

Highly selective one-pot conversion of THP and MOM ethers to acetates by indium triiodide-catalysed deprotection and subsequent transesterification by ethyl acetate

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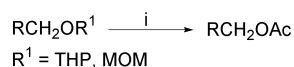
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A simple and efficient method is developed for the chemoselective one-pot conversion of tetrahydropyranyl (THP) and methoxymethyl (MOM) ethers of primary alcohols to the corresponding acetates by indium triiodide-catalysed deprotection and subsequent acetylation by ethyl acetate through a transesterification process.

Introduction

The protection and subsequent deprotection of a functional group is usual practice in a multistep synthetic strategy and a switchover of one protective group to another is also often required as demanded by the reaction conditions in subsequent steps. Thus, a direct method for this transformation bypassing the intermediate step of going back to the parent functionality is becoming much more important in order to improve the overall synthetic efficiency.¹ Tetrahydropyranyl (THP) and methoxymethyl (MOM) ethers are widely used in organic synthesis as hydroxy-protecting groups because they are stable under a variety of reaction conditions including strongly basic media; however, they are not suitable for use in a relatively strongly acidic environment.² On the other hand, acetate, another important hydroxy-protecting moiety, can tolerate acidic reagents. Thus, switchover of THP and MOM ethers to acetate is sometimes considered useful in certain steps. Although only a limited number of methods have been reported recently for this purpose,^{3,4} they involve traditional reagents such as acetyl chloride,^{3a} acetic anhydride⁴ and titanium tetrachloride,^{3b} which being corrosive and hazardous need replacement by 'greener' chemicals. In addition, the reported procedure for the conversion of MOM ether to acetate lacks operational simplicity and is not free from side reactions.⁴ Recently, we have discovered a unique use of ethyl acetate with a catalytic amount of indium triiodide for acetylation of alcohols and amines through transesterification⁵ and we envisaged the potential of this combination for direct conversion of acid-labile hydroxy-protecting groups to acetates. This prompted us to initiate a systematic investigation in this direction and we now report that THP and MOM ethers of primary alcohols are converted to the corresponding acetates very efficiently through a one-pot indium triiodide-catalysed reaction with ethyl acetate (Scheme 1).⁶



Scheme 1 Reagents and conditions: i, In, I₂, EtOAc, reflux.

Results and discussion

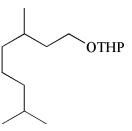
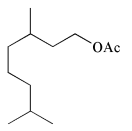
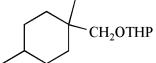
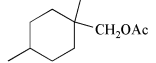


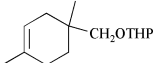
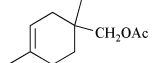
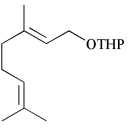
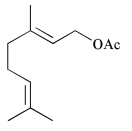
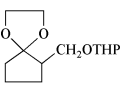
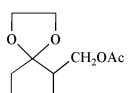
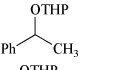
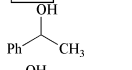
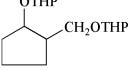
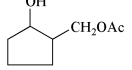
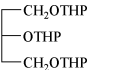
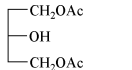
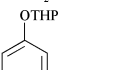
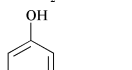
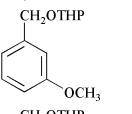
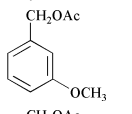
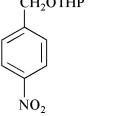
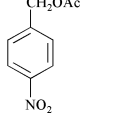
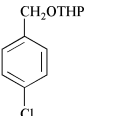
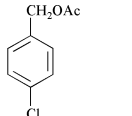
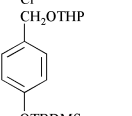
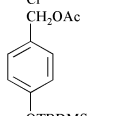
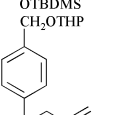
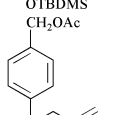
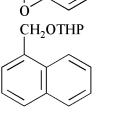
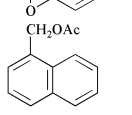
In a general experimental procedure, the THP or MOM ether was heated at reflux in ethyl acetate in the presence of a catalytic amount (20 mol%) of indium triiodide generate *in situ*

by the reaction of indium metal and iodine⁷ (a small excess of either In or I₂ does not make any difference to the normal course of reaction) for a certain period of time as required to complete the reaction. The reaction mixture was then quenched with water and extracted with diethyl ether. Usual work-up and column chromatography over silica gel furnished pure acetate.

A wide range of structurally different THP and MOM ethers were subjected to this procedure to produce the corresponding acetates. The results are summarised in Tables 1 and 2. It was found that THP and MOM ethers of primary alcohols underwent smooth conversion to acetates while those of secondary alcohols and phenols furnish only the parent hydroxy compounds by simple deprotection. Obviously, the ethers first undergo deprotection by Lewis acid (indium triiodide) and then acetylation by ethyl acetate through transesterification. So, it is reasonable to assume that ethers of secondary alcohols and phenols after initial deprotection failed to proceed to acetylation with this reagent system. This is very much consistent with our earlier observation⁵ that secondary alcohols and phenols do not undergo acetylation by indium triiodide-catalysed transesterification by ethyl acetate. However, this chemoselective conversion of THP and MOM ethers of primary hydroxy groups to the corresponding acetates, in the presence of secondary and phenolic ones which undergo deprotection only, is of much synthetic utility. On the other hand, deprotection of THP and MOM ethers of secondary alcohols and phenols by a mild Lewis acid (indium triiodide) provides a practical alternative to many existing procedures using relatively strong acids.² The present reaction conditions are tolerable to a variety of sensitive functionalities and moieties such as nitro, chloro, iodo, methoxy, furan, thiophene, *etc.* Several hydroxy-protecting groups including OTBDMS, O-allyl and O-benzyl also remained unaffected during this conversion. The reactions are, in general, very clean and high-yielding and no side product has been isolated in any reaction.

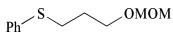
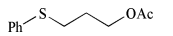
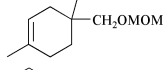
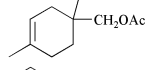
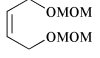
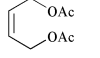
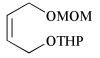
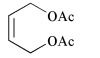
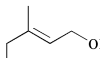
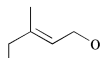
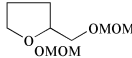
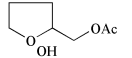
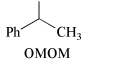
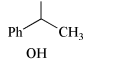
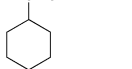
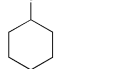
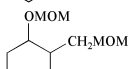
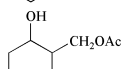
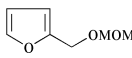
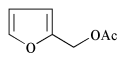
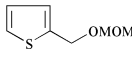
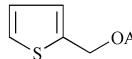
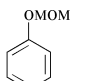
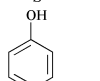
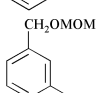
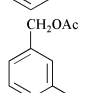
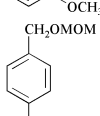
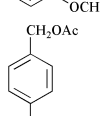
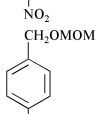
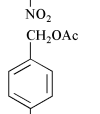
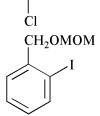
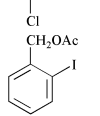
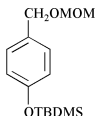
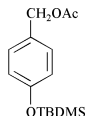
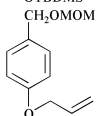
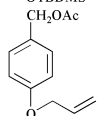
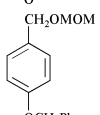
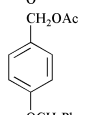
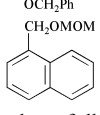
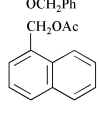
In conclusion, the present procedure using ethyl acetate and a catalytic amount of indium triiodide provides a convenient and efficient method for one-pot conversion of THP and MOM ethers to acetates. The significant advantages offered by this procedure are: (a) operational simplicity; (b) 'green' methodology involving no toxic or hazardous chemicals; (c) remarkable chemoselectivity for THP and MOM ethers of primary alcohols; (d) mild reaction conditions compatible with several sensitive functional groups and hydroxy-protecting ethers; and (e) high yield. We believe that this will present a better and more viable alternative to the existing

Table 1 Direct conversion of THP ether to acetate

Entry	Substrate	t/h	Product	Yields (%) ^a
1	PhCH ₂ OTHP	15	PhCH ₂ OAc	80
2	PhCH ₂ CH ₂ OTHP	12	PhCH ₂ CH ₂ OAc	82
3	PhCH ₂ CH ₂ CH ₂ CH ₂ OTHP	12	PhCH ₂ CH ₂ CH ₂ OAc	82
4	<i>n</i> -BuOTHP	14	<i>n</i> -BuOAc	78
5	<i>n</i> -hexOTHP	14	<i>n</i> -hexOAc	78
6	ClCH ₂ CH ₂ OTHP	12	ClCH ₂ CH ₂ OAc	75
7	ClCH ₂ CH ₂ CH ₂ OTHP	13	ClCH ₂ CH ₂ CH ₂ OAc	82
8	MeOCH ₂ CH ₂ OTHP	12	MeOCH ₂ CH ₂ OAc	76
9	EtOCH ₂ CH ₂ OTHP	12	EtOCH ₂ CH ₂ OAc	78
10	THPO(CH ₂) ₄ OTHP	15	AcO(CH ₂) ₄ OAc	78
11		13		78
12		15		75
13		12		80
14		13		75
15		12		78
16	H—C≡C—CH ₂ OTHP	14	H—C≡C—CH ₂ OAc	78
17		14		80
18		20		82
19		18		80
20		18		78
21		20		75
22		13		80
23		14		82
24		14		82
25		12		78
26		12		78
27		14		80

^a Yields refer to those of pure isolated products fully characterised by spectral data.

Table 2 Direct conversion of MOM ether to acetate

Entry	Substrate	t/h	Product	Yield (%) ^a
1	PhCH ₂ OMOM	16	PhCH ₂ OAc	82
2	PhCH ₂ CH ₂ OMOM	18	PhCH ₂ CH ₂ OAc	85
3	ClCH ₂ CH ₂ CH ₂ OMOM	18	ClCH ₂ CH ₂ CH ₂ OAc	84
4	EtOCH ₂ CH ₂ OMOM	17	EtOCH ₂ CH ₂ OAc	82
5		17		82
6		17		82
7		15		84
8		15		80
9		15		78
10	H-C≡C-CH ₂ OMOM	15	H-C≡C-CH ₂ OAc	78
11		16		85
12		20		85
13		20		84
14		20		80
15		16		84
16		15		80
17		20		75
18		16		80
19		18		82
20		17		82
21		16		84
22		16		72
23		15		80
24		17		82
25		16		85

^a Yields refer to those of pure isolated products fully characterised by spectral data.

Table 3 IR, ^1H and ^{13}C NMR data of some selected acetates

Entry	$\nu_{\text{max}}/\text{cm}^{-1}$	$\delta_{\text{H}}/\text{ppm}$	$\delta_{\text{C}}/\text{ppm}$
6 (Table 1)	1739	4.32 (t, 2H, J 5.6), 3.68 (t, 2H, J 5.6), 2.10 (s, 3H)	170.1, 63.7, 41.8, 20.9
7 (Table 1)	1740	4.21 (t, 2H, J 6.1), 3.60 (t, 2H, J 6.3), 2.11–2.07 (m, 2H), 2.06 (s, 3H)	170.9, 61.9, 41.3, 33.0, 19.5
10 (Table 1)	1738	3.95 (t, 4H, J 3.2), 1.90 (s, 6H), 1.57 (t, 4H, J 3.2)	171.2 (2), 64.1 (2), 22.5 (2), 21.0 (2)
11 (Table 1)	1744	4.12–4.01 (m, 2H), 1.97 (s, 3H), 1.46–0.79 (m, 19H)	171.3, 63.3, 38.5, 35.8, 28.9, 24.9, 22.8, 22.2, 22.1, 20.2, 20.0, 19.8
12 (Table 1)	1742	3.78 (q, 2H, J 10.6), 2.01 (s, 3H), 1.59–0.84 (m, 15H)	171.3, 72.0, 31.2, 30.3, 27.8, 25.4, 24.3, 23.7, 23.1, 22.3, 19.4
14 (Table 1)	1743	5.23–5.22 (m, 1H), 3.79 (q, 2H, J 10.3), 2.01 (s, 3H), 1.89–1.34 (m, 9H), 0.87 (s, 3H)	171.6, 133.1, 119.3, 72.2, 39.3, 34.4, 30.8, 27.0, 23.3, 22.7, 20.9
17 (Table 1)	1739	4.12–4.05 (m, 2H), 3.89 (s, 4H), 2.10 (s, 3H) 1.89–1.38 (m, 7H)	171.3, 119.3, 65.0, 64.9, 64.7, 45.3, 35.4, 30.7, 22.7, 20.9
19 (Table 1)	3419, 1741	4.15–4.12 (m, 3H), 2.03 (s, 3H), 1.96–0.85 (m, 8H)	171.1, 78.3, 64.6, 44.7, 32.1, 25.6, 22.9, 20.8
22 (Table 1)	1739	7.27–7.22 (m, 1H), 6.92–6.81 (m, 3H), 5.05 (s, 2H), 3.79 (s, 3H), 2.08 (s, 3H)	170.1, 159.9, 137.7, 133.7, 129.6, 122.0, 120.5, 66.2, 55.2, 21.0
25 (Table 1)	1741	7.01 (d, 2H, J 8.4), 6.60 (d, 2H, J 8.4), 4.81 (s, 2H), 1.87 (s, 3H), 0.78 (s, 9H), 0.03 (s, 6H)	169.1, 154.1, 128.8 (2), 127.0, 118.4 (2), 64.4, 24.1 (3), 19.4, 16.6, –6.0 (2)
26 (Table 1)	1736	7.24 (d, 2H, J 9.0), 6.85 (d, 2H, J 9.0), 6.06–5.96 (m, 1H), 5.41–5.23 (m, 2H), 5.01 (s, 2H), 4.50 (d, 2H, J 5.1), 2.04 (s, 3H)	170.5, 157.4, 132.0, 128.8 (2), 127.0, 116.3, 113.3 (2), 67.4, 64.7, 19.7
5 (Table 2)	1739	7.31–7.14 (m, 5H), 4.13 (t, 2H, J 6.2), 2.94 (t, 2H, J 7.1), 2.01 (s, 3H), 1.95–1.87 (m, 2H)	172.1, 136.4, 129.8, 129.6, 129.3, 126.5, 96.5, 63.1, 30.6, 28.6, 21.2
11 (Table 2)	1743	4.15–3.77 (m, 5H), 1.99 (s, 3H), 1.97–1.88 (m, 3H), 1.63–1.57 (m, 1H)	170.9, 76.7, 68.7, 66.7, 28.3, 25.9, 21.1
16 (Table 2)	1740	7.28–6.93 (m, 3H), 5.22 (s, 2H), 2.03 (s, 3H)	170.9, 138.3, 128.6, 127.3, 127.2, 60.8, 21.2
21 (Table 2)	1745	7.83 (d, 1H, J 7.9), 7.37–7.32 (m, 2H), 7.00 (t, 1H, J 7.7), 5.1 (s, 2H), 2.13 (s, 3H)	170.6, 139.8, 138.7, 130.2, 130.1, 128.6, 96.5, 70.3, 21.2
24 (Table 2)	1737	7.38–7.22 (m, 7H), 6.90 (d, 2H, J 8.2), 5.05 (s, 2H), 4.99 (s, 2H), 1.99 (s, 3H)	171.0, 159.2, 137.3 (2), 130.9 (2), 129.0 (2), 128.8, 127.8, 127.3, 96.6 (2), 70.3, 66.4, 21.4

methodologies^{3,4} and thus it will find useful applications in the synthesis of complex natural products where such conversions are needed under mildly acidic conditions.

Experimental

Indium metal (ingot from SRL Mumbai, India) was cut into small slices, and used directly without any treatment. Iodine crystals were used as obtained commercially. Ethyl acetate was dried over CaCl_2 and distilled before use. THP and MOM ethers were prepared following reported procedures.^{8,9}

General procedure for conversion of THP and MOM ethers to acetates

A THP or MOM ether (2 mmol) as a solution in ethyl acetate (2 cm^3) was added to indium triiodide (20 mol%), prepared *in situ* by refluxing indium metal and iodine in ethyl acetate (3 cm^3), and the mixture was then refluxed for a certain period of time as required to complete the reaction (monitored by TLC). The reaction mixture was then quenched with water and extracted with diethyl ether (4 \times 10 cm^3). The combined extract was washed successively with aq. sodium thiosulfate and brine, and dried (Na_2SO_4). Evaporation of the solution and purification by column chromatography over silica gel furnished the corresponding acetate. The product acetates were easily characterised by IR, ^1H and ^{13}C NMR data. The spectral data of many of these acetates are already reported^{3a,5,10,11} and our products have data in good agreement with those. The spectral and analytical data of some selected acetates whose spectra are not available for comparison are presented in Table 3.

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