Cesium Fluoride Catalyzed Trifluoromethylation of Esters, Aldehydes, and Ketones with (Trifluoromethyl)trimethylsilane

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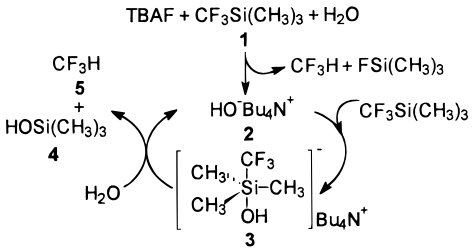
The low reactivity of carboxylic esters toward (trifluoromethyl)trimethylsilane (TMS−CF_3) was investigated. A universal cesium fluoride catalyzed procedure for nucleophilic trifluoromethylation was developed. At room temperature (25 °C), with catalytic amounts of cesium fluoride, carboxylic esters were found to react to give the silyl ether intermediates, which afforded the trifluoromethyl ketones after hydrolysis. Sulfonic, sulfinic, and selenic esters also show good reactivity, giving novel trifluoromethylated compounds. The trifluoromethylation method was also applied to aldehydes and ketones, which were transformed to trifluoromethyl silyl ether intermediates and afforded trifluoromethylated alcohols in excellent yields after acid hydrolysis. Ethylene glycol dimethyl ether was used as solvent for solid or high boiling substrates, and benzonitrile was used for the low boiling substrates.

Introduction

The incorporation of fluorine into molecules results in profound changes in the physical and chemical properties of molecules. These changes affect the biological activity of the molecules. (Trifluoromethyl)trimethylsilane (**1**) (TMS−CF_3) was first reported in 1989 as a nucleophilic trifluoromethylating agent to transform aldehydes and ketones to trifluoromethyl alcohols.[1] Since then the trifluoromethylating ability of TMS−CF_3 has been extensively demonstrated by introducing the trifluoromethyl group at carbon, sulfur, phosphorus, and nitrogen centers,[2] and even at ruthenium,[3] a transition metal center. The trifluoromethylated organic, inorganic, and organometallic compounds that were obtained have been used in the fields of pharmaceutical, agrochemical, and polymer chemistry.[4]

Simple nonactivated carboxylic esters were reported to show sluggish reactivity toward TMS−CF_3,[5] which suggested that it might be difficult using this reagent to prepare most of the trifluoromethyl ketones, which are of biological interest as enzyme inhibitors,[6] building blocks for trifluoromethyl heterocycles,[7] or monomers for novel polymer materials.[8] We report here a straightforward, high-yield, CsF-catalyzed route for the trifluoromethylations of carboxylic, sulfonic, sulfinic, and selenic esters, as well as aldehydes and ketones with TMS−CF_3.

Scheme 1



Results and Discussion

In our experience with TMS−CF_3, CF_3H (**5**) was always detected in the reaction mixture when a trace amount of water was present or with protonic solvents, e.g., CH_3CN. In some cases, **5** was isolated quantitatively. TBAF hydrate or TBAF/THF (water <5% weight) was used as a catalyst in most of the previously reported reactions of TMS−CF_3. Consequently water could have been responsible for the reported lack of reactivity of the esters with TMS−CF_3.[5] Initially we followed the literature procedure, with TBAF (hydrate or solution in THF, water <5% weight) as an initiator in reactions of the esters with TMS−CF_3. All of the TMS−CF_3 was consumed, and quantitative amounts of **4** and **5** were isolated. Apparently water competed with the esters for the trifluoromethyl anion formed in the reaction (Scheme 1). Fortunately, because of their higher reactivity, most ketones and aldehydes were not affected by trace amounts of water on reaction with TMS−CF_3.

While our work was in progress, Prakash et al. succeeded in rerunning the same reactions of carboxylic esters and TMS−CF_3 to prepare trifluoromethyl ketones by simply adding activated molecular sieves and changing the solvent from THF to nonpolar and aprotic solvents.[9] But the success of this method depended on the use of carefully dried solvents and reagents, and an inert atmoshphere (argon), as well as on control of the

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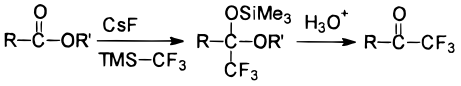
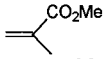
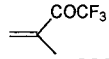
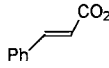
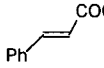
Scheme 2



7a-g **8a-g** **9a-f**

a: R = Ph, R' = Me **b**: R = Me, R' = Et
c: R = $PhCH_2CH_2$, R' = Et **d**: R = $H_2C=C(Me)$, R' = Me
e: R = PhCH=CH, R' = Me **f**: R = PhC≡C, R' = Et
g: R = PhC≡C, R' = Me

Table 1. Cesium Fluoride Catalyzed Trifluoromethylation[a] Reactions of Esters with TMS−CF_3

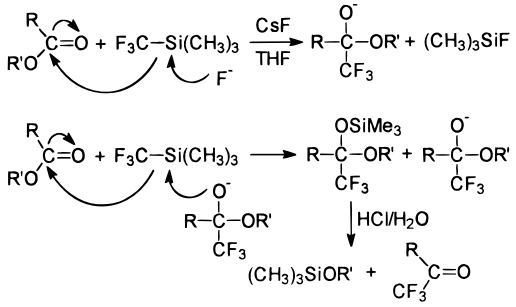
entry	substrate	solvent	T (°C)	t (h)	product	yield (%)[b]	ref
I	Ph−C(=O)−OMe **7a**	neat	25	1	Ph−C(=O)−CF_3 **9a**	90	11
II	CH_3−C(=O)−OEt **7b**	neat/ PhCN	25	1	CH_3−C(=O)−CF_3 **9b**	86	12
III	$PhCH_2CH_2$−C(=O)−OEt **7c**	neat	25	4	$PhCH_2CH_2$−C(=O)−CF_3 **9c**	90	13
IV	 **7d**	neat	25	3	 **9d**	84	8
V	 **7e**	glyme[c]	25	3	 **9e**	90	14, 15a
VI	Ph−≡−CO_2Et **7f**	neat	25	3	Ph−≡−$COCF_3$ **9f**	87	15
VII	Ph−≡−CO_2Me **7g**	neat	25	3	Ph−≡−$COCF_3$ **9f**	86	15
VII	MeO−S(=O)−OMe **7h**	neat/ PhCN	50	0.5	F_3C−S(=O)−CF_3 **9h**	77	16
IX	MeO−Se(=O)−OMe **7i**	neat/ PhCN	50	2	F_3C−Se(=O)−CF_3 **9i**	84	17
X	Ph−S(=O)−OMe **7j**	neat	100	6	Ph−S(=O)−CF_3 **9j**	85	18
XI	Ph−S(=O)(=O)−OMe **7k**	neat	100	6	Ph−S(=O)(=O)−CF_3 **9k**	85	19
XI	CH_3−S(=O)(=O)−OMe **7l**	PhCN	100	6	CH_3−S(=O)(=O)−CF_3 **9l**	88	20

[a] All the reactions were carried out with 10.0 mM of substrate, 10.25 mM of TMS-CF_3 and 0.1 mM of CsF; [b] isolated; [c] ethylene glycol dimethyl ether.

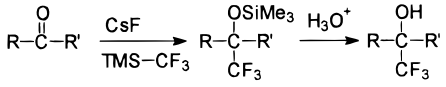
temperature to avoid double addition products. Also, rather long reaction times were needed to complete the reactions. This method did not succeed with compounds that possess a triple bond (e.g., methyl phenyl propiolate).

We have used potassium fluoride successfully as the initiator for reactions of TMS−CF_3 with many inorganic substrates.[10] In this study we found that CsF is a very good initiator for the trifluoromethylation of esters, aldehydes, and ketones. Within 1−4 h, esters **7a**−**g** reacted with TMS−CF_3 to give the corresponding trifluoromethylated silyl ethers (**8a**−**g**), which upon acid hydrolysis afforded the products noted in excellent isolated yields (**9a**−**f**) (Scheme 2, Table 1).[8,11−15] Known compounds were identified by comparing their spectral data with the literature. It should be mentioned that no double addition products were formed, indicating that,

Scheme 3



Scheme 4



10a-e **11a-e** **12a-e**

a: R = Me, R' = Me **b**: R = Ph, R' = Me
c: R = Me, R' = H **d**: R = Ph, R' = H
e: R = PhCH=CH, R' = H

under these conditions, the esters are more reactive than the products formed.

The mechanism for the nucleophilic trifluoromethylation of esters, shown in Scheme 3, involves fluoride ion initiation to give the trifluoromethylated oxyanion ester intermediate, which then catalyzes the subsequent reaction.[9]

Sulfonic, sulfinic, and selenic esters also showed good reactivity via this method (Table 1, **9h**−**l**).[16−20] Synthesis of compound **9j** has been reported in the literature[18] by the reaction of PhSOCl with TMS−CF_3 in 53% yield. With $PhSO_2Me$ (**7j**), which is more stable than PhSOCl, this method provided a facile route to trifluoromethyl sulfoxide. These trifluoromethylated sulfur compounds are attracting attention because they are key intermediates for the synthesis of trifluoromethyl sulfonium salts that are used as electrophilic trifluoromethylating agents.[21]

The method described in this paper was also applicable to the trifluoromethylation of aldehydes and ketones (Scheme 4, Table 2), which are more reactive than the esters. The reactions of aldehydes or ketones (**10a**−**e**) with TMS−CF_3 at room temperature in the presence of a catalytic amount of CsF led to the formation of trifluoromethylated silyl ethers (**11a**−**e**), which upon hydrolysis with 4 N HCl afforded the products **12a**−**e** in excellent isolated yields (Table 2).[5,22−24] Compound **10f** and **10g** have been reported to be unreactive with TMS−CF_3 in the presence of CsF in acetonitrile.[25] The products **12f** and **12g** were isolated in good yields (Table 2).[5,25] No

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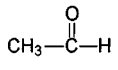
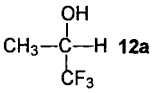
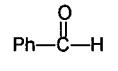
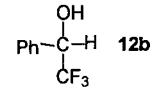
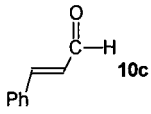
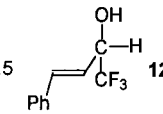
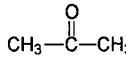
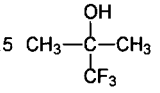
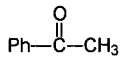
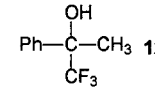
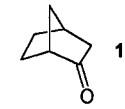
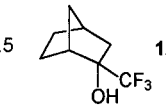
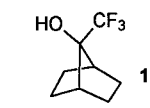
Table 2. Cesium Fluoride Catalyzed Trifluoromethylation[a] of Aldehydes and Ketones at Room Temperature

entry	substrate	solvent	t (h)	product	yield (%)[b]	ref.
I	 **10a**	neat	1	 **12a**	85	22
II	 10b	neat	6	 **12b**	88	5
III	 **10c**	glyme[c]	1.5	 **12c**	92	23
IV	 **10d**	neat	1.5	 **12d**	89	24
V	 **10e**	neat	5	 **12e**	93	5
VI	 **10f**	glyme[c]	1.5	 **12f**	95	5
VII	 **10g**	glyme[c]	1	 **12g**	90	25

[a] All the reactions were carried out with 10.0 mM of substrate, 10.25 mM of TMS-CF_3 and 0.1 mM of CsF; [b] isolated; [c] ethylene glycol dimethyl ether.

other products were isolated. Known compounds were identified by comparing spectral data with the spectral data reported in the literature.

Although the effect of solvent has been examined,[2] we have found that no solvent was required for the reaction of low boiling liquid substrates. When necessary we used ethylene glycol dimethyl ether as the solvent (with solids and some high boiling liquids) and benzonitrile for low boiling substrates. The use of these solvents allowed ease of separation of the desired products from the reaction mixture.

Conclusion

A general, efficient, CsF-catalyzed process for trifluoromethylation of carboxylic, sulfonic, sulfinic, and selenic esters was developed. At room temperature (25 °C), with catalytic amounts of cesium fluoride, carboxylic esters were found to react to give the silyl ether intermediates, which afforded the trifluoromethyl ketones after hydrolysis. Sulfonic, sulfinic, and selenic esters also show good reactivity giving trifluoromethylated compounds. The trifluoromethylation method was also applied to aldehydes and ketones, which were transformed to trifluoromethyl silyl ether intermediates and afforded trifluoromethylated alcohols in excellent yields after acid hydrolysis. We have successfully reacted TMS−CF_3 with esters and other substrates that have been reported to be unreactive in the literature.

Experimental Section

General Comments. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded in $CDCl_3$ on a spectrometer operating at 200, 50, and 188 MHz, respectively. Chemical shifts are reported in ppm relative to the standard: $CFCl_3$ for ^{19}F, and trimethylsilane/$CHCl_3$ for ^{1}H and ^{13}C NMR spectra. IR spectra were recorded using NaCl plates. Mass spectra were measured at 70 ev.

Materials. (Trifluoromethyl)trimethylsilane (TMS−CF_3) was prepared by the literature procedure.[25] Cesium fluoride was purchased from Aldrich and was finely powdered and used directly from the oven, where it was stored at 200 °C. Benzonitrile and ethylene glycol dimethyl ether were purchased from Aldrich and used as received. All of the substrates (esters, aldehydes, and ketones) were purified by distillation/recrystallization before use.

General Trifluoromethylation Procedure for Esters. At room temperature, CsF (0.1 mM) was added to a mixture of ester (10 mM) and TMS−CF_3 (10.25 mM). The reaction was monitored by ^{19}F NMR. After complete disappearance of the TMS−CF_3 resonance (−67.4 ppm) hydrolysis was carried out over 3 h by using 4 N HCl (4 mL). The resulting product was extracted with ether (30 mL). After removing the ether the trifluoromethylated ketones were found in good to excellent yields (Table 1).

1,1,1-Trifluoro-4-phenyl-2-butanone (9c): Colorless liquid; IR (film) 1760 (s, C=O) cm^1; ^{1}H NMR ($CDCl_3$) δ 3.10 (m, 4H), 7.21 (m, 5H); ^{19}F NMR ($CDCl_3$) δ −80.2 (s); MS (EI) *m/z* (species, rel int) 202 (M^+, 85), 133 ($M^+ - CF_3$, 100), 105 ($PhCH_2CH_2^+$, 30), 91 ($PhCH_2^+$, 60); HRMS calcd for $C_{10}H_9F_3O$ (M^+) 202.0605, found 202.0603.

***trans*-1,1,1-Trifluoro-4-phenyl-3-buten-2-one (9e):** Colorless liquid; IR (neat) 1608 (s, C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.39 (d, 1H, J = 16 Hz)), 7.65 (m, 5H); 8.10 (d, 1H, J = 16 Hz); ^{19}F NMR ($CDCl_3$) δ −85.0 (s); MS (EI) *m/z* (species, rel int) 200 (M^+, 80), 131 ($M^+ - CF_3$, 100), 103 ($PhCH{=}CH^+$, 60), 77 ($C_6H_5^+$, 22).

1,1,1-Trifluoro-4-phenyl-3-butyn-2-ethoxy-2-trimethylsilyl ether (8f): Yellow liquid; 95% yield; ^{1}H NMR ($CDCl_3$) δ 0.31 (s, 9H), 1.30 (t, J = 7 Hz), 3.85 (q, J = 3.5 Hz), 7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 1.08, 15.01, 60.60, 81.10, 87.02, 91.00 (q, J_{C-C-F} = 28.5 Hz), 122.50 (q, J_{C-F} = 286), 128.48, 129.62, 131.84; ^{19}F NMR ($CDCl_3$) δ −84.42 (s); MS (EI) *m/z* (species, rel int) 297 (M^+ − F, 10), 271 (M^+ − OEt, 47), 247 ($M^+ - CF_3$, 100), 129 ($PhC{=}CCO^+$, 9), 73 ($SiMe_3^+$, 3).

1,1,1-Trifluoro-4-phenyl-3-butyn-2-one (9f): Yellow liquid; 87% yield; IR (film) 2250 (s, C=C), 1760 (s, C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.52 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 83.34, 100.48, 114.86 (q, J_{C-F} = 286.5 Hz), 118.07, 128.7, 132.48, 133.90, 168.00 (q, J_{C-F} = 28.0 Hz); ^{19}F NMR δ −80.17 (s); MS (EI) *m/z* (species, rel int) 198 (M^+, 4), 129 ($M^+ - CF_3$, 100), 101 ($M^+ - COCF_3$, 10).

General Trifluoromethylation Procedure for Sulfonic, Sulfinic, and Selenic Esters. Ester (10.0 mM) and TMS−CF_3 (10.25 mM) were taken in a Schlenk flask, and powdered CsF (0.1 mM) was added at room temperature. The reaction mixture was heated until the ^{19}F NMR spectrum of the mixture showed the complete disappearance of TMS−CF_3 resonance (67.4). The product was distilled from the reaction mixture and identified by comparing the spectral data reported in the literature.

Phenyl trifluoromethyl sulfoxide: Colorless liquid; ^{1}H NMR ($CDCl_3$) δ 8.33−7.56 (m, 5H), ^{19}F NMR ($CDCl_3$) δ −78.5 (q, J = 12 Hz).

Methyl trifluoromethyl sulfoxide: ^{1}H NMR ($CDCl_3$) δ 3.10 (q, J_{H-F} = 1), ^{19}F NMR ($CDCl_3$) δ −79.6 (q, J = 13).

General Trifluoromethylation Procedure for Aldehydes and Ketones. In a typical reaction, the aldehyde or ketone (10 mM) and (trifluoromethyl)trimethylsilane (10.25 mM) were placed in a flask, and CsF (0.0015 g, 0.1 mM) was added as solid. The reaction was exothermic, and the solution changed from colorless to yellowish. It was stirred at 25 °C for 3 h and was hydrolyzed with 4 N HCl solution (6 mL) for 2 h at room temperature. The reaction mixture was diluted with water (20 mL), and the products were extracted with ether (25 mL). The ether extract was dried over anhydrous $MgSO_4$ and filtered. Removal of ether at reduced pressure gave the products in good yield.

***trans*-1,1,1-Trifluoro-4-phenyl-3-buten-2-ol:** Colorless solid; IR (neat) 3350 (broad, OH), 1600 (s, C=C) cm^{-1}; ^{1}H NMR

($CDCl_3$) δ 2.45 (s, broad, 1H), 4.62 (m, 1H), 6.18 (dd, 1H, J = 16 Hz, 3.3 Hz), 6.84 (d, 1H, J = 16 Hz), 7.32 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 71.60 (q, J_{C-C-F} = 32 Hz), 124.16 (q, J_{C-F} = 280); ^{19}F NMR ($CDCl_3$) δ −79.33 (s); MS (EI) *m*/*z* (species, rel int) 202 (M^+, 47), 185 ($M^+ - OH$, 32) 133 ($M^+ - CF_3$, 100), 103 ($PhCH{=}CH^+$, 30), 91 ($PhCH_2^+$, 60); HRMS calcd for $C_{10}H_9F_3O$ (M^+) 202.0605, found 202.0607.

2-(Trifluoromethyl)bicyclo[2.2.1]heptan-2-ol: Colorless liquid, IR (film) 3395 (s, broad, OH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.1−1.7 (m, 4H), 1.47−2.05 (m, 4H), 2.26 (br s, 1H, OH), 2.48 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 22.4, 27.4, 36.4, 39.0, 41.1, 42.9, 79.5 (q, J_{C-C-F} = 28.2 Hz), 126.7 (q, J_{C-F} = 283.4); ^{19}F NMR ($CDCl_3$) δ −81.4 (s); MS (EI) *m*/*z* (species, rel int) 180 (M^+, 2), 163 ($M^+ - HO$, 60), 162 ($M^+ - H_2O$, 10) 111 ($M^+ - CF_3$, 10); HRMS calcd for $C_8H_{11}F_3O$ (M^+) 180.0761, found 180.0751.

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Supporting Information Available: Copies of ^{19}F NMR spectra of **8a, 8f, 9c, 9f, 9k, 9l, 11a−11f, 12a−12f**; ^{1}H NMR spectra of **8a, 8f, 9f, 9k, 9l, 11a, 11b, 11d, 11e, 12a−12c, 12e,** and ^{13}C NMR spectra of **8a, 8f, 9f, 11b, 11d, 12a−12e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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