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Ethyl acetate as an acetyl surrogate for the iodine catalyzed acetylation of alcohols

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ABSTRACT

The use of readily available ethyl acetate in the presence of iodine as an alternative acetylating agent is reported. Amines and phenols were unreactive under the examined reaction conditions, indicating that the method is highly chemoselective.

Introduction

Acetylation is one of the most essential transformations in organic synthesis. Protection of the hydroxyl functionality by an acetyl group has advantages over various protecting groups in view of its easy introduction, stability towards acidic reaction conditions, and mild removal by alkaline hydrolysis.[1]

Acetic anhydride[2] is the most commonly used acetyl source, albeit acetyl chloride and vinyl acetate[3] find applications in the acetylation of alcohols and amines. In the acetylation of alcohols, acetyl donors, such as acid anhydrides or acid chlorides, are activated with a stoichiometric quantity of an amine base in the presence of a basic catalyst. The Fischer esterification of acetic acid with alcohols in the presence of various Lewis acids[4] is also known, however it has not drawn as much attention.

The acetylation of alcohols using ethyl acetate as an acetyl surrogate is intriguing despite its low electrophilicity. However, the use of ethyl acetate in the place of commonly used acetic anhydride can be complicated by reversible *trans*-esterification. Therefore, selection of a suitable catalyst to avoid reversibility is vital. Hatano and Ishihara accomplished the acetylation of alcohols with ethyl acetate in the presence of catalytic La(O*i*-Pr)$_3$ and 2-(2-methoxyethoxy)ethanol.[5] Matta and co-workers used ethyl acetate for the selective acetylation of primary over secondary alcohols in sugar diols in the presence of Woelm neutral alumina at 60–65 °C.[6] The use of CBr_4/triphenylphosphine[7] and distannoxane[8] have also been reported. More recently, Singha and co-workers reported the selective acetylation of primary alcohols using ethyl acetate in the presence of KO*t*-Bu.[9] Unfortunately, many of the aforesaid methods suffer from drawbacks such as high cost, requiring azeotropic reflux in hexane,[5] poor environmental compatibility,[7,8] long reaction times,[7,8] and poor reactivity profiles.[6,7] As a result, there is still demand for the development of reactions using ethyl acetate as an acetylating agent. Herein, we report preliminary observations on the iodine catalyzed acetylation of alcohols employing ethyl acetate as an acetyl surrogate as well as solvent (Scheme 1).

Initially, a solution of the model compound benzyl alcohol (0.108 g, 1 mmol) and iodine (10 mol%) in ethyl acetate (excess) was stirred at room temperature; no conversion was observed after 24 h (Table 1, entry 1). Heating the reaction to 40 °C and 60 °C gave the acetylated product in 30% and 50% yield, respectively (Entries 2, 3). The reaction took only 2 h at reflux to give the acetylated product in 97% yield (Entry 5). Next, the effect of catalyst loading was examined. The reaction employing 5 mol% catalyst gave **1a** in 72% yield after a prolonged reaction time (Entry 4). Further increasing the catalyst loading to 15 mol% did not result in any significant increase in yield (Entry 6). The reaction did not proceed in the absence of iodine, even after heating at reflux for 24 h (Entry 9).

After optimization of the reaction conditions, the substrate scope of the protocol was explored (Table 2).[8] Both aliphatic and benzylic alcohols showed high to excellent conversion to the corresponding acetates. Functional groups such as nitro (Entries 2–4), cyano (Entry 6) and acetonide (Entry 22) were not affected. Secondary alcohols also reacted well to give the acetylated products

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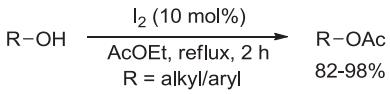


Scheme 1. Alcohol acetylation.

Table 1
Reaction conditions optimization.[a]

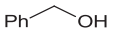
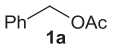
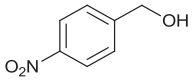
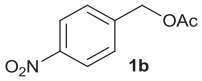
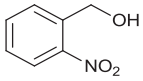
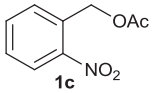
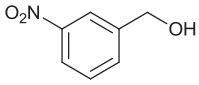
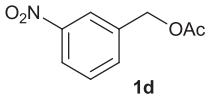
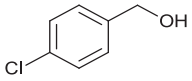
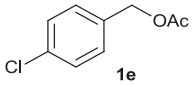
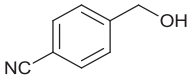
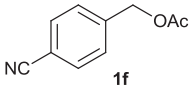
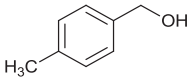
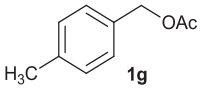
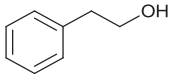
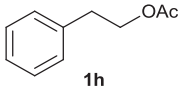
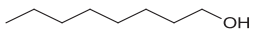
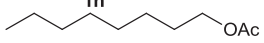
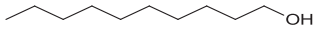
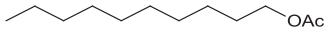
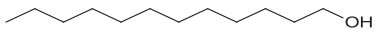
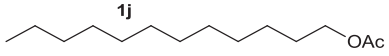
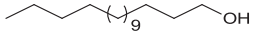
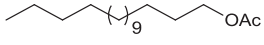
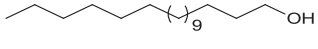
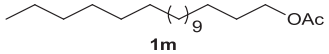
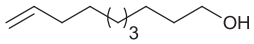
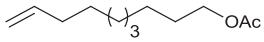
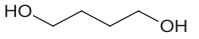
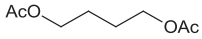
Entry	Iodine (mol%)	EtOAc (mL)	Temp.	Time (h)	Yield **1a** (%)[b]
1	10	2	22 °C	24	0
2	10	2	40 °C	24	30
3	10	2	60 °C	24	50
4	5	2	Reflux	12	72
5	10	2	Reflux	2	97
6	15	2	Reflux	2	96
7	10	3	Reflux	2	96
8	10	1	Reflux	2	62
9	0	2	Reflux	24	0

[a] Reagents and conditions: benzyl alcohol (1 mmol).
[b] Isolated yield.

in good to excellent yields (Entries 15–20). However, tertiary alcohols remained unreacted even after prolonged reaction times. This inertness towards tertiary alcohols may be attributed to steric repulsion between ethyl acetate and the hindered alcohol.[3] The double bond was also not affected, as observed in the case of 9-decen-1-ol where the acetate derivative was formed in 98% yield (Entry 13). As expected, *o*-cresol, aniline, and *n*-hexylamine (Entries 23–25) did not undergo acetylation, thereby making the protocol highly chemoselective.

Since the hydroxyl group and ethyl acetate can compete to react with *in-situ* formed HI, the reaction of β-cholesterol with ethyl acetate was carried out under the developed reaction conditions. If the hydroxyl group of cholesterol reacts with HI, it should generate a carbocation which upon reaction with ethyl acetate should, in principle, give a mixture of diastereomeric acetate derivatives (Scheme 2). Interestingly, the product was found to be β-cholesteryl acetate (**2a**) as evident from the specific rotation (observed $[\alpha]_D^{24} = -42$, c 2.0 $CHCl_3$) and melting point (108–109

Table 2
Substrate scope.[a]

Entry	Substrate	Product	Time (h)	Yield **1** (%)[b]
1		 **1a**	2	97
2		 **1b**	2.5	90
3		 **1c**	2.5	90
4		 **1d**	2.5	90
5		 **1e**	2	93
6		 **1f**	2	97
7		 **1g**	2	95
8		 **1h**	2	95
9		 **1i**	2	97
10		 **1j**	2	98
11		 **1k**	2	98
12		 **1l**	2	98
13		 **1m**	2.5	98
13		 **1n**	2	98
14		 **1o**	2	97

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