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Highly selective acylation of alcohols and amines by an indium triiodide-catalysed transesterification process

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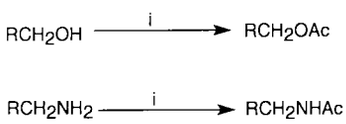
A very simple method has been developed for the acylation of alcohols and amines by ethyl acetate through an indium triiodide-catalysed transesterification process. Using this method acylation of a primary OH group in the presence of secondary and phenolic OH groups, and of a primary NH_2 in the presence of secondary NH and primary OH have been achieved with high selectivity.

The acylation of alcohols and amines is one of the most frequently used transformations in organic synthesis as it provides an efficient and inexpensive means for protecting hydroxy and amino groups in a multistep synthetic process.[1] Acetyl chloride and acetic anhydride are usually employed as the acylating agents in the presence of a convenient acidic[2] or basic[3] catalyst. However, both of these reagents, being corrosive and a lachrymator respectively, are not always ideal. Moreover, the acidic conditions in Lewis acid acylations lead to the cleavage of sensitive functional groups such as acetals and TBDMS ethers. On the other hand, most of the acidic and basic catalysts lack the ability to select between primary and secondary hydroxy and amino groups. Thus, acylation by transesterification with an ester or an enol ester constitutes a simple and practical alternative. A variety of procedures involving different catalysts have been developed for this purpose[4] and this process is under constant review to make it more effective and selective.[5]

The reactions involving indium(III) halides have been the subject of current interest because of their unique capability to impart high regio- and chemoselectivity in various chemical transformations.[6] Our recent experience with indium triiodide[6h] thus prompted us to explore the utility of this Lewis acid for the acylation of alcohols and amines. We were particularly interested in selectivity[5b,7] for substrates having more than one OH or NH_2 group, since selective monoacylation of diols and diamines is often needed in the synthesis of complex natural products and unfortunately is not always clean because of competing diacylation.[5e] We have discovered that indium triiodide catalyzes the acylation of primary alcohols and amines with ethyl acetate very efficiently (Scheme 1).



Scheme 1 *Reagents and conditions*: i, In, I_2, EtOAc, reflux.

Results and discussion

In a typical experimental procedure, the alcohol was heated under reflux in ethyl acetate in the presence of a catalytic amount of indium triiodide, generated *in situ* from indium metal and iodine, for a certain period of time as required to complete the reaction (monitored by TLC). The reaction mixture was then extracted with ether. The ether extract, after being washed with sodium thiosulfate and brine, was evaporated to furnish the product.

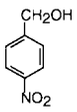
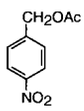
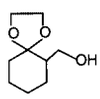
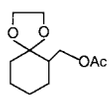
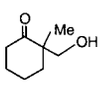
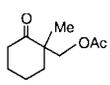
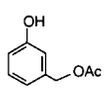
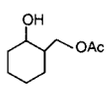
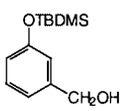
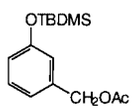
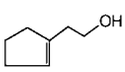
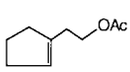
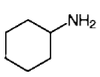
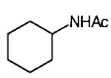
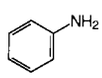
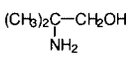
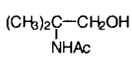
A wide range of structurally varied alcohols and amines were subjected to acylation by this procedure. The results are reported in Table 1. It was found that primary alcohols (entries 1–9) underwent smooth acylation whereas phenol (entry 10) and secondary alcohols (entries 12, 13) remained inert even after prolonged treatment (20 h) under the present experimental conditions. Thus, selective acylation of a primary OH group is achieved efficiently in compounds containing phenolic (entry 11) and secondary (entries 14, 15) hydroxy functionalities together with the primary hydroxy group in the same molecule and no appreciable diacetate (less than 5%) was isolated in each case. A tertiary alcohol on the other hand, suffered dehydration under these conditions (entry 18). The reaction conditions are mild enough not to induce any isomerisation of the double or triple bond in allylic and propargylic (propargyl = prop-2-ynyl) alcohols (entries 6, 7). More significantly, acid-sensitive functionalities such as ketal (entry 8) and TBDMS ether (entry 16) remained unaffected. In addition, a variety of other functional groups like OEt (entry 4), NO_2 (entry 5) and keto carbonyl (entry 9) also survived under the present reaction conditions.

Like primary alcohols, primary amines (entries 19, 20) were also readily acylated by this procedure. However, secondary and aromatic amines did not undergo any change (entries 21, 22). Very interestingly, in a competitive acylation reaction with an equimolar mixture of benzyl alcohol and benzylamine by this procedure, the amine is acylated selectively leaving behind the alcohol almost unaffected (acylation of OH group is less than 5% by ^{1}H NMR). Thus, acylation of amino alcohols produced the corresponding acetamides only (entries 23, 24, 25); the hydroxy moiety remained untouched. This selective acylation of a primary NH_2 over a primary OH by this process is of considerable synthetic importance and is difficult to achieve with many other reagents.[2,3]

The reactions are, in general, very clean giving very good yields, and no side product has been isolated. The reactions proceeded well with 0.1 equivalent of InI_3 and use of an increased amount of catalyst does not make much difference. The outcome of acylations either with preformed InI_3 or with *in situ* formed InI_3 (as mentioned in the experimental procedure) is more or less same.

In conclusion, the present procedure using indium triiodide provides a novel and efficient method for acylation of primary alcohols and amines. The notable advantages of this procedure are: (a) operational simplicity; (b) excellent selectivity for primary OH over secondary and phenolic OH groups, and for NH_2 groups over NH and primary OH; (c) general applicability; (d) reaction conditions tolerant to several acid-sensitive functional groups such as acetal and TBDMS ether and (e)

Table 1 InI_3-Catalysed acetylation of alcohols and amines by EtOAc

Entry	Alcohol/Amine	*t*/h	Product	Yield (%)[a]
1	$PhCH_2OH$	14	$PhCH_2OAc$	82
2	$PhCH_2CH_2OH$	12.5	$PhCH_2CH_2OAc$	80
3	$CH_3(CH_2)_{14}CH_2OH$	15	$CH_3(CH_2)_{14}CH_2OAc$	81
4	$EtOCH_2CH_2OH$	14	$EtOCH_2CH_2OAc$	78
5		16		79
6		12.5		80
7	≡–CH_2OH	13.5	≡–CH_2OAc	75
8		14		78
9		13.5		82
10		20	No reaction	
11		15		83
12	$PhCH(OH)Pr^n$	20	No reaction	
13	Me_2CHOH	20	No reaction	
14		14		80
15		16		85
16		15.5		85
17		12.5		80
18	Me_3COH	12	$Me_2C{=}CH_2$	75
19	$PhCH_2NH_2$	10	$PhCH_2NHAc$	82
20		13		80
21		20	No reaction	
22	Dicyclohexylamine	20	No reaction	
23	$HOCH_2CH_2NH_2$	15	$HOCH_2CH_2NHAc$	82
24		15		80
25	$HOCH_2(CH_2)_3CH_2NH_2$	16	$HOCH_2(CH_2)_3CH_2NHAc$	83

[a] Refers to yields of pure isolated products properly characterised by spectral data.

good yields. We believe this will present a better and more practical alternative to the existing methodologies for selective acylation of primary alcohols and amines and thus will find useful applications in the synthesis of complex natural products where selective protection of hydroxy and amino groups is required.

Experimental

Indium metal (Ingot, SRL, India) was cut into small slices and used directly without any treatment. Iodine crystal was used as obtained commercially. Ethyl acetate was dried over $CaCl_2$ and distilled before use. Alcohols and amines were obtained commercially or prepared by standard methods.

General procedure for acylation

Representative procedure. Benzyl alcohol (108 mg, 1 mmol) was heated at reflux in ethyl acetate (5 cm^3) in the presence of indium metal slices (12 mg, 0.1 mmol) and iodine (38 mg, 0.15 mmol) for 14 h (monitored by TLC). The reaction mixture was then extracted with ether (4 × 10 cm^3). The ether extract was washed successively with a solution of sodium thiosulfate, brine, and dried (Na_2SO_4). Evaporation of ether produced the

Table 2 IR and ^{1}H NMR data of some selected acetates and acetamides

Entry	ν_{max}/cm^{-1}	δ_H/ppm
5	1730	2.16 (s, 3H), 4.8 (s, 2H), 7.47–7.51 (m, 2 H), 8.16–8.20 (m, 2H)
6	1725	2.1 (s, 6H), 4.5–4.65 (d, 4H, *J* 9), 5.7–5.85 (t, 2H, *J* 9)
7	1725	2.0 (s, 3H), 2.2 (t, 1H, *J* 3), 4.2 (d, 2H, *J* 3)
8	1720	1.1–2.0 (m, 6H), 2.2 (s, 3H), 2.4–2.7 (m, 3H), 4.0 (s, 4H), 4.05–4.15 (broad d, 2H)
9	1725, 1715	1.1 (s, 3H), 1.7–1.95 (m, 6H), 2.1 (s, 3H), 2.2–2.4 (broad t, 2H), 4.1–4.2 (d, 2H, *J* 6)
11	1715	2.07 (s, 3H), 5.01 (s, 2H), 6.76–6.85 (m, 4H), 7.13–7.17 (m, 1H)
14	1715	2.06 (s, 3H), 3.65–3.70 (m, 1H), 4.04 (d, 5H, *J* 3)
15	1725	1.2–2.0 (m, 9H), 2.15 (s, 3H), 3.15–3.4 (m, 2H), 4.8 (broad d, 2H)
23	1680	2.0 (s, 3H), 2.8 (broad s, 1H), 3.3 (t, 2H, *J* 12), 3.65 (t, 2H, *J* 12) 7.0 (broad s, 1H)
24	1675	1.25 (s, 6H), 2.0 (s, 3H), 3.0 (broad s, 1H), 3.75 (s, 2H), 6.2 (broad s, 1H)

crude product which was purified by column chromatography over silica gel to furnish pure benzyl acetate (oil, 123 mg, 82%) which is in full agreement with spectral data of an authentic sample.

The reaction was also carried out with preformed InI_3 in which a mixture of indium metal and iodine was refluxed in ethyl acetate for half an hour and then benzyl alcohol was added. The results in both the procedures are the same.

The first procedure is followed for acylation of all the substrates included in Table 1. Gram-scale reactions also afforded analogously good yields. All the products are simple and known compounds and are easily identified by comparison of their spectra with those of authentic samples.[8] However, IR and ^{1}H NMR data of some selected acetates and acetamides whose spectra are not available for comparison are presented in Table 2.

Acknowledgements

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