Iodine as an Acetyl Transfer Catalyst†

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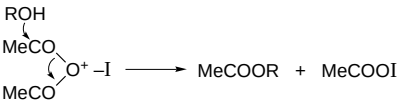
Ruli Borah, Nabajyoti Deka and Jadab C. Sarma*

Organic Chemistry Division, Regional Research Laboratory, Jorhat - 785006, Assam, India

Iodine catalyses the acetylation of amines, phenols and alcohols, including tertiary ones, with acetic anhydride in excellent yield.

The protection of hydroxy and amino groups by converting them into acetates is one of the most fundamental and widely used transformations in organic chemistry. Protection of such functional groups is often necessary during the course of various transformations in a synthetic sequence especially in the construction of polyfunctional molecules such as nucleosides, carbohydrates, steroids and natural products. Although several reagents[1] are available for the acetylation of alcohols, an acetic anhydride–pyridine mixture is most commonly used for this purpose. 4-Dimethylaminopyridine (DMAP)[2] is also used and is more efficient and has wider scope. Recently reagents like $CoCl_2$–acetic anhydride,[3] MgI_2–diethyl ether–acetic anhydride,[4] functional polymers[5] and polymer support reagents[6] have been reported as alternative and versatile acylating agents. In most of these cases either a low yield is observed or stringent reaction conditions are necessary.

We report here a mild, convenient and efficient catalyst for the acetylation of alcohols. When an alcohol was treated with acetic anhydride in the presence of a catalytic amount of iodine at room temperature, the corresponding acetate was obtained in excellent yield. The reaction proceeded rapidly at ambient temperature with high yields of acetates also from tertiary alcohols, (Table 1). The reaction was fast at high temperatures (refluxing chloroform or dichloromethane, entry 7) and also at high concentrations of acetic anhydride. The problem of β-elimination in β-hydroxy carbonyl compounds to yield α, β-unsaturated carbonyl compounds as side products as observed during base catalysed acetylation[3] was not evident here; in contrast the yield of acetate was found to be almost quantitative (Table 1, entry 13). The acetylation of 4-hydroxy-4-methylpentan-2-one (entry 13) was even faster than that of 2-methylpentane-3,4-diol (entry 6) or 4-acetoxy-2-methylpentan-2-ol (entry 14). Polarization of the acetic anhydride by forming a complex with iodine followed by nucleophilic attack of the alcohol may give the acetate and the unstable acylhypohalite which eliminates iodine to continue the reaction (Scheme 1).



Scheme 1

In a blank experiment, cholesterol was treated with acetic anhydride for 10 h. No corresponding acetate was observed, clearly indicating the importance of iodine as a catalyst in the system.

Table 1

Entry	Compound	*t*/min	*T*/°C	Yield[a] (%)	ν_{max}/cm^{-1}	δ_H (60 MHz)
1	Cetyl alcohol	30	r.t.	10[b]	1725	2.05 (s, 3 H), 3.85 (t, 2 H, *J* 6 Hz)
		15 h	r.t.	90[b]		
2	Octadecan-1-ol	30	r.t.	10[b]	1720	2.0 (s, 3 H), 3.8 (t, 2 H, *J* 6 Hz)
		15 h	r.t.	86[b]		
3	Benzyl alcohol	30	r.t.	20[b]	1725	1.95 (s, 3 H), 4.8 (s, 2 H)
		15 h	r.t.	100		
4	Cyclohexanol	20	r.t.	100	1725	2.0 (s, 3 H), 4.8 (brs, 1 H)
5	Cholestanol	20	r.t.	100	1725	1.85 (s, 3 H), 4.4 (br, 1 H)
		3	42	100		
6	$MeCH(OH)CH_2CMe_2OH$	30	r.t.	60[b]	(2°) + 3 (diac)	1.8 (s, 3 H), 4.85 (sex, 1 H, *J* 6 Hz)
		90	r.t.	95	(1:1)	
7	Cholesterol	10	r.t.	100	1725	1.9 (s, 3 H), 4.4 (brs, 1 H)
		2	42	100		
8	Diosgenin	60	r.t.	95	1730	1.85 (s, 3 H), 4.25 (brs, 1 H)
9	Carveol	30	r.t.	90	1725	1.95 (s, 3 H), 4.9 (brs, 1 H)
10	α-Ionol	30	r.t.	100	1725	1.95 (s, 3 H), 4.8–5.3 (brs, 4 H)
11	PhCH(OH)Me	20	r.t.	100	1725	1.8 (s, 3 H), 5.5 (q, 1 H, *J* 6 Hz)
12	(20*R*)-20-hydroxypregna-5,16-dien-3β-yl acetate	120	r.t.	65[b]	1725	1.85 (s, 6 H), 4.35 (br, 2 H)
13	$MeC{=}O)CH_2CMe_2OH$	30	r.t.	95	1725	2.0 (s, 3 H)
14	$MeCH(OAc)CH_2CMe_2OH$	180	r.t.	90[b]	1730	1.8 (s, 3 H), 1.85 (s, 3 H), 4.85 (m, 1 H)
15	Butylamine	100	r.t.	78	1650	2.0 (s, 3 H), 7.8 (br5, 1 H)
16	Aniline	105	r.t.	77	1660	2.0 (s, 3 H), 7.7 (br, 1 H)
17	Phenol	30	r.t.	90	1745	1.95 (s, 3 H)
18	Resorcinol	30	r.t.	80	1745	2.0 (s, 3 H)

[a]All yields refer to isolated products which were characterised by direct comparison with authentic samples and also by spectral analysis. [b]Remainder is unreacted starting material.

Both aliphatic and aromatic amino groups as well as phenols are also acetylated by this system in excellent yield.

The reagent combination of acetic anhydride–pyridine or acetic anhydride–DMAP is not suitable for acetylation of base sensitive compounds.[3] Pyridine and DMAP are both toxic and in the case of polar compounds are sometimes difficult to remove from the reaction mixture after work-up. The present reagent combination circumvents these

*To receive any correspondence.

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problems and offers a quick and efficient method of acetylation.

Experimental

Melting points were determined on a Buchi capillary apparatus. IR spectra were recorded on a Perkin Elmer 237B IR Spectrophotometer. NMR spectra were recorded on Varian 360L instrument. Mass spectra were recorded on a INCOS 50 GC-MS instrument.

General Procedure.—In a typical reaction, a stirred solution of substrate (1 mmol) in acetic anhydride (5 mmol) [dichloromethane–chloroform (2 ml) was added to aid solubilization when necessary] was treated with a catalytic amount of iodine (0.1 mmol) at room temperature. On completion of the reaction (monitored by TLC), the mixture was diluted with water and extracted with chloroform or dichloromethane. The extract was washed successively with a solution of sodium thiosulfate and dilute sodium hydrogen carbonate followed by water. The extract was dried over anhydrous sodium sulfate and evaporated at reduced pressure. The residue was purified by preparative TLC if necessary.

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