An extremely fast and efficient acylation reaction of alcohols with acid anhydrides in the presence of trimethylsilyl trifluoromethanesulfonate as catalyst

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Alcohols are converted to esters in a fast, clean and efficient reaction with acid anhydrides in the presence of trimethylsilyl trifluoromethanesulfonate.

Trimethylsilyl trifluoromethanesulfonate (TMSOTf) in the presence of acetic anhydride has been used for the selective cleavage of the ring carbon–oxygen bond of methyl β-D-glycopyranosides, and for the replacement of the anomeric methoxy group of methyl α-D-pyranosides by an acetoxy group with concomitant peracetylation of the free hydroxy groups.[1,2] This methodology has been subsequently extended by Fraser-Reid to the acetolysis of 1,6-anhydro sugars in acetic anhydride using triethylsilyl trifluoromethanesulfonate as catalyst.[3] During our studies of the squalestatins, the fungal metabolites which are potent inhibitors of squalene synthase,[4] we attempted the cleavage of the ketal moiety of the dimethyl ester **1** with Ac_2O–TMSOTf. No cleavage of the ketal group was observed; however, to our astonishment, a clean and extremely fast conversion to the diacetate **2** had occurred. Considering the complexity of the substrate and the fact that the reaction was over in 5 min at 0 °C, whereas the analogous reaction catalysed by 4-(dimethylamino)pyridine (DMAP) required several hours at 20 °C to go to completion, we decided to exploit the potential of this new methodology for the acylation of a variety of alcohols.

Treatment of the primary alcohols octadecan-1-ol **3** and 3-phenylpropan-1-ol **4** with Ac_2O (1.5 equiv.) and TMSOTf (2 mol%) in CH_2Cl_2 at 0 °C provided the corresponding acetate esters **5** and **6** in quantitative yield in 30 s! (Table 1, entries 2 and 3).

Treatment of the secondary alcohols 3β-cholestanol **7** and 3β-cholesterol **8** with Ac_2O (1.5 equiv.) and TMSOTf (2 mol%) in CH_2Cl_2 at 20 °C provided the corresponding acetates **9** and **10** in 2 min and in excellent yields (entries 4 and 5). Similarly high yields were obtained with (+)-(1*S*,2*R*,5*S*)-menthol **11** and (*S*)-1-phenylethanol **12** to provide the corresponding acetates **13** and **14** respectively (entries 6 and 7). Furthermore, fluocinolone acetonide **15** possessing a primary and a hindered axial secondary alcohol group was acetylated within 30 min to give the diacetate **16** in 99% yield (entry 8). Moreover, ergocalciferol **17** was acetylated in 5 min to give the acetate **18** (entry 9).

Tertiary alcohols are also cleanly, efficiently and rapidly converted using 2 mol% TMSOTf and Ac_2O in CH_2Cl_2. Thus, treatment of 3-methylpent-1-yn-3-ol **19** gave the acetate **20** (>80%), whereas the squalestatine derivative **21** provided diacetate **22** (98%) (entries 10 and 11).

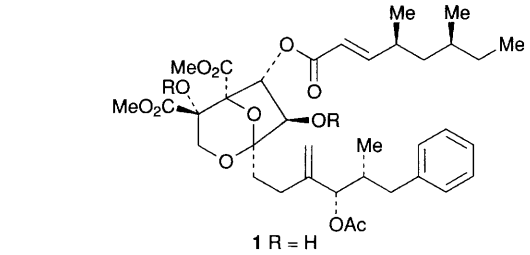
Finally, the acylation of menthol with acid anhydrides other than acetic was examined. Thus, (+)-menthol **11** was reacted with propionic, isobutyric and pivalic anhydrides to give the corresponding esters **23**, **24** and **25** respectively (entries 12–14) in excellent yields. Finally, acylation of diol **26** possessing the hindered 11β- and 17α-hydroxy groups with propionic anhydride (entry 15) gave the 17β-mixed anhydride of the dipropionate ester **27** in 94% yield, which upon ammonolysis gave **27** in 55% yield.

In conclusion, we have described a mild, highly efficient and extremely fast acylation procedure for a variety of functionalised alcohols using a catalytic amount of TMSOTf and acid anhydrides. This method is much faster than the now standard method of Steglich[5] utilising DMAP. Furthermore our method is very clean, and chromatography is not necessary, as all the by-products are water soluble and are removed upon aqueous work-up. Recent procedures for the acylation of alcohols by acid anhydrides include the tributylphosphine- catalysed method of Vedejs,[6] and the Lewis acid-catalysed methods of Mukaiyama.[7,8] Mukaiyama has also reported a novel esterification of carboxylic acids and alcohols in the presence of octamethylcyclotetrasiloxane and a catalytic amount of titanium(IV) chloride tris(trifluoromethanesulfonate).[9] Very recently a procedure similar to ours but utilising a catalytic amount of scandium trifluoromethanesulfonate as Lewis acid instead of TMSOTf has been described by Yamamoto.[10] The cost of TMSOTf, however, is a fraction of that of scandium trifluoromethanesulfonate, which makes the current procedure very attractive indeed.

Table 1 Acylation of alcohols with acid anhydrides in the presence of TMSOTf[a]

Entry	Alcohol	$(RCO)_2O$ (equiv.)	Product	TMSOTf (mol%)	*T*/°C	*t*/min	Yield (%)
1	**1**	Ac_2O (solvent)	**2**	3	0	5	95
2	**3**	Ac_2O (1.5)	**5**	2	0	0.5	100
3	**4**	Ac_2O (1.5)	**6**	2	0	0.5	100
4	**7**	Ac_2O (1.5)	**9**	2	20	2	98
5	**8**	Ac_2O (1.5)	**10**	2	20	2	88
6	**11**	Ac_2O (1.5)	**13**	2	0	5	95
7	**12**	Ac_2O (1.5)	**14**	2	0	5	95
8	**15**	Ac_2O (6)	**16**	4	20	30	99
9	**17**	Ac_2O (3)	**18**	2	0	5	71
10	**19**	Ac_2O (2)	**20**	2	0	60	>80
11	**21**	Ac_2O (solvent)	**22**	3	0	5	98
12	**11**	$(EtCO)_2O$ (3)	**23**	2	20	10	91
13	**11**	$(Pr^iCO)_2O$ (3)	**24**	2	20	10	91
14	**11**	$(Bu^tCO)_2O$ (3)	**25**	2	20	10	95
15	**26**	$(EtCO)_2O$ (9)	**27**	2	20	120	55

[a] Typical experimental procedure. A solution of alcohol (1 mmol) in CH_2Cl_2 (2 cm^3) was treated with acetic anhydride (0.14 cm^3, 1.5 mmol) at 0 °C, followed by a CH_2Cl_2 solution of trimethylsilyl trifluoromethanesulfonate (1 mol dm^{-3}, 0.02 cm^3). The reaction upon completion (TLC) is treated with saturated aq. $NaHCO_3$, and the aqueous phase was extracted with CH_2Cl_2. The organic extracts were washed with aq. $NaHCO_3$ (× 3) and water, dried and the solvent evaporated. Generally, the products are very clean and do not require any further purification, unless a large excess of anhydride was used, in which case percolation through silica gel removed any trace of anhydride.



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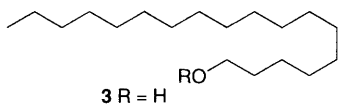

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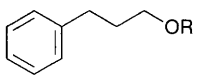

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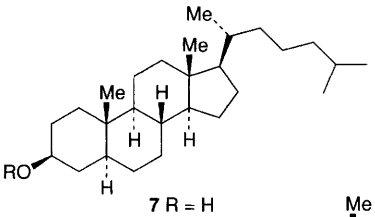

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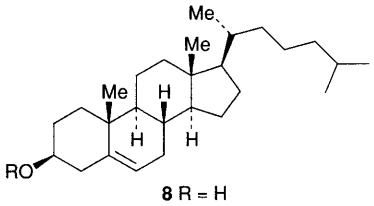

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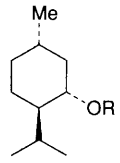

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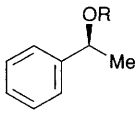

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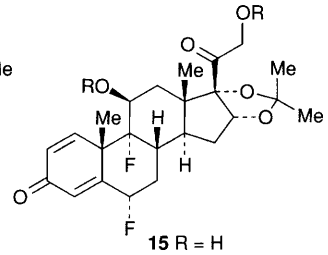

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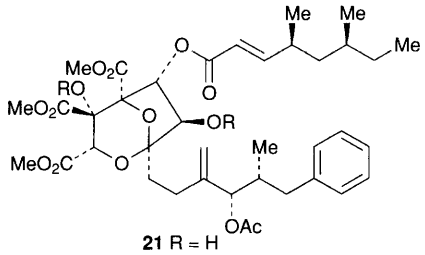

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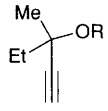

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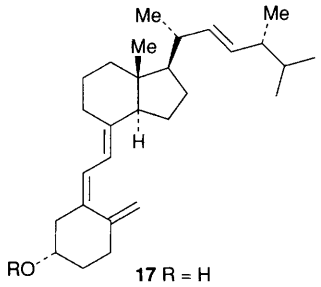

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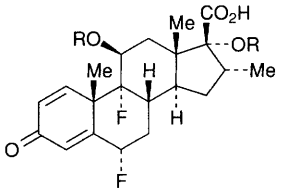

26 R = H
27 R = EtCO

References

1 P. Angibeaud and J.-P. Utille, *J. Chem. Soc., Perkin Trans. 1*, 1990, 1490.
2 P. Angibeaud, C. Bosso and J.-P. Utille, *Carbohydr. Res.*, 1990, **198**, 403.
3 M. Zottola, V. Rao and B. Fraser-Reid, *J. Chem. Soc., Chem. Commun.*, 1991, 969.
4 N. S. Watson and P. A. Procopiou, *Squalene Synthase Inhibitors: Their Potential as Hypocholesterolaemic Agents*, in *Progress in Medicinal Chemistry*, ed. G. P. Ellis and D. K. Luscombe, Elsevier, Amsterdam, 1996, vol. 33, ch. 7, pp. 331–378.
5 G. Höfle, W. Steglich and H. Vorbrüggen, *Angew. Chem., Int. Ed. Engl.*, 1978, **17**, 569.
6 E. Vedejs, N. S. Bennett, L. M. Conn, S. T. Diver, M. Gingras, S. Lin, P. A. Oliver and M. J. Peterson, *J. Org. Chem.*, 1993, **58**, 7286.
7 T. Mukaiyama, I. Shiina and M. Miyashita, *Chem. Lett.*, 1992, 625.
8 I. Shiina, S. Miyoshi, M. Miyashita and T. Mukaiyama, *Chem. Lett.*, 1994, 515.
9 J. Izumi, I. Shiina and T. Mukaiyama, *Chem. Lett.*, 1995, 141.
10 K. Ishihara, M. Kubota, H. Kurihara and H. Yamamoto, *J. Org. Chem.*, 1996, **61**, 4560.

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