

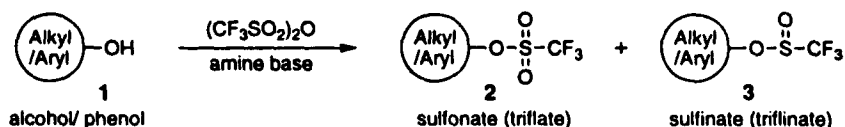
Formation of Sulfinate Esters in the Synthesis of Triflates ^{1,2)}

Thomas Netscher* and Patrick Bohrer

Vitamin Research and Technology Development
F. Hoffmann-La Roche, Ltd., CH-4070 Basel, Switzerland

Abstract. On standard treatment of sterically congested alcohols and phenols with triflic anhydride in the presence of amines, trifluoromethanesulfinyl esters were unexpectedly found. Depending on the reaction conditions and the structures of both hydroxy compound and base, esterified products (yields <5% to 99%) containing 0% to 89% (!) of sulfonates were obtained. The mechanisms of these reactions are discussed. The results of the present study indicate how to avoid unwanted sulfonate formation in triflate synthesis. Copyright © 1996 Elsevier Science Ltd

The trifluoromethanesulfonate (triflate) group belongs to the most activating functional groups for nucleophilic substitution reactions in organic chemistry, documented by well-known solvolytic data,³ as well as many mechanistic and preparative applications. In order to take advantage of the exceptionally high reactivity of the corresponding alkylating reagents in several projects, e.g. the synthesis of vitamin E active compounds,⁴ we used standard methods for converting different alcohols **1** to sulfonic esters **2** by treatment with triflic anhydride and amine bases in an organic solvent.^{3,5} However, we met problems in synthesizing pure products. TLC results and out-of-range microanalyses urged us to look for by-products which could be characterized as the corresponding trifluoromethanesulfinyl esters (triflinates) **3**. Authentic reference materials were prepared from trifluoromethanesulfinyl chloride⁶ for comparison.



We studied the mechanism of this esterification reaction⁷ with the aim to find conditions to avoid the unwanted formation of trifluoromethane sulfinates which react with C/O-nucleophiles under S-O- rather than C-O-scission (as expected for triflates). In our opinion, it is not very surprising that the formation of sulfinates during the synthesis of triflates has, to our knowledge, not been described in the literature so far. We only have information on unpublished results of colleagues.^{8,9} Many triflates are very reactive and thermally labile compounds¹⁰ which are often prepared in situ, but not isolated; in most cases, (unknown) by-products might be considered to be due to decomposition. Often sulfinates are not easily detected side by side with sulfonates, because of their similar properties. The present studies could be performed only with a series of alcohols (1a to 1e) which bear an asymmetric center adjacent to the OH-group. This allowed the detection of the sulfinate esters as a pair of diastereomers by an appropriate analytical method (¹H/¹⁹F-NMR, GC, HPLC). The Figure shows a typical HPLC elution profile of a crude product containing both S^{VI} and S^{IV} esters.

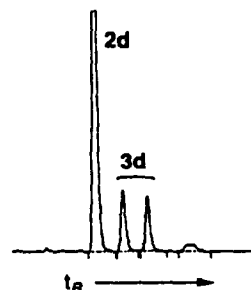


Figure. HPLC of a Crude Product from Synthesis.

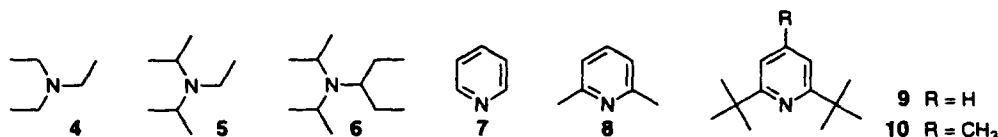
Table. Selected Esterification Reactions of Sterically Crowded Alcohols and Phenols with Tf₂O and a Base.

Alcohol, Phenol	1 (R = H)	Temp. °C	Base	Solvent	Yield (%)	Ratio
Sulfonate Ester	2 (R = SO ₂ CF ₃)	(Time)			Sulfonate	Sulfonate:
Sulfinate Ester	3 (R = SOCF ₃)				+Sulfinate	Sulfinate
					(2+3) ^a	(2:3) ^f
a		0	NEt ₃ (4)	CH ₂ Cl ₂	<5 ^b	?
		-78	NEt ₃	CH ₂ Cl ₂	<5 ^b	?
		0	NEt ₃	Et ₂ O	≈5 ^b	≈50:≈50
		-78	NEt ₃	Et ₂ O	11 ^b	>95:<5
		-78 (1h)→0	Lutidine (8)	Et ₂ O	>91 ^b	>99:<1
		-78 (1h)→0	DIPPA (6)	Et ₂ O	92 ^b	>99:<1
b		0	NEt ₃ (4)	CH ₂ Cl ₂	14 ^{c,d}	11.4:88.6
		-78 (1h)→rt	NEt ₃	CH ₂ Cl ₂	14 ^d	55.7:44.3
		-78 (1 h)	NEt ₃	CH ₂ Cl ₂	5 ^d	97.0:3.0
		-78 (7 h)	NEt ₃	CH ₂ Cl ₂	6 ^d	93.5:6.5
		-20 (1h)→rt	Pyridine (7)	-	96 ^e	>99.5:<0.5
		-10	Pyridine	-	≈100 ^b	? ¹¹
		0 (1h)→rt (1h)	DIPPA (6)	CH ₂ Cl ₂	98 ^b	98.9:1.1
					92 ^e	99.4:0.6
c		0	NEt ₃ (4)	CCl ₄	70 ^b	≈85:≈15
		-20	NEt ₃	CCl ₄	78 ^b	>99:<1
		?	?	?	32	? ¹²
		0	DIPPA (6)	CCl ₄	94 ^b	>99:<1
d		0	NEt ₃ (4)	CH ₂ Cl ₂	82 ^e	84.0:16.0
		-78	NEt ₃	CH ₂ Cl ₂	98 ^e	>99.5:<0.5
		0	NEt ₃	CCl ₄	98 ^e	99.2:0.8
		rt	NEt ₃	ClF ₂ CCCl ₂ F	85 ^e	92.8:7.2
		0	Lutidine (8)	CH ₂ Cl ₂	99 ^e	>99.5:<0.5
		0	Pyridine (7)	CH ₂ Cl ₂	99 ^e	>99.5:<0.5
		0	i-Pr ₂ NEt (5)	CH ₂ Cl ₂	95 ^e	98.2:1.8
		0	DIPPA (6)	CH ₂ Cl ₂	96 ^e	>99.5:<0.5
e		0	NEt ₃ (4)	CH ₂ Cl ₂	99 ^b , 86 ^d	≈99:≈1
		-15 (0.3h)→rt	NEt ₃	CH ₂ Cl ₂	91 ^d	≈98:≈2
		-15	NEt ₃	CH ₂ Cl ₂	?(>63)	? ¹³
		0	DIPPA (6)	CH ₂ Cl ₂	90 ^d	>99:<1
f		0 (1h)→rt (1.5h)	NEt ₃ (4)	CH ₂ Cl ₂	88 ^d	95.4:4.6
		0 (1h)→rt (2d)	DIPPA (6)	CH ₂ Cl ₂	89 ^d	>99.7:<0.3

^a) Difference to 100% = starting material (exception see ^c). - ^b) Crude. - ^c) Mainly polar products, acetal opening? - ^d) Chromatographed. - ^e) Crystallized. - ^f) Determination of ratio: **a**, **c** ¹H-NMR, **b**, **f** GC, **d** HPLC, **e** ¹H-NMR and quant. MS. - Method: 1.) 1.0 equiv. **1** (typically: 5 mmol dissolved in 10-20 ml of solvent), 2.) 1.5 equiv. base, 3.) 1.2 equiv. Tf₂O, 1 h stirring if not stated otherwise, then addition of 2N H₂SO₄. - Tf = SO₂CF₃, Lutidine = 2,6-Lutidine, DIPPA = N,N-Diisopropyl-3-pentylamine, rt = room temperature (20-22°C).

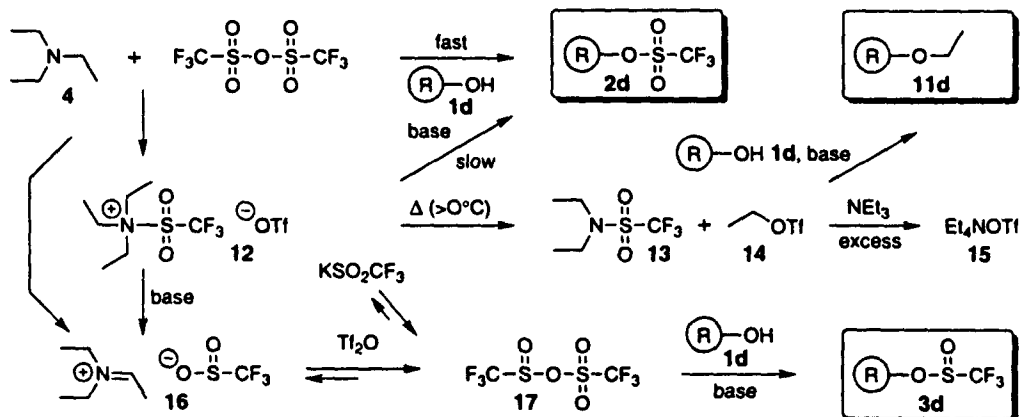
Secondary alcohols **1a-c** possessing considerable steric hindrance about the hydroxyl group have been investigated as to their reactions with triflic anhydride in the presence of amines **4-10**, and compared to neopentyl-type alcohol **1d**, less hindered primary alcohol **1e**, and phenol **1f** (Table). If Tf₂O was added to a

solution of alcohol and base, the yields of the reactions varied from <5% to almost quantitative, and the esterified products isolated contained up to 89% of the unwanted sulfinate. The ratio of sulfonate to sulfinate (2:3) depends not only on the reaction conditions, but also on the structure of the base used, and generally increases with the lowering of the reaction temperature. Inverse addition (alcohol to a mixture of Ti_2O and base) produces even higher amounts of sulfinate 3.



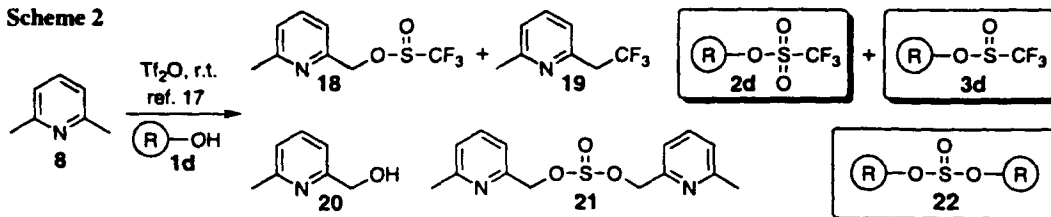
In particular, triethylamine (4), and to a less extent the more sterically hindered Hünig's base (5), as well as 2,6-lutidine (8), showed this effect. A mechanism for the action of 4 as a $\text{S}^{\text{VI}} \rightarrow \text{S}^{\text{IV}}$ reducing agent is proposed in Scheme 1: esterification reactions of alcohol 1d delivered, besides triflate 2d, sulfinate 3d and - not less surprisingly - ethyl ether 11d. The salt 12, primarily formed from triethylamine and triflic anhydride, is indicated to not be the primary trifyl source in these esterification reactions, as generally accepted in the literature.^{3,14} This compound (m.p. 52-54°C) is stable at -30°C for months and gives only a slow and sluggish conversion with alcohol 1d. Instead, it decomposes rapidly above 0°C (neat or in solution) to sulfonamide 13 and ethyl triflate 14, which then reacts with the starting alcohol to yield the ethyl ether 11d. Triethylamine is supposed to induce formation of iminium salt 16 either from 12 or directly by reduction of Ti_2O , and leads to the formation of tetraethylammonium triflate 15. Further evidence for the pathway via the mixed anhydride 17 could be obtained from a control experiment: treatment of the alcohol with KSO_2CF_3 , triflic anhydride and 2,6-di-tert-butyl-4-methylpyridine (10) afforded triflate 2d and trifinate 3d in a 1:2 ratio.

Scheme 1



Pyridine (7) is the most common base for triflation of alcohols.^{5,11} Since it can act as a nucleophile and form pyridinium salts from the triflates prepared in situ,¹⁵ hindered pyridines like 2,6-di-tert-butylpyridine (9) and 2,6-di-tert-butyl-4-methylpyridine (10) were recommended.^{15,16} Good results were obtained when using these bases which have, however, the drawbacks of high price and difficult handling. The less hindered 2,6-lutidine (8) also reacts to give sulfinate esters, but by a different mechanism than triethylamine does: it is known¹⁷ that treatment of 8 with Ti_2O in CCl_4 gives 19 and sulfinate ester 18 to some extent (Scheme 2). When alcohol 1d was added to a mixture of 2,6-lutidine and Ti_2O in CH_2Cl_2 , sulfinate 3d was formed, although in small amounts (5:95 with sulfonate 2d). In addition, alcohol 20 and sulfites 21 and 22 have been identified.

Scheme 2

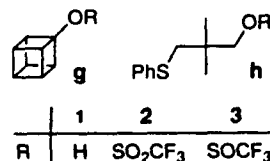


How can unwanted formation of sulfinate esters be avoided? Examples from the Table show that the attachment of additional alkyl groups in position α to the nitrogen atom of trialkylamines (4 \rightarrow 5 \rightarrow 6) suppresses side reactions, presumably by increasing the bulkiness of the base and lowering the acidity of α -hydrogens still present. But even when using the "simple" bases triethylamine or lutidine, sulfinate formation can be retarded effectively by choosing the appropriate conditions. This also makes plausible the mechanism proposed in Scheme 1 (direct esterification reaction of the alcohol with Ti_2O).

The formation of sulfinate esters does not appear to be a problem when starting from non-hindered primary alcohols (e.g. 1e). However, it can become a major reaction pathway with sterically more crowded primary (neopentyl-type) alcohols (1d), secondary alcohols (1a,b,c), and phenols (1f). Beside yield loss, two further aspects have to be kept in mind when choosing the conditions for the preparation of triflates: (1) in the case of carbohydrate diols the selectivity of monotriflation can depend substantially on base and solvent used,¹⁸ and (2) CAUTION! unexpectedly exothermic redox processes may lead to potentially hazardous situations in the laboratory.⁹ Steric hindrance is, therefore, an important factor not only in reactions of sulfonic esters,¹⁹ but also in their preparation.

References and Notes

- 1 This paper is dedicated to Professor Horst Prinzbach on the occasion of his 65th birthday.
- 2 Presented in part at the 9th International Conference on Organic Synthesis, Montreal, Canada, June 28 - July 2, 1992, Poster MW-44, and 204th National Meeting of the American Chemical Society, Washington, DC, USA, August 23-28, 1992, Division of Organic Chemistry, Paper 276.
- 3 P.J. Stang, M. Hanack, L.R. Subramanian, *Synthesis* **1982**, 85, and cit. lit.
- 4 Th. Netscher, P. Bohrer, *Chimia* **1993**, 47, 295.
- 5 Ch.D. Beard, K. Baum, V. Grakauskas, *J. Org. Chem.* **1973**, 38, 3673.
- 6 J.B. Hendrickson, P.L. Skipper, *Tetrahedron* **1976**, 32, 1627.
- 7 We thank Dr. R.K. Müller and Dr. H.J. Mayer (Basel) for the support of these studies and Prof. J.E. Baldwin (Oxford) for stimulating discussions.
- 8 In the preparation of cubyl triflate 2g, sulfinate 3g was found (5-20%) when DIBAH was involved. J. Zhou, Ph.E. Eaton, Univ. of Chicago, personal communication, August 22 and October 19, 1992.
- 9 Treatment of neopentyl alcohol 1h with NEt_3 and Ti_2O in CH_2Cl_2 at 0°C on a 0.1-mol scale resulted in a violent, highly exothermic reaction. Sulfinate 3h was isolated from the partly carbonized residue. P. Mohr, F. Hoffmann-La Roche, Basel, personal communication, July 28, 1992.
- 10 Discussion of stability and analytics: W. Walther, Th. Netscher, *J. Chromatogr. Sci.* **1994**, 32, 418.
- 11 L.D. Hall, D.C. Miller, *Carbohydr. Res.* **1976**, 47, 299.
- 12 M. Yamashita, Y. Soeda, N. Suzuki, M. Yamada, K. Tsunekawa, T. Oshikawa, S. Inokawa, *Bull. Chem. Soc. Jpn.* **1983**, 56, 1871.
- 13 H. Kotsuki, I. Kadota, M. Ochi, *J. Org. Chem.* **1990**, 55, 4417; *Tetrahedron Lett.* **1989**, 30, 3999.
- 14 P.J. Stang, W. Treptow, *Synthesis* **1980**, 283.
- 15 M.G. Ambrose, R.W. Binkley, *J. Org. Chem.* **1983**, 48, 674; Y. Al-Abed, N. Naz, K.M. Khan, W. Voelter, *Angew. Chem.* **1996**, 108, 581; *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 523.
- 16 B. Kanner, *Heterocycles* **1982**, 18, 411.
- 17 R.W. Binkley, M.G. Ambrose, *J. Org. Chem.* **1983**, 48, 1776.
- 18 S. Knapp, A.B.J. Naughton, C. Jaramillo, B. Pipik, *J. Org. Chem.* **1992**, 57, 7328. We thank Prof. Knapp for a preprint of this paper.
- 19 Th. Netscher, R. Schwesinger, B. Trupp, H. Prinzbach, *Tetrahedron Lett.* **1987**, 28, 2115.



(Received in Germany 9 September 1996; accepted 24 September 1996)