An efficient synthesis of cholesterol formate

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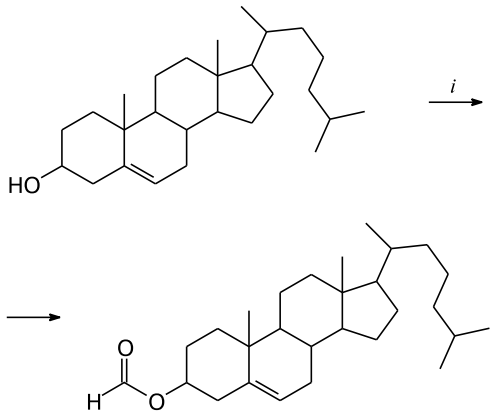
Cholesterol formate is an important compound in the chemistry of steroids. It is used in biochemical investigations of model membrane vesicles.[1] Recently, cholesterol formate has been isolated from the red alga *Grateloupia turuturu* Yamada and this may be of chemotaxonomic significance for this organism.[2] This compound is employed as a component in liquid-crystal optical filters.[3] Formyl protection is widely used in cholesterol chemistry because of its selective removal under mild conditions (K_2CO_3, methanol, 20 °C) in the presence of other ester protecting groups.[4] That is why a search for new convenient routes to cholesterol formate is of relentless interest.

Common reagents employed for O-formylation of cholesterol include DMF—benzoyl chloride,[5] DMF—triarylphosphine—halogen,[6] $EtOCHO—Cu(NO_3)_2 \cdot 3H_2O$,[7] $MeOCHO—Ph_3P—CBr_4$,[8] $CCl_3CHO—K_2CO_3$,[9] $EtOCHO—PCl_3—SiO_2$),[10] and $DMF—POCl_3$.[11] Usually, they are used in large molar excesses with respect to cholesterol. For instance, formylation of cholesterol with $DMF—POCl_3$ (the Vilsmeier complex), which is poorly reproducible and inefficient for alcohols,[5] is carried out in the presence of its four- to fivefold molar excess (~20 °C, 3 h, 64% yield).[11]

In our recent synthesis of 1-vinylpyrrole-2-carbaldehydes,[12] we found that the complex DMF—oxalyl chloride is a milder and more efficient formylating reagent than the classic Vilsmeier system.

Our investigations in the borderland between the chemistry of pyrroles and steroids,[13] including novel approaches to their vinylation[14] and formylation,[12,15] led us to a convenient and efficient route to cholesterol formate. At a molar ratio cholesterol : DMF—oxalyl chloride of 1 : 1.5, the reaction in CH_2Cl_2 at ~20 °C is completed in 40 min to give the target product in 97% yield (Scheme 1).

Scheme 1



i. DMF—oxalyl chloride, CH_2Cl_2

Cholesterol formate. Dimethylformamide (0.29 g, 3.9 mmol) and $(COCl)_2$ (0.49 g, 3.9 mmol) were mixed at 0—5 °C. After 10 min, CH_2Cl_2 (15 mL) and a solution of cholesterol (1.0 g, 2.6 mmol) in CH_2Cl_2 (15 mL) were added at room temperature to the resulting crystalline complex. The reaction mixture was stirred at room temperature for 30 min. The excess of the reagent was decomposed with a solution of NaOAc (1.3 g) in water (35 mL) for 30 min. The organic layer was separated and organic materials from the aqueous layer was extracted with CH_2Cl_2 (5×10 mL). The organic layer and the extracts were washed with saturated aqueous $NaHCO_3$ (3×10 mL) and water (3×10 mL) and dried with $MgSO_4$. Column chromatography on neutral Al_2O_3 in hexane—ether (2 : 1) gave cholesterol formate (1.05 g, 97%) as white crystals, m.p. 112—113 °C (*cf.* Ref. 11: 112—113 °C). Found (%): C, 81.23; H, 11.14. $C_{28}H_{46}O_2$. Calculated (%): C, 81.10; H, 11.18. The ^1H and ^{13}C NMR and IR spectra of the compound obtained are identical with those cited in Ref. 11.

Thus, the complex DMF—oxalyl chloride is a highly efficient and economical reagent for formylation of cholesterol as well.

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