

The simultaneous use of immobilised reagents for the one-pot conversion of alcohols to carboxylic acids

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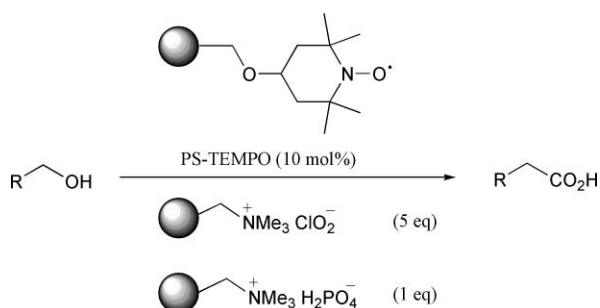
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The simultaneous use of selected immobilised oxidising reagents in a single reaction vessel provides an efficient method for the conversion of primary alcohols to the corresponding carboxylic acids.

During our work on the use of solid-supported reagents and scavengers for the multi-step preparation of chemical libraries,¹ heterocyclic systems² and natural products,³ we became aware of the deficiency of these reagents to effect the conversion of alcohols to their corresponding carboxylic acids.⁴ This is an important transformation in organic synthesis⁵ and while there are many immobilised reagents for the oxidation of alcohols to aldehydes,⁶ their further oxidation to acids has not been well established. Recently we developed a partial solution to this problem using a phosphate buffered silica-gel supported potassium permanganate or a polymer-supported chlorite system to oxidise aldehydes to acids. These methods also tolerated a reasonable range of functional groups.⁷

Here we report on a new one-pot multi-reagent sequence that facilitates the direct oxidation of alcohols to carboxylic acids⁸ (Scheme 1).



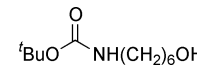
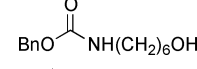
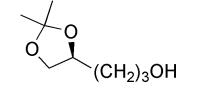
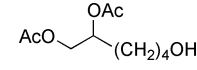
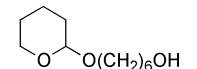
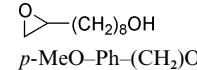
Scheme 1 KBr (0.1 eq.), NaOCl (4 mol%), MeCN–H₂O 3 : 1 at RT.

A typical procedure⁹ for this oxidation involves reacting the primary alcohol at room temperature with a combination of 4-(polystyrylmethyloxy)-2,2,6,6-tetramethylpiperidin-1-yloxy free radical (PS-TEMPO) (10 mol%),¹⁰ resin bound chlorite⁷ and buffered with immobilised hydrogen phosphate in aqueous acetonitrile (1 : 3, water–acetonitrile, v/v) containing potassium bromide (0.1 eq.) and 4 mol% sodium hypochlorite.

The polymer-supported chlorite reagent was easily obtained from Amberlyst IRA 900 by ion exchange with sodium chlorite solution.¹¹ The polymer-supported hydrogen phosphate was prepared using the same procedure except the resin washing procedure omitted the use of tetrahydrofuran and diethyl ether.

After the specified reaction times the reaction mixtures were filtered then evaporated, generally yielding oils. The oils were then redissolved in the minimum quantity of 25% methanol in chloroform and the solution passed through a short pad of silica gel to clean out the salts. After evaporation, the acids were obtained as essentially pure products. In this way several alcohols have been converted to their corresponding acids in good to excellent yield (Table 1).

Table 1 Results using conditions set out in Scheme for the oxidation of alcohols to carboxylic acids^a

Starting material	Time/h	Yield (%)
Ph(CH ₂) ₃ OH	24	95
	36	Quant.
	36	Quant.
	36	76
	48	98
BnO(CH ₂) ₅ OH	24	Quant.
	24	98
	20	Quant.
<i>p</i> -MeO-Ph-(CH ₂)OH	48	92
PhCH ₂ OH	24	88
<i>p</i> -O ₂ N-Ph-CH ₂ OH	20	77
<i>p</i> -MeO-Ph-(CH ₂) ₂ OH	36	94

^a All of the reported carboxylic acids were either commercially available or were known in the literature.

Reaction times varied from 20 up to 48 hours before completion was observed. It is clear from the table that ester, epoxide, acetal and benzyl groups withstand these reaction conditions.

The carboxylic acid products are readily obtained and the process could be easily adapted for automation to deliver acids on demand. Obviously the simultaneous use of supported reagents¹² adds to the power of these methods for organic synthesis and many other such processes and reagent combinations can be envisaged.

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- 8 For a useful discussion of the oxidation of primary alcohols to carboxylic acids in the solution phase with sodium chlorite catalysed by TEMPO and bleach see M. Zhao, J. Li, E. Mano, Z. Song, D. M. Tschaen, E. J. J. Grabowski and P. J. Reider, *J. Org. Chem.*, 1999, **64**, 2564.
- 9 A typical procedure for the oxidation of an alcohol to a carboxylic acid: prior to use PS-TEMPO (18.8 mg, 0.030 mmol) was washed with acetonitrile (2 × 2 ml). To a suspension of washed PS-TEMPO, PS-Chlorite (0.7 g, 1.5 mmol), PS-Dihydrogen phosphate (154 mg, 0.30 mmol) and potassium bromide (3.6 mg, 0.030 mmol) in acetonitrile (1 ml) was added NaOCl (8.5 mg, 0.012 mmol) as an aqueous solution in water (0.5 ml). After 10 min at room temperature the alcohol (0.3 mmol) was added as a solution in acetonitrile (1 ml). The mixture was stirred at room temperature (24–48 h) then passed through a short pad of Celite (1 g). The precipitate was washed with acetonitrile (30 ml) and the washings concentrated *in vacuo*. The residue was dissolved in acetonitrile (0.5 ml) and passed through a short pad of silica (0.3 g) eluting with 25% MeOH in CHCl₃ (10 ml). The filtrate was concentrated to give the desired carboxylic acid derivative.
- 10 TEMPO polystyrene is available from the Novabiochem Polymer-Supported Reagents catalogue (2001, p. 26).
- 11 Preparation of PS-chlorite: Polymer-supported chloride (Fluka, 4 mmol g⁻¹, 10 g) was washed with water (500 ml). The resin was added to sodium chlorite solution (2.0 M, 100 ml) and shaken at 25 °C for 24 h. The resin was collected by filtration, and washed with water (50 ml × 2), THF (50 ml × 2) and Et₂O (50 ml × 2) to obtain 18.6 g of PS-chlorite.
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