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Formation of Sulfinate Esters in the Synthesis of Triflates [1,2]

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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 sulfinates were obtained. The mechanisms of these reactions are discussed. The results of the present study indicate how to avoid unwanted sulfinate 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 chloride[6] for comparison.

1 alcohol/ phenol — **2** sulfonate (triflate) — **3** sulfinate (triflinate)

We studied the mechanism of this esterification reaction[7] 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 We only have information on unpublished results of colleagues.[8,9] Many triflates are very reactive and thermally labile compounds[10] which are often prepared in situ, but not isolated; in most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 ($^1H/^{19}F$-NMR, GC, HPLC). The **Figure** shows a typical HPLC elution profile of a crude product containing both S^{VI} and S^{IV} esters.

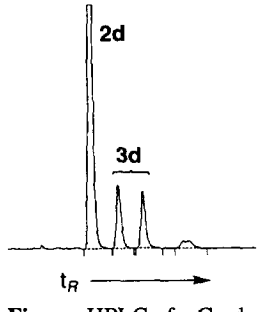
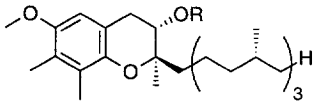
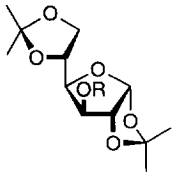
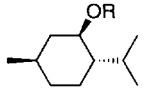
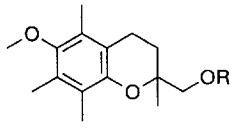
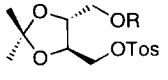
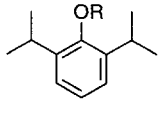


Figure. HPLC of a Crude Product from Synthesis.

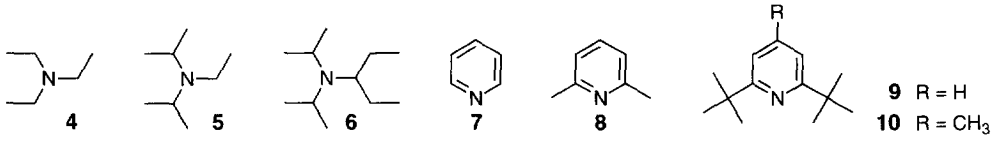
Table. Selected Esterification Reactions of Sterically Crowded Alcohols and Phenols with Tf_2O and a Base.

	Alcohol, Phenol **1** (R = H) Sulfonate Ester **2** ($R = SO_2CF_3$) Sulfinate Ester **3** ($R = SOCF_3$)	Temp. °C (Time)	Base	Solvent	Yield (%) Sulfonate +Sulfinate (**2**+**3**)[a]	Ratio Sulfonate: Sulfinate (**2**:**3**)[f]
a		0	NEt_3 (**4**)	CH_2Cl_2	<5[b]	?
		-78	NEt_3	CH_2Cl_2	<5[b]	?
		0	NEt_3	Et_2O	≈5[b]	≈50:≈50
		-78	NEt_3	Et_2O	11[b]	>95:<5
		-78 (1h)→0	Lutidine (**8**)	Et_2O	>91[b]	>99:<1
		-78 (1h)→0	DIPPA (**6**)	Et_2O	92[b]	>99:<1
b		0	NEt_3 (**4**)	CH_2Cl_2	14[c,d]	11.4:88.6
		-78 (1h)→rt	NEt_3	CH_2Cl_2	14[d]	55.7:44.3
		-78 (1 h)	NEt_3	CH_2Cl_2	5[d]	97.0:3.0
		-78 (7 h)	NEt_3	CH_2Cl_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_2Cl_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_2Cl_2	82[e]	84.0:16.0
		-78	NEt_3	CH_2Cl_2	98[e]	>99.5:<0.5
		0	NEt_3	CCl_4	98[e]	99.2:0.8
		rt	NEt_3	ClF_2CCCl_2F	85[e]	92.8:7.2
		0	Lutidine (**8**)	CH_2Cl_2	99[e]	>99.5:<0.5
		0	Pyridine (**7**)	CH_2Cl_2	99[e]	>99.5:<0.5
		0	i-Pr_2NEt (**5**)	CH_2Cl_2	95[e]	98.2:1.8
		0	DIPPA (**6**)	CH_2Cl_2	96[e]	>99.5:<0.5
e		0	NEt_3 (**4**)	CH_2Cl_2	99[b], 86[d]	≈99:≈1
		-15 (0.3h)→rt	NEt_3	CH_2Cl_2	91[d]	≈98:≈2
		-15	NEt_3	CH_2Cl_2	?(>63)	?[13]
		0	DIPPA (**6**)	CH_2Cl_2	90[d]	>99:<1
f		0 (1h)→rt (1.5h)	NEt_3 (**4**)	CH_2Cl_2	88[d]	95.4:4.6
		0 (1h)→rt (2d)	DIPPA (**6**)	CH_2Cl_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** ^{1}H-NMR, **b**, **f** GC, **d** HPLC, **e** ^{1}H-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. Tf_2O, 1 h stirring if not stated otherwise, then addition of 2N H_2SO_4. - Tf = SO_2CF_3, Lutidine = 2,6-Lutidine, DIPPA = N,N-Diisopropyl-3-pentylamine, rt = room temperature (20-22°C).

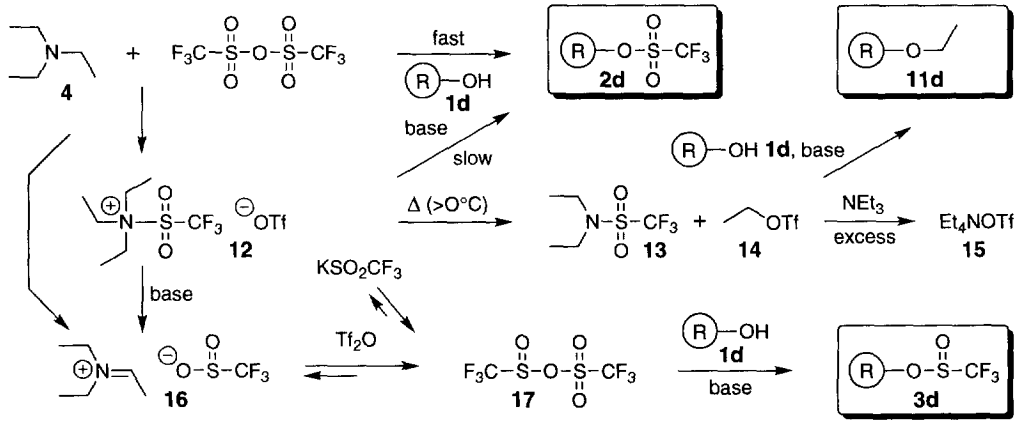
Secondary alcohols **1a-c** possessing considerable steric hindrance about the hydroxyl group have been investigated as to their reactions with triflic anhydride in the presence of amines **4-10**, and compared to neopentyl-type alcohol **1d**, less hindered primary alcohol **1e**, and phenol **1f** (**Table**). If Tf_2O 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 Tf_2O and base) produces even higher amounts of sulfinate **3**.



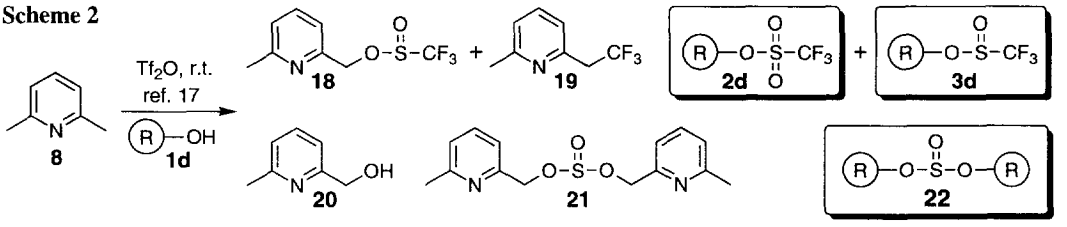
In particular, triethylamine (**4**), and to a less extent the more sterically hindered Hünig's base (**5**), as well as 2,6-lutidine (**8**), showed this effect. A mechanism for the action of **4** as a $S^{VI} \rightarrow S^{IV}$ reducing agent is proposed in **Scheme 1**: esterification reactions 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 Tf_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 triflinate **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 known[17] that treatment of **8** with Tf_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 Tf_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**→**5**→**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 Tf_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.

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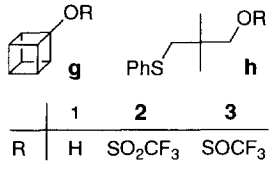

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