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Montmorillonite Clay Catalysis. Part 13.[1] Etherification of Cholesterol Catalysed by Montmorillonite K-10†

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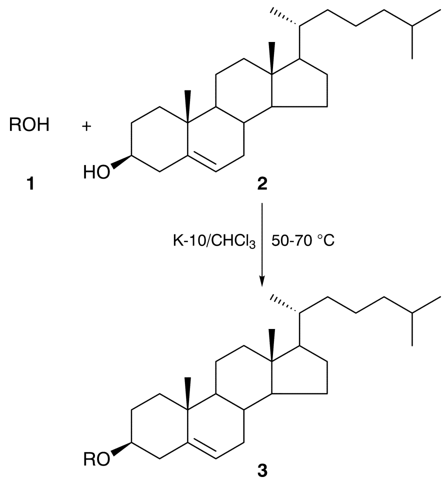
The preparation of cholesteryl ethers from alcohols and phenols with cholesterol is carried out at 50–70 °C by using montmorillonite K-10 as an acid catalyst in chloroform or cyclohexane.

We are currently interested in the etherification of sterols as steryl ethers have been discovered in some sediments.[2–4] Steryl ethers may be useful as liquid crystals[5] and might have biological activities.[6] However, etherification of sterols directly with alcohols or phenols has received little attention.[7]

Montmorillonite clays have been used as efficient catalysts for a variety of organic reactions.[8] Previously, we reported a facile preparation of disteryl ethers from a series of sterols catalysed by montmorillonite K-10.[9] Recently, we have also investigated the arylation of cholesterol with a variety of aromatic compounds catalysed by montmorillonite K-10.[10] However, when phenols were employed as substrates for the latter reaction, aryl cholesteryl ethers were obtained instead of aryl cholestenes. We report here a simple and convenient procedure for the etherification of cholesterol with alcohols and phenols catalysed by montmorillonite K-10. As shown in Table 1, in the presence of montmorillonite K-10, a series of alcohols (**1a**–**1f**) and phenols (**1i**–**1o**) were heated with cholesterol in chloroform to give the corresponding ethers in moderate to excellent yield. Primary and secondary alcohols (**1a**–**1f**) were treated with cholesterol **2** to give good to excellent yields of the corresponding ethers (**3a**–**3f**). We focused on the reaction of phenylmethanol with cholesterol; it gave cholesteryl benzyl ether **3d** in 99% yield. Akiyama *et al.* reported the cleavage of cholesteryl benzyl ether in 88% yield by $AlCl_3$–*N*,*N*-dimethylaniline.[11] Thus, an alternative method for protection of the cholesterol hydroxy group with benzyl ethers has been developed.



Scheme 1

It is noteworthy that butan-2-ol **1e** provided a pair of epimers of (1′*R*)- and (1′*S*)-1′-methylpropyl 3*β*-cholesteryl ether (**3e**) in equal amounts. The two epimers were inseparable on silica gel TLC, but they could be distinguished by ^1H NMR (500 MHz) spectroscopy.

Tertiary alcohols such as *tert* butyl alcohol **1g** and triphenylmethanol **1h** did not react with cholesterol under these conditions.

Phenols (**1i**–**1o**) were treated with cholesterol to give the corresponding aryl cholesteryl ethers (**3i**–**3o**). The hindering effect of the substituted phenols was a major factor interfering with the reaction yield. The *ortho*-substituted phenols gave markedly lower yields (entries **l**, **m**, **n**; **j**, **k**).

Phenols with electron-withdrawing groups, *e.g.* 4-nitrophenol, 2,4,6-tribromophenol, 2,4-dichlorophenol, salicylaldehyde and vanillin, failed to react.

Table 1 Etherification of cholesterol catalysed by montmorillonite K-10

Entry	Alcohol or phenol	Cholesterol/alcohol or phenol (mol/mol)	*t*/h	*T*/°C	Product **3** yield (%)	Mp/°C
a	Methanol	1/10	13	55	69	84–85
b	*n*-Butanol	1/2	13	55	99	76–78
c	Decyl alcohol	1/2	5	55	81	58–59
d	Phenylmethanol	1/2.7	12	55	99	108–110
e	Butan-2-ol	1/2	9	55	82	110–111
f	Pentan-3-ol	1/3	8	55	91	192–194
g	*tert*-butyl alcohol	1/2	6	55	0	
h	Triphenylmethanol	1/2	3.5	50	0	
i	Phenol	1/4	2.5	50	65	155–157
j	4-Chlorophenol	1/2	2.5	70	65	156–157
k	2-Chlorophenol	1/4	10	50	33	117.5–118.5
l	4-Methylphenol	1/3.8	3.5	50	81	151–153
m	3-Methylphenol	1/2	9	45	53	119.5–120.5
n	2-Methylphenol	1/2	8	50	33	98–99
o	4-Methoxyphenol	1/2	5	50	76	124–127

It is also noteworthy that the catalyst could be reused after being washed with diethyl ether and activated at 120 °C for 2 h.

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Some steryl ethers have been discovered in sediments[2–4] and their origin is still unclear. The formation of cholesteryl ethers under montmorillonite catalysis may have geochemical implications,[12] since montmorillonite clay is an important class of clay mineral and is widespread in geological samples.[13–14] Thus we presume that steryl ethers in sediments were formed from natural sterols and alcohols catalysed by acidic clay minerals.

In conclusion, the present procedure on the solid surface of montmorillonite K-10 provides a very convenient etherification of cholesterol. The operational simplicity, mild conditions, good yields and low cost make this procedure a useful and attractive alternative to the currently available methods.

Experimental

Melting points were uncorrected. Elemental analyses were determined on a Hearu CHN-Rapid instrument. Infrared spectra were recorded on Perkin-Elmer 983G and FTS-40 IR spectrometers. ^1H and ^{13}C NMR spectra were measured on Bruker AC-80, Bruker AM-400 and Varian INOVA-500 spectrometers, using $CDCl_3$ as solvent and tetramethylsilane as internal reference. *J* values are in Hz. Mass spectra were obtained on a VG-7070E spectrometer, election impact, 70 eV.

Typical Procedure.—A mixture of methanol (**1a**, 320 mg, 10.0 mmol), chloroform (10 ml), cholesterol (**2**, 386 mg, 1.0 mmol) and montmorillonite K-10 (0.8 g, from Aldrich, activated at 120 °C overnight prior to use) was stirred at 55–60 °C on an oil bath for 13 h. After completion, the catalyst was removed by filtration and washed with diethyl ether. Evaporation of the solvent yielded crude cholesteryl methyl ether. The crude product was purified by short column chromatography on silica gel to give cholesteryl methyl ether (**3a**, 275 mg, 69%).

n-Butyl cholesteryl ether **3b**, δ_H (500 MHz) 0.674 (3 H, s, 18-H$_3$), 0.862, 0.866 (6 H, 2d, *J* 6.5, 26, 27-H$_6$), 0.912 (3 H, d, *J* 6.0, 21-H$_3$), 0.917 (3 H, t, *J* 7.3, 4′-H$_3$), 0.998 (3 H, s, 19-H$_3$), 3.126 (1 H, m, $W_{1/2}$ 22.5, 3α-H), 3.458 (2 H, t, *J* 7.0, 1′-H$_2$), 5.344 (1 H, m, 6-H).

Decyl cholesteryl ether **3c** (Found: C, 84.71; H, 12.51; $C_{37}H_{66}O$ requires C, 84.43; H, 12.62%); δ_H (400 MHz) 0.674 (3 H, s, 18-H$_3$), 0.862, 0.866 (6 H, 2d, *J* 6.6, 26, 27-H$_6$), 0.913 (3 H, d, *J* 6.5, 21-H$_3$), 0.999 (3 H, s, 19-H$_3$), 3.125 (1 H, m, $W_{1/2}$ 24.8, 3α-H), 3.446 (2 H, t, *J* 6.7, 1′-H$_2$), 5.345 (1 H, m, 6-H).

Benzyl cholesteryl ether **3d**, δ_H (500 MHz) 0.675 (3 H, s, 18-H$_3$), 0.861, 0.866 (6 H, 2d, *J* 6.5, 26, 27-H$_6$), 0.912 (3 H, d, *J* 6.0, 21-H$_3$), 1.013 (3 H, s, 19-H$_3$), 3.281 (1 H, m, $W_{1/2}$ 23.0, 3α-H), 4.557, 4.570 (2 H, 2d, J_{AB} 12.0, 1′-H$_2$), 5.349 (1 H, m, 6-H), 7.347 (5 H, s, Ph-H$_5$).

2-Butyl cholesteryl ether **3e**, δ_H (500 MHz) 0.674 (3 H, s, 18-H$_3$), 0.862, 0.867 (6 H, 2d, *J* 6.0, 26, 27-H$_6$), 0.896 [1.5 H, t, *J* 7.5, (*R*)-3′- or (*S*)-3′-Me], 0.903 [1.5 H, t, *J* 7.5, (*S*)-3′- or (*R*)-3′-Me], 0.913 (3 H, d, *J* 6.0, 21-H$_3$), 1.002 (3 H, s, 19-H$_3$), 1.115 [1.5 H, d, *J* 6.3, (*R*)-1′- or (*S*)-1′-Me], 1.115 [1.5 H, d, *J* 6.3, (*S*)-1′- or (*R*)-1′-Me], 3.192 (1 H, m, $W_{1/2}$ 22.4, 3), 3.425 (1 H, m, 1′-H), 5.342 (1 H, m, 6-H).

3-Pentyl cholesteryl ether **3f** (Found: C, 84.09; H, 12.45; $C_{32}H_{56}O$ requires C, 84.14; H, 12.36%); ν_{max}/cm^{-1} 1084; δ_H (500 MHz) 0.675 (3 H, s, 18-H$_3$), 0.862, 0.867 (6 H, 2d, *J* 6.5, 26, 27-H$_6$), 0.919 (3 H, d, *J* 6.5, 21-H$_3$), 0.893, 0.902 (6 H, 2t, *J* 7.0, 3′-H$_3$ and 1′-CH$_2$C*H*$_3$), 1.004 (3 H, s, 19-H$_3$), 3.177 (2 H, m, $W_{1/2}$ 25.3, 3α-H and 1′-H), 5.337 (1 H, m, 6-H); *m*/*z* 456 (M$^+$, 11%), 369 (38), 57 (100).

Phenyl cholesteryl ether **3i**, ν_{max}/cm^{-1} 1231, 1040; δ_H (80 MHz) 0.69 (3 H, s, 18-H$_3$), 0.87 (6 H, d, *J* 6.0, 26, 27-H$_6$), 0.93 (3 H, d, *J* 6.1, 21-H$_3$), 1.06 (3 H, s, 19-H$_3$), 4.06 (1 H, m, $W_{1/2}$ 26.7, 3α-H), 5.41 (1 H, m, 6-H), 6.83–7.18 (5 H, m, Ar-H$_5$); *m*/*z* 462 (M$^+$, 1%), 369 (100).

4-Chlorophenyl cholesteryl ether **3j** (Found: C, 79.42; H, 10.15; Cl, 7.15; $C_{33}H_{49}ClO$ requires C, 79.72; H, 9.93; Cl, 7.13%); ν_{max}/cm^{-1} 1237, 1038; δ_H (80 MHz) 0.69 (3 H, s, 18-H$_3$), 0.86 (6 H, d, *J* 6.0, 26, 27-H$_6$), 0.91 (3 H, d, *J* 6.4, 21-H$_3$), 1.05 (3 H, s, 19-H$_3$), 4.06 (1 H, m, $W_{1/2}$ 21.8, 3α-H), 5.38 (1 H, m, 6-H), 6.80 (2 H, d, J_{AB} 9.0, 2′,6′-H$_2$), 7.19 (2 H, d, J_{AB} 9.0, 3′,5′-H$_2$); δ_C (100 MHz, DEPT, number of carbon) 39.51 (1), 28.22 (2), 77.52 (3), 39.75 (4), 140.10 (5), 122.48 (6), 31.93 (7), 31.88 (8), 50.19 (9), 36.81 (10), 21.07 (11), 28.13 (12), 42.32 (13), 56.75 (14), 24.28 (15), 38.55 (16), 56.16 (17), 11.86 (18), 19.40 (19), 35.77 (20), 18.72 (21), 36.18 (22), 23.82 (23), 37.12 (24), 28.01 (25), 22.55 (26 or 27), 22.81 (27 or 26), 156.33 (1′), 117.24 (2′), 129.31 (3′), 125.37 (4′), 129.31 (5′), 117.24 (6′); *m*/*z* 369 (100%).

2-Chlorophenyl cholesteryl ether **3k** (Found: C, 79.63; H, 9.98; Cl, 7.10; $C_{33}H_{49}ClO$ requires C, 79.72; H, 9.93; Cl, 7.14%); ν_{max}/cm^{-1} 1250, 1035; δ_H (80 MHz) 0.69 (3 H, s, 18-H$_3$), 0.87 (6 H, d, *J* 6.0, 26, 27-H$_6$), 0.93 (3 H, d, *J* 6.0, 21-H$_3$), 1.07 (3 H, s, 19-H$_3$), 4.16 (1 H, m, $W_{1/2}$ 23.4, 3α-H), 5.42 (1 H, m, 6-H), 6.87–7.29 (4 H, m, Ar-H$_4$); *m*/*z* 369 (100%).

4-Methylphenyl cholesteryl ether **3l** (Found: C, 85.87; H, 10.94; $C_{34}H_{52}O$ requires C, 85.65; H, 10.99%); ν_{max}/cm^{-1} 1234, 1040; δ_H (80 MHz) 0.69 (3 H, s, 18-H$_3$), 0.87 (6 H, d, *J* 6.0, 26, 27-H$_6$), 0.93 (3 H, d, *J* 6.1, 21-H$_3$), 1.05 (3 H, s, 19-H$_3$), 2.27 (3 H, s, 4′-CH$_3$), 4.06 (1 H, m, $W_{1/2}$ 23.4, 3α-H), 5.38 (1 H, m, 6-H), 6.78 (2 H, d, J_{AB} 8.5, 2′,6′-H$_2$), 7.05 (2 H, d, J_{AB} 8.5, 3′,5′-H$_2$); *m*/*z* 476 (M$^+$, 6%), 369 (100).

3-Methylphenyl cholesteryl ether **3m** (Found: C, 85.95; H, 10.83; $C_{34}H_{52}O$ requires C, 85.65; H, 10.99%); ν_{max}/cm^{-1} 1255, 1055; δ_H (80 MHz) 0.69 (3 H, s, 18-H$_3$), 0.87 (6 H, d, *J* 6.0, 26, 27-H$_6$), 0.93 (3 H, d, *J* 6.0, 21-H$_3$), 1.06 (3 H, s, 19-H$_3$), 2.48 (3 H, s, 3′-CH$_3$), 4.10 (1 H, m, $W_{1/2}$ 23.1 Hz, 3α-H), 5.38 (1 H, m, 6-H), 6.73 (3 H, m, 2′,4′,6′-H$_3$), 7.14 (1 H, t, *J* 8.4, 5′-H); *m*/*z* 476 (M$^+$, 8%), 369 (100).

2-Methylphenyl cholesteryl ether **3n** (Found: C, 85.90; H, 10.78; $C_{34}H_{52}O$ requires C, 85.65; H, 10.99%); ν_{max}/cm^{-1} 1235, 1040; δ_H (80 MHz) 0.69 (3 H, s, 18-H$_3$) 0.86 (6 H, d, *J* 6.0, 26, 27-H$_6$), 0.93 (3 H, d, *J* 6.0, 21-H$_3$), 1.07 (3 H, s, 19-H$_3$), 2.21 (3 H, s, 2′-CH$_3$), 4.13 (1 H, m, $W_{1/2}$ 23.2, 3α-H), 5.41 (1 H, m, 6-H), 6.81–7.19 (4 H, m, Ar-H$_4$); *m*/*z* 476 (M$^+$, 2%), 369 (100).

4-Methoxyphenyl cholesteryl ether **3o** (Found: C, 82.61; H, 10.47; $C_{34}H_{52}O_2$ requires C, 82.87; H, 10.64%); ν_{max}/cm^{-1} 1040; δ_H (80 MHz) 0.69 (3 H, s, 18-H$_3$), 0.86 (6 H, d, *J* 6.0, 26, 27-H$_6$), 0.93 (3 H, d, *J* 6.0, 21-H$_3$), 1.05 (3 H, s, 19-H$_3$), 3.76 (3 H, s, 4′-OCH$_3$), 3.95 (1 H, m, $W_{1/2}$ 23.4, 3α-H), 5.35 (1 H, m, 6-H), 6.82 (4 H, s, Ar-H$_4$); δ_C (100 MHz, DEPT) 39.51 (1), 31.93 (2), 78.21 (3), 39.76 (4), 140.45 (5), 122.14 (6), 31.93 (7), 31.88 (8), 50.19 (9), 36.62 (10), 21.07 (11), 28.22 (12), 42.31 (13), 56.75 (14), 24.48 (15), 38.65 (16), 56.15 (17), 11.85 (18), 19.41 (19), 35.77 (20), 18.71 (21), 36.18 (22), 23.82 (23), 37.18 (24), 28.00 (25), 22.55 (26), 22.81 (27), 153.70 (1′), 117.52 (2′), 114.58 (3′), 151.66 (4′), 114.58 (5′), 117.52 (6′), 55.65 (-OCH$_3$); *m*/*z* 492 (M$^+$, 13%), 369 (100).

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