehyde **4a** (0.64 g, 3 mmol) in 2-propanol (30 ml). Product **6a** crystallized out over 2-3 min and was filtered off after 2 h. The product was washed with 2-propanol, dried, and crystallized from CCl_4.

Cholesteryl Ester of 4-Nicotinoyloxycinnamic Acid (6b). Triethylamine (0.5 ml) was added to solution of salt **1** (3 mmol) and aldehyde **4b** (3 mmol) in 2-propanol (25 ml). Product **6b** began to crystallize out immediately and was filtered off after 2 h. The crude product was washed with 2-propanol and recrystallized from heptane. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm, *J* (Hz): 9.40 (1H, s, H_{Het}); 8.88 (1H, m, H_{Het}); 7.71 (2H, m, C_6H_4); 7.60 (2H, m, C_6H_4); 7.49 (1H, m, H_{Het}); 6.45 (1H, *J* = 19.5, =CHCO); 5.42 (1H, m, =<u>CH</u>C_6H_4); 4.76 (1H, m, H_{Chol}); 2.40-0.69 (44H, m, H_{Chol}).

Cholesteryl Ester of 3-Methoxy-4-furoyloxycinnamic Acid (6c). Triethylamine (0.5 ml) was added to solution of salt **1** (2.2 g, 3 mmol) and aldehyde **4c** (0.65 g, 3 mmol) in 2-propanol (30 ml). A precipitate of product **6c** began to form during the first 5 min and was filtered off after 3 h. The crude product was dried and crystallized from heptane. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm, *J* (Hz): 7.68 (1H, m, H_{Fur}); 7.4 (1H, *J* = 7.3, H_{Fur}); 7.16 (3H, m, C_6H_3); 6.60 (1H, m, H_{Fur}); 6.44 (1H, *J* = 19.2, =CHCO); 5.42 (1H, m, =<u>CH</u>C_6H_3); 4.76 (1H, m, H_{Chol}); 3.86 (3H, s, OCH_3); 2.40-0.69 (44H, m, H_{Chol}).

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