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Full Papers

Catalytic Mesylation of Alcohols: A Highly Productive Process for Trifluoroethyl Mesylate

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Abstract:

"Intermediate" Lewis acids are efficient catalysts for mesylation of trifluoroethanol (TFE) by mesyl chloride at 80 °C. In the absence of solvent, trifluoroethyl mesylate (TFEMes) is obtained in a chemical yield of 98% with total conversion of TFE. The only coproduct of the reaction, hydrochloric acid, simply distills from the reaction mixture. Distillation of TFEMes allows for recycle of the catalyst without any treatment.

Introduction

Trifluoroethoxy group CF_3CH_2 is widely present in active molecules in the pharmaceutical, agrochemical, and performances markets. There are different ways to introduce the CF_3CH_2 moiety into a molecule: nucleophilic substitution of a leaving group (halogen, nitro) by trifluoroethanol or nucleophilic substitution of an activated trifluoroethanol derivatives such as mesylate, tosylate, triflate.[1] Trifluoroethyl mesylate (TFEMes) is a good compromise between reactivity and price to introduce the CF_3CH_2 group for large-scale production.[2] Our goal to develop an industrial process for TFEMes prompted us to find a new and very efficient means of mesylation and, more generally, esterification of electron-poor alcohols.

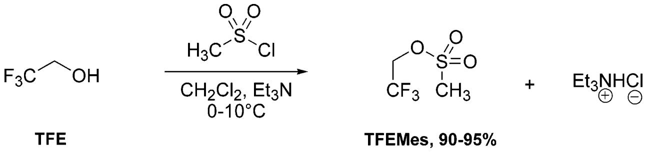
Results and Discussion

Classical Synthesis of Trifluoroethyl Mesylate. Mesylation of alcohols such as trifluoroethanol (TFE) is a very classical reaction:[3] use of an organic base, generally an amine like triethylamine, pyridine, or diisopropylethylamine, in stoichiometric amount, leads to good performances of esterification with mesyl chloride as shown in Scheme 1.

From the process point of view this approach includes several process units as shown in the flow sheet (Figure 1).

This process produces aqueous wastes containing the corresponding chlorhydrate salts of the amine, in our case triethylamine. These wastes must be treated because of their toxicity for microorganisms used for purification of water. Thus, the aqueous phases have to be neutralised to a basic pH to release the amine, which must be distilled and, if possible, recycled. In the case of triethylamine these last steps are very time- and energy consuming. Use of an amine such as diisopropylethylamine permits an easier recycling due to its lower solubility in water than that of triethylamine.

Scheme 1. **Classical synthesis of TFEMes**



Other important criteria for an efficient process are the volume efficiency and throughput. Analysis of the reaction step shows that in theory only 30% of the total weight of the medium is really necessary to synthesise TFEMes: TFE (14% of the weight) and mesyl chloride (16% of the weight). The base (Et_3N) and the solvent occupy 70% of weight and volume of the vessel.

These statements prompted us to try to find a more efficient process, with the following goals:

(i) Increase the volume efficiency and throughput
(ii) Reduce the number of unit operations
(iii) Keep a good yield of TFEMes.

Our first approach was to remove solvent and to change the nature of the base.[4]

In the absence of solvent, with triethylamine as the base, mesylation of TFE occurred, but quickly the reaction mixture became pasty and difficult to stir.

Replacing triethylamine with an inorganic base presents the advantage of limiting the aqueous waste treatment issues. Attempts were made to use sodium hydroxide in inert solvents such as chlorobenzene or potassium carbonate in acetonitrile. The performances of these systems are presented in Table 1.

With sodium hydroxide in chlorobenzene the yield of TFEMes was too low to reach an economical process. Partial hydrolysis of mesyl chloride by NaOH explains limitation on the yield. Surprisingly, the use of a usual phase transfer catalysis[5] contributed to a decrease in the yield of TFEMes.

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(1) Langlois, B.; Desbois, M. *L'actualité Chimique* **1987**, 151.

(2) Camps, F.; Coll, J.; Messeguer, A.; Pericas, M. A. *Synthesis* **1980**, 727.

(3) (a) Crossland, R. K.; Servis K. L. *J. Org. Chem.* **1970**, *35*, 3195. (b) Prescher, D.; Rhumann, T. *J. Fluorine Chem.* **1996**, *79*(2), 145. (c) King, J. F.; Gill, M. S. *J. Org. Chem.* **1998**, *63*, 808.

(4) DSC analysis of an equimolar mixture of TFE and mesyl chloride without base showed a very small exotherm above 150 °C, but no traces of TFEMes were detected in the cell content.

10.1021/op050105s CCC: $33.50

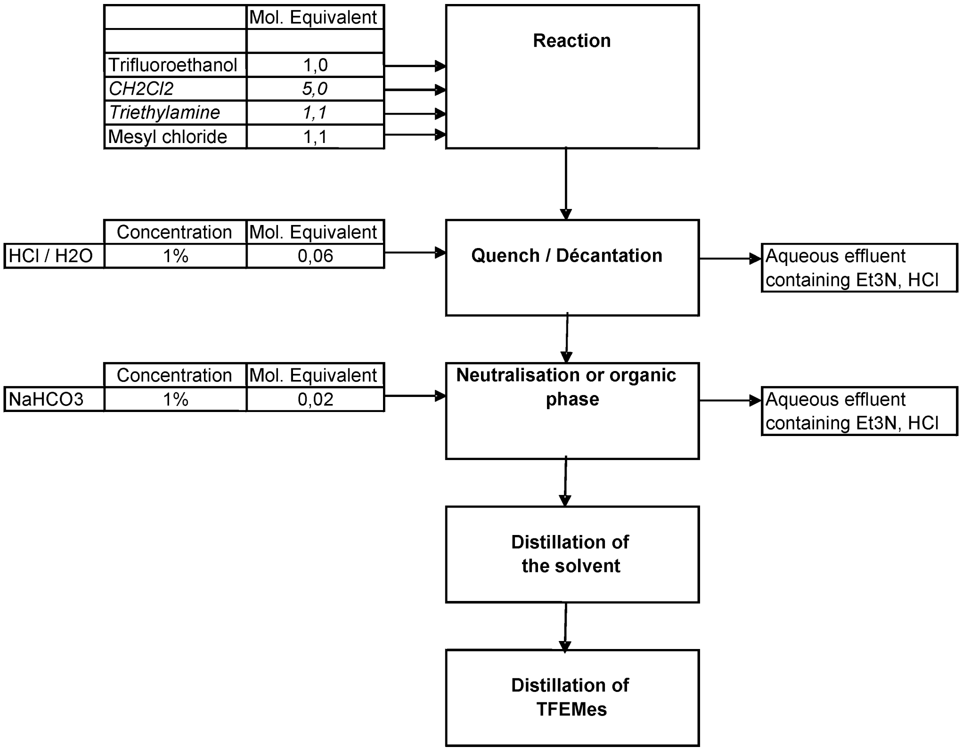

Figure 1. **Flow sheet of TFEMes synthesis using Et_3N.**

Table 1. **Comparison of inorganic bases with Et_3N (CMS/TFE: 1/1)**

base	solvent	temp (°C)	yield TFEMes[b] (%)
NaOH (1.1 mol equiv)	chlorobenzene	50	74
NaOH (1.1 mol equiv) and TBAC[a] (5% mol)	chorobenzene	50	61
K_2CO_3 (1.1 mol equiv)	CH_3CN	65	82

[a] Tetrabutylammonium chloride. [b] GC with internal standard.

A better yield of TFEMes was obtained with K_2CO_3 in acetonitrile, but performances were still inferior to those of the classical route.

Taking the following results into account and looking at economic impacts on the process, which is highly dependent on the volume efficiency, we tried to proceed without solvent using weak bases in catalytic amount. The idea was to regenerate the base by thermal decomposition of its chlorhydrate salt (Scheme 2).

The results obtained were somewhat disappointing. None of the amine bases tested at 80−100 °C during 10 h (triethylamine, diisopropylethylamine, pyridine, DMAP, imidazole, TMEDA) allowed to get satisfactory yields of TFEMes (<2% GC, with internal standard). Better conversion of TFE was observed at higher temperature but with a poor selectivity, indicating that side reactions occurred. Same observations were made with the use of phosphites such as trimethyl phosphite. Running the reaction with 5 mol % of triphenylphospine in a batch manner or slowly adding either TFE or CMS at 100 °C gave up to 68% of conversion of TFE in 10 h with 39% yield of TFEMes. Even though encouraging, this result was not good enough for the purposes of a future industrial process.

To improve mesyl chloride electrophilicity, we decided, on the basis of the previous results, to explore the possibility of its catalytic activation using Lewis acids (Scheme 3). Such mesyl chloride activation is known in the literature for Friedel−Crafts-type reactions.[6] Nevertheless, in the current case we had to deal with a better Lewis base (TFE) than aromatic rings, which can compete with mesyl chloride for the Lewis acid coordination.

A screening of several Lewis acids[7] was scheduled, and the results were compared, following the HSAB classification, to extract a correlation if any.[8] The experiments have been run in a batch manner using 5 mol % of catalyst at 80−85 °C. Reactions were monitored by GC using an internal standard.

Generally, complete recovery of starting material was observed with hard Lewis acids such as $AlCl_3$, $FeCl_3$, $MgCl_2$, $ZrCl_4$, $BF_3.Et_2O$, $ZrCl_4$, H^+, etc... In some cases up to 25% of conversion of TFE has been observed but without any formation of TFEMes ($TiCl_4$, $SiCl_4$), indicating that TFE has probably replaced the chlorine ion as ligand.

Formation of TFEMes occurred with some borderline Lewis acids such as $BiCl_3$ (12%), $ZnCl_2$ (44%), or $SnCl_2$ (32%), but with various selectivities (conversion of TFE: 37, 66, and 38% respectively, Table 2). The same metal cations tested with other ligands gave lower yields of TFEMes.[7]

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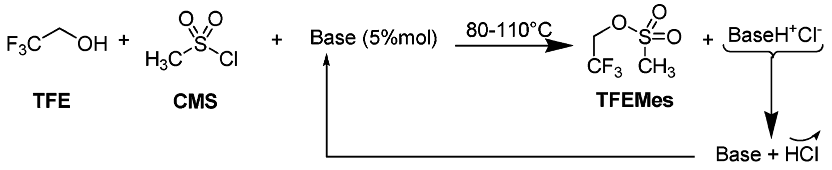
(5) Tappe, H. *Synthesis* **1979**, 822−823; Szeja, W. *Synthesis* **1980**, 577.

(6) Olah, G. A.; Lin, H. C. *Synthesis* **1974**, 342.

(7) Around 50 Lewis acids have been tested, essentially metal ion with chlorine ligands. When formation of TFEMes was observed with metal-chloride salt, other counterions have been tested (Br^-, OTf^-, $TFSI^-$, oxide,...). Better results were always obtained with chlorine derivatives.

(8) (a) Pearson, R. G. *J. Am. Chem. Soc.* **1963**, *85*, 3533. (b) Tse-Lok Ho *Chem. Rev.* **1975**, *75*, 1.

Scheme 2. **Catalytic base principle**



Scheme 3. **Acid catalysis principle**

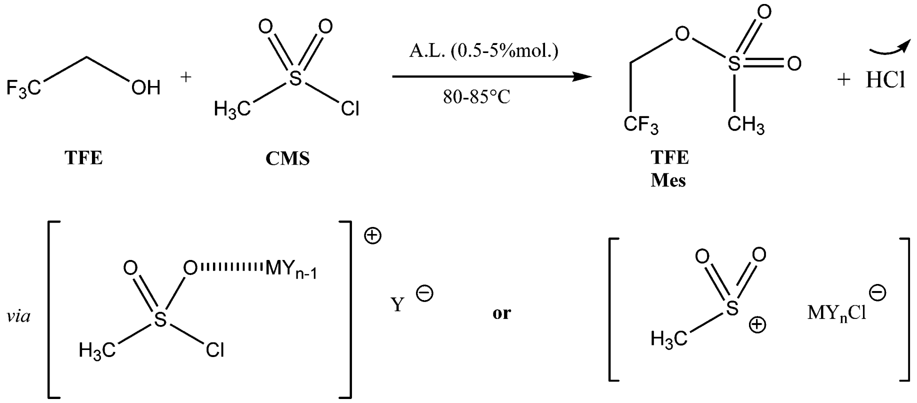


Table 2. **Test of some soft and borderline Lewis acids**

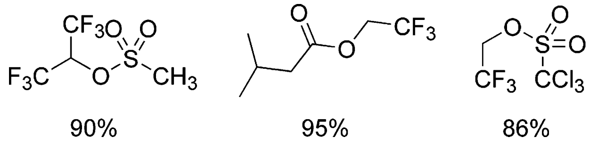
Lewis acid	mol equiv	temp (°C)	time (h)	conversion TFE (%)	yield TFEMes (%)
$BiCl_3$	0.05	80−85	9	37	12
$ZnCl_2$ [a]	0.05	80−85	8	66	44
$TeCl_4$ [a]	0.05	80−85	6	62	42
$SnCl_2$ [a]	0.05	80−85	4	38	32
$SbCl_5$ [a]	0.05	80−85	**3.5**	**98**	**91**

[a] Batch conditions (CMS/TFE: 1.1).

Finally, the best results were obtained with borderline $TeCl_4$ and $SbCl_5$ Lewis acids (Table 2), the last one giving singular excellent yield and selectivity. Taking into account that both mesyl chloride and TFE are present in the reaction mixture (batch reaction), these results suggest that $SbCl_5$ intrinsically possesses adequate Lewis acidity to activate CMS without reacting with TFE hydroxyl function.

Catalytic amounts of $SbCl_5$ led to direct mesylation of trifluoroethanol in high yields without any other reagent and any solvent. Optimisation of the reaction conditions allowed synthesis of TFEMes on 3-kg scale (98% yield) without any scale-up issues and the use of a reduced amount of catalyst (0.05 mol %).[9−11] Direct distillation from the reaction mixture permits isolation of pure TFEMes, and the residue containing catalyst can be reused for a new reaction.[12] This additionally contributes to reduction of the global amount of catalyst needed. The reaction is globally athermic due to HCl evolution all along the reaction.[13]

Scheme 4. **Esters formed using $SbCl_5$ catalytic process**



To determine limits and expectations of this chemistry, several esters were synthesized using the same catalytic process.[9] Some examples of the products synthesised using $SbCl_5$ as catalyst are represented in Scheme 4.

In comparison with the classical chemistry and process (solvent, amine) the $SbCl_5$-catalysed process presents several advantages:

(i) maximum productivity because no solvent or base is used

(ii) reduction of process unit: only reaction and distillation instead of five process units in the classical process

(iii) very efficient reduction of amounts of wastes: with Lewis acid the amount of waste is estimated to be 15 kg per ton of TFEMes instead of 3 tons per ton of TFEMes in the triethylamine process.

Conclusion

Some soft and borderline Lewis acids, especially $SbCl_5$, are efficient catalysts for mesylation of trifluoroethanol by mesyl chloride. In the absence of solvent, trifluoroethyl mesylate is obtained with a chemical yield of 98%. The amount of catalyst required is very low (0.05 mol %), and it can be recycled for several batches since the residue is keeping out of moisture. Hydrochloric acid, which is the only side product, distills from the reaction mixture, giving a global athermic reaction. No scale-up issue has been identified. In comparison with the classical process using a stoichiometric base, such as triethylamine, the $SbCl_5$ catalytic

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(9) Vastra, J.; Saint-Jalmes, L. (Rhodia Chimie). WO 02/28826, 2002.

(10) From an environmental and an economical point of view it was important to reduce as much as possible the amount of $SbCl_5$ to be handled. Furthermore, the catalyst could be easily recycled since it stays in the distillation residue.

(11) Alkaline hydrolysis of the residue gives antimony oxide (Sb_2O_5) which can be used as halogen-free flame retardant in clothing.

(12) The residue has been successfully reused three times in the laboratory without loss of yield.

(13) Heat of reaction was determined by Mettler RC1 experimentation ($\Delta H_r = -0.2$ kcal/mol of mesyl chloride).

process leads to an optimum productivity, to a reduction of process units, and a drastic reduction in the amount of wastes generated. This type of chemistry has been extended to esterification of some electron-poor alcohols.[9]

Experimental Section

General Procedure. Trifluoroethyl mesylate is commercially available from Fluka (2,2,2-trifluoroethyl methanesulfonate, RN CAS 25236-64-0). All reagents were obtained at industrial scale and used without further purification. ^{1}H NMR spectra were determined on a 200 MHz spectrometer. Each compound prepared herein was characterized by GC, GC−MS, and ^{1}H NMR spectroscopy.

Gas Chromatography. Gas chromatography was carried out using a Varian CP-3800 gas chromatograph equipped with a catharometer detector and a column DB-210 (30 m × 0.53 mm × 1 μm). All samples were examined under the following temperature gradient: temp 1, 40 °C (5 min); temp 2, 140 °C (5 min); rate 5 °C/min. Conversions and yields were determined by calibration curves using standard solutions of each component; internal standard is *n*-decane. GC−MS data were acquired using a HP 5890 series II gas chromatograph using the same temperature gradient as described for GC analysis.

Safety. $SbCl_5$ is an irrating and corrrosive reagent. Although it is less toxic than its Sb(III) analogue, it must be handled with care, and any trace of moisture must be avoided. $SbCl_5$ can be destroyed with basic aqueous medium controlling the exotherm.[11]

2,2,2-Trifluroethyl Methanesulfonate (Trifluroethyl Mesylate, TFEMes). $SbCl_5$ (0.49 g; 1.5 mmol) is slowly added to mesyl chloride (62.3 g, 544 mmol) at room temperature. An exotherm is noted. The medium is warmed to 80 °C, and trifluoroethanol (50.5 g, 504.7 mmol) is added over 5 h. HCl evolution is observed all along the addition. The reaction mixture is then maintained at 80 °C for 1.5 h to remove remaining HCl. Analysis by GC of aliquot showed total conversion of trifluoroethanol and formation of TFEMes with 98% yield. Trifluoroethanol mesylate is purified by distillation on seven plates column, bp: 99 °C/ 35 mmHg.

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