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# Synthesis of esters by selective methanolysis of the trifluoromethyl group

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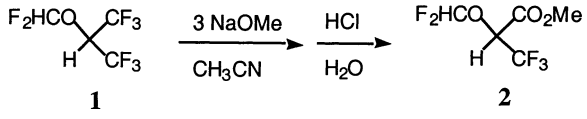
**Abstract**—The trifluoromethyl group of certain compounds containing one or two trifluoromethyl groups can be converted to the carbomethoxy group by treatment with sodium methoxide followed by aqueous acidic work-up. α-Trifluoromethyl esters can be obtained by selective methanolysis of the 1,1,1,3,3,3-hexafluoroisopropyl group in some cases. The structural requirements for the transformation are delineated, and a mechanistic study confirms the proposed mechanism, a dehydrofluorination–addition–elimination process. © 2002 Elsevier Science Ltd. All rights reserved.

We disclose here a method for the conversion of the trifluoromethyl group into a carbomethoxy group. The trifluoromethyl group is normally very resistant to attack by both electrophilic and nucleophilic reagents, but when the molecule bearing this group contains a properly positioned hydrogen atom—one which can be lost in an initial dehydrofluorination reaction—and certain other structural features, all the fluorine atoms may be lost. Alcoholysis under basic conditions of compounds containing a trifluoromethyl group has been shown to yield carboxylic esters,[1–7] sometimes through the intermediacy of orthoesters[2–4] or ketene acetals.[1] There have also been reports of application of these reaction conditions to compounds containing multiple trifluoromethyl groups.[3,8–11] In two of these cases, the observed chemoselectivity is not surprising because only one of the groups is proximate to an active hydrogen atom.[3,8] However, there have been four examples of chemoselective hydrolysis or alcoholysis of molecules containing multiple equivalent trifluoromethyl groups.[9–12]

All of the examples cited above involve the transformation of molecules of a limited structural type—or even just one particular molecule—under a number of different conditions. It would be desirable to have one set of conditions that would be applicable to a broader class of molecules containing trifluoromethyl groups, and also have that method be chemoselective when applied to molecules containing multiple trifluoromethyl groups. We report here that a modification of the conditions for the alcoholysis of α-trifluoromethyl-β,β-difluorostyrenes[13] can be applied to the methanolysis of several different types of substrates containing one or two trifluoromethyl groups, and in the case of substrates with two, the process occurs chemoselectively.

Treatment of fluoroether **1** with sodium methoxide in methanol—conditions similar to those which had been successfully applied by others[9–11] to related substrates—gave a complex mixture of products rather than predominantly the desired ester **2** (Scheme 1). In an attempt to produce the carboxylic acid derivative of ester **2**, recourse was made to hydrolysis of fluoroether **1** with aqueous solutions of various metal hydroxides in a number of different co-solvents, but the yields of the acid were in all cases very low. These reactions were complicated by hydrolysis of both the difluoromethoxy group and the other trifluoromethyl group. However, when treated with 3 equiv. of sodium methoxide in acetonitrile[13] as solvent, ester **2** was isolated in 55% yield after brief treatment with aqueous acid during work-up. The ester was purified by either fractional distillation or radial chromatography. Application of the methanolysis conditions to other substrates gave synthetically useful yields of esters (Table 1). The reaction works for a fairly wide variety of structural types, as long as the aforementioned active hydrogen atom is




**1** **2**

**Scheme 1.** Methanolysis of fluoroether **1**.

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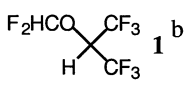
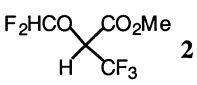
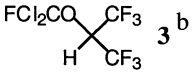
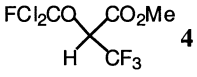
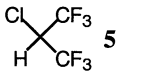
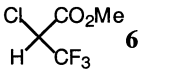
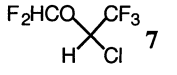
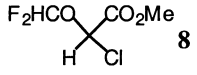
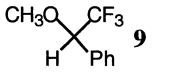
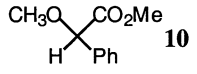
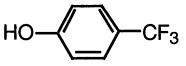
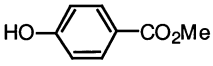
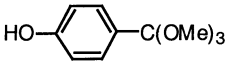
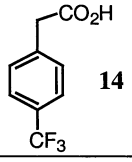
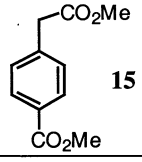
**Table 1.** Methanolysis reactions

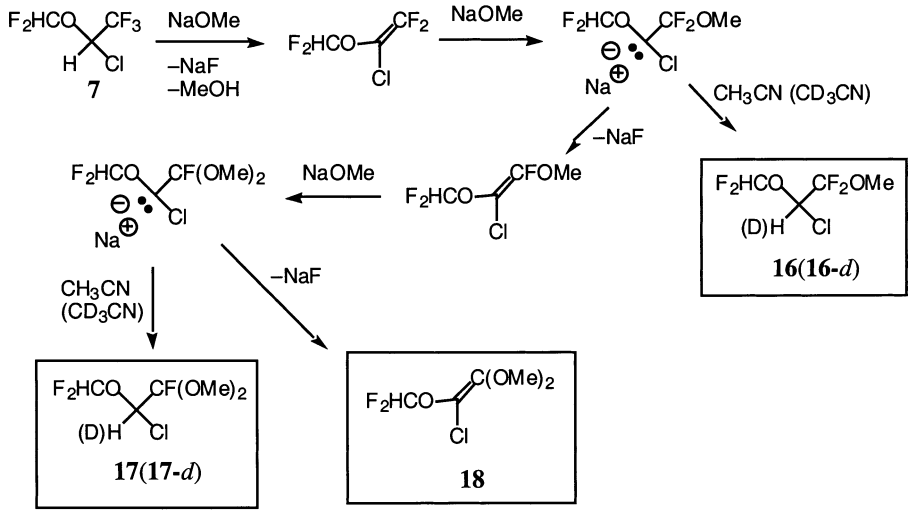
| entry | substrate | equiv. NaOMe | temp. (°C) | time (h) | product | crude yield[a] | isolated yield |
|---|---|---|---|---|---|---|---|
| 1 |  **1**[b] | 3 | -45 to r.t. | 1 |  **2** | 62% | 55% |
| 2 |  **3**[b] | 3 | -45 to r.t. | 1 |  **4** | 70% | 45% |
| 3 |  **5** | 3 | -45 to r.t. | 1 |  **6** | 89% | 23%[c] |
| 4 |  **7** | 4 | 0 to r.t. | 18 |  **8** | 71% | 52% |
| 5 |  **9** | 3 | reflux | 22[d] |  **10** | - | 59% |
| 6 |  **11** | 3 | reflux | 2 |  **12** or  **13** | - | 49% or 53%[e] |
| 7 |  **14** | 4 | reflux | 20 |  **15** | - | 51%[f] |

[a] Determined by $^{1}H$ and $^{19}F$ NMR analysis, except for entry 3, which was determined by quantitative GC analysis.
[b] Speers, L.; Szur, A. J.; Terrell, R. C.; Treadwell, J.; Ucciardi, T. R. *J. Med. Chem.* **1971**, *14*, 593–595.
[c] After washing with water to remove acetonitrile, and distillation.
[d] Treatment with acid after reflux period was 1.5 h at rt.
[e] Yield of orthoester **13** when acidic work-up is omitted.
[f] The crude product was treated with excess methanol/cat. sulfuric acid for 2 h at reflux.

present, and the functional groups around the trifluoromethyl group are sufficiently electron-withdrawing. In the cases of the substrates which contain two trifluoromethyl groups, entries 1–3, small amounts of diesters which are the result of methanolysis of both trifluoromethyl groups were detected in the crude reaction mixtures. The discrepancies in the crude and isolated yields for these cases and also the case of entry 4 are due to either simple handling losses or due to thermal instability of the esters during distillation. For the case of entry 3, separation of the volatile ester **6** from the acetonitrile solvent was problematic and resulted in a low isolated yield of product.

The substrates in Table 1 were chosen based on the presence of electron-withdrawing groups positioned around the trifluoromethyl group. When the substrate lacks these structural features, the reaction fails. For example, 1,1,1,3,3,3-hexafluoroisopropyl methyl ether, which lacks the two fluorine atoms of its analog ether **1**, gives a complex mixture of products containing very little of the corresponding ester when subjected to the reaction conditions. This and other bits of evidence point to a dehydrofluorination–addition–elimination sequence as the most probable mechanism by which the transformation occurs. In the case of the commercial anesthetic isoflurane (**7**), if the aqueous acidic work-up is left out and the crude reaction mixture is simply filtered to remove the by-product salts, followed by removal of the solvent under reduced pressure, then three products are seen, difluoroether **16**, monofluoroether **17** and enol ether **18** (Scheme 2). The use of 4 equiv. of sodium methoxide is required for the best yields of monofluoroether **17** (50% crude yield) and enol ether **18** (27% crude yield), both of which are converted to ester **2** after brief exposure to aqueous acid; difluoroether **16** is resistant to hydrolysis and remains as a troublesome contaminant in ester **2** if only 3 equiv. of sodium methoxide are used.

The observation of these intermediates led to a labeling study to elucidate the mechanism. When the methanoly-



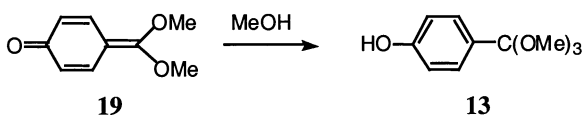

**Scheme 2.** Labeling study and proposed mechanism for production of **16**, **17**, and **18**.

sis reaction producing compounds **16**, **17**, and **18** was run in acetonitrile-$d_3$ as solvent, and the aqueous acidic work-up was omitted, the products had incorporated deuterium to give difluoroether **16**-*d* and monofluoroether **17**-*d* as determined by $^1$H NMR analysis: In **16**-*d*, the triplet at 5.87 ppm, assigned to the proton on the carbon atom bearing the chlorine atom in **16**, had disappeared, while for **17**-*d*, the doublet at 5.87 ppm, assigned to the corresponding proton in **17**, had also disappeared. The notion of this addition–elimination process is further bolstered by the isolation of orthoester **13** if the acidic treatment is omitted from the reaction which produces aromatic ester **12** (Table 1). Orthoester **13** is most likely formed by initial dehydrofluorination of phenol **11** followed by successive addition–elimination steps, eventually giving enol ether **19** (Scheme 3). At this point, all 3 equiv. of sodium methoxide are used up, and an equivalent of methanol has been produced by the initial dehydrofluorination. Enol ether **19** is especially activated for addition of methanol across the unsaturated system because the aromaticity of the ring is reestablished. A similar process is probably at work in the case of acid **14**.

To conclude, we have found a method for the methanolysis of the trifluoromethyl group which shows signs of being generally applicable to compounds which contain both an appropriately positioned active hydrogen atom and an electron-withdrawing group. When the substrate contains two trifluoromethyl groups, chemoselectivity was seen. The method is primarily useful for the synthesis of α-trifluoromethyl carboxylic esters.

**Representative experimental procedure. Ester 2**:

Sodium hydride (30.2 g, 60% in mineral oil, 0.75 mol) was added portionwise with rapid mechanical stirring to a solution of methanol (29 mL, 0.72 mol) in 500 mL anhydrous acetonitrile under $N_2$ in an ice bath. The mixture was stirred at rt for 100 min, at which point very little gas production was apparent. The resulting white slurry was cooled to −45°C, and fluoroether **1** (52.3 g, 0.240 mol) was added dropwise over a period of 40 min, keeping the reaction temperature <−35°C. The mixture was stirred for 30 min at −45°C, and then was removed from the cold bath for 65 min. The resulting off-white slurry was suction filtered, washing with 100 mL acetonitrile. The filtrate was treated with 1 L of 1 M HCl solution with rapid mechanical stirring for 20 min, giving a biphasic mixture. The bottom phase (57.0 g of clear colorless liquid), which contained both product and acetonitrile, was removed and dried over $CaCl_2$; the upper aqueous phase was extracted with 2×200 mL of ether, and the combined ether extracts were dried over $MgSO_4$. The ether was removed under reduced pressure at rt with a minimum pressure of 150 mmHg, giving a mixture of product and acetonitrile which was shaken with 300 mL water. The resulting bottom phase was dried over $MgSO_4$ giving 10.8 g clear colorless liquid which contained product and acetonitrile. The two product-containing liquids were combined and fractionally distilled under vacuum using a silvered, vacuum-jacketed 1×24 cm column packed with ceramic saddles, and a reflux-splitter head. The acetonitrile was first removed at 150 mmHg, and then the pressure was reduced gradually to 50 mmHg. Ester **2** (28 g, 55% yield) was collected at 59°C as a clear colorless liquid.




**19** **13**

**Scheme 3.** Proposed formation of orthoester **13**.

**Physical and spectral data for new compounds**:

All NMR spectra were recorded in $CDCl_3$ solvent, reporting in units of ppm relative to tetramethylsilane for the $^1$H and $^{13}$C spectra, and relative to fluorotrichloromethane for the $^{19}$F spectra. The $^{19}$F spectra are proton-coupled and the $^{13}$C spectra are proton-decoupled.

Compound **2**: bp = 59°C/50 mmHg; $^1$H: 3.90 (s, 3H), 5.00 (q, $J$ = 6.5 Hz, 1H), 6.45 (t, $J$ = 71 Hz); $^{19}$F (H-cou-

pled): −74.6 (dt, $J=6.5$, 20 Hz, 3F), −85.7 (dq, $J=71$, 2.0 Hz, 2F); $^{13}$C (H-decoupled): 54.0 (s), 70.0 (qt, $J=35$, 55 Hz), 116 (t, $J=267$ Hz), 122 (q, $J=280$ Hz). 164 (q, $J=1.8$ Hz). Compound **4**: bp = 76°C/40 mmHg; $^{1}$H: 3.96 (s, 3H), 5.11 (q, $J=6.3$ Hz, 1H); $^{19}$F (H-coupled): −12.4 (q, $J=2.1$ Hz, 1F), −74.0 (dd, $J=6.3$, 2.1 Hz, 3F); $^{13}$C (H-decoupled): 54.1 (s), 74.3 (qd, $J=35$, 2.5 Hz), 121 (q, $J=282$ Hz), 125 (d, $J=314$ Hz). 165 (br s). Compound **8**: bp = 63°C/20 mmHg; $^{1}$H: 3.90 (s, 3H), 6.12 (s, 1H), 6.49 (dd, $J=73$, 70 Hz, 1H); $^{19}$F (H-coupled): −85 to −90 (m); $^{13}$C (H-decoupled): 54.0 (s), 79.0 (t, $J=5.2$ Hz), 116 (dd, $J=266$, 262 Hz), 165 (s). **16**: bp = 45°C/30 mmHg; $^{1}$H: 3.68 (s, 3H), 5.87 (t, $J=4.2$ Hz, 1H), 6.41 (dd, $J=73$, 71 Hz, 1H); $^{19}$F (H-coupled): −85 to −90 (m, 2F), −88.9 (t, $J=4.2$ Hz, 2F); $^{13}$C (H-decoupled): 50.5 (t, $J=7.3$ Hz), 81.3 (tt, $J=42$, 5.4 Hz), 115 (t, $J=265$ Hz), 120 (t, $J=265$ Hz). **17**: bp = 77°C/30 mmHg; $^{1}$H: 3.57 (s, 6H), 5.87 (d, $J=3.2$ Hz, 1H), 6.43 (dd, $J=74$, 71 Hz, 1H); $^{19}$F (H-coupled): −85 to −90 (m, 2F), −100 (br s, 1F); $^{13}$C (H-decoupled): 50.9 (d, $J=6.0$ Hz), 83.5 (dt, $J=50$, 4.8 Hz), 116 (dd, $J=263$, 262 Hz), 117 (d, $J=247$ Hz). **18**: $^{1}$H: 3.70 (s, 3H), 3.72 (s, 3H), 6.34 (t, $J=74$ Hz, 1H); $^{19}$F (H-coupled): −85.0 (d, $J=74$ Hz).

## Acknowledgements

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