$Al(HSO_4)_3$ Catalyzed Acetylation and Formylation of Alcohols

F. Shirini,* M. A. Zolfigol,† M. Abedini, and P. Salehi‡

Department of Chemistry, College of Science, Guilan University, Rasht-Iran
†Department of Chemistry, College of Science, Bu-Ali Sina University, Hamadan-Iran
‡Department of Phytochemistry, Medicinal Plants Research Institute, Shahid Beheshti University, Evin, Tehran 1983963113, Iran
Received June 30, 2003

Key Words : $Al(HSO_4)_3$, Acetic acid, Acetylation, Formic acid, Formylation

Functional group protection and deprotection is important in synthetic organic chemistry.[1] Amongst protecting groups for alcohols, the esters are the most important with acetate being the simplest and easiest of all. Acetylation[2] is most commonly performed using[3,4] reagents such as Ac_2O or AcCl in the presence of base, procedures which are not environmentally friendly. The use of HOAc/mineral acid for acetylation suffers from the problem of reversibility. Later modifications involving the use of Lewis acids[5-10] in combination with Ac_2O is inherently wasteful since half of the every acid anhydride molecules lost as a carboxylic acid and the use of HOAc (as solvent)-lanthanide triflates[11-13] whilst efficient, is expensive.

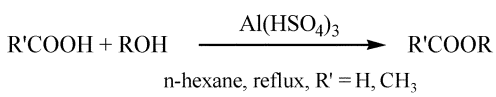
Formylation is a very important process in organic chemistry. Although various formylation reagents have been reported previously,[14-23] there are still serious limitations for the preparation of formates due to the drastic reaction conditions, the use of uncommon reagents, formation of undesirable or toxic by-products, the application of expensive catalysts for preparation of formylating agents and thermal instability of the reagents. Due to the instability of the anhydride and acid chloride of formic acid, formylation of alcohols by formic acid is an important synthetic reaction.

In continuation of our studies on the applications of inorganic acidic salts,[24,25] herein we wish to report an efficient method for the acetylation and formylation of alcohols with acetic and formic acids in the presence of a catalytic amounts of $Al(HSO_4)_3$. All reactions were performed under mild and heterogeneous conditions in *n*-hexane (Table 1, Scheme 1).

The acetylation of alcohols with acetic acid (1 mol equiv.) was performed in the presence of a catalytic amounts of $Al(HSO_4)_3$ in refluxing n-hexane to produce the desired esters in good to high yields (Table 1). Benzylic alcohols carrying both electron- withdrawing and electron-releasing groups and aliphatic alcohols were acetylated without formation of any side products with 0.1 mol equiv. of catalyst. We have observed that $Al(HSO_4)_3$ can bring about the acetylation of (−)-menthol with high yield and retention of the configuration with acetic acid in refluxing *n*-hexane (Table 1, entry 13).

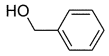
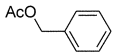
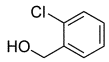
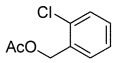
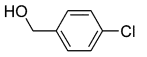
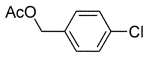
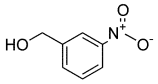
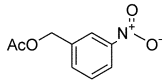
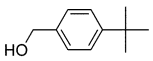
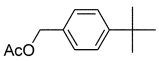
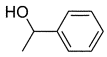
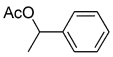
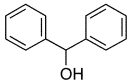
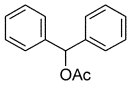
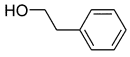
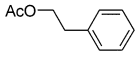
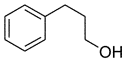
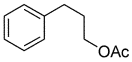
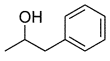
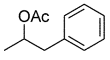
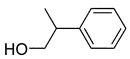
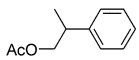
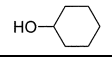
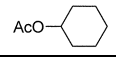
The formylation of alcohols in *n*-hexane, using formic acid (1 mol equiv.) can be performed at room temperature in the presence of 0.3 mol equiv. of $Al(HSO_4)_3$ with good to high yields (Table 1).

In addition, we have found that $Al(HSO_4)_3$, can be reused several times without loss of activity, simply by filtering the catalyst, washing with dichloromethane and acetone, drying and immediately reusing. The yield of benzyl acetate from the acetylation of benzyl alcohol promoted by the recovered



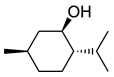
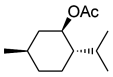
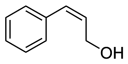
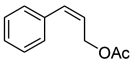
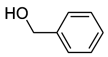
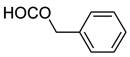
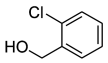
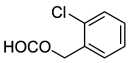
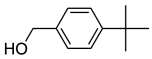
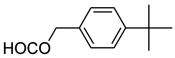
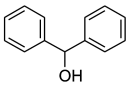
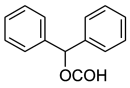
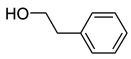
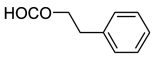
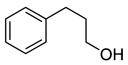
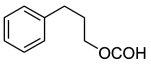
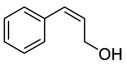
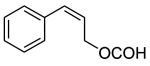
Scheme 1

Table 1. Acetyaltion[a] and formylation[b] of alcohols in the presence of $Al(HSO_4)_3$

Entry	Substrate	AcOH/ HCO_2H	Product	Time (h)	Yield %[c]
1		AcOH		0.5	92
2		AcOH		2.5	80
3		AcOH		3.5	90
4		AcOH		3.7	92
5		AcOH		0.33	85
6		AcOH		0.42	90
7		AcOH		2.5	80
8		AcOH		0.25	93
9		AcOH		0.33	90
10		AcOH		3.2	75
11		AcOH		0.67	90
12		AcOH		1	80

*To whom correspondence should be addressed. e-mail: shirini @guilan.ac.ir; Fax: +98-131-3220066

Table 1. Continued

Entry	Substrate	AcOH/ HCO_2H	Product	Time (h)	Yield %[c]
13		AcOH		1.5	75
14		AcOH		2.5	80
15		AcOH		4.7	–[d]
16		HCO_2H		1	92
17		HCO_2H		2	75
18		HCO_2H		1	90
19		HCO_2H		2.5	80
20		HCO_2H		0.33	90
21		HCO_2H		0.5	85
22	Cholesterol	HCO_2H	Cholesterol formate	0.67	75
23		HCO_2H		3	–[d]

[a]Acetylation reactions were performed in the presence of 0.1 mmol of $Al(HSO_4)_3$ under reflux conditions. [b]Formylation reactions were performed in the presence of 0.3 mmol of $Al(HSO_4)_3$ at room temperature. [c]Isolate yield. [d]Mixture of products = Starting material + unidentified products.

catalyst for 3 times was 87%.

This methodology is not useful for the acetylation and formylation of allylic alcohols (Table 1, entries 15, 23).

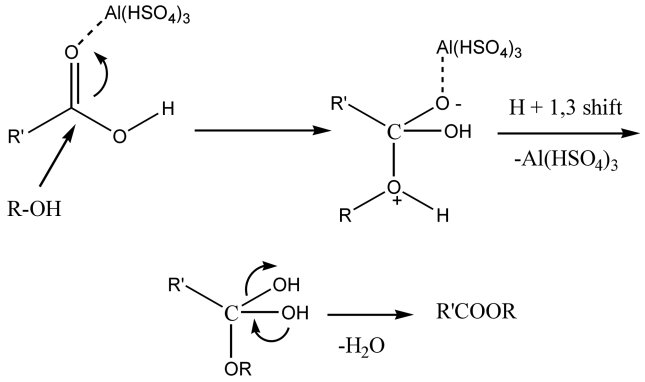
The actual mechanism of the reaction is not clear. However, the plausible role of the $Al(HSO_4)_3$ may be the activation of acyl and formyl moieties by coordination, triggering the acetylation and formylation process with concomitant regeneration of $Al(HSO_4)_3$, followed by the loss of water (Scheme 2).

In order to show the ability of this method we have compared some of the results with some of those reported in the literature (Table 2).[26,27]

In conclusion, we have shown that $Al(HSO_4)_3$ is a good reagent for acetylation and formylation of a variety of alcohols under mild reaction conditions. The reactions are clean and the products yields are good to high and the procedure is easy.

Experimental Section

General. Chemicals were purchased from Merck, Fluka, BDH and Aldrich Chemical Companies. Products were separated and purified by different chromatography techniques, and were identified by the comparison of their mp, bp, IR, NMR and refractive index with those reported for the authentic samples.[28-30] All yields refer to the isolated products. The purity determination of the substrates and reaction monitoring were accomplished by TLC on silica gel polygram SILG/UV 254 plates. Column chromatography was carried out on Merck kisselgel 60H.



Scheme 2

Table 2. Comparison of some of the results obtained by the acetylation and formylation in the presence of $Al(HSO_4)_3$ (1), with some of those reported by $AcOH/Cu(OTf)_2$ (2)[26] and chloral/K_2CO_3/acetone (3)[27]

Entry	Product	(t/h) (Yield%)		
		(1)	(2)	(3)
1	$PhCH_2OAc$	(0.5)(92)	(8)(94)	–
2	$PhCH(CH_3)OAc$	(0.42)(90)	(14)(94)	–
3	$PhCH_2OCHO$	(1)(92)	–	(4.5)(62)

Preparation of $Al(HSO_4)_3$. A 500 mL suction flask was equipped with a constant pressure dropping funnel. A gas outlet was connected to a vacuum system through an absorbing solution (water) and an alkali trap. Anhydrous aluminum chloride (66.7 g, 0.5 mol) was charged into the flask and concentrated sulfuric acid (147.1 g, 1.5 mol) was added dropwise over a period of 40 min at room temperature. HCl gas was evolved immediately. After completion of the addition of the H_2SO_4, the mixture was shaken for 30 min, meanwhile, the residual HCl was exhausted by suction. A white solid material was thus obtained (158.5 g). $Al(HSO_4)_3$ was characterized by the determination of its H^+ content by titration with NaOH (Calcd 0.95%, Found 0.96%) and SO_4^- by precipitation with Ba^{2+} (Calcd 90.57%, Found 09.48%). Al^{3+} was determined by two methods; conversion to Al_2O_3 (Calcd 8.48%, Found 8.31%) and spectrophotometric determination by complex formation with aluminon (Calcd 8.48%, Found 8.38%).[31]

General procedure for acetylation and formylation of alcohols using acetic acid and formic acids. A mixture of the substrate (1 mmol), acid (1 mmol) and $Al(HSO_4)_3$ (0.1-0.3 mmol) in *n*-hexane (5 mL) was stirred at room temperature or under reflux conditions for the specified time (Table). The reaction was monitored by TLC. After completion of the reaction, the mixture was filtered and the solid residue was washed with dichloromethane (10 mL). Evaporation of

the solvent followed by column chromatography on silica gel gave the corresponding esters from good to high yields.

Acknowledgement. We are thankful to Guilan University Research Council for the partial support of this work.

References

1. Greene, T. W.; Wuts, P. G. *Protective Group s in Organic Synthesis*, 3rd ed.; John Wiley & Sons Inc.: New York, 1991.
2. Haslam, E. *Tetrahedron* **1980**, *36*, 2409.
3. Muzler, J. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.: Oxford: Pergamon Press: 1991; Vol. 6, p 323.
4. Trost, B. M. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259.
5. Izumi, J.; Shiina, I.; Mukaiyama, T. *Chem. Lett.* **1995**, 141.
6. Vedejs, E.; Daugulis, J. *J. Org. Chem.* **1996**, *61*, 5702.
7. Iranpoor, N.; Firouzabadi, H.; Zolfigol, M. A. *Synth. Commun*. **1998**, *28*, 1923.
8. Chandrasekahar, S.; Ramachander, T.; Takhi, M. *Tetrahedron Lett*. **1998**, *39*, 3263.
9. Ganesam, B.; Small, V. R., Jr. *J. Org. Chem.* **1974**, *39*, 3728.
10. Tyryshkin, N. I.; Vedernikov, A. N.; Solomonov, B. N.; Garifzyanova, G. G. *J. Gen. Chem. USSR* **1992**, *62*, 303.
11. Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H. *J. Org. Chem.* **1996**, *61*, 4560.
12. Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H. *Synlett* **1996**, 265.
13. Barrett, A. G. M.; Broddock, C. D. *J. Chem. Soc., Chem. Commun*. **1997**, 351.
14. Ringold, H. J.; Loeken, B.; Rosenkranz, G.; Sondheimer, F. *J. Am. Chem. Soc*. **1956**, *76*, 816.
15. McOmie, J. F. W. *Protective Groups in Organic Chemistry*; Plenum: London, 1973; p 111.
16. Caputo, R.; Ferreri, C.; Palumbo, G. *Synth. Commun*. **1987**, *17*, 1629.
17. Barluenga, J.; Campos, P. J.; Gonzalez-Nunez, E.; Asensio, G. *Synthesis* **1985**, 425.
18. Fernandez, I.; garica, B.; Munoz, S.; Pedro, J. R.; Salud, R. *Synlett* **1993**, 489.
19. Katritzky, A. R.; Chang, H.-X.; Yang, B. *Synthesis* **1995**, 503.
20. Gramani, J. C.; Remuson, R. *Synthesis* **1982**, 264.
21. Neveux, M.; Bruneau, C.; Dixneuf, P. H. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1197.
22. Staab, H. A.; Polenski, B. *Liebigs Ann. Chem.* **1962**, *655*, 95.
23. Effenbergger, F.; Muck, A. O.; Bessey, E. *Chem. Ber.* **1980**, *113*, 2086.
24. Shirini, F.; Zolfigol, M. A.; Mallakpour, B.; Mallakpour, S. E.; Hajipour, A. R. *Aust. J. Chem.* **2001**, *54*, 405.
25. Shirini, F.; Zolfigol, M. A.; Mallakpour, B.; Mallakpour, S. E.; Hajipour, A. R.; Mohammadpour-Baltork, I. *Tetrahedron Lett.* **2002**, *43*, 1555.
26. Chandra, K. L.; Saravanan, P.; Singh, R. K.; Singh, V. K. *Tetrahedron* **2002**, *58*, 1369.
27. Ram, R. N.; Meher, N. K. *Tetrahedron* **2002**, *58*, 2997.
28. Aldrich Catalogue, *Handbook of Fine Chemicals*; 1990-1991.
29. *CRC Handbook of Chemistry and Physics*, 54th ed.; CRC Press: Boca Raton, 1973.
30. Bilestine *Handbook of Organic Chemistry*, 4th ed.; Springer: Berlin, 1998.
31. Vogel, A. I. *Quqntitative Inorganic Analysis*; Longman: London, 1972; pp 462, 472, 792.