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$Al(OTf)_3$ as a highly efficient catalyst for the rapid acetylation of alcohols, phenols and thiophenols under solvent-free conditions

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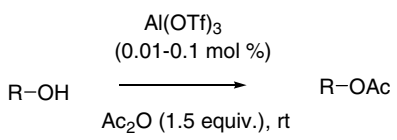
Abstract—Aluminium triflate (0.01–0.1 mol %) was found to be an efficient catalyst for the acylation of alcohols, phenols, thiols and sugars with acetic anhydride in high yields under solvent-free conditions in a short reaction time at room temperature. Racemization of optically active alcohols and epimerization of sugars were not observed. The acylation efficacy of various acyl donors was also investigated.

Acylation of alcohols and phenols is an important and routinely utilized transformation in organic synthesis.[1] Despite a number of precedents, new efficient methodologies for acylation are still in demand. Acid anhydrides have been the most commonly used reagents in the presence of an acid or base catalyst.[2] Although a number of methods are available for the preparation of acetates, the use of acetic acid or a protic acid or acetic anhydride and pyridine are the most commonly used reagents.[1] 4-(Dimethylamino)pyridine (DMAP) and 4-pyrrolidinopyridine (PPY) catalyze the acetylation of alcohols.[3] Further, other catalysts such as $CoCl_2$,[4] $TaCl_5$–SiO_2,[5] $ZnCl_2$,[6a] ZnO,[6b,c] $InCl_3$,[7a] $ZrCl_4$,[7b] $LiClO_4$,[7c] Ru-catalysts,[7d] $Mg(ClO_4)_2$,[7e] SmI_2,[7f] $CeCl_3$,[7g] $ZrOCl_2{\cdot}8H_2O$,[7h] montmorillonite,[8a] TMS–Cl,[8b] PTSA,[9a] NH_2SO_3H,[9b] distannoxane,[9c] ionic liquids,[9d] solid supported reagents and lipase enzymes[9e] and various triflates[10] have been used for acetylation of alcohols.

Most of the above procedures can be applied for the acylation of various acid/base sensitive substrates. Recently, perchlorates[7c,e] were reported to catalyze the acetylation of alcohols; however, perchlorates, particularly of lithium, are known to be explosive and moisture sensitive. More recently, molecular iodine,[11a] 3-nitrobenzeneboronic acid[11b] and $La(NO_3)_3{\cdot}6H_2O$[11c] catalyzed acetylations of alcohols were also reported. Although a large number of methods for acetylation are available, many suffer from limitations such as long reaction times, harsh reaction conditions, use of expensive, moisture sensitive and toxic catalysts, formation of side products and poor yields of the desired products. In view of the demands of organic synthesis, there is still a need to develop mild and efficient protocols for the acetylation of alcohols.

$Al(OTf)_3$ has been used for the Friedel–Crafts alkylation and acylation of aromatic compounds.[12a] In recent years, it was found to be an efficient catalyst for epoxide ring opening,[12b,c] esterification of carboxylic acids with alcohols,[12d] thiol protection[12e] and silylation of alcohols and phenols.[12f] Herein, we report that a number of alcohols, phenols and thiophenols can be acetylated with acetic anhydride, in excellent yields, in the presence of 0.1 mol % of $Al(OTf)_3$ at room temperature under solvent-free conditions in short times (10–40 s) (Scheme 1). Encouraged by the success of this reaction various primary, secondary, benzylic and cyclic alcohols and phenols were subjected to acylation in excellent yields. The product structures were established from their



Scheme 1.

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Table 1. Acetylation of alcohols and phenols catalyzed by 0.1 mol % aluminium triflate[a]

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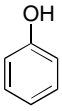
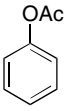
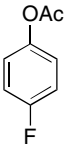
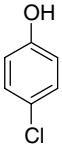
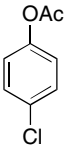
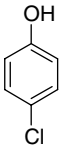
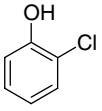
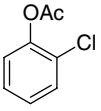
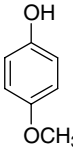
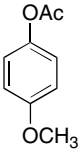
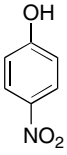
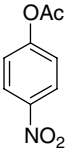
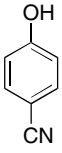
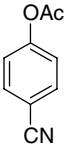
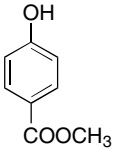
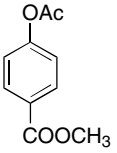
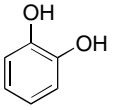
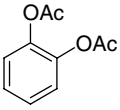
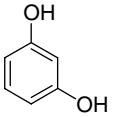
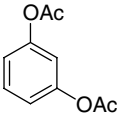
1			15	96
2			20	98
3a			10	99
3b	 (12.85 g scale)		15	96
4			10	95
5			10	99
6			25	95
7			30	96
8			20	99
9			30	95
10			30	95

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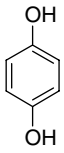
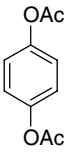
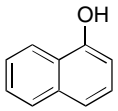
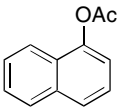
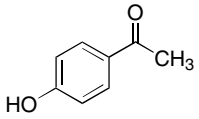
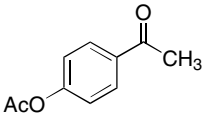
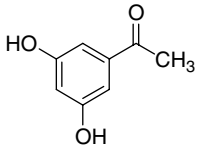
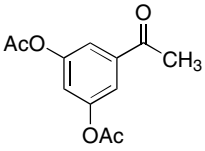
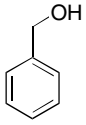
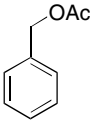
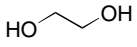
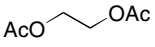
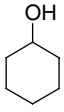
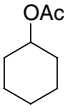
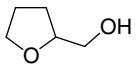
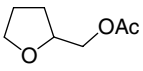
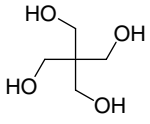
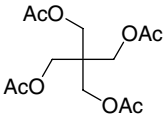
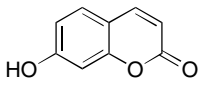
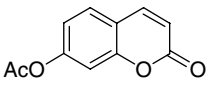
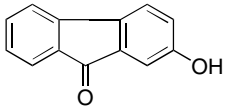
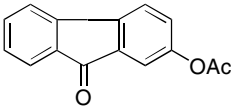
Entry	Substrate	Product	Time (s)	Yield[b] (%)
11			25	96
12			30	90
13			10	98
14			20	96
15			15	98
16			30	95
17			20	96
18			20	96
19			30	95
20			20	98[c]
21			15	95

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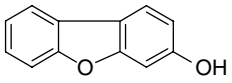
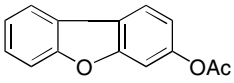
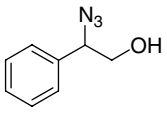
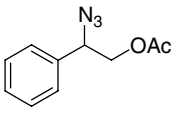
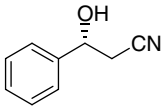
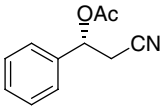
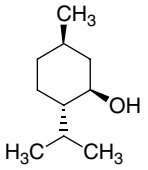
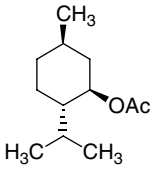
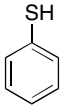
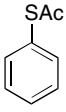
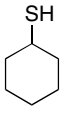
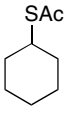
Table 1 (*continued*)

Entry	Substrate	Product	Time (s)	Yield[b] (%)
22			15	98[c]
23			20	98
24			20	99
25			20	98
26			10	98
27			15	95
28	D-Mannitol	Hexa-*O*-acetyl-D-mannitol	40	95[c]

[a] All the reactions were performed using 1.5 equiv of acetic anhydride unless otherwise stated.
[b] Isolated yields.
[c] To solubilize solid substrates, 5 equiv of acetic anhydride was added.

spectral properties[13] (NMR, mass and IR) and by comparison with available literature data. In the absence of a catalyst, using the same reaction conditions, the corresponding products were obtained in low yields (25–40%) even after prolonged reaction times of 1.5 h. The general applicability and efficiency of this reaction is evident from the wide range of compounds studied (Table 1). Deactivated substrates, such as aromatic and benzylic alcohols, could also be acetylated rapidly. For example, strongly deactivated *p*-nitrophenol and *p*-cyanophenol (Table 1, entries 6 and 7) quantitatively afforded the corresponding acetates within 25–30 s.

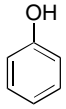
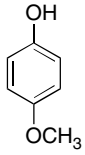
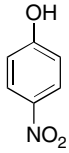
Furthermore, when stereogenic centres were present in the substrates, racemization or epimerization were not observed to any extent in the acetylated products.[14] In order to increase the scope of the present method, a large scale acylation of phenol was carried out (Table 1, entry 3b) using 0.01 mol % of the catalyst, the reaction proceeded rapidly and in high yield.

We have also investigated the acetylating efficiency of other acylating agents such as isopropenyl acetate, vinyl acetate and acetic acid using the same catalyst on unsubstituted phenol and electron rich and electron deficient phenols. All the phenols afforded good yields of acetates in 5–7 min in the presence of isopropenyl acetate (1.5 equiv) and $Al(OTf)_3$ (0.5 mol %) at room temperature (Table 2). However, when vinyl acetate was used as the acylating agent, *p*-methoxy and *p*-nitrophenols gave 50–70% yields after prolonged reaction times of 2 h (Table 2, entries 2 and 3) and phenol was not acetylated under the same conditions (Table 2, entry 1). Acetylation of phenols did not take place in the presence of acetic acid using $Al(OTf)_3$ at room temperature (Table 2).

In conclusion, we have shown that $Al(OTf)_3$ is an efficient and versatile catalyst for the acylation of alcohols, phenols, thiols, thiophenols and sugars using acetic anhydride under solvent-free conditions at room temperature. The advantages of this method over earlier reported processes includes its simplicity, clean and rapid reactions, high yields, absence of organic solvents, large scale synthesis and retention of chirality.

Typical experimental procedure: To a mixture of alcohol/phenol (2 mmol) and acetic anhydride (3 mmol), $Al(OTf)_3$ (0.01–0.1 mol %) was added. The reaction mixture was stirred at room temperature for the appropriate

Table 2. Acetylating efficacy of various acyl donors catalyzed by 0.5 mol % $Al(OTf)_3$ under solvent-free conditions

Entry	Substrate	Acetic anhydride		Isopropenyl acetate		Vinyl acetate		Acetic acid	
		T[a] (s)	Y[b] (%)	T[a] (min)	Y[b] (%)	T[a] (h)	Y[b] (%)	T[a] (h)	Y[b] (%)
1		15	96	7	95	2	0	2	0
2		10	99	7	90	2	70	2	0
3		25	95	5	95	2	50	2	0

[a] Time.
[b] Isolated yields after purification.

amount of time (Tables 1 and 2). Completion of the reaction was monitored by TLC after quenching with a saturated solution of $NaHCO_3$ and the products were extracted into ethyl acetate (3×25 mL). The combined organic layer was washed with water, dried over anhydrous Na_2SO_4 and concentrated in vacuo. If necessary the product was purified by column chromatography on silica gel in hexane/ethyl acetate. All products were characterized by comparison of their spectral data and physical properties with those of authentic samples.

Large scale acetylation: To a mixture of *p*-chlorophenol (12.85 g, 0.1 mol) and acetic anhydride (14.18 mL, 0.15 mol) (entry 3b) at room temperature, was added $Al(OTf)_3$ (4.7 mg, 0.01 mol %). After 15 s, a saturated solution of $NaHCO_3$ was added to the reaction mixture and the acetylated product was isolated by the above described method.

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13. *Selected spectral data for the acetylated products: Tetrahydro-2-furanylmethyl acetate* (entry 18), semi solid, ^{1}H NMR ($CDCl_3$, Me_4Si, 300 MHz) δ (ppm): 4.02–4.14 (m, 2H), 3.92–4.00 (m, 1H), 3.86 (q, $J = 6.80$ Hz, 1H), 3.77 (q, $J = 7.55$ Hz, 1H), 2.08 (s, 3H, $COCH_3$), 1.84–2.07 (m, 3H), 1.54–1.68 (m, 1H). IR (KBr) (ν/cm^{-1}): 2955, 2874, 1742 (OC=O), 1370, 1237 (CO–O), 1040. EI-MS: M^+ 144. Anal. Calcd for $C_7H_{12}O_3$: C, 58.32; H, 8.39. Found: C, 58.39; H, 8.36. *3-(Acetyloxy)-2,2-di[(acetyloxy)methyl]propyl acetate* (entry 19), mp 78–80 °C, ^{1}H NMR ($CDCl_3$, 300 MHz) 2.08 (s, 12H, $4COCH_3$), 4.10 (s, 8H). IR (KBr) (ν/cm^{-1}): 2975, 2906, 1738 (OC=O), 1236 (CO–O), 1041. LC-MS: 327 $[M+Na]^+$. Anal. Calcd for $C_{13}H_{20}O_8$: C, 51.38; H, 6.62. Found: C, 51.45; H, 6.58. *2-Oxo-2H-7-chromenyl acetate* (entry 20), mp 143–145 °C, ^{1}H NMR ($CDCl_3$, Me_4Si, 200 MHz) δ (ppm): 7.68 (d, $J = 9.37$ Hz, 1H), 7.48 (d, $J = 8.59$ Hz, 1H), 7.12 (d, $J = 2.34$ Hz, 1H), 7.04 (dd, $J = 8.59$, 2.34 Hz, 1H), 7.38 (d, $J = 9.37$ Hz, 1H), 2.35 (s, 3H, $COCH_3$). IR (KBr) (ν/cm^{-1}): 1742 (OC=O), 1621, 1203, 1186 (CO–O), 848. EI-MS: M^+ 204. Anal. Calcd for $C_{11}H_8O_4$: C, 64.71; H, 3.95. Found: C, 64.75; H, 3.94. *9-Oxo-9H-2-fluorenyl acetate* (entry 21), mp 158–159 °C, yellow crystalline solid. ^{1}H NMR ($CDCl_3$, Me_4Si, 200 MHz) δ (ppm): 7.62 (d, $J = 7.81$ Hz, 1H), 7.48 (d, $J = 7.81$ Hz, 2H), 7.44 (s, 1H), 7.35 (d, $J = 2.34$ Hz, 1H), 7.24–7.32 (m, 1H), 7.15 (dd, $J = 8.59$, 2.34 Hz, 1H), 2.31 (s, 3H, $COCH_3$). ^{13}C NMR ($CDCl_3$, Me_4Si, 75 MHz) δ (ppm): 192.5, 169.0, 151.4, 143.8, 141.6, 135.5, 134.8, 134.3, 128.8, 127.3, 124.4, 121.0, 120.2, 118.0, 20.9. IR (KBr) (ν/cm^{-1}): 3060, 1762 (OC=O), 1716 (C=O), 1600, 1455, 1196, 1126 (CO–O), 1013, 736. EI-MS: M^+ 238; M^+-42 (196, base peak). Anal. Calcd for $C_{15}H_{10}O_3$: C, 75.62; H, 4.23. Found: C, 75.69; H, 4.21. *Dibenzo[b,d]furan-3-yl acetate* (entry 22), mp 110–112 °C, ^{1}H NMR ($CDCl_3$, Me_4Si, 300 MHz) δ (ppm): 7.86 (d, $J = 7.55$ Hz, 1H), 7.63 (d, $J = 2.26$ Hz, 1H), 7.50–7.55 (m, 2H), 7.42 (dt, $J = 8.31$, 1.51 Hz, 1H), 7.24–7.34 (m, 1H), 7.12 (dd, $J = 9.06$, 2.26 Hz, 1H), 2.33 (s, 3H, $COCH_3$). IR (KBr) (ν/cm^{-1}): 1755 (OC=O), 1446, 1222, 1158 (OC–O), 1012, 745. EI-MS: M^+ 226. Anal. Calcd for $C_{14}H_{10}O_3$: C, 74.33; H, 4.46. Found: C, 74.39; H, 4.43.

14. (*R*)-3-Acetyloxy-3-phenylpropanenitrile (entry 24): A white solid; mp 120–121 °C {lit.[15a] mp 121–124 °C}; $[\alpha]_D^{25}$ +70 (*c* 1.0, $CHCl_3$) {lit.[15a] $[\alpha]_D^{30}$ +71.9 (*c* 1.0, $CHCl_3$)}. Menthyl acetate (entry 25): $[\alpha]_D^{25}$ +79 (*c* 1.0, $CHCl_3$) {lit.[15b] $[\alpha]_D$ +80}. 1,2,3,4,5,6-Hexa-*O*-acetyl-D-mannitol (entry 28): A white crystalline solid; mp 121–122 °C {lit.[15c] mp 123–124 °C} $[\alpha]_D^{25}$ +26 (*c* 1.0, $CHCl_3$) {lit.[15c] $[\alpha]_D^{30}$ +27 (*c* 1.0, $CHCl_3$)}.

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