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The Use of Chloroacetic Acid in the Mitsunobu Reaction.

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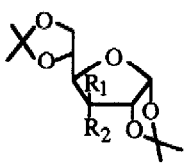
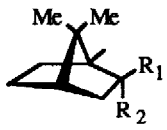
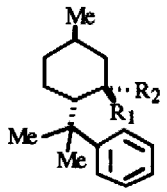
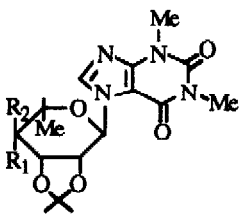
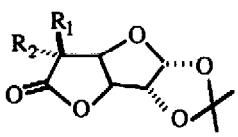
Abstract: Reaction of chloroacetic acid with TPP-DEAD was found to be very effective for the inversion of sterically congested alcohols, including carbohydrates and nucleosides.

The reaction of hydroxy compounds with carboxylic acids in the presence of diethyl azodicarboxylate and triphenylphosphine has been widely used for the inversion of a variety of alcohols.[1] However, the reaction often proceeds in low yields, and can even be completely ineffective in the case of sterically congested alcohols.[2] It has been found that the use of *p*-nitrobenzoic acid results in some improved yields, but it too is ineffective with substrates in which the alcohol moiety is flanked by two substituents or for alcohols with large α-substituents.[2] Recent mechanistic studies[3,4,5] have provided some additional insight into the intermediates involved in this esterification with inversion of configuration.

We report herein a modification of this reaction, using chloroacetic acid as the carboxylic acid partner, which gives dramatically improved yields of the inverted products, even in the case of substrates having sterically hindered hydroxyl groups.

The five substrates **1a-5a** (Table) were chosen for their known inability, or great resistance, to undergo inversion at their free alcoholic site. The C-3 secondary alcohol of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (**1a**) is known to be very difficult to invert.[6,7] Previous results[6] indicated that when **1a** was heated in the presence of TPP-DEAD-PhCOOH, the only product was 3-O-benzoyl-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose, in which the configuration of the alcohol was retained. In contrast, when it was subjected to our modified conditions,[8] the inverted product (**1b**) was obtained in 67% yield as ascertained by typical ^{1}H- NMR features (strong downfield shift for H-3, enhanced value of H3/H4 coupling constant) and by a strong dextrorotatory value for the deacylated product.[9]

Table.

Substrates: **a** ; Products: **b**		Yield[a]	$[\alpha]_D^{20}$	^{1}H Nmr of the products ($CDCl_3$ in ppm from TMS)
	**1a**: R_1= -OH R_2= -H **1b**: R_1= -H R_2= -$OCOCH_2Cl$	67%	+ 38 c = 1 $CHCl_3$	δ 5.81 (1H, d, J=3.7Hz); 5.32 (1H, d, J= 2.3Hz); 4.55 (1H, d, J= 3.7Hz); 4.20 (2H, m); 4.10 (2H, s); 4.02 (1H, m); 1.52 (3H, s); 1.46 (3H, s); 1.31 (6H, s).
	**2a**: R_1= -H R_2= -OH **2b**: R_1= -$OCOCH_2Cl$ R_2= -H	73%	+ 41 c = 1 $CHCl_3$	δ 4.95 (1H, m; 4.08 (2H, s); 2.39 (2H, m); 1.92 (1H, m); 1.79 (1H, m); 1.7 (1H, m); 1.30 (2H, m); 1.0-0.8 (9H, m).
	**3a**: R_1= -OH R_2= -H **3b**: R_1= -H R_2= -$OCOCH_2Cl$	61%	+ 33 c = 1 $CHCl_3$	δ 7.35 (5H, m); 5.92 (1H, m); 3.51 (2H, s); 2.09 (1H, m); 1.95-1.8 (2H, m); 1.7 (1H, m)
	**4a**: R_1= -OH R_2= -H **4b**: R_1= -H R_2= -$OCOCH_2Cl$	82%	−43 c = 1 MeOH	δ 5.80 (1H, d, J= 8.9Hz); 5.12 (1H, d, J= 3.6Hz); 4.75-4.65 (3H, m); 4.15 (2H, s); 3.61 (3H, s); 3.41 (3H, s); 1.6-1.2 (12H, m).
	**5a**: R_1= -OH R_2= -H **5b**: R_1= -H R_2= -$OCOCH_2Cl$	76%	+55 c = 1 $CHCl_3$	δ 5.98 (1H, d, J= 3.7Hz); 5.12 (2H, dd, J= 3.6, 0.5Hz); 4.85 (2H, m); 4.18 (2H, s); 1.6 (3H, s); 1.42 (3H, s).

[a]All the reactions were carried out with 2 equivalents of TPP, DEAD, chloroacetic acid in toluene. Yields refer to isolated products.

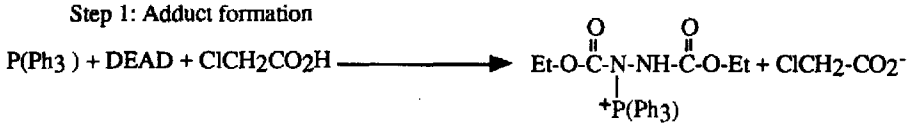
Borneol (**2a**) reacted under the same conditions to give a 73% yield of the isobornyl chloroacetate (**2b**). The case of the couple (-) 8-phenylmenthol (**3a**) and (+) 8-phenylneomenthol (**3'a**) appears particularly interesting because of their current use as valuable chiral auxiliary reagents.[10a,b] Compound **3b** was previously prepared in 47% overall yield from (+) pulegone.[10c] We found that direct nucleophilic displacement at C-1 of phenylmenthol (**3a**) with chloroacetic acid gave a 61% yield of the chloroacetate of phenylneomenthol (**3b**).

In a similar way the talosyl nucleoside **4a**[11] gave an 82% yield of the inverted product **4'a**, while it did not react when other carboxylic acids were used.

The synthesis of 1,2-O-isopropylidene-β-L-idofurano-6,3-lactone has formerly been carried out by either multistep procedures involving separation of diastereoisomers[12] or nucleophilic displacement of the trifluoromethanesulfonyl derivative.[13a] Reaction with carboxylate nucleophiles, however, invariably led to by-products.[13b,c] Our chloroacetate modification yielded in 76% the 5-chloroacetate of idofuranolactone (**5b**), which significantly, could be cleaved without elimination by mild alkaline hydrolysis.

The substantial improvement in the yield of this reaction observed with chloroacetic acid, accords with the mechanistic study by Hughes et al. (scheme),[4] who pointed out that the rates of the alcohol activation (step 2) and of the SN2 reaction (step 3) were very comparable using this acid. Accordingly, neither the alcohol nor the oxyphosphonium species are accumulated in the reaction medium, thus minimizing side reactions such as esterification and elimination.

Step 1: Adduct formation



Step 2: Alcohol activation

Step 3: SN2 reaction

Aside from giving good yields of inverted products, several types of which were previously not readily obtainable, the chloroacetate modification of the Mitsunobu reaction described in this paper offers the additional advantage of mild and selective subsequent hydrolysis,[14, 15] which can be important in the field of natural product chemistry.

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8. ***Typical experimental procedure.*** To a solution of diacetone glucose (**1a**, 130 mg; 0.5 mmol) in anhydrous toluene (5 ml), triphenylphosphine (262.5 mg, 1 mmol) and dry chloroacetic acid (97 mg, 1 mmol) were added. To this stirred solution diethyl azodicarboxylate (0.157 ml, 1 mmol) was added dropwise, causing a slightly exothermic reaction. The resulting pale yellow solution was stirred at room temperature for 12 h. The volatile components were then removed *in vacuo* and the residue purified by flash chromatography (silica gel, hexane/ethyl acetate 10%) to give in 67% yield the chloroacetate of diisopropylidene allofuranose(**1b**). Deacylation of **1b** with 2M methanolic ammonium hydroxide gave a product, which was identical to a commercial sample of diisopropylidene-α-D-allofuranose.
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