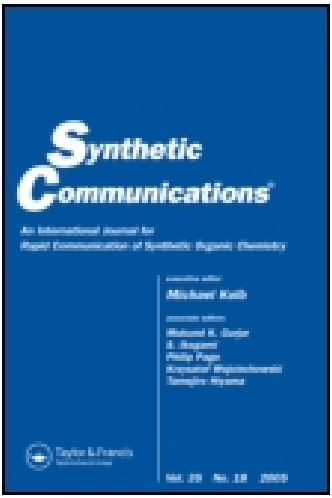

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A Fast and Convenient Procedure for the Acetylation of Alcohols

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A Fast and Convenient Procedure for the Acetylation of Alcohols

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ABSTRACT

Treatment of different steroidal and aliphatic alcohols with $BF_3 \cdot OEt_2$ and acetic anhydride for 5 seconds produced complete acetylation in high to quantitative yields.

Key Words: O-Acetylation; $BF_3 \cdot OEt_2$.

Acetylation of alcohols is the most common procedure for the protection of the hydroxyl group. Although a wide variety of procedures are known,[1] new methodologies are always desirable. Acetylation of tertiary alcohols

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is particularly important, due to the fact that this functionality is prone to elimination or to carbocationic rearrangement when drastic conditions are employed. For example, attempts to acetylate the 3β,6β-diacetoxy-5α-cholestan-5-ol (Fig. 1) led to the rearranged product instead of acetylation.[2]

During our recent studies on the reactivity of the spiroketal side chain of different steroidal sapogenins through $BF_3 \cdot OEt_2$ and acetic anhydride,[3,4] we found that in addition to the reaction involving the spiroketal moiety, free hydroxyl groups were also acetylated in quantitative yields (Fig. 2). Owing to this observation, we decided to explore this reaction as an alternative procedure for the acetylation of different alicyclic and aliphatic alcohols.

Treatment of solutions or suspensions of different alcohols in methylene chloride (Table 1, entries a–d) or ethyl acetate (Table 1, entries e–g) with $BF_3 \cdot OEt_2$ and acetic anhydride for 5 seconds resulted in acetylation of all hydroxyl groups (Eq. 1). The acetylation reactions were run, with similar results, using 2 mmol of substrate, but can be scaled up to 20 mmol. Using these conditions, even tertiary hydroxyl groups were acetylated (see Table 1, entry d).

(1)

Table 1 shows the results of the acetylation of steroidal and nonsteroidal alcohols. Although ^1H and ^{13}C NMR indicated that the crude products were pure enough for synthetic purposes, chromatographic purifications using silica gel were carried out to eliminate the yellowish coloring developed during the reactions.

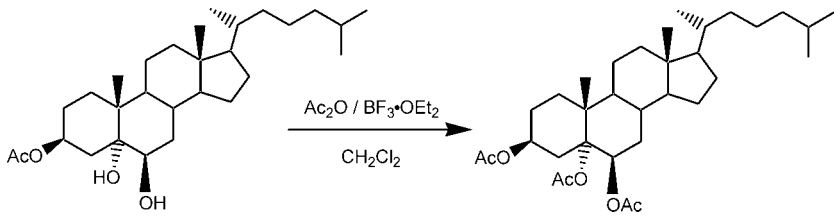


Figure 1. Formation of an *abeo*-cholestane.

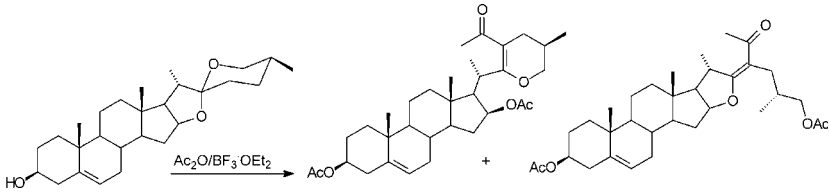
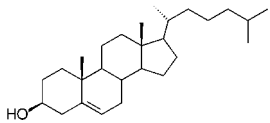
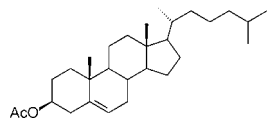
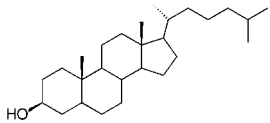
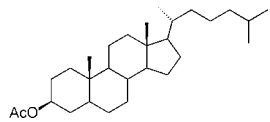
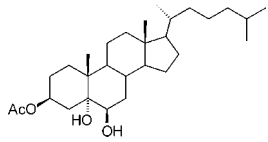
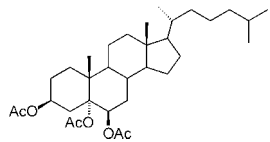
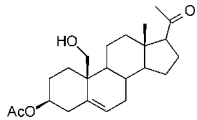
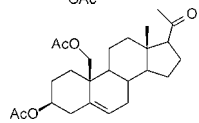
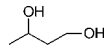
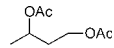
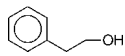
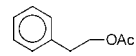


Figure 2. Acetolysis of steroidal sapogenins.

EXPERIMENTAL

NMR spectra were registered in $CDCl_3$ on a Varian Mercury spectrometer at 400 MHz for ^1H or 100 MHz for ^{13}C. Chemical shifts are expressed in ppm downfield from TMS. Melting points were obtained on a Mel-Temp apparatus and were not corrected.

Table 1. Starting materials and products of acetylation.

Entry	Starting alcohol (1)	Product (2)	Yield[a]
a			85%
b			91%
c			75%
d			85%
e			100%
f			100%
g			100%

[a]Yields (mol%) are given after chromatographic purification.

General Procedure for the Acetylation of Alcohols

To a solution or suspension of alcohols 1a–g (2 mmol, in all experiments) in 5 mL of either CH_2Cl_2 (Entries a–d) or AcOEt (Entries e–g), Ac_2O (1 mL) and $BF_3 \cdot OEt_2$ (0.5 mL) were added in this order. The mixture was stirred for 5 seconds, poured into ice/water, stirred for 15 min, and extracted with selected solvents (2 × 10 mL). The organic layer was washed with water (3 × 15 mL), 10% aqueous $NaHCO_3$ (3 × 15 mL) and water (3 × 15 mL), dried (anh. Na_2SO_4), and evaporated to afford the desired acetylated product 2a–h.

Cholesteryl acetate, 2a. M.p 113–115°C. Lit[5] 114–115°C. ^{1}H NMR: 5.4 (1H, m, H-6), 4.6 (1H, m, H-3), 2.03 (3H, s, CH_3-AcO), 1.02 (3H, s, CH_3-19), 0.91 (3H, d, $J_{20-21} = 6.2$ Hz, CH_3-21), 0.86 (3H, d, $J_{25-26} = 6.6$ Hz, CH_3-26), 0.86 (3H, d, $J_{25-27} = 6.6$ Hz, CH_3-27). ^{13}C NMR: 37.06 (C-1), 27.86 (C-2), 73.95 (C-3), 38.18 (C-4), 139.45 (C-5), 122.51 (C-6), 31.93 (C-7), 31.98 (C-8), 50.06 (C-9), 36.65 (C-10), 21.14 (C-11), 39.58 (C-12), 42.36 (C-13), 57.70 (C-14), 24.38 (C-15), 28.33 (C-16), 56.14 (C-17), 11.98 (C-18), 19.42 (C-19), 35.88 (C-20), 18.83 (C-21), 36.26 (C-22), 23.95 (C-23), 39.79 (C-24), 28.10 (C-25), 22.94 (C-26), 22.69 (C-27), 170.25 ($CH_3\underline{C}OO$), 21.55 ($\underline{C}H_3COO$).

5α-Cholestanyl acetate, 2b. M.p 108–109°C. Lit[5] 110–111°C. ^{1}H NMR: 4.7 (1H, m, H-3), 2.02 (3H, s, CH_3-AcO), 0.89 (3H, d, $J_{20-21} = 6.6$ Hz, CH_3-21), 0.85 (3H, d, $J_{25-26} = 6.6$ Hz, CH_3-26), 0.83 (3H, d, $J_{25-27} = 6.6$ Hz, CH_3-27). ^{13}C NMR: 36.80 (C-1), 27.54 (C-2), 73.72 (C-3), 34.08 (C-4), 44.67 (C-5), 28.68 (C-6), 32.07 (C-7), 35.86 (C-8), 54.21 (C-9), 35.86 (C-10), 21.29 (C-11), 40.01 (C-12), 42.62 (C-13), 56.40 (C-14), 24.29 (C-15), 28.33 (C-16), 56.25 (C-17), 12.18 (C-18), 12.33 (C-19), 35.51 (C-20), 18.77 (C-21), 36.21 (C-22), 23.93 (C-23), 39.56 (C-24), 28.09 (C-25), 22.93 (C-26), 22.67 (C-27), 170.40 ($CH_3\underline{C}OO$), 21.58 ($\underline{C}H_3COO$).

5α-Cholestan-3β,5,6β-triol triacetate, 2c. M.p 149–151°C. Lit[6] 149–150°C. ^{1}H NMR: 5.86 (1H, dd, $J_{6e-7e} = 2.56$, $J_{6e-7a} = 2.94$ Hz, H-6), 4.7 (1H, m, H-3), 2.81(1H, ddd, $J_{4a-4e} = 13.56$, $J_{4e-3a} = 5.13$, $J_{4e-2e} = 1.8$ Hz H-4e), 2.07, 2.068, 2.0 (3H, s, $3CH_3$-AcO), 1.20 (3H, s, CH_3-19), 0.91 (3H, d, $J_{20-21} = 6.6$ Hz, CH_3-21), 0.86 (3H, d, $J_{25-26} = 6.6$ Hz, CH_3-26), 0.85 (3H, d, $J_{25-27} = 6.6$ Hz, CH_3-27), 0.69 (3H, s, H-18). ^{13}C NMR: 31.90 (C-1), 26.53 (C-2), 69.93 (C-3), 30.17 (C-4), 86.55 (C-5), 69.46 (C-6), 31.34 (C-7), 30.17 (C-8), 45.23 (C-9), 39.85 (C-10), 21.14 (C-11), 39.72 (C-12), 42.71 (C-13), 55.85 (C-14), 24.08 (C-15), 28.20 (C-16), 56.07 (C-17), 12.30 (C-18), 17.16 (C-19), 35.76 (C-20), 18.72

(C-21), 36.14 (C-22), 23.79 (C-23), 39.51 (C-24), 28.04 (C-25), 22.61 (C-26), 22.87 (C-27), 169.93, 169.22, 169.07 ($CH_3\underline{C}OO$), 22.23, 21.34, 21.33 ($\underline{C}H_3COO$).

3β, 19-Diacetoxypreg-5-en-20-one, 2d. M.p 101–103°C. Lit[5] 104–105°C. ^{1}H NMR: 5.6 (1H, m, H-6), 4.6 (1H, m, H-3), 4.49 (1H, d, $J = 12$ Hz H-19), 3.96(1H, d, $J = 12$ Hz H-19), 2.13 (3H, s, H-21), 2.04, 2.03 (3H, s, CH_3-AcO), 0.650 (3H, s, H-18). ^{13}C NMR: 33.49 (C-1), 27.88 (C-2), 73.16 (C-3), 38.09 (C-4), 134.32 (C-5), 126.34 (C-6), 31.23 (C-7), 32.89 (C-8), 49.93 (C-9), 39.73 (C-10), 21.71 (C-11), 38.91 (C-12), 44.03 (C-13), 57.31 (C-14), 24.45 (C-15), 22.84 (C-16), 63.51 (C-17), 13.39 (C-18), 64.32 (C-19), 209.039 (C-20), 31.57 (C-21), 170.40, 170.28 ($2CH_3\underline{C}OO$), 21.46, 21.15 ($2\underline{C}H_3COO$).

Heptyl acetate, 2e. B.p. 184–185°C/580 mmHg, Lit.[7] 193°C/760 mm Hg, ^{1}H NMR: 4.05 (2H, t, $J_{1-2} = 6.4$ Hz, H-1), 2.04 (3H, s, $C\underline{H}_3$-AcO), 1.67 (2H, q, $J = 6.4$ Hz, H-2), 1.0 (8H, m, H-3,6), 0.89 (3H, t, $J = 7.2$ Hz, H-7). ^{13}C NMR: 64.55 (C-1), 31.71 (C-2), 28.92 (C-3), 28.60 (C-4), 25.89 (C-5), 22.59 (C-6), 14.08 (C-7), 170.89 ($CH_3\underline{C}OO$), 21.00 ($\underline{C}H_3COO$).

($\pm$)-1,3-Butanediol diacetate, 2f. B.p.102–103°C/26 mm Hg, Lit.[8] 92–94°C/13 mm Hg. ^{1}H NMR: 5.0 (1H, m, H-3), 4.11 (2H, t, $J_{1-2} = 5.9$ Hz, H-1), 2.05, 2.04 (3H, s, $2C\underline{H}_3$-AcO), 1.88 (2H, m, H-2), 1.26 (3H, d, $J_{4-3} = 6.2$ Hz, H-4). ^{13}C NMR: 60.67 (C-1), 34.66 (C-2), 67.69 (C-3), 20.04 (C-4), 170.62, 170.18 ($2CH_3\underline{C}OO$), 21.21, 20.88 ($2\underline{C}H_3COO$).

2-Phenylethanol acetate, 2g. B.p.109–111°C/26 mmHg, Lit.[8] 118–120°C/13 mmHg. ^{1}H NMR: 7.32–7.20 (5H, aromatics), 4.27 (2H, t, $J_{1-2} = 7.2$ Hz, H-2), 2.93 (2H, t, $J_{2-1} = 7.2$ Hz, H-1), 2.03 (3H, s, $C\underline{H}_3$-AcO). ^{13}C NMR: 35.10 (C-1), 64.89 (C-2), 137.56, 128.69, 128.30, 126.37 (aromatics), 170.74 ($CH_3\underline{C}OO$), 21.03 ($\underline{C}H_3COO$).

In summary, the mixture $BF_3 \cdot OEt_2$/acetic anhydride constitutes a useful alternative for the fast acetylation of alcohols in high yields.

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