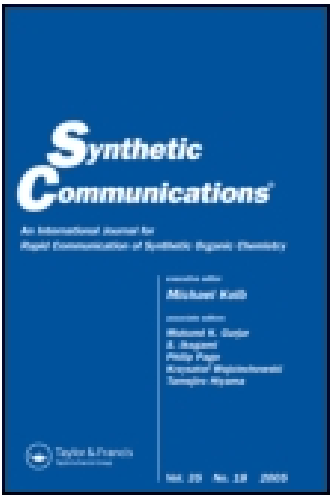

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Potassium Fluoride Assisted Selective Acetylation of Alcohols with Acetic Acid

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Potassium Fluoride Assisted Selective Acetylation of Alcohols with Acetic Acid

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ABSTRACT

Potassium fluoride promotes the acetylation of primary and secondary alcohols with acetic acid in excellent yield. Phenols are not affected under this reaction conditions. The groups like double bond, chloro, methoxy, benzyloxy, thiol, and nitro remain unaffected.

Key Words: Potassium fluoride; Acetic acid; Acetylation; Alcohols.

INTRODUCTION

The acetylation of alcohols is an important and frequently used transformation in organic synthesis.[1] The direct acetylation of alcohols with acetic acid

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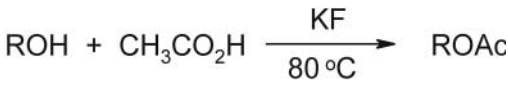
is carried out in the presence of mineral acids or sulfonic acids. Generally, this method is avoided because it is reversible in nature and the byproduct water has to be removed by azeotropic distillation or addition of dehydrating agent to drive the reaction forward direction. The main disadvantage of this method is that acid sensitive groups are not tolerated.[2] Moreover, the use of strong mineral acids leads to highly acidic waste streams posing an environmental problem for industrial processes. These limitations make preferable the use of more reactive derivatives of carboxylic acid, such as acid chloride[3] or (mixed) anhydride,[4] in the presence of tributylphosphine[5] or pyridine derivatives.[6] Recently, Lewis acid catalyst such as titanium(IV) chloride *tris*(trifluoromethanesulfonate),[7] scandium(III), and lanthanide(III) triflates have been reported as catalyst for the direct acetylation of alcohols with acetic acid.[8] In a recent work, direct acylation of alcohols with carboxylic acids using H_2SO_4 supported on silica is reported.[9] However, the use of mineral acid, expensive transition metal catalyst and acetic anhydride makes these methods unsuitable for routine work. More recently, Yamamoto[10] and co-workers disclosed that $HfCl_4$ could be used as a catalyst for the direct esterification of carboxylic acids with alcohols. Although yield is high in this method, it suffers from some inconvenience. As the system is sensitive to water and thus rigorous dehydration by soxhlet extraction with molecular sieve is indispensable.

Potassium fluoride has long been used as a useful reagent in organic synthesis.[11] In this communication, some of the results obtained from the acetylation of alcohols using easily available and cheap reagents KF and AcOH have been disclosed (Sch. 1). Under the reaction condition, neither elimination nor fluorinated products were observed. The use of acetic acid rather than acetic anhydride or acetyl chloride is both economically and environmentally advantageous. The reaction is generalized through entries 1–18 (Table 1).

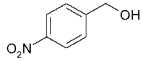
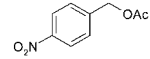
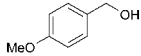
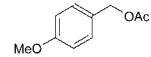
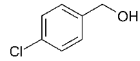
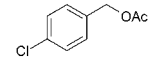
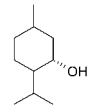
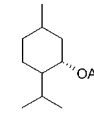
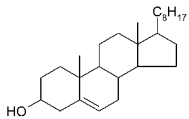
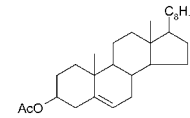
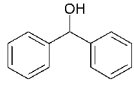
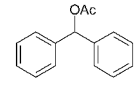
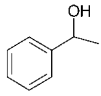
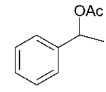
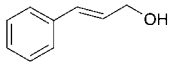
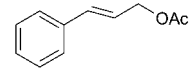
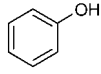
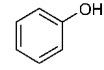
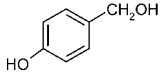
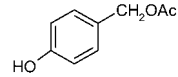
It was observed that primary and secondary alcohols can be acetylated readily with a very high yield and neither fluorinated nor eliminated products were identified. This is due to the fact that the hydrogen bonding between fluoride ion and hydroxyl group of acetic acid reduces nucleophilicity and basicity of the fluoride ion. In the case of tertiary alcohol, the reaction becomes sluggish and takes longer time with the formation of elimination pro-



where R=Alkyl, Aryl

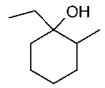
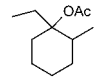
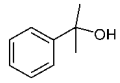
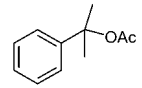
Scheme 1.

Table 1. Direct acetylation of various alcohols with acetic acid in the presence of potassium fluoride.

Entry	Substrate[a]	*t* (hr)	Product[b]	Yield[a] (%)
1		1.5		98
2		3		97
3		1.5		98
4		3		97
5	$CH_3(CH_2)_{14}CH_2OH$	3	$CH_3(CH_2)_{14}CH_2OAc$	96
6	$CH_3(CH_2)_8CH_2OH$	3	$CH_3(CH_2)_8CH_2OAc$	98
7		7		95
8		5		97
9		7		98
10		7		94
11		5		98
12		4		97
13	$PhCH_2O(CH_2)_5OH$	3.5	$PhCH_2O(CH_2)_5OAc$	99
14	$HSCH_2CH_2OH$	3	$HSCH_2CH_2OAc$	92
15		9		0
16		7		94

(*continued*)

Table 1. Continued.

Entry	Substrate[a]	*t* (hr)	Product[b]	Yield[a] (%)
17		9		34[b]
18		9		41[b]

[a]Yields are isolated yields. The compounds were characterized by GC, ^{1}H NMR, and IR spectroscopy and by comparisons with the literature.
[b]Olefins are the byproduct.

ducts and the reaction ends up with a low yield (Table 1). However, phenols are not affected and alcoholic group can be selectively acetylated. More importantly, the hydroxyl group residing in chiral center could be acetylated with retention of configuration (entry 7). The groups like double bond, chloro, nitro, methoxy, benzyloxy, thiol, etc. remain unaffected. Moreover, the reaction does not require any dry glassware and inert atmosphere. The operation is quite simple, because the dehydrating systems like Dean–Stark apparatus or agent like molecular sieve is not necessary. The purification process is very simple, as both potassium fluoride and acetic acid are water-soluble and final product does not require any tedious purification procedures.

CONCLUSION

In conclusion, we have developed a new, high yielding, and selective methodology for the direct acetylation of primary and secondary alcohols with acetic acid and potassium fluoride. The ease of use of potassium fluoride, and low cost of both acetic acid and KF; and clean, easy work up of the product mixture makes this protocol important for both industrial and general purposes.

TYPICAL EXPERIMENTAL PROCEDURE

In a typical reaction benzyl alcohol (0.35 g, 3.1 mmol), KF (0.22 g, 3.8 mmol), and acetic acid (5 mL) were heated at 80°C in a round bottom flask. The reaction was monitored by TLC and GC. After completion (1.5 hr) of the reaction, the reaction mixture was diluted with water (20 mL),

and extracted with ethyl acetate (2 × 50 mL). The organic layer was washed with aqueous $NaHCO_3$ (30 mL) and brine (20 mL), dried (Na_2SO_4), and evaporated to dryness and finally passed through a short silica gel column to give benzyl acetate (0.45 g, 98%); ^{1}H NMR (60 MHz, $CDCl_3$): δ 2.0 (s, 3H, $-O-CO-CH_3$), 4.9 (s, 2H, $-CH_2-O-$), 7.19 (m, 5H, aromatic); IR: 3026, 1741, 1228, 1029 cm^{-1}.

***p*-Nitrobenzyl acetate (2b).** ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.17 (s, 3H, $-O-CO-CH_3$), 5.20 (s, 3H, O-CH_2^-), 7.52 (d, $J = 5.50$ Hz, 2H, aromatic), 2H, 8.22 (d, $J = 5.62$ Hz, 2H, aromatic); IR: 3098, 1741, 1516, 1347, 1244, 1055 cm^{-1}.

***p*-Methoxybenzyl acetate (3b).** ^{1}H NMR (60 MHz, $CDCl_3$): δ 1.95 (s, 3H, $-O-CO-CH_3$), 3.6 (s, 3H, O-CH_3), 4.8 (s, 2H, $-CH_2-O-$), 6.85 (m, 4H, aromatic); IR: 2950, 1736, 1516, 1245, 1173, 1040 cm^{-1}.

***p*-Chlorobenzyl acetate (4b).** ^{1}H NMR (60 MHz, $CDCl_3$): δ 1.95 (s, 3H, $-O-CO-CH_3$), 4.8 (s, 2H, $-CH_2-O-$), 7.0 (m, 4H, aromatic); IR: 2960, 1746, 1495, 1383, 1234, 1096, 1014 cm^{-1}.

Cetyl acetate (5b). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, $J = 6.3$ Hz, 3H, $-CH_3$), 1.26 (m, 30H, $-CH_2-$), 1.62 (m, 2H, $-CH_2-$), 2.05 (s, 3H, $O-COCH_3$), 4.05 (t, $J = 6.90$ Hz, 2H, $-OCH_2-$); IR: 2924, 2853, 1747, 1465, 1373, 1240, 1040 cm^{-1}.

Menthyl acetate (7b). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.77 (d, $J = 6.9$ Hz, 3H, 2-CH_3), 0.90 (d, $J = 7.2$ Hz, 6H, 2-CH_3), 1.00–1.90 (m, 9H, 3-CH–, 3-CH_2-), 2.09 (s, 3H, $-OCOCH_3$), 4.67 (dt, $J = 10.8$ and 4.5 Hz, 1H, O–CH–); IR: 2955, 1741, 1244, 1029 cm^{-1}; $[\alpha]_D^{25}$ -79.42° (*c* 1.6 g/100 mL, $CHCl_3$) [Lit.[12] $[\alpha]_D^{20}$ -80.5° (*c* 2 g/100 mL, $CHCl_3$)].

Cholesteryl acetate (8b). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.68 (s, 3H, $-CH_3$), 0.86 (d, $J = 4.4$ Hz, 6H, 2-CH_3), 0.91 (d, $J = 4.6$ Hz, 3H, $-CH_3$), 1.00 (s, 3H, $-CH_3$), 1.20–1.80 (m, 26H, $-CH_2-$, –CH–), 2.03 (s, 3H, O-$COCH_3$), 2.30 (d, $J = 5.06$ Hz, 2H, $-CH_2-$), 4.60 (m, $J = 4$, 1H, –O–CH–), 5.37 (m, 1H, –CH═C–); IR: 2955, 1741, 1470, 1372, 1255, 1045 cm^{-1}.

Cyclododecyl acetate (9b). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25–1.54 (m, 18H, 9-CH_2-), 1.71 (m, 4H, 2-CH_2-), 2.04 (s, 3H, $-OCOCH_3$), 5.0 (m,1H, –O–CH–); IR: 2934, 1741, 1475, 1239, 1024 cm^{-1}.

1-Acetoxy-1,1-diphenyl-methane (10b). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.16 (s, 3H, O-CO-CH_3), 6.88 (s, 1H, O–CH–), 7.31 (m, 10H, 2Ph); IR: 3042, 1741, 1377, 1239, 1025 cm^{-1}.

Cinnamyl acetate (12b). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.90 (s, 3H, $-O-COCH_3$), 4.72 (d, $J = 6.30$ Hz, 2H, O–CH_2-), 4.05 (dt, $J = 12.90$ and 6.60 Hz, 2H, –CH–), 6.64 (d, $J = 15.90$ Hz, –CH–), 7.31 (s, 5H, –Ph); IR: 2955, 1741, 1244, 1029 cm^{-1}.

4-Benzyloxy pentyl acetate (13b). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.42 (m, 2H, $-CH_2-$), 1.62 (m, 4H, 2-CH_2-), 2.04 (s, 3H, $-O-COCH_3$), 3.47

(t, $J = 6.30$ Hz, 2H, O–CH_2–), 4.05 (t, $J = 6.60$ Hz, 2H, O–CH_2–), 4.50 (s, 2H, –CH_2Ph), 7.30 (s, 5H, –Ph); ^{13}C NMR (300 MHz, $CDCl_3$): 171.2, 138.5, 128.3 (2C), 127.6 (2C), 127.5, 72.9, 70.1, 64.5, 29.12, 28.41, 22.67, 20.98; IR: 2930, 2853, 1737, 1240, 1096, 1061, 1030 cm^{-1}.

2-Acetoxy ethane thiol (14b). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.05 (s, 3H, O–CO–CH_3), 2.75 (dt, $J = 9.00$ and 6.00 Hz, 2H, S–CH_2–), 4.19 (t, $J = 6.6$ Hz, 2H, –CH_2–); IR: 2542, 1741, 1377, 1239, 1025 cm^{-1}.

4-Hydroxy benzyl acetate (15b). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.09 (s, 3H, –O–CO–CH_3), 5.03 (s, 2H, –CH_2–O–), 5.43 (br, 1H, OH), 6.82 (d, $J = 8.80$ Hz, 2H, aromatic), 7.25 (d, $J = 8.80$ Hz, 2H, aromatic); IR: 3406, 2955, 1716, 1516, 1235, 1030 cm^{-1}.

1-Ethyl-2-methyl-cyclohexyl acetate (16b). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (m, 6H, 2-CH_3), 1.25–1.41 (m, 11H, 1-CH–, 5-CH_2–), 2.16 (s, 3H, –$OCOCH_3$); IR: 2929, 1736, 1459, 1275, 1131, 1070 cm^{-1}.

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