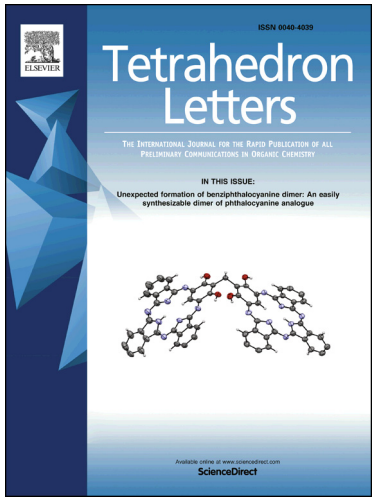

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LETTERS

Isopropenyl acetate: a cheap and general acylating agent of alcohols under metal-free conditions

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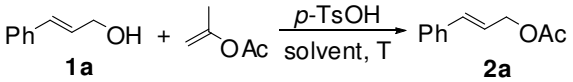
Abstract— Functionalized primary, secondary and tertiary alcohols are efficiently acetylated by isopropenyl acetate and catalytic *p*-TsOH.

Keywords: *Acetates; Protecting groups; Isopropenyl acetate; Alcohols.*

Acetylation of hydroxyl groups is an important and frequently used transformation in organic synthesis.[1] In synthetic sequences, acetylation is often a useful step performed by using acetyl chloride or acetic anhydride in the presence of stoichiometric amounts of bases such as tertiary amines,[2a] 4-(dimethylamino)pyridine,[2b] and tributyl phosphine.[2c] On the other hand, protic acids such as recyclable sulfonic acid catalysts,[3a] and Lewis acids, such as scandium trifluoromethansulfonate,[3b] copper (II) trifluoromethansulfonate,[3c] zinc chloride[3d] and cobalt chloride[3e] are well known to catalyze the acylation of alcohols and phenols in the presence of acetic anhydride. Transesterification with enol esters[4] as acylating agents is a possible alternative since the resultant enolate is converted to aldehyde or ketone, which is unable to take part to the reverse reaction. Organometallic catalysts,[5] basic iminophosphoranes,[6] *N*-heterocyclic carbenes[7] or tetraethylammonium hydrogen carbonate[8] have been employed to this end, but they suffer from some limitations such as poor air stability or low availability of the catalyst, high catalyst loading and incompatibility with acid-sensitive substrates. In recent years, iodine[9] has also been proposed as Lewis acid catalyst for the acetylation of alcohols under solvent free conditions.

More than sixty years ago, Hagemeyer and Hull reported[4a] some examples of alcohols acetylation by transesterification with an excess of isopropenyl acetate in the presence of sulfuric acid as catalyst. In continuation of our studies[10] on the protection of hydroxyl, amino and thiol groups, these results encouraged us to study and develop a practical, mild and general procedure that would be applied to a variety of alcohols replacing solfuric acid with *para*-toluenesulfonic acid (*p*-TsOH). Preliminary experiments were carried out on cinnamic alcohol **1a** under different reaction conditions (Scheme 1).



Scheme 1. Model study of acetylation of cinnamic alcohol **1a**

Thus, alcohol **1a** was treated with 4 equivalents of isopropenyl acetate (IPA) in dichloromethane at room temperature in the presence of 0.02 equivalents of *p*-TsOH (Table 1, entry 1).

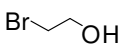
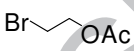
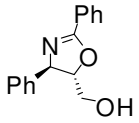
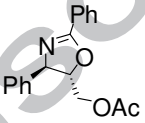
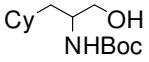
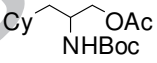
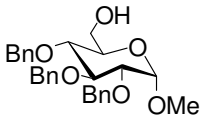
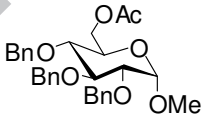
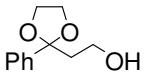
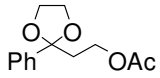
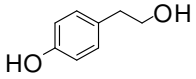
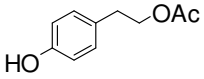
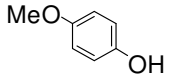
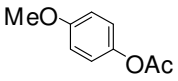
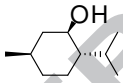
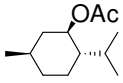
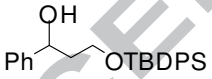
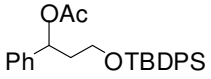
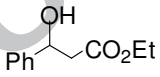
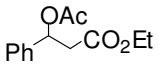
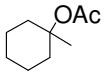
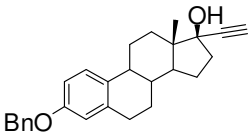
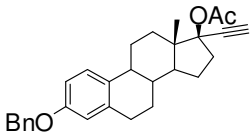
Table 1. Screening conditions for the acetylation of cinnamic alcohol **1a** with 4 equiv. of IPA in different solvents and catalytic *p*-TsOH (0.02 equiv).

Entry	Solvent	T (°C)	Time (h)	**2a**, Yield (%)[a]
1	CH_2Cl_2	rt	24	--
2	CH_2Cl_2	60	16	87
3	EtOAc	60	24	85
4	THF	60	24	50
5	MeCN	rt	16	97

[a] Yields of isolated product.

After 24 h, we did not observe any formation of the corresponding acetyl ester derivative **2a** (Table 1, entry 1). In contrast, the reaction performed at 60 °C (oil bath temperature) gave the expected product with 87% yield (Table 1, entry 2). When 2 equiv. of IPA were used or IPA was used as solvent (solvent free conditions), the final yield decreased, while no improvement was observed by using 6 equiv. of IPA. However, satisfactory yields were obtained operating in tetrahydrofuran or ethyl acetate at 60 °C (Table 1, entry 3-4), while, no conversion of the starting material was observed with the same solvents at room temperature. Surprisingly, the reaction performed in acetonitrile at room temperature (Table 1, entry 5) gave complete conversion of the starting alcohol **1a** into the corresponding acetyl ester **2a** (16 h, monitored by thin-layer chromatography, TLC).

Table 2. Acetylation of alcohols **1b**-**m** with IPA promoted by catalytic *p*-TsOH.

Entry	Alcohol		Solvent	T (°C)	Time (h)	Acetyl ester[a]		Yield (%)[b]
1		**1b**	CH_2Cl_2	rt	17		**2b**	84[c]
2		**1c**	CH_2Cl_2	60	24		**2c**	60[d]
3		**1d**	CH_2Cl_2	rt	17		**2d**	65
4		**1e**	CH_2Cl_2	rt	15		**2e**	97[c]
5		**1f**	CH_2Cl_2	60	14		**2f**	93[e]
6		**1g**	CH_2Cl_2	rt	4		**2g**	69[f]
7		**1h**	CH_2Cl_2	rt	36		**2h**	73
8		**1i**	MeCN	rt	17		**2i**	98[c]
9		**1j**	CH_2Cl_2	rt	16		**2j**	84[c]
10		**1k**	CH_2Cl_2	rt	16		**2k**	85
11		**1l**	CH_2Cl_2	60	15		**2l**	81[c]
12		**1m**	CH_2Cl_2	rt	14		**2m**	96[c]

[a] All the products were characterized by ^1H and ^{13}C NMR and mass spectroscopy.

[b] Yields of isolated products.

[c] 0.04 equiv of *p*-TsOH was employed.

[d] 0.5 equiv of *p*-TsOH was employed.
[e] Isolated as a 5:1 mixture with deprotected ketone (^{1}H NMR).
[f] Diacetylated product was also isolated in 30% yield after column chromatography.

When, the crude reaction mixture was poured in 10% aqueous sodium hydrogen carbonate, extracted with ethyl acetate and dried over sodium sulfate, pure acetyl ester **2a** was obtained in 98% yield after column chromatography on silica gel. Replacing *p*-TsOH with milder acids, such as acetic and cictric acid, there was no conversion of the starting material. We also found that this protocol can be successfully applied to a variety of differently substituted alcohols[11] and the results obtained are collected in Table 2. Thus, the preparation of ester **2a** and the data reported in Table 2 clearly demonstrate that the acetylation of primary alcohols **1a**-**h** proceed smoothly in dichloromethane or acetonitrile to afford the corresponding acetyl esters **2a**-**h** in good to excellent yields at room reaction temperature. For alcohols **1c** and **1f** a gentle reflux was necessary to promote the reaction. It is noteworthy that the mild experimental conditions employed are compatible with different functional groups such as double bound, alogen, ether, *tert*-butoxycarbonyl and acetonide groups. Interestingly, the reaction works well also with substrates possessing acid labile groups (compound **1c** and **1d**). In the case of compound **1c** a non-catalytic amount of *p*-TsOH (0.5 equiv) was added to advance the reaction. The acetylation of alcohol **1f** gave an inseparable 5:1 mixture of the protected ketone **2f** together with deprotected acetoxy ketone. In this case partial hydrolysis of the ketal group occurred. The phenolic compound **1g** containing also an alcoholic hydroxyl group (Table 2, entry 6) reacted with IPA to give the protected alcoholic hydroxyl group derivative **2g** in good yield together with some diprotected product, thus showing that hydroxyl group of phenol is less reactive than that of the alcohol. This fact was confirmed by the long reaction time (36 h) required to acetylate the phenolic compound **1h** (Table 2, entry 7). The scope of the present investigation was extended to the protection of some representative secondary and tertiary alcohols as **1i**-**k** and **2l**-**m** respectively. Functionalized secondary and tertiary alcohols also gave the corresponding acetyl ester derivatives in excellent yields. The various functionalities present in the secondary and tertiary alcohols (e.g. *tert*-butyl(diphenyl)silyl, carbethoxy and carbon-carbon triple bond) were compatible with the mild reaction conditions employed. Thus, the hydroxyl groups of silyl ether **1j** and β-hydroxy ester **1k** were successfully protected as acetyl derivatives (Table 2, entries 9 and 10) and no dehydration products were observed. It should be noted that tertiary alcohol **1l** and *O*-benzyl ethinylestradiol (**1m**), which might be subjected to dehydration or rearrangement reactions, gave the corresponding acetyl derivatives **2l** and **2m** in high yields. In the case of tertiary alcohol **1l**, a gentle reflux was necessary to promote the reaction.

In conclusion, we have shown that an almost forgotten system for acetylation such as IPA and *p*-TsOH is able to acetylate various alcohols under mild conditions. The results confirm that IPA can be considered as a valid alternative to acetic anhydride or acetyl chloride as acetylating reagent. However, the use of IPA significantly increases the range of acetylation substrates, making it highly effective even on alcohols containing acid labile functional groups and under metal-free and mild reaction conditions.

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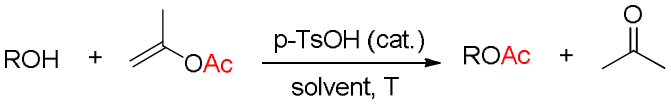
11. *General procedure for the protection of alcohols **1** as acetyl-derivatives*. A mixture of the alcohol **1** (1 mmol), isopropenyl acetate (0.45 mL, 4 mmol) and *p*-TsOH (4 mg, 0.02 mmol) in dichloromethane or acetonitrile (4 mL) was stirred at the indicated temperature (see Table 1 and Table 2). Reaction times ranged from 16 to 36 h. After completion of the reaction (TLC monitoring) the mixture was poured into 10 mL of 10% aqueous sodium hydrogen carbonate solution. The aqueous phase was extracted with ethyl acetate (3x10 mL) and the combined organic phases were washed with 10 mL of brine, dried over sodium sulfate and then evaporated under vacuum. Purification by silica gel column chromatography afforded the pure acetyl ester **2**. Physical and spectral data of known compounds were consistent with the ones reported in literature. Physical and spectral data of not previously described compounds are reported below. **2-[(*tert*-Butoxycarbonyl)amino]-3-cyclohexylpropyl acetate** (**2d**): Yield 65%; oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ= 4.55-4.38 (m, 1H), 4.10-3.88 (m, 3H), 2.10 (s, 3H), 1.90-1.57 (m, 5H), 1.48 (s, 9H), 140-1.10 (m, 6H), 1.08-0.78 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ= 170.9, 155.3, 79.2, 66.7, 46.9, 39.4, 34.0, 33.6, 32.7, 28.2 (3C), 26.3, 26.2, 26.0, 20.7. GC-MS (EI): *m/z* (%)= 226 (35) $[M-73]^+$, 170 (100), 126 (95), 102 (27), 81 (12), 67 (10), 57 (88). ν_{max}/cm^{-1} 3343, 2922, 1746, 1524, 1366, 1235, 1172, 1046, 756. **2-(2-Phenyl-1,3-dioxolan-2-yl)ethyl acetate** (**2f**): Yield 93%; oil; Obtained as 5:1 mixture with deprotected ketone, only the signals of the new compound **2f** are indicated below. ^{1}H NMR (200 MHz, $CDCl_3$): δ= 7.55-7.20 (m, 5H), 4.17 (t, 2H, J= 7.28 Hz), 4.07-3.91 (m, 2H), 3.85-3.68 (m, 2H), 2.28 (t, 2H, J= 7.28 Hz), 1.93 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ= 170.8, 141.8, 133.2, 128.1 (2C), 125.4 (2C), 108.7, 64.3 (2C), 60.1, 38.8, 20.7. GC-MS (EI): *m/z* (%)= 149 (100) $[M-87]^+$, 105 (73), 99 (26), 77 (37). **3-{[*tert*-Butyl(diphenyl)silyl]oxy}-1-phenylpropyl acetate** (**2j**): Yield 84%; oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ= 7.75-7.60 (m, 5H), 7.49-7.25 (m, 10H), 6.02 (dd, 1H, J= 8.32 and 5.80 Hz), 3.80-3.55 (m, 2H), 2.28-1.98 (m, 2H), 2.02 (s, 3H), 1.08 (m, 9H). ^{13}C NMR (50 MHz, $CDCl_3$): δ= 170.1, 140.6, 135.5 (2C), 135.3 (2C), 133.5 (2C), 130.2, 129.6 (2C), 128.4 (2C), 127.8 (2C), 127.6 (2C), 126.5 (2C), 73.1, 59.9, 39.1, 26.8 (3C), 21.2, 19.1. ν_{max}/cm^{-1} 3070, 2931, 1736, 1428, 1236, 1111, 737. GC-MS (EI): *m/z* (%)= 241 (100) $[M-191]^+$, 181 (12), 77 (16). **Ethyl 3-(acetyloxy)-3-phenylpropanoate** (**2k**): Yield 85%; oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ= 7.42-7.22 (m, 5H), 6.18 (dd, 1H, J= 8.97 and 5.33 Hz), 4.13 (q, 2H, J= 7.11 Hz), 2.98 (dd, 1H, J= 15.70 and 8.97 Hz), 2.74 (dd, 1H, J= 15.70 and 5.33 Hz), 2.07 (s, 3H), 1.22 (t, 3H, J= 7.11 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ= 169.8, 169.7, 139.2, 128.6 (2C), 128.3, 126.5 (2C), 72.1, 60.7, 41.4, 21.0, 14.1. ν_{max}/cm^{-1} 2983, 1743, 1373, 1230, 1024, 764. GC-MS (EI): *m/z* (%)= 236 (5), 193 (100), 147 (48), 131 (52), 120 (41), 105 (84), 77 (34), 51 (11). **(17b)-3-(Benzyloxy)-17-ethynylestra-1(10),2,4-trien-17-yl acetate** (**2m**) m.p. 185-187 °C; ; ^{1}H NMR (200 MHz, $CDCl_3$): δ= 7.50-7.19 (m, 6H), 6.89-6.70 (m, 2H), 5.30 (s, 2H), 2.98-2.72 (m, 3H), 2.68 (s, 1H), 2.50-1.69 (m, 11H), 2.09 (s, 3H), 1.65-1.22 (m, 4H), 0.92 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ= 169.6, 156.7, 137.9, 137.2, 132.6, 128.5 (2C), 127.8, 127.4 (2C), 126.3, 114.7, 112.2, 84.4, 83.3, 74.8, 69.8, 47.8, 47.7, 43.4, 39.0, 37.3, 33.0, 29.7, 27.2, 26.3, 23.2, 21.4, 13.4. ν_{max}/cm^{-1} 2942, 2359, 1733, 1498, 1456, 1254, 1031, 730.



- Protection of primary, secondary and tertiary alcohols
- Mild and metal-free reaction conditions
- Acetylation in the presence of acid sensitive moieties