An Extremely Powerful Acylation Reaction of Alcohols with Acid Anhydrides Catalyzed by Trimethylsilyl Trifluoromethanesulfonate†

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Trimethylsilyl trifluoromethanesulfonate is an excellent catalyst for the acylation of alcohols with acid anhydrides. Highly functionalized primary, secondary, tertiary, and allylic alcohols, and phenols, were acylated cleanly and efficiently and in a fraction of the time used under the standard DMAP conditions.

Introduction

Esterification of alcohols using acid anhydrides in pyridine has been known and extensively used by organic chemists for nearly 100 years.[1] In 1969 Steglich and Höfle published the now standard method of catalyzing the acylation of alcohols by DMAP.[2] This was a significant advance over the use of pyridine or triethylamine alone, as DMAP caused an acylation rate increase of 10000-fold. A number of sterically hindered secondary and tertiary alcohols that were previously difficult to acylate could now be acylated with relative ease. Vedejs disclosed in 1993 the use of tributylphosphine as a catalyst for the acylation of base-sensitive alcohols.[3] In addition a number of Lewis acids are also known to catalyze the acylation of alcohols with acid anhydrides.[4−9] More recently Yamamoto has reported the use of scandium trifluoromethanesulfonate, $Sc(OTf)_3$, a commercially available and moisture stable Lewis acid, as an extremely active catalyst for the acylation of alcohols with acid anhydrides.[10] This method is truly catalytic in $Sc(OTf)_3$ (only 2 mol % or less is used) and is capable of acylating alcohols which are only slowly acylated by DMAP catalysis. We have recently reported in a preliminary communication that trimethylsilyl trifluoromethanesulfonate (TMSOTf) is an extremely powerful acylation catalyst.[11] Herein we disclose the functional group tolerance, solvent effects, and selectivity of this method, together with a comparison with Yamamoto's $Sc(OTf)_3$ method.

Table 1. Acylation of Alcohols with Acid Anhydrides in the Presence of TMSOTf

entry	alcohol	$(RCO)_2O$ (equiv) (solvent)[a]	product (ref)	TMSOTf (mol %)	temp (°C)	time min	yield (%)
1	**1a**	Ac_2O (1.5) (A)	**1b**[29]	2	0	0.5	100
2	**2a**	Ac_2O (1.5) (A)	**2b**[30]	2	0	0.5	100
3	**3a**	Ac_2O (1.5) (A)	**3b**	2	0	0.5	100
4	**4a**	Ac_2O (1.5) (A)	**4b**[31]	2	20	2	96
5	**5a**	Ac_2O (1.5) (A)	**5b**[32]	2	20	2	88
6	**6a**	Ac_2O (1.5) (A)	**6b**[33]	2	0	5	95
7	**6a**	$(EtCO)_2O$ (3) (A)	**6c**[34]	2	20	10	91
8	**6a**	$(^iPrCO)_2O$ (3) (A)	**6d**[10b]	2	20	10	91
9	**6a**	$(^tBuCO)_2O$ (3) (A)	**6e**[35]	2	20	10	95
10	**6a**	succinic (1.1) (A)	**6f**[14,36]	2	20	30	88
11	**6a**	$(PhCO)_2O$ (1.5)(A)	**6g**[37]	2	20	92 h	96
12	**6a**	$(PhCO)_2O$(1.5) (A)	**6g**[37]	30	20	150	94
13	**7a**	Ac_2O (1.5) (A)	**7b**[38]	2	0	5	95
14	**8a**	Ac_2O (3) (A)	**8b**[39]	2	0	5	71
15	**9a**	Ac_2O (1.5) (C)	**9b**[40]	1	−15	5	100
16	**10**	Ac_2O (1.1) (A)	**12**[41]	2	20	5	100
17	**10**	Ac_2O (6) (A)	**11**	4	20	30	99
18	**13a**	Ac_2O (3.4) (A)	**12**	20	20	15	90
19	**14a**	Ac_2O (5) (solv)	**14b**[29]	5	−10	2	100
20	**16a**	Ac_2O (2) (A)	**16b**[42]	2	0	60	>80
21	**17a**	Ac_2O (solv)	**17b**[43]	3	0	5	95
22	**18a**	Ac_2O (solv)	**18b**[44]	3	0	5	98
23	**19a**	Ac_2O (8) (A)	**21**	10	20	75	97
24	**22**	$(EtCO)_2O$ (9) (A)	**23**[45]	2	20	120	55
25	**25a**	Ac_2O (2) (B)	**25b**[16]	2	20	15	87
26	**26a**	Ac_2O (2.5)(AB)	**26b**[46]	2	20	60	100
27	**29a**	Ac_2O (1.5) (A)	**29b**[47]	2	0	15	86
28	**30a**	Ac_2O (5) (C)	**30b**[48]	0.5	−10	10	100
29	**31a**	Ac_2O (5) (C)	**31b**[49]	0.5	−10	5	100
30	**32a**	Ac_2O (5) (solv)	**32b**[15]	0.5	−10	5	ND[b]
31	**34a**	Ac_2O (2) (A)	**34b**[50]	2	20	3	98
32	**34a**	$(PhCO)_2O$ (2) (A)	**34g**[10b]	10	20	60	90
33	**35**	Ac_2O (1) (A)	**37**[22,23]	2	20	84 h	88
34	**40a**	Ac_2O (1.5) (A)	**40b**[51]	1	0	5	96

[a] Solvents: A = CH_2Cl_2, B = MeCN, C = EtOAc. [b] ND: not determined.

Results and Discussion

Simple unfunctionalized alcohols such as octadecanol (**1a**), 3-phenylpropanol (**2a**), and 3-(4-bromophenyl)propanol[12] (**3a**) were investigated first (Table 1). Acetic anhydride (1.5 equiv) was added to a solution of the

† Dedicated to my great teacher, Sir Derek H. R. Barton, on the occasion of his 80th birthday.

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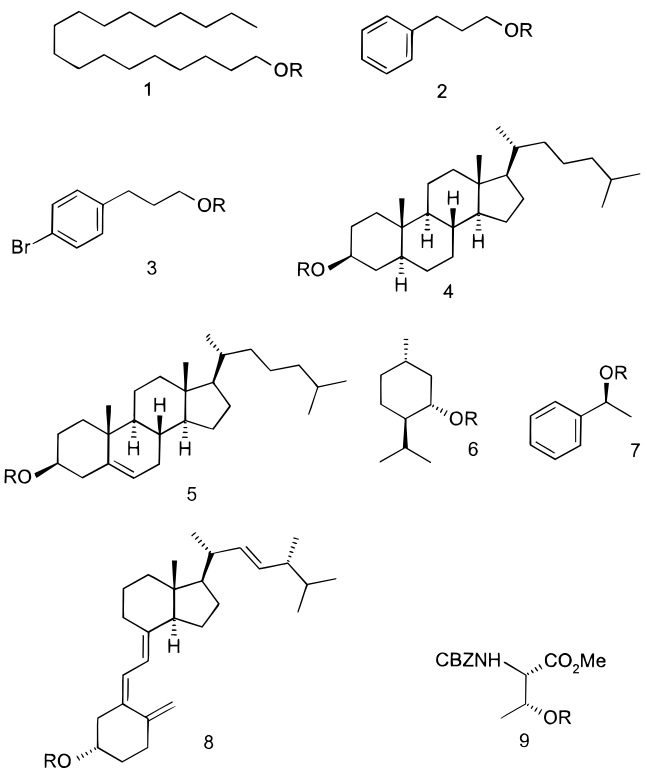
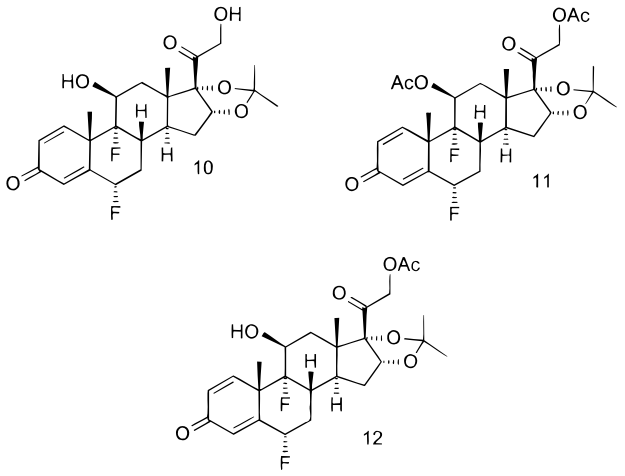
alcohol in CH_2Cl_2 at 0 °C, followed by 2 mol % TMSOTf, added as a freshly made 1 M solution in CH_2Cl_2. In all of these cases the alcohol was acetylated in less than 30 s and in quantitative yield! The secondary alcohols 5α-cholestan-3β-ol (**4a**), 3β-cholesterol (**5a**), (+)-(1*S*,2*R*,5*S*) menthol (**6a**), and (S)-1-phenylethanol (**7a**) were acetylated under the same conditions or at room temperature in excellent yields. The acetylation proceeded with



complete retention of configuration as evidenced by the absence of diastereoisomeric acetate products. The conjugated triene, ergocalciferol (**8a**) was acetylated in 71% yield without any isomerization of the sensitive triene system. Treatment of *N*-(benzyloxycarbonyl)-L-threonine methyl ester (**9a**) with 1.5 equiv of Ac_2O and TMSOTf (1 mol %) in EtOAc at −15 °C gave the acetate **9b** in quantitative yield without any acylation on nitrogen or cleavage of the CBZ group. The glucocorticoid fluocinolone acetonide (**10**) possesses two hydroxy groups, a primary hydroxyl at C21 and a secondary at C11. The primary hydroxy group is rapidly and selectively acetylated with Ac_2O in pyridine. The secondary 11β-hydroxy group, however, is axial and sterically hindered, because of 1,3-diaxial interactions with the two methyl groups at C10 and C13. Acetylation of **10** with excess Ac_2O in the presence of DMAP (0.1 equiv) gave the 11β,21-diacetate **11** after 8 h. When the reaction was carried out using 1.1 equiv of Ac_2O and 2 mol % TMSOTf, the 21-acetate **12** was produced within 5 min and in quantitative yield, indicating that selectivity between primary and secondary hydroxy groups can be achieved. The selective acetylation of the primary hydroxy group of **10** was repeated on a 22 mmol scale. Reaction of **10** with 6 equiv



of Ac_2O and 4 mol % TMSOTf gave the diacetate **11** in 30 min and 99% yield. Considering the complexity of the functional groups present in **10**, including the acid sensitive dienone, the rapidity and selectivity of this reaction are remarkable. The acetylation of fluocinolone acetonide with Ac_2O in the presence of $Sc(OTf)_3$ was also examined for comparison. Thus, in the presence of 4 equiv of Ac_2O and 0.6 mol % $Sc(OTf)_3$ acetylation of the primary hydroxy group took place within 0.5 h, without any trace of the diacetate, even though an excess of anhydride was present. After 20 h there was only 44% diacetate and 56% monoacetate **12**. Extra quantities of Ac_2O (4 equiv) and $Sc(OTf)_3$ (0.6 mol %) were added, and 2 h later the diacetate constituted 52% of the reaction mixture. The reaction went to completion after a total of 39 h; however, a pale orange coloration developed which was removed after recrystallizing the product twice from acetone−diethyl ether to give the diacetate **11** in 32% yield. These results demonstrate that TMSOTf is a more powerful catalyst than $Sc(OTf)_3$. Acetylation of fluocinolone acetonide 21-mesylate[13] **13a** with 3.4 equiv of Ac_2O required a much higher amount of TMSOTf (0.2 equiv) than was usually necessary for the reaction to go to completion.

Tertiary alcohols such as *tert*-butyl alcohol or 1-methylcyclohexanol (**14a**) are not acetylated with Ac_2O in pyridine. Addition of DMAP, however, allows the reaction to proceed, but at a slow rate. Thus, **14a** requires 14 h to go to completion, and its acetate is obtained in 86% yield.[2a] Yamamoto reported an enhancement of the acetylation rate of the same alcohol using $Sc(OTf)_3$.[10b] Thus, at − 20 °C and with 5 equiv of Ac_2O and 1 mol % $Sc(OTf)_3$ 91% of acetate **14b** was obtained after 5 h, together with 9% 1-methylcyclohexene (**15**).[10b] In contrast, reaction of **14a** with 5 equiv of Ac_2O and 5 mol % TMSOTf was complete within 2 min at −10 °C and in quantitative yield, and no olefin **15** was detected. 3-Methylpent-1-yn-3-ol (**16a**) with 2 equiv of Ac_2O at 0 °C gave the corresponding acetate **16b** in >80% yield. The highly functionalized squalestatin derivatives **17a** and **18a** were converted to their respective 4,7-diacetates in quantitative yields, by performing the reaction in Ac_2O as solvent, and using 3 mol % TMSOTf at 0 °C. The analogous reaction catalyzed by DMAP requires 14 h to go to completion. The glucocorticoid **19a** possessing the 11β-hydroxy group and the extremely sterically hindered 17α-

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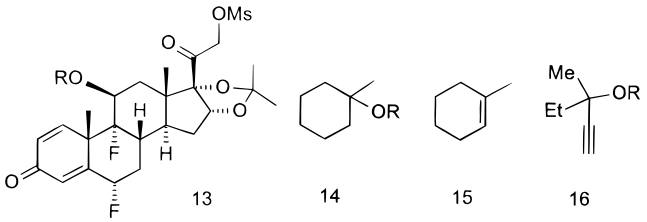

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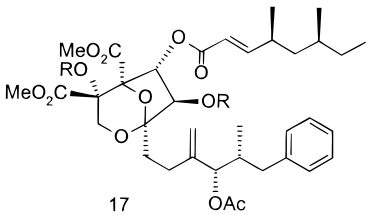

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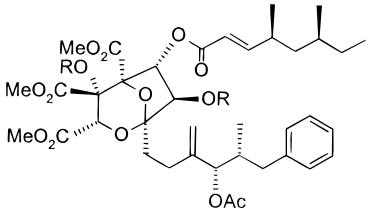

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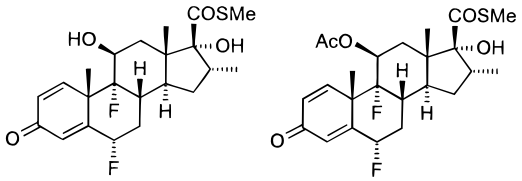
hydroxy group requires 7 h to form the 11β-acetate **20** and more than 5 days to form the diacetate **21** using the standard DMAP conditions. In contrast, TMSOTf (10 mol %) catalyzes this reaction within 1.25 h and in excellent yield (97%).



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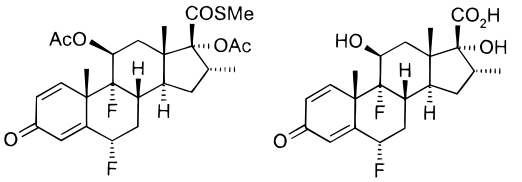

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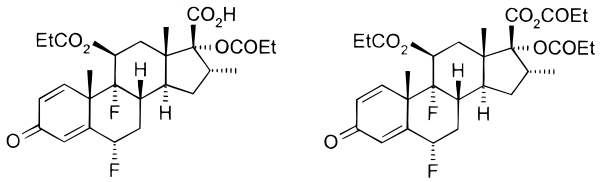

23 24

Menthol (**6a**) was acylated with other acid anhydrides in order to examine the generality of this procedure, and the results are summarized in Table 1. All acid anhydrides except benzoic behaved similarly and reacted very rapidly to give esters **6b**−**g** in high yields (88−96%). In the case of succinic anhydride the DMAP method is reported[14] to require 24 h to go to completion, whereas the TMSOTf method required 0.5 h. Furthermore, DMAP does not catalyze the acylation of sterically hindered alcohols such as *tert*-butyl alcohol with pivalic anhydride;[15] however, TMSOTf takes only 10 min to produce **6e** in 95% yield. In the case of benzoic anhydride (1.5 equiv) the reaction was relatively slow at 20 °C (92 h, 96% yield) using 2 mol % TMSOTf. The reaction was speeded up, however, by using more catalyst. Thus, complete reaction (94% yield) was obtained within 2.5 h when 30 mol % TMSOTf was used. This result is in agreement with the data reported by Yamamoto[10b] using $Sc(OTf)_3$. The glucocorticoid **22** was acylated with propionic anhydride (9 equiv) and TMSOTf (2 mol %) in CH_2Cl_2 to give two products by TLC. On treatment with aqueous ammonia the less polar product disappeared and the 11β,17α-dipropionate-17β-carboxylic acid **23** was obtained (55%). The less polar product was assumed to be the 17β-mixed anhydride **24**.

The acetylation of allylic alcohols under acid-catalyzed conditions is always problematical because of allylic rearrangement, in addition to the formation of elimination products. Yamamoto[10b] also observed some of these side reactions with $Sc(OTf)_3$. Thus, we were interested to explore the behavior of TMSOTf in the acetylation of these alcohols. The sterically hindered primary alcohol (1R)-(−)-myrtenol (**25a**) is reported to require overnight heating in refluxing Ac_2O and pyridine.[16] However, treatment of **25a** with 2 equiv of Ac_2O in CH_3CN at 20 °C for 15 min gave the acetate **25b** in 87% yield. The esterification of cephalosporin alcohols such as **26a** is not trivial. Under the classical esterification conditions using base catalysis, inseparable mixtures of Δ^2 and Δ^3 cephalosporin esters **27** and **26b** are obtained[17] which require an oxidation−reduction sequence to put the double bond back into conjugation with the ester group.[18] Alternatively, under acid catalysis, the lactone **28** is formed.[17,19] However, treatment of **26a** with 2.5 equiv of Ac_2O in CH_2Cl_2−MeCN and 2 mol % TMSOTf at 20 °C gave cephalothin diphenylmethyl ester **26b** in quantitative yield, without any trace of lactonization or deconjugation. The cyclic allylic alcohol **29a** gave the cyclohexenyl acetate **29b** in 86% yield. The acid sensitive cinnamyl alcohol **30a** under the usual conditions of TMSOTf-catalyzed acetylation gave a mixture of products. However, when the reaction was repeated using 5 equiv of Ac_2O and 0.005 equiv of TMSOTf at −10 °C in EtOAc, it gave, after 10 min, a quantitative yield of the primary allylic acetate, without any trace of products arising from allylic rearrangement. Similar results were obtained with 4-bromocinnamyl alcohol[20] **31a**. Attempted acetylation of the even more acid labile tertiary allylic alcohol linalool (**32a**)

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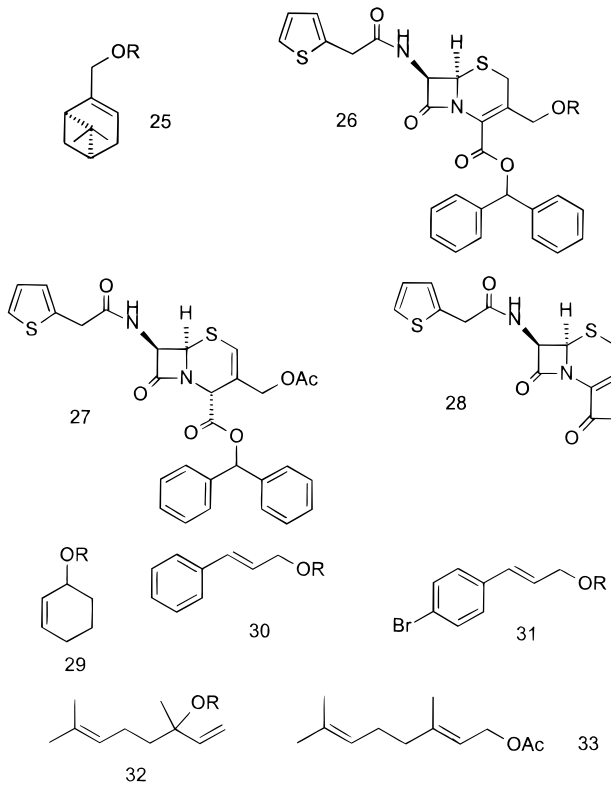
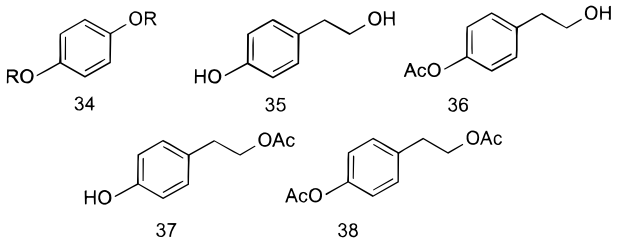


with Ac_2O (5 equiv used as solvent) and TMSOTf (0.5 mol %) at 0 °C gave predominantly geranyl acetate **33**, whereas at −20 °C there was no reaction at all. However, at −10 °C an exothermic reaction took place (temperature rose to +1 °C before it fell back to −10 °C). The reaction was quenched after 5 min with the addition of ethanol, and the product composition was examined by NMR. This indicated that a mixture had formed which contained linalyl acetate (**32b**) and starting material (**32a**) but no **33**. In contrast Yamamoto reported that acetylation of linalool with Ac_2O as solvent and 2 mol % $Sc(OTf)_3$ at −20 °C for 2.5 h gave linalyl acetate (**32b**) (68%) and geranyl acetate (**33**) (8%).[10b]

In addition to the esterification of aliphatic alcohols we examined the acylation of phenols. Thus, 1,4-hydroquinone (**34a**) reacted with 2 equiv of Ac_2O and 2 mol % TMSOTf to give the diacetate **34b** in 98% yield in an exothermic reaction. Similarly, reaction with benzoic anhydride (2 equiv) gave the dibenzoate **34g** in 90% yield. It is noteworthy that acylation of phenols with benzoic anhydride is much faster than the analogous reaction with aliphatic alcohols.

In general, phenolic alcohols are predominantly acylated in the presence of aliphatic alcohols under basic conditions. This is attributable to the greater nucleophilicity of phenols under basic conditions, where the phenol is expected to be ionized. A reversal of chemoselectivity was reported by Yamamoto for the $Sc(OTf)_3$-catalyzed esterification.[10b] It was therefore of interest to investigate the chemoselectivity of our TMSOTf-catalyzed esterification. The acetylation of 2-(4-hydroxyphenyl)ethanol (**35**) using 1 equiv of Ac_2O and pyridine is reported[21] to give mainly 2-(4-acetoxyphenyl)ethanol **36**. We repeated this reaction using 1 equiv of Ac_2O, 1.4 equiv of triethylamine, DMAP (0.1 equiv) in CH_2Cl_2 at 0



°C and we obtained a mixture which after chromatography gave the diacetate **38** (22%), 2-(4-acetoxyphenyl)-ethanol (**36**) (39%), 2-(4-hydroxyphenyl)ethyl acetate (**37**) (3%). When the reaction was repeated using Ac_2O and TMSOTf (2.5mol %) in CH_2Cl_2 at 20 °C, after 1 h HPLC indicated a mixture in the ratio of 22:48:30 (**35**:**37**:**38**). After stirring for 21 h, the starting material (**35**) was consumed, and the mixture of products was 88:12 monoacetate (**37**):diacetate (**38**), and after a total of 3.5 days the ratio improved further to 93:7. Clearly, an equilibrium reaction was set up which eventually provided the thermodynamic product with the acetate group ending up on the alcohol group. This is a significant result as alternative methods for the preparation of **37** involve a protection−deprotection sequence[22] for the phenolic group of **35**, or a selective lipase-mediated deacylation[23] of the phenolic acetate of diacetate **38**. Direct methods involve the use of EtOAc in the presence of Woelm, neutral, chromatographic alumina (10 g/mmol),[24] or the use of 3-acetyl-2-oxazolone in the presence of zirconium acetylacetonate.[25]

The effect of solvents on the acetylation of the steroidal alcohol **13a** with Ac_2O (3.5 equiv) and TMSOTf (0.1 equiv) at 20 °C over a period of 3 h was investigated by examination of the reaction mixture by HPLC. The results are summarized in Table 2. Acetone and methyl isobutyl ketone gave very dark colored solutions, presumably enolization of the carbonyl group had occurred, which gave rise to aldol condensation products. THF is known[26] to react with TMSOTf and gave a viscous polymeric material. Clearly, the best solvents for this reaction are acetonitrile, dioxane, EtOAc, cyclohexane, and toluene. Unfortunately, for the majority of examples mentioned in this study we had used CH_2Cl_2, which gave a slower rate of acylation than the solvents indicated above. It is interesting to note that the $Sc(OTf)_3$-catalyzed acetylation of 2-octanol proceeded faster in acetonitrile and very slowly in chloroform.[10b]

TMSOTf in the presence of Ac_2O 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.[27] For this reason we were interested to find out whether a chemoselective acetyla-

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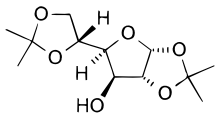
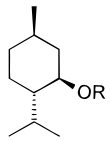
Table 2. Effect of Solvent on Acylation of Alcohol 13a by Ac_2O (3.5 equiv) and TMSOTf (0.1 equiv) at 20 °C

entry	solvent	13b (%)	entry	solvent	13b (%)
1	cyclohexane	91	7	acetone	21
2	toluene	89	8	dioxane	95
3	Et_2O	27	9	MeCN	95
4	CH_2Cl_2	57	10	methyl isobutyl ketone	42
5	$CHCl_3$	67	11	$^iPr_2O$	0
6	EtOAc	91	12	THF	0

tion would occur rather than reaction at the acetal center. We investigated the acetylation of diacetone glucose **39** in CH_2Cl_2 in the presence of 1 equiv of Ac_2O and 2 mol % TMSOTf at 0 °C. Unfortunately, a mixture was formed indicating that reaction had taken place at both the acetal and hydroxy groups.



39



40

Finally, we speculated about the mechanism of our esterification procedure and in particular we were interested to find out whether the reaction was catalyzed by TMSOTf itself or by trifluoromethanesulfonic acid (TfOH) arising by hydrolysis of TMSOTf. When (−)-(1*R*,2*S*,5*R*)-menthol (**40a**) was treated with Ac_2O (1.5 equiv) and TfOH (2 mol %) in CH_2Cl_2 at 0 °C there was only a trace of product (<1%). However, when the same reaction mixture was treated with 1 mol % TMSOTf a rapid reaction occurred, and the acetate **40b** was obtained in 96%, indicating that the active catalyst was indeed TMSOTf. The mechanism of this reaction was not investigated further. However, a plausible reaction mechanism is presented in Scheme 1. The alcohol reacts

Scheme 1

$$R^1OH + TMSOTf \rightarrow R^1OTMS + TfOH$$

$$(R^2CO)_2O + TfOH \rightarrow R^2COOTf + R^2CO_2H$$

$$R^1OTMS + R^2COOTf \rightarrow R^2COOR^1 + TMSOTf$$

with TMSOTf to form the TMS-ether and TfOH. The latter reacts with the anhydride to form the active acylating species, which could be a mixed anhydride or the acylium ion. This species then reacts with the TMS-ether to form the ester and regenerate TMSOTf which reenters the catalytic cycle. The silicon obviously plays a crucial role in the last step which may involve a pentacoordinate silicon species which facilitates the remarkable reaction rate.

Mukaiyama has described the use of catalytic amounts of Lewis acids, such as $Sn(OTf)_2$, $TiCl_4$, and $AgClO_4$, for the preparation of esters from equimolar amounts of silyl carboxylates and silyl ethers.[7] Acetylium ion, derived from trimethylsilyl acetate, was detected by NMR spectroscopy in that study. The observed difference in reactivity of benzoic anhydride in Yamamoto's[10b] and our own studies is compatible with the greater stability of alkyl- vs aromatic-substituted acylium ions.[28]

Conclusion

We have demonstrated that TMSOTf is an excellent catalyst for the fast and efficient acylation of alcohols and phenols with acid anhydrides. The reaction is clean, and chromatography is not required. TMSOTf is a far more powerful catalyst than DMAP and also more powerful than $Sc(OTf)_3$. Furthermore, the cost of TMSOTf is a fraction of that of $Sc(OTf)_3$. It is cheaper to use TMSOTf than DMAP as a catalyst since 2 mol % or less TMSOTf is normally used, whereas at least 10 mol % DMAP plus at least 1 equiv of tertiary base are generally used in the classical Steglich esterification. The reaction is extremely fast, selective, and mild. The following functional groups are well tolerated: acetylene, allylic ester, aromatic ring, carbamate, diene, enone, ester, α,β-unsaturated ester, ether, halide, ketal, ketone, nitrile, sulfonate ester, thioester and triene. The selectivity of acylation for a hydroxyphenol is for the alcohol group and is complementary to that of DMAP. Aliphatic and aromatic acid anhydrides work equally well; however, aromatic anhydrides require either longer reaction times or more catalyst. The best solvents are MeCN, EtOAc, dioxane, toluene, and cyclohexane. We have provided examples from a number of highly functionalized alcohols of pharmaceutical importance, which should make this new esterification procedure a very attractive alternative to established methodologies.

Experimental Section

TMSOTf was purchased from Aldrich and was stored under nitrogen in a flask stoppered with a rubber septum. TMSOTf stored in this way lasted for over a year, without any loss of its activity. It was used either neat for larger scale reactions, or as a freshly made 1 M solution in CH_2Cl_2 for smaller scale reactions. Organic solutions were dried over $MgSO_4$. Solvents were removed by rotary evaporation at or below 40 °C. TLC was conducted on Merck 0.25 mm Kieselgel F_{254} plates. Products were visualized under UV light and/or by staining with aqueous 1% $KMnO_4$ solution. Analytical HPLC was conducted on a Phenomenex Prodigy ODS-2 (15 cm × 0.46 cm column) eluting with 0.05% aqueous TFA−MeCN using a gradient (15 → 95% MeCN over 16 min) with a flow rate of 1.5 mL/min. NMR spectra were recorded on a Bruker AM250 or a DPX250. Filament-assisted thermospray positive ion mass spectrometry (TSMS) was performed on an HP Engine 5989A, and electrospray positive ion (ESMS) on a VG Autospec instrument.

General Procedure for the TMSOTf-Catalyzed Esterification Reaction. All the following compounds that do not have experimental details associated with them were prepared by the following typical experimental procedure:

A solution of alcohol (1 mmol) in CH_2Cl_2 (2 mL) was treated with acid anhydride (1.5 mmol) at 0 °C, followed by a CH_2Cl_2 solution of TMSOTf (1 M; 20 μL). The reaction upon completion (TLC or HPLC) was treated with saturated aqueous $NaHCO_3$, and the two phases were separated. In the cases where an excess of acid anhydride was used, the reaction was quenched with stoichiometric quantities of methanol, followed by washing with $NaHCO_3$. The organic extracts were washed with water and dried, and the solvent was evaporated. Generally, the products are very clean and do not require any further purification.

3-(4-Bromophenyl)propyl acetate (3b): IR (KBr) 1738, 1241 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.87−1.98 (m, 2H), 2.05 (s, 3H), 2.65 (t, J = 7 Hz, 2H), 4.07 (t, J = 7 Hz, 2H), 7.06 (d, J = 8 Hz, 2H), 7.40 (d, J = 8 Hz, 2H); TSMS *m/z* 274, 276 (M + NH_4)$^+$. Anal. Calcd for $C_{11}H_{13}BrO_2$: C, 51.38; H, 5.10. Found: C, 51.35; H, 5.14%.

6α,9α-Difluoro-11β,21-dihydroxy-16α,17α-(isopropylidenedioxy)-3,20-dioxopregnane-1,4-diene-11β,21-diyl di-

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acetate (11): ^{1}H NMR ($CDCl_3$) δ 0.84, 1.23, 1.38, 1.44, 2.14 and 2.16 (6s, 3H each), 4.73 (d, J = 18 Hz, 1H), 4.97 (d, J = 18 Hz, 1H), 5.01 (d, J = 5 Hz, 1H), 5.25 and 5.45 (2m, 1H), 5.49 (m, 1H), 6.39 (dd, J = 10 and 2 Hz, 1H), 6.45 (s, 1H), 6.79 (d, J = 10 Hz, 1H); TSMS m/z 537 $(M + H)^+$. Anal. Calcd for $C_{28}H_{34}F_2O_8$ C, 62.68; H, 6.39. Found: C, 62.86; H, 6.34%.

11β-(Acetyloxy)-6α,9α-difluoro-21-hydroxy-16α,17α-(isopropylidenedioxy)-3,20-dioxopregnane-1,4-diene-21-yl methanesulfonate (13b): IR (KBr) 1749, 1731, 1671 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.79, (s, 3H), 1.13 (s, 3H), 1.38 (s, 6H), 2.10 (s, 3H), 3.28 (s, 3H), 4.91 (m, 1H), 4.99 (d, J = 18 Hz, 1H), 5.27 (m, 1H), 5.35 (d, J = 18 Hz, 1H), 5.53 and 5.72 (2m, 1H), 6.14 (s, 1H), 6.35 (dd, J = 10 and 2 Hz, 1H), 6.83 (d, J = 10 Hz, 1H), 5.77 (CH_2Cl_2); TSMS m/z 573 $(M + H)^+$. Anal. Calcd for $C_{27}H_{34}F_2O_9S.0.33CH_2Cl_2$ C, 54.65; H, 5.82; S, 5.34. Found: C, 54.53; H, 5.80; S, 5.25%.

11β-(Acetyloxy)-6α,9α-difluoro-17α-hydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioic Acid, Methyl Ester (20). A solution of diol[45] **19** (213 mg, 0.5 mmol) in CH_2Cl_2 (2 mL), triethylamine (1.5 mL, 10.76 mmol), and Ac_2O (0.6 mL, 6.3 mmol) was treated with DMAP (9.1 mg, 0.075 mmol), and the mixture was stirred at 20 °C for 7 h. The reaction mixture was diluted with EtOAc, and 2 M HCl was added. The organic phase was washed with 2 M HCl, $NaHCO_3$, and brine, dried, and evaporated to dryness. The residue was recrystallized twice from MeOH to give **20** (49 mg, 21%) as white crystals: IR (KBr) 3484, 1744, 1731, 1681, 1667 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.96 (s and d, J = 7 Hz, 6H), 1.37 (s, 3H), 2.10 (s, 3H), 2.27 (s, 3H), 3.0−3.2 (m, 1H), 5.24 (m, 0.5 H), 5.37−5.49 (m, 1.5H), 6.37 (dd, J = 10 and 2 Hz, 1H), 6.42 (s, 1H), 6.75 (dd, J = 10 and 1 Hz, 1H); ESMS m/z 469 $(M + H)^+$ (30%), 936 $(2M + H)^+$ (100%). Anal. Calcd for $C_{24}H_{30}F_2O_5S$ C, 61.52; H, 6.45; S, 6.84. Found: C, 61.54; H, 6.66; S, 6.70%.

11β,17α-(Diacetyloxy)-6α,9α-difluoro-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioic acid, methyl ester (21): IR (KBr) 1746, 1672 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.94 (s, 3H), 1.02 (d, J = 7 Hz, 3H), 1.37 (s, 3H), 2.07 (s, 3H), 2.11 (s, 3H), 2.35 (s, 3H), 3.3−3.5 (m, 1H), 5.24 (m, 0.5H), 5.4−5.52 (m, 1.5 H), 6.38 (dd, J = 10 and 1 Hz, 1H), 6.45 (s, 1H), 6.79 (d, J = 10 Hz, 1H); TSMS m/z 511 $(M + H)^+$. Anal. Calcd for $C_{26}H_{32}F_2O_6S$ C, 61.16; H, 6.32; S, 6.28. Found: C, 60.99; H, 6.33; S, 6.23%.

6α,9α-Difluoro-16α-methyl-3-oxo-11β,17α-bis(propionyloxy)-androsta-1,4-diene-17β-carboxylic Acid (23). A mixture of the carboxylic acid[45] **22** (192 mg, 0.5 mmol) in CH_2Cl_2 (2 mL) and propionic anhydride (0.57 mL, 4.5 mmol) was treated at 20 °C with a solution of TMSOTf in CH_2Cl_2 (1 M; 20 μL), and the mixture was stirred for 2 h. The reaction mixture was diluted with CH_2Cl_2 and treated with aqueous concentrated ammonia for 5 min. The two phases were separated, and the organic solution was retreated with ammonia. TLC indicated removal of the less polar product and the formation of a polar product. The organic layer was washed with 2 M HCl, dried, and evaporated to a white solid (140 mg, 55%): ^{1}H NMR ($CDCl_3$) δ 0.94 (d, J = 7 Hz, 3H), 1.00 (s, 3H), 1.12 (t, J = 7 Hz, 6H), 1.37 (s, 3H), 3.32 (m, 1H), 5.26 and 5.45 (2m, 1H), 5.47 (m, 1H), 6.38 (dd, J = 10 and 2 Hz, 1H), 6.44 (s, 1H), 6.80 (d, J = 10 Hz, 1H); TSMS m/z 509 $(M + H)^+$. Anal. Calcd for $C_{27}H_{34}F_2O_7 \cdot 1.75H_2O$: C, 60.05; H, 7.00. Found: C, 60.12; H, 6.96%.

Effect of Solvent in the Acetylation of Mesylate 13a. Twelve reactions were set up using alcohol **13a** (160 mg, 0.3 mmol) in a solvent (5 mL), acetic anhydride (0.1 mL, 1.06 mmol), and TMSOTf in CH_2Cl_2 (1 M; 30 μL, 0.1 equiv), and the mixtures were stirred at 20 °C for 3 h. Aliquots were taken out, diluted in CH_3CN (150 μL) and MeOH (50 μL), and examined by HPLC. The results are shown in Table 2.

Acetylation of 2-(4-hydroxyphenyl)ethanol (35) using as follows:

(a) Ac_2O and DMAP. 2-(4-Hydroxyphenyl)ethanol (**35**) (1.38 g, 10 mmol) and Ac_2O (0.95 mL, 10 mmol) in CH_2Cl_2 (30 mL) were treated with Et_3N (2 mL, 10 mmol) and DMAP (122 mg, 1 mmol) at 20 °C, and the mixture was stirred for 4 d. Analytical HPLC indicated a mixture t_R = 5.531 min 53.5%, 6.626 min 13.3%, and 8.670 min 33.2%. The mixture was diluted with CH_2Cl_2 and washed with 2 M HCl, $NaHCO_3$, H_2O, dried, and chromatographed on silica gel eluting with ethyl acetate−cyclohexane (1:3, 1:1) to give the diacetate[21,23] (**38**) (500 mg, 22%) t_R = 8.664 min: ^{1}H NMR ($CDCl_3$) δ 2.05 (s, 3H), 2.30 (s, 3H), 2.94 (t, J = 7 Hz, 2H), 4.28 (t, J = 7 Hz, 2H), 7.02 (d, J = 8 Hz, 2H), 7.24 (d, J = 8 Hz, 2H); ESMS m/z 240 $(M + NH_4)^+$

the *O*-aryl acetate[21] (**36**) (705 mg, 39%), t_R = 5.585 min: ^{1}H NMR ($CDCl_3$) δ 1.85 (br s, 1H), 2.29 (s, 3H), 2.83 (t, J = 7 Hz, 2H), 3.80 (t, J = 7 Hz, 2H), 7.01 (d, J = 8 Hz, 2H), 7.22 (d, J = 8 Hz, 2H); ESMS m/z 198 $(M + NH_4)^+$ and the *O*-alkyl acetate[22,23] (**37**) (54 mg, 3%), t_R = 6.547 min: ^{1}H NMR ($CDCl_3$) δ 2.04 (s, 3H), 2.85 (t, J = 7 Hz, 2H), 4.23 (t, J = 7 Hz, 2H), 6.22 (s, 1H), 6.75 (d, J = 8 Hz, 2H), 7.05 (d, J = 8 Hz, 2H); ESMS m/z 198 $(M + NH_4)^+$

(b) TMSOTf. 2-(4-Hydroxyphenyl)ethanol (**35**) (1.38 g, 10 mmol) in CH_2Cl_2 (10 mL) and Ac_2O (0.95 mL, 10 mmol) was treated with TMSOTf in CH_2Cl_2 (1 M; 0.25 mL) at 20 °C. The reaction mixture was checked by HPLC after 1 h and indicated a mixture (22:48:30). After stirring for 21 h, the starting material was consumed and the mixture of products was 88:12. After stirring for a total of 3.5 d the ratio improved to 93:7. The mixture was washed with water and brine, dried, and evaporated to give **37** (1.577 g, 88%): ^{1}H NMR ($CDCl_3$) δ 2.05 (s, 3H), 2.85 (t, J = 7 Hz, 2H), 4.24 (t, J = 7 Hz, 2H), 5.92 (s, 1H), 6.77 (d, J = 8 Hz, 2H), 7.07 (d, J = 8 Hz, 2H).

Supporting Information Available: ^{1}H NMR data (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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