Nucleophilic Substitution of (Alkoxymethylene)dimethylammonium Chloride with Carboxylate Salts: a Convenient Procedure for the Synthesis of Esters with Inversion of Configuration

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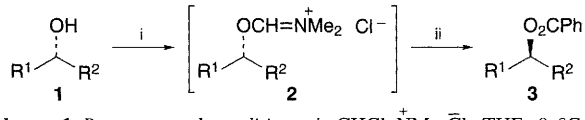
Secondary alcohols are converted into benzoate esters with inversion of configuration *via* sequential reaction with (chloromethylene)dimethylammonium chloride and potassium benzoate.

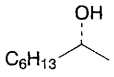
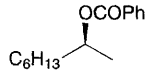
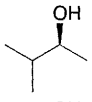
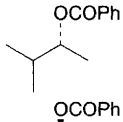
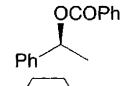
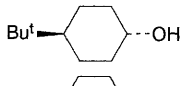
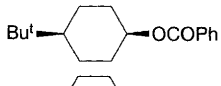
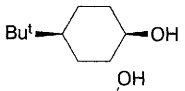
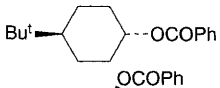
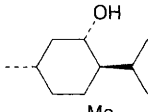
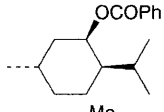
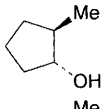
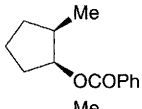
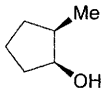
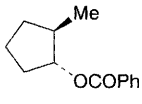
The conversion of secondary alcohols into esters with net inversion of configuration is a transformation of considerable importance in synthesis. The Mitsunobu reaction is the process *par excellence* for this conversion.[1] In the reaction an alcohol is treated with diethyl azodicarboxylate, triphenylphosphine and a carboxylic acid to provide the target ester. The Mitsunobu reaction is applicable for a diverse array of secondary alcohols and has been extended to lactonisation and macrolactonisation reactions. In addition, the carboxylic acid component can be replaced with alternative nucleophiles to provide varied products of S_N2 substitution. There are however disadvantages with the process. Firstly, diethyl azodicarboxylate is a hazardous chemical that precludes its safe use on a large scale. Secondly, the side products triphenylphosphine oxide and diethyl hydrazinedicarboxylate are of considerable mass and as such the Mitsunobu reaction scores badly from the viewpoint of atom economy.[2] Recently, one of us reported the use of Vilsmeier chemistry to effect the stereospecific cyclisation of hydroxyphenols to provide benzodioxans, dihydrobenzopyrans and dihydrobenzofurans *via* (alkoxymethylene)dimethylammonium salts and intramolecular S_N2 displacement by phenoxide.[3] Herein we report the extension of this chemistry to the conversion of secondary alcohols into esters with inversion of stereochemistry.

Reaction of a series of secondary alcohols **1** with (chloromethylene)dimethylammonium chloride, generated from DMF and oxalyl chloride,[4] gave the corresponding salts **2**. These were allowed to react with potassium benzoate at 67 °C to provide the corresponding benzoate esters **3** (Scheme 1 and Table 1).† Additionally, the reaction was extended to 5α-cholestan-3β-ol **4** (Scheme 2). Thus the sterol **4** was smoothly converted into the 3α ester **5**[5] (65%). Saponification gave 5α-cholestan-3α-ol **6**[6] and this in turn was esterified using the Vilsmeier methodology to produce the 3β ester **7** (53%) along with alkene **8**[7] (18%). In all cases with the exception of entry 3 (Table 1), the reactions were highly stereoselective and cleanly gave the products of S_N2 inversion. In each case the ester was authenticated by comparison with data for authentic samples. Enantiomeric purities for esters **3** (entries 1–3, Table 1) were determined by comparisons of optical rotations with literature data. Additionally, diastereoselectivities for all other esterification reactions were established by HPLC and ^{1}H NMR spectroscopy. Several factors need further comment. Firstly, tetrahydrofuran was found to be a better solvent for the reaction than dichloro-



Scheme 1 *Reagents and conditions*: i, $CHCl{=}\overset{+}{N}Me_2\bar{Cl}$, THF, 0 °C; ii, $PhCO_2K$, THF, 67 °C, 3 d

Table 1 Esterification of Secondary Alcohols with Inversion of Stereochemistry

Entry	Alcohol	Product	Yield (%)	e.e./d.e. (%)	Ref.
1			91	98	11
2			73	97	‡
3			88	51	12
4			64	97	13
5			46	97	
6			70	95	1d
7			80	97	
8			74	97	14

methane. Secondly, it is clear that the reaction proceeds with clean inversion of stereochemistry in all cases but one. The esterification of α-methylbenzyl alcohol proceeded with only partial inversion (e.e. = 51%). It is reasonable to speculate that this example involved either a mixed S_N2/S_N1 reaction or took place partially *via* the corresponding benzylic chloride. In several cases, small amounts of the formate with retention of configuration were detected. This is consistent with the S_N2 displacement of salt **2** to provide the ester **3** being slow and with hydrolysis of any remaining imidate **2** taking place on work-up. Finally, the esterification of axial alcohols proceeded in lower yields due to competing elimination reactions.

The imidate methodology in this paper should be of use as an alternative to the Mitsunobu reaction particularly for larger scale use and especially since the side products are innocuous (DMF and potassium chloride). The method is mechanistically similar to the synthesis of glycosides[8] and benzyl, allyl and *tert*-butyl ethers[9] *via* trichloroacetimidate activation. Recently, Zard and coworkers have described the use of *O*-alkyl *S*-prop-2-ynyl dithiocarbonates and carboxylic acids in the synthesis of esters with inversion of configuration.[10] This elegant method is a convenient alternative to Mitsunobu esterification.

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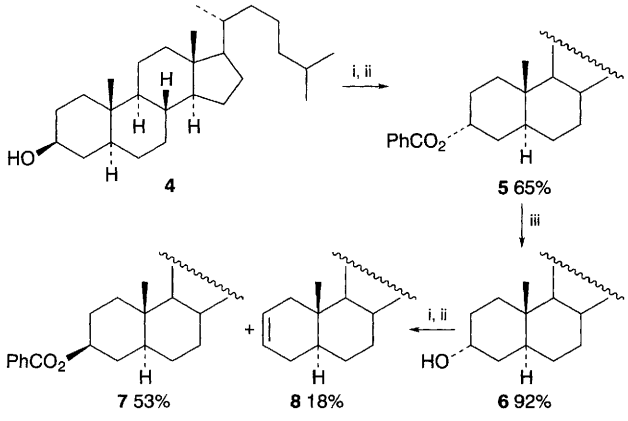

Scheme 2 *Reagents and conditions*: i, $CH{=}\overset{+}{N}Me_2\bar{C}l$, THF, 0 °C; ii, $PhCO_2K$, THF, 67 °C, 3 d ; iii, KOH, THF, EtOH, H_2O, 67 °C, 3 h

Footnotes

† In a typical procedure, oxalyl chloride (0.600 ml, 6.88 mmol) was added dropwise with stirring to a solution of DMF (0.550 ml, 7.10 mmol) in dry dichloromethane (12 ml) at 0 °C under nitrogen. After 5 min, the solvent was evaporated under reduced pressure at room temp. to leave a colourless solid. This solid was cooled to 0 °C and suspended in dry THF (10 ml) under nitrogen. (*R*)-Octan-2-ol (0.94 ml, 6.05 mmol) and potassium benzoate (4.82 g, 30.1 mmol) were added sequentially. The reaction mixture was heated to reflux for 3 d, cooled and filtered. The residue, after rotary evaporation, was chromatographed (silica pentanes–ethyl acetate 20 : 1) to provide (*S*)-2-octyl benzoate (1.29 g, 91%) as a colourless oil.

‡ (*S*)-3-Methylbutan-2-yl benzoate was prepared from (*S*)-3-methyl-butan-2-ol and benzoyl chloride in pyridine; $[\alpha]_D^{25}$ +36.0 (*c* 0.8, CH_2Cl_2).

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