

Indium triiodide catalysed one-step conversion of tetrahydropyranyl ethers to acetates with high selectivity

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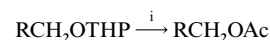
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A very simple and efficient method has been developed for the chemoselective one-step conversion of tetrahydropyranyl ethers of primary alcohols to the corresponding acetates through an indium triiodide catalysed transesterification process in ethyl acetate.

The conversion of one protective group to another is often required in a multistep organic synthesis 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) ether is one of the most useful protective groups for the hydroxy functionality as it is stable under a variety of reaction conditions including strong basic media; however it is not suitable for use in an acidic environment. On the other hand, acetate, another important hydroxy protecting moiety, can tolerate acidic reagents. Thus, switch-over of a THP ether to an acetate is sometimes considered useful in organic synthesis. Although a couple of methods are available in the literature for this purpose,² these involve corrosive and hazardous reagents such as acetyl chloride,^{2a} acetic anhydride and titanium tetrachloride.^{2b} Our recent experience with indium triiodide³ thus prompted us to explore the utility of this Lewis acid catalyst for this useful transformation and we have discovered that THP ethers of primary alcohols are converted

to the corresponding acetates very efficiently through a one-step indium triiodide catalysed reaction in ethyl acetate (Scheme 1).



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

In a simple experimental procedure, the THP ether was heated at reflux in ethyl acetate in the presence of a catalytic amount (20 mol%) of indium triiodide generated *in situ* (a small excess of either In or I₂ does not affect the reaction) for a certain period of time as required to complete the reaction. The reaction mixture was then quenched with water and extracted with ether. Usual workup and column chromatography over silica gel furnished pure acetate.

A wide range of structurally varied THP ethers were subjected to this procedure to give the corresponding acetates in high yields. The results are reported in Table 1. It was found that this direct conversion method proceeds very efficiently with the THP ethers of primary alcohols, whereas THP ethers from secondary alcohol (entry 18) and phenol (entry 21) undergo simple deprotection to produce the parent hydroxy compound. Obviously, the THP ethers first undergo deprotection and then acetylation through transesterification with ethyl acetate in the presence of the Lewis acid catalyst, indium triiodide. The THP

Table 1 One-step conversion of THP ether to acetate

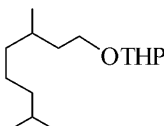
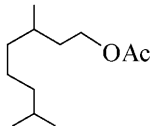
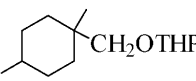
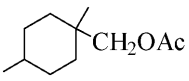
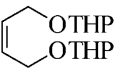
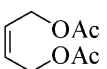
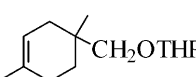
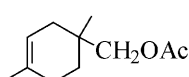
Entry	Substrate	Time/h	Product	Yield (%) ^a
1	PhCH ₂ OTHP	15	PhCH ₂ OAc	80
2	PhCH ₂ CH ₂ OTHP	12	PhCH ₂ CH ₂ OAc	82
3	PhCH ₂ CH ₂ CH ₂ OTHP	12	PhCH ₂ CH ₂ CH ₂ OAc	82
4	<i>n</i> -BuOTHP	14	<i>n</i> -BuOAc	78
5	<i>n</i> -HexOTHP	14	<i>n</i> -HexOAc	78
6	ClCH ₂ CH ₂ OTHP	12	ClCH ₂ CH ₂ OAc	75
7	ClCH ₂ 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

Table 1 (Contd.)

Entry	Substrate	Time/h	Product	Yield (%) ^a
15		12		78
16	H≡C-CH ₂ OTHP	14	H≡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.

ethers of secondary alcohol and phenol after initial deprotection remained inert under the present reaction conditions, which is consistent with our earlier observation^{3b} of no acetylation of secondary alcohols and phenol by this indium triiodide catalysed transesterification process.

Thus, chemoselective conversion of the THP ether of a primary hydroxy group to the corresponding acetate in the

presence of a secondary one which undergoes only deprotection, is achieved with high efficiency (entries 19, 20). Nevertheless, this selectivity is of considerable synthetic potential. The reaction conditions are mild enough not to induce any isomerisation of the double (entries 13–15) and triple bonds (entry 16). Most significantly, acid-sensitive functionalities such as ketal (entry 17) and TBDMS ether (entry 25) remained

unaffected. In addition, a variety of other functionalities like Cl, OMe, OEt, O-allyl and NO₂, also survived under the present reaction conditions.

In conclusion, the present procedure using indium triiodide provides a simple and efficient method for direct conversion of THP ethers to acetates. The significant advantages of this procedure are: (a) operational simplicity; (b) no involvement of toxic or hazardous chemicals; (c) excellent selectivity for THP ethers of primary alcohols; (d) reaction conditions acceptable to several acid-sensitive functional groups including acetal and TBDMS ether; and (e) good yield. We believe this will present a better and more practical alternative to the existing methodologies and thus will find useful applications in the synthesis of complex natural products where such a conversion is needed.

Experimental

Indium triiodide was first prepared by refluxing indium metal slices (46 mg, 0.4 mmol) and iodine (152 mg, 0.6 mmol) in ethyl acetate (3 cm³) for half an hour. Then the THP ether of 2-phenylethyl alcohol (412 mg, 2.0 mmol) (entry 2) in ethyl acetate (2 cm³) was added and refluxed for 12 h (monitored by TLC). The reaction mixture was then quenched with water and extracted with ether (4 × 10 cm³). The ether extract was washed successively with sodium thiosulfate solution and brine, and dried (Na₂SO₄). Evaporation of solvent and purification by

column chromatography over silica gel furnished the corresponding acetate (269 mg, 82%), the identity of which was established by comparison with the spectra (IR and NMR) of an authentic sample.

This procedure was followed for all the substrates included in Table 1.

Acknowledgements

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