Nucleophilic substitution of (alkoxymethylene)dimethylammonium chloride with potassium phthalimide; a convenient procedure for the synthesis of imides with inversion of configuration

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Secondary alcohols are converted into their phthalimido derivatives with inversion of configuration *via* sequential reaction with (chloromethylene)dimethylammonium chloride and potassium phthalimide.

The Mitsunobu reaction is the process *par excellence* for the conversion of secondary alcohols into esters with inversion of stereochemistry.[1] In this reaction an alcohol is treated with diethyl azodicarboxylate, triphenylphosphine and a carboxylic acid to provide the required ester. The reaction can be extended to a wide range of nucleophiles in addition to carboxylic acids to provide a variety of S_N2 substitution products. The stereoselective preparation of amines from the corresponding alcohol can be effected *via* formation of the phthalimido derivative.[2] There are however disadvantages associated with the Mitsunobu reaction. Diethyl azodicarboxylate is unstable and potentially explosive and the by-products, triphenylphosphine oxide and diethyl hydrazinedicarboxylate, are of considerable mass making the process non-ideal from the point of view of atom economy.[3] 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.[4] This Vilsmeier chemistry has also been extended to the conversion of alcohols into esters with inversion of stereochemistry.[5,6] Herein we report a further application of this methodology to form the phthalimide derivatives of secondary alcohols.

Treatment of a series of secondary alcohols **1** with (chloromethylene)dimethylammonium chloride, generated from oxalyl chloride and dimethylformamide,[7] provided the corresponding imidate salts **2**. These were then treated with potassium phthalimide at 60–70 °C to provide the phthalimide derivative **3** with inversion of stereochemistry (Scheme 1 and Table 1).† Enantiomeric purities (entries 1, 5, and 6) were established by HPLC. Clean inversion of stereochemistry was observed for entries 1 and 5 but substitution of (*R*)-1-phenylethanol proceeded with partial racemisation (entry 6, 72% ee). It is reasonable to speculate that this example either involved a mixed S_N2/S_N1 reaction or took place partially *via* the corresponding benzylic chloride. Several solvents were examined in these reactions of which acetonitrile was found to be superior. No reaction was observed in THF whereas reaction in DME or DMF gave the desired product in moderate yield. Furthermore the use of DMF as solvent led to partial racemisation in the preparation of (*S*)-*N*-2-octylphthalamide (58% ee). It is reasonable to assume that such partial racemisation was the result of partial substitution *via* 2-octyl chloride or *via* nucleophilic participation of the solvent (DMF) leading to inverted imidates. The imidate methodology in this paper should be of use as an alternative to the Mitsunobu reaction particularly for larger scale applications as 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.

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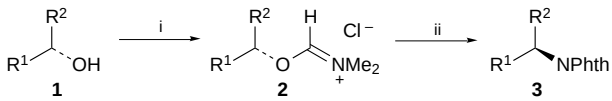
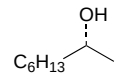
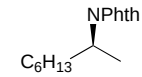
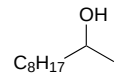
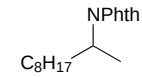
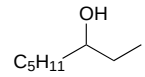
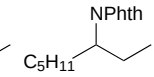
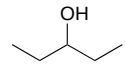
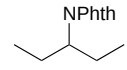
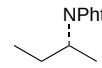
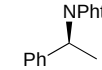
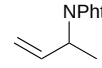
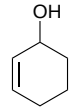
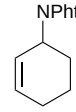


Scheme 1 *Reagents and conditions*: i, $CHCl{=}NMe_2{}^+Cl^-$, MeCN, 0 °C; ii, KPhth, 60–70 °C, 1–3 d

Table 1 Formation of phthalimido derivatives with inversion of stereochemistry[a]

Entry	Substrate	Product[b]	Yield (%)	ee[c] (%)	Ref.
1			95	96 $[\alpha]_D$ +14.0 (*c* 1.1, $CHCl_3$)	10[e]
2			77	—[d]	‡
3			90	—[d]	§
4			91	—[d]	11[e]
5			92	92 $[\alpha]_D$ –12.8 (*c* 1.1, $CHCl_3$)	12[e]
6			73	72 $[\alpha]_D$ –31.4 (*c* 0.5, $CHCl_3$)	12[e]
7			98	—[d]	13[e]
8			34	—[d]	14[e]

[a] All reactions performed with 7 equiv. of potassium phthalimide in acetonitrile for 1–3 d; [b] NPhth = phthalimido derivative; [c] Determined by HPLC on a chiral stationary phase; [d] Racemic substrate employed; [e] The spectroscopic data were identical to those reported in the literature.

Footnotes

† In a typical procedure, oxalyl chloride (0.10 cm^3, 1.15 mmol) was added dropwise with stirring to a solution of DMF (0.09 cm^3, 1.17 mmol) in dry dichloromethane (1 cm^3) at 0 °C under nitrogen. After 5 min, the white solid was suspended in dry acetonitrile (30 cm^3) and (*R*)-octan-2-ol (0.16 cm^3, 1.0 mmol) and potassium phthalimide (1.3 g, 7 mmol) were added sequentially. The reaction mixture was heated to 65 °C for 16 h cooled and filtered. The residue, after rotary evaporation, was chromatographed on silica gel (5% ethyl acetate in hexanes) to provide (*S*)-*N*-2-octylphthalimide (0.25 g, 95%) as a colourless oil.

‡ *Selected data* for *N*-2-decylphthalimide: R_f = 0.40 (light petroleum–ethylacetate, 10 : 1); δ_H (300 MHz; $CDCl_3$) 0.84 (3 H, t, *J* 6.7 Hz, CH_3), 1.24 (12 H, m, 6 × CH_2), 1.47 (3 H, d, *J* 6.9 Hz, CH_3), 1.74 (1 H, m, CH_2), 2.05 (1 H, m, CH_2), 4.34 (1 H, m, CH), 7.70 (2 H, m, PhH), 7.82 (2 H, m, PhH); δ_C (75 MHz; $CDCl_3$) 14.1, 18.7, 22.6, 26.8, 29.2, 29.2, 29.4, 31.8, 33.7, 47.5, 123.0, 132.1, 133.8, 168.6; υ_{max} (thin film)/cm^{-1} 2927s, 2856m, 1774m, 1710s; *m/z* (CI^+; NH_3), 305 (*M* + NH_4^+, 100), 288 (*M* + H^+, 45%); HRMS: $C_{18}H_{25}NO_2$ requires: 287.1885. Found: 287.1873.

§ *Selected data* for *N*-3-octylphthalimide: R_f = 0.23 (light petroleum–ethyl acetate 20 : 1); δ_H (300 MHz; $CDCl_3$) 0.86 (6 H, m, 2 × CH_3), 1.26 (6 H, m, 3 × CH_2), 1.82 (1 H, m, CH_2), 2.06 (1 H, m, CH_2), 4.12 (1 H, m, CH), 7.72 (2 H, m, PhH), 7.83 (2 H, m, PhH); δ_C (75 MHz; $CDCl_3$) 11.1, 14.0, 22.5, 25.6, 26.4, 31.5, 32.2, 54.0, 123.1, 131.9, 133.8, 168.9; υ_{max} (thin film)/cm^{-1} 2960s, 2931s, 2860m, 1770s, 1711s; *m/z* (CI^+; NH_3), 277 (*M* + NH_4^+, 100), 260 (*M* + H^+, 69%); HRMS: $C_{16}H_{21}NO_2$ requires: 259.1572. Found: 259.1583.

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