A green method for selective acetylation of primary alcohols using ethyl acetate and solid potassium carbonate

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A simple and selective acetylation of primary alcohols in the presence of other reactive functionalities such as secondary alcohol, phenol, acetonide and amine is described using mild ethyl acetate as the acetyl-transfer agent and solid potassium carbonate as the catalyst.

Keywords: transesterification, selective acetylation, ethyl acetate, K_2CO_3, green chemistry

Esterification is one of the fundamental reactions in organic chemistry.[1] There are several methods available to carry out this reaction. In the methods where stoichiometric quantities of the components, namely the alcohol and acid are used, the acid is activated as an acyl halide, acyl cyanide, anhydride or ketene.[2,3] While this approach is advantageous in terms of the quantities, the problem lies with the moisture-sensitive, corrosive and hazardous nature of the acid derivatives. A green replacement for the acid component is required. Alternatively, one of the components can be used in excess and these methods include Fischer esterification[4] and transesterification.[5] The latter method has received a lot of attention of late. Different catalysts and different acyl transfer agents are being studied to make this method more efficient and selective.[6–13] While acidic catalysts affect functional groups like acetals, strong basic catalysts pose problems such as β-elimination and other side reactions, especially if high nucleophilicity is associated with basicity. In either case, the catalyst in insoluble solid form offers advantages of easy work-up and minimal generation of waste.

With the available and widely used catalysts (acidic and basic), chemoselectivity has been an issue, necessitating separation and purification steps. While trying to acylate a primary hydroxyl group, other functional groups like a secondary alcohol, phenol and amine would come into competition. Although there are methods in which ethyl acetate is used as the acetyl transfer agent, the promoting agents are either highly basic and hazardous such as sodium hydride[14] or protic/Lewis acidic conditions[15] are used. Neutral alumina[16] has been used for the conversion of primary hydroxyalkylphenols to acetoxyalkylphenols, but this method also transformed primary arylamines to corresponding acetamides and hence these methods are not compatible with some functional groups.

Here we report a simple, selective and efficient transesterification method for preparing the acetate esters of primary alcohols using ethyl acetate as the acetyl-transfer agent as well as solvent and solid potassium carbonate as the catalyst under basic heterogeneous conditions (Scheme 1 and Table 1).

Results and discussion

Simple primary alcohols such as 1-heptanol (entry 1) and benzyl alcohol (entry 2) resulted in the corresponding acetate esters in good yield and in short time. Next we tried the method on *cis* butene-1,4-diol (entry 3) and butyne-1,4-diol (entry 4). Here also the reactions proceeded smoothly and in good yields.

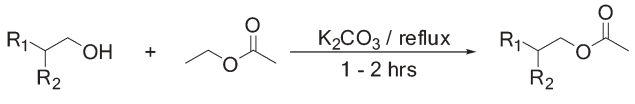
As a test of selectivity we tried the methodology on a wide range of compounds (entries 5–17) which underwent smooth *O*-acetylation under the given conditions and in all cases only the primary hydroxyls were esterified leaving the other hydroxyls intact. We were expecting some products corresponding to the acetylated secondary hydroxyl, at least, by way of acetyl migration. However, that was not the case.

To test the chemoselectivity, dithiothreitol (entry 18), 2-hydroxybenzyl alcohol (entry 19) and 3-aminobenzyl alcohol (entry 20) were subjected to the reaction conditions. Here also only primary selectivity was the feature. The other functionalities, *viz:* phenolic –OH and primary amine functionalities did not react.

As a special case with a possibility of β-elimination, we tried 9-fluorenylmethanol (entry 21), which underwent smooth esterification without any elimination reaction. Resorcinol (entry 22), triphenylmethanol (entry 23), benzylamine (entry 24), cyclohexylmethanamine (entry 25) and octylamine (entry 26) did not react under these reaction conditions. When the reaction was carried out using catalytic amount of conc. H_2SO_4 and ethyl acetate at 40 °C as described by Pi-Hui Liang[15] *et al.*, the acetonides (entries 7–9) were not stable and were hydrolysed.

Surprisingly, replacing potassium carbonate by organic bases like tributylamine, pyridine and also Dowex 550 resin failed to bring about any satisfactory result as tested on xylose monoacetonide (**9**) keeping all other parameters identical (Table 2).

In summary, the reported method is highly chemoselective for acetylating primary alcohols in the presence of secondary alcoholic, phenolic acetonide and amine functionalities. The method employs easily available, inexpensive potassium carbonate in solid form as catalyst and ethyl acetate as both the acetyl-transfer agent and solvent, which offers advantages of easy work-up with minimal waste generation. The reaction does not involve sensitive/toxic/hazardous reagents and are generally very clean, good yielding without any side products.



R_1, R_2 = Alkyl or Aryl groups comprising Secondary-OH, Phenolic-OH and -NH_2 functionalities

Scheme 1 Selective acetylation of alcohols.

Experimental

A mixture of alcohol (10 mmol), ethyl acetate (10 mL) and anhydrous potassium carbonate (10 mmol) was placed in a round bottom flask and refluxed until completion of the reaction (monitored by TLC). The reaction mass was cooled, filtered and the solvent was removed *in vacuo* to dryness. The residue was dissolved in minimum amount of methylene dichloride and passed a through plug of silica column eluting with *tert*-butyl ether to isolate the product.

The structure of the products was confirmed by b.p., m.p. and ^{1}H and ^{13}C NMR spectra (provided in the supplementary data). In multifunctional systems, the position of the acetyl group was ascertained by

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Table 1 Acetylation of alcohols using ethyl acetate and solid potassium carbonate

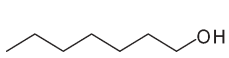
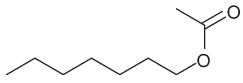
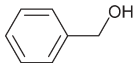
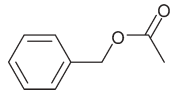
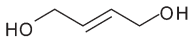
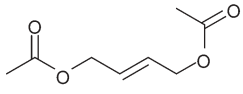
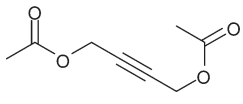
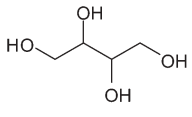
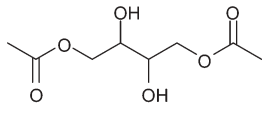
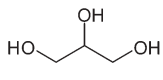
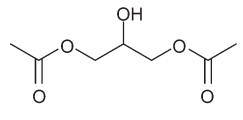
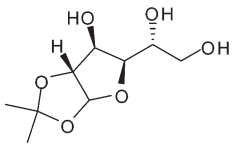
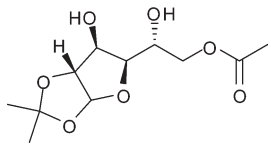
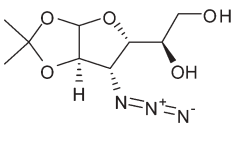
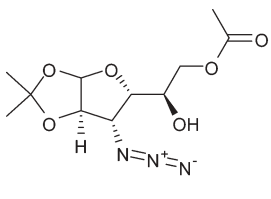
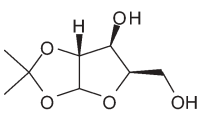
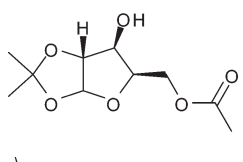
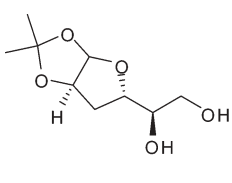
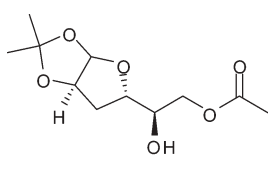
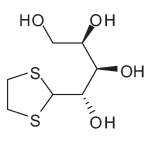
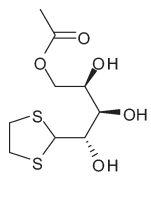
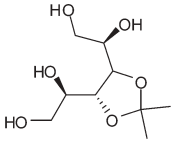
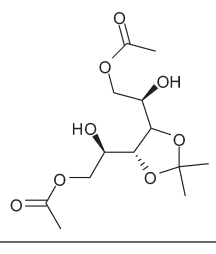
Entry no.	Substrate	Product	Time /h	Yield /%[a]
1.			1	85
2.			1	90
3.			1.5	79
4.			1	80
5.			2	78
6.			2	78
7.			2	80
8.			4*	75
9.			2	90
10.			1	88
11.			1.5	76
12.			1	79

Table 1 Continued

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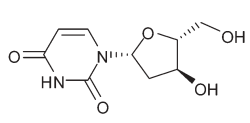
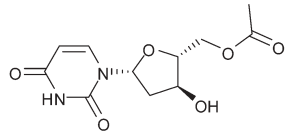
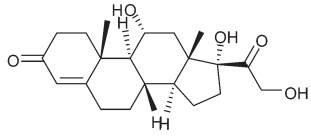
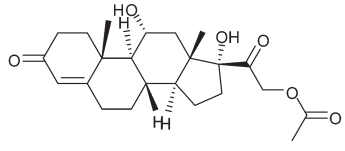
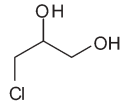
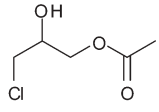
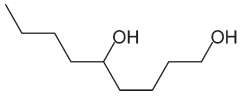
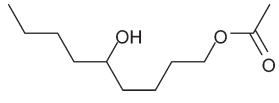
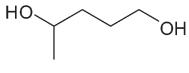
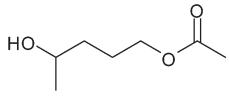
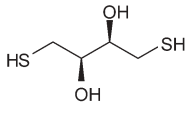
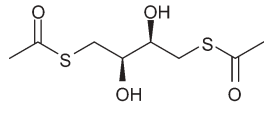
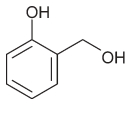
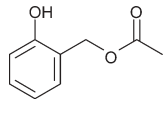
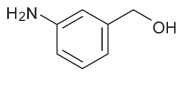
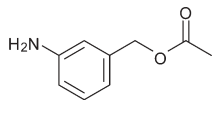
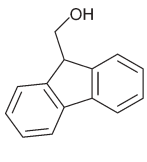
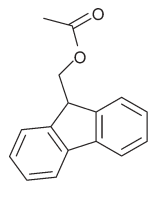
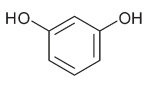
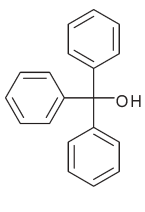
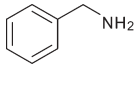
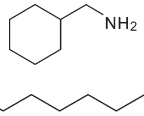
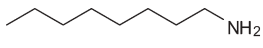
13.			1	70
14.			1	67
15.			1	85
16.			1	88
17.			1	86
18.			1.5	79
19.			2	85
20.			1	90
21.			1	91
22.		No reaction	4hr	Nil
23.		No reaction	5hr	Nil
24.		No reaction	4hr	Nil
25.		No reaction	4hr	Nil
26.		No reaction	4hr	Nil

[a]Yield refers to isolated product.
*Reaction mass was warmed to 40 °C for 4h.

Table 2 Acetylation of alcohol (entry 9) using other bases and resin with ethyl acetate

No.	Base	Time /h	Yield /%
1.	Tributyl amine	4	15
2.	Pyridine	4	16
3.	Dowex resin	4	33

the downfield shift of the carbinol proton in comparison with the shift in the starting materials.

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