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Molecular iodine catalyzed selective acetylation of alcohols with vinyl acetate

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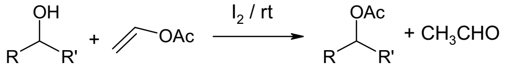
Abstract—Molecular iodine is found to catalyze the acetylation of alcohols efficiently with vinyl acetate. The reaction is mild and selective with good to high yields. Molecular iodine displays significant functional group tolerance, being compatible with methoxy, double bonds, spiroketals, ketals and phenolic hydroxyl functions.

Acetylation of hydroxy groups is an important and frequently used transformation in organic synthesis.[1] Acetyl chloride[2] and acetic anhydride[3] are usually employed as acetylating agents in the presence of tributylphosphine[4] or pyridine derivatives.[5] Lewis acid catalysts such as Sc(OTf)$_3$,[6] TMSOTf,[7] Cu(OTf)$_2$,[8] TaCl$_4$,[9] In(OTf)$_3$,[10] CoCl$_2$[11] and yttria–zirconia based Lewis acids[12] have been reported to be efficient catalysts for this reaction. Although these catalysts are effective, the acidic conditions in acetic anhydride and the Lewis acid can lead to cleavage of acid sensitive groups. Transesterification with esters is an alternative method for the acetylation of alcohols under mild conditions, but due to the reversibility, high yields cannot be achieved. In this connection, vinyl acetate is a reagent of choice, since the resultant enolate is converted to acetaldehyde, which is unable to participate in the reverse reaction. Several approaches towards the transformation of alcohols to acetates using vinyl acetate are known. Among these, the use of Cy$_2^*$Sm(thf)$_2$,[13] distanoxanes,[14] iminophosphoranes,[15] *N*-hetero-cyclic carbenes,[16] TsOH or concd H$_2$SO$_4$,[17] PdCl$_2$–CuCl$_2$,[18] Et$_2$Zn[19] and enzymes[20] is reported. However, the use of expensive and toxic metal precursors is a serious concern in the aspect of green chemistry. *N*-Heterocyclic carbenes are quite effective, but they are difficult to prepare. Hence, there is a need to develop more efficient methods and reagents as catalysts.

In recent years, molecular iodine has drawn considerable attention as an inexpensive, non-toxic, non-metallic and readily available catalyst for various organic transformations under mild and convenient conditions in excellent yields and with high selectivity.[21]

In continuation of our interest in iodine chemistry,[22] we chose this catalyst for the acetylation of alcohols with vinyl acetate. Kaimal and his group have reported that transesterification of alcohols can be performed with esters in the presence of molecular iodine at reflux.[23] We argued that if the carbonyl group and double bond of vinyl acetate were activated by iodonium ions and simultaneously reacted with a nucleophile, then acetylated products would be obtained in shorter times under these mild conditions. This proved to be the case when benzyl alcohol and vinyl acetate were stirred at room temperature with a catalytic amount of molecular iodine (10 mol %) yielding the corresponding acetate in good yield[24] (Scheme 1).

In order to evaluate the efficiency of iodine as a catalyst, the generality of the reaction was studied using various aliphatic, benzylic and allylic alcohols (Table 1). Both primary and secondary alcohols can be converted to the corresponding acetates in good yields. Electron donating groups accelerate the reaction of benzylic



Where R = R' = H, alkyl, aryl

Scheme 1.

Keywords: Molecular iodine; Catalyst; Selective; Alcohol; Acetate; Vinyl acetate.

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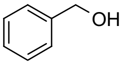
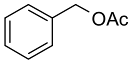
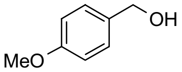
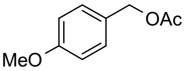
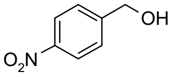
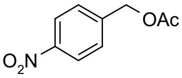
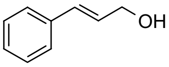
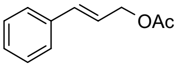
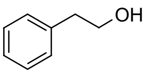
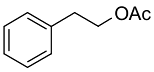
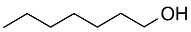
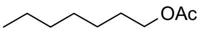
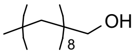
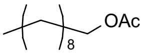
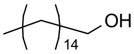
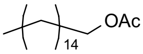
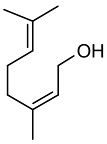
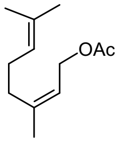
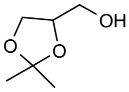
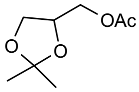
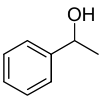
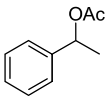
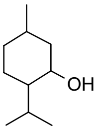
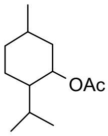
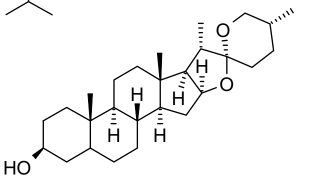
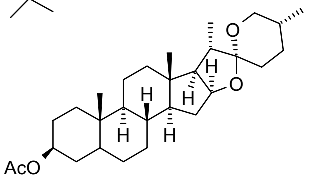
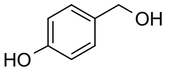
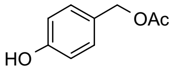
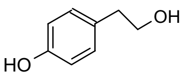
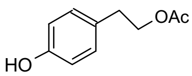
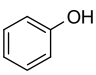
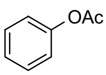
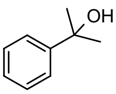
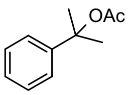
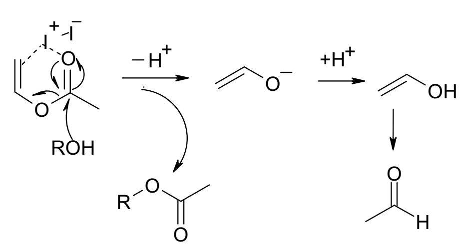
Table 1. Acetylation of alcohols with vinyl acetate using molecular iodine

Entry	Substrate	Time (h)	Product	Yield (%)[a]
1		4		97
2		1.5		98
3		6		93[b]
4		4		91
5		4.5		96
6		4		89
7		4		91
8		4		93[b]
9		4.5		89
10		7		87
11		5		93
12		4.5		94[b]
13		4		78[b]
14		2		95[b]
15		2		92[b]
16		3		Trace
17		12		0

[a] Yield refers to isolated yield. The compounds were characterized by ^{1}H NMR, ^{13}C and IR spectroscopy and by comparison with literature data.
[b] 4 equiv of vinyl acetate was used.



Scheme 2.

alcohols. Sterically hindered secondary alcohols (entries 11, 12 and 13) can also be acetylated in good yields. Entries 10 and 13 testify the mildness of this method towards acid sensitive groups. Phenols gave only trace amounts of acetylated products and therefore alcohols can be chemoselectively acetylated (entries 14 and 15). Tertiary alcohols were found to react slowly under these reaction conditions. Tertiary butyl alcohol gave only an 18% yield after a prolonged reaction time (24 h), while the tertiary benzylic alcohol (entry 17) remained unreacted. The reaction was completed quickly when carried out neat and also worked well in solvents such as toluene and THF, but took longer. Thus, the reaction of menthol was complete within 4.5 h with 94% yield when carried out in the presence of 4 equiv of vinyl acetate. On the other hand, the same reaction took 13 h to complete when carried out in THF giving a 92% yield. Interestingly, no iodo product was observed in the case of olefinic substrates (entries 4 and 9). The advantage of this reaction is that like acetic anhydride or acetyl chloride, it does not generate any acidic waste; as a result, the reaction medium is neutral. The only by-product, acetaldehyde can be removed by evaporation.

The reaction is a transesterification reaction as is evident from the formation of acetaldehyde, which was confirmed by ^{1}H NMR of the crude reaction mixture. The following mechanism can be proposed for the reaction. Both the carbonyl and double bond of vinyl acetate are activated by iodine, making the carbonyl group more susceptible to nucleophilic attack (Scheme 2). The inertness of the tertiary alcohol towards this reagent may be attributed to steric repulsion between the reagent and the hindered alcohol.

In conclusion, an efficient catalytic acetylation reaction using vinyl acetate as the acetylating agent under mild, neat and neutral conditions has been developed. A variety of primary and secondary alcohols were acetylated in good yields. Under these reaction conditions, functional groups such as methoxy, olefinic, spiroketal, ketal and phenolic remain unaffected. Thus, the catalytic acetylation of alcohols with iodine offers an additional method using vinyl acetate instead of acetic anhydride or acetyl chloride as the acetylating agent.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.03.182.

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24. Typical procedure for the molecular iodine catalyzed acetylation of alcohols (entry 2): Molecular iodine (0.1 mmol, 25.4 mg) was added to a mixture of *p*-methoxybenzyl alcohol (1 mmol, 138.16 mg) and vinyl acetate (3 mmol, 258 mg), which was stirred at room temperature under a nitrogen atmosphere. When the reaction was complete (TLC), it was extracted with ethyl acetate (10 ml) and washed with saturated sodium thiosulfate solution (4 ml). The organic layer was dried over sodium sulfate and purified by column chromatography. The products were characterized by spectroscopic methods. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.07 (s, 3H, –O–CO–CH_3), 3.80 (s, 3H, O–CH_3), 5.04 (s, 2H, –CH_2–O–), 6.88 (d, $J = 8.40$ Hz, 2H, –ArH), 7.30 (d, $J = 8.40$ Hz, 2H, –ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.96, 55.10, 65.94, 113.80, 127.80, 129.80, 159.28, 170.52; IR: 2950, 1736, 1516, 1245, 1173, 1040 cm^{-1}.