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CsF-Catalyzed Nucleophilic Trifluoromethylation of *trans*-Enones with Trimethyl(trifluoromethyl)silane: A Facile Synthesis of *trans*-α-Trifluoromethyl Allylic Alcohols

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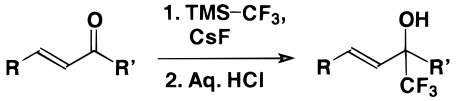
ABSTRACT



R = Ph, CH_3; R' = Ph, CH_3

Reactions of *trans*-enones, R–C═C–COR′ (R = Ph, Me, –C═CH–CH═C–S; R′ = Ph, Me, Et, CF_3) (1a–e), with TMS-CF_3 in the presence of catalytic amounts of cesium fluoride (CsF) in ethylene glycol dimethyl ether led to the formation of the corresponding *trans*-α-trifluoromethyl silyl ethers, R–C═C–C(OSiMe_3)(CF_3)R′ (R = Ph, Me, –C═CH–CH═C–S; R′ = Ph, Me, Et, CF_3) (2a–e), in essentially quantitative yield. On hydrolysis with aqueous HCl, the corresponding *trans*-α-trifluoromethyl allylic alcohols, R–C═C–C(OH)(CF_3)R′ (R = Ph, Me, –C═CH–CH═C–S; R′ = Ph, Me, Et, CF_3) (3a–e), were formed in >90% isolated yield. Under similar reaction conditions, 2-cyclohexen-1-one (1f) also gave trifluoromethyl allylic alcohols (3f) in 92% yield. The intermediates (2a–f) and products (3a–f) are liquids and were characterized by IR, ^{1}H, ^{19}F and ^{13}C NMR, MS, and high-resolution mass spectroscopy (HRMS).

Because fluorine is the most electronegative element and the van der Waals radius of fluorine is close to that of hydrogen, the introduction of a fluorine-containing group into an organic molecule brings about some remarkable changes in its physical and chemical properties.[1] In addition, novel reactivities are observed as a result of the introduction of fluorine or fluorinated groups into organic molecules. Many new fluorinated materials that take advantage of these useful changes, e.g., drugs and agrochemicals, have been designed[2] and synthesized.[3]

Allylic alcohols are particularly useful intermediates for the synthesis of biologically active compounds.[4] Consequently, reactions leading to the formation of allylic alcohols, especially fluorinated alcohols are of great interest. A number of methods are available for the preparation of allylic alcohols,[5] but techniques for the synthesis of α-trifluoromethyl allylic alcohols are rare.[6] Shen et al. reported the synthesis of some α-trifluoromethyl allylic alcohols by the reaction of a ylide anion with aldehydes, but the yields were low (46−55%).[6]

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(2) (a) Welch, J. T., Eswarakrishnan, S., Eds. *Fluorine in Bioorganic Chemistry*; John Wiley & Sons: New York, 1991. (b) Goldman, P. *Science* **1969**, *164*, 1123.

(3) Hudlický, M.; Pavlath, A. E. *Chemistry of Organic Fluorine Compounds II. A Critical Review*; ACS Monograph 187; American Chemical Society: Washington, DC, 1995.

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(5) Ono, N.; Kamimura, A.; Kaji, A. *Tetrahedron Lett.* **1984**, *25*, 5319 and references therein.

(6) Shen, Y.; Wang, T. *Tetrahedron Lett.* **1989**, *30*, 7203.

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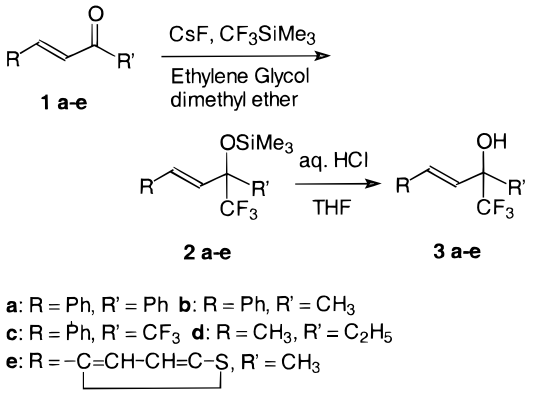
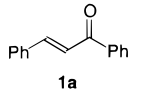
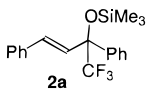
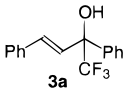
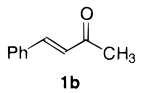
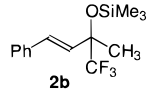
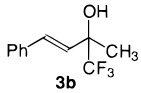
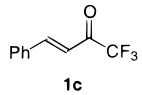
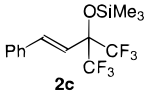
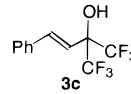
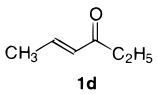
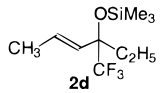
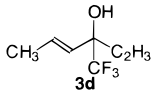
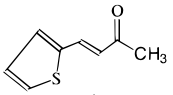
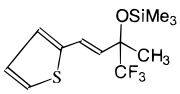
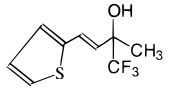
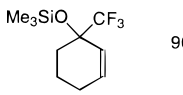
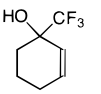
Recently, we reported several highly successful new cesium fluoride-catalyzed nucleophilic trifluoromethylation reactions.[7−10] We have now extended this chemistry to the facile synthesis of *trans*-α-trifluoromethyl allylic alcohols in excellent isolated yields by the CsF-catalyzed nucleophilic trifluoromethylation of enones with TMS−CF_3. Initially, we studied the optimization of the reaction conditions (Scheme 1) by using *trans*-chalcone (benzylideneacetophenone) (**1a**)

Scheme 1



as a substrate. Reactants **1a** and TMS-CF_3 were dissolved in ethylene glycol dimethyl ether. The mixture was cooled to 0 °C, and a catalytic amount of CsF was added. The reaction mixture was allowed to warm slowly to room temperature over 1 h. The reaction was monitored by ^{19}F NMR and was found to be complete in 3 h, giving the *trans*-1,1,1-trifluoro-2,4-diphenyl-3-buten-2-trimethylsilyl ether (**2a**)[11] intermediate, in 99% yield. Hydrolysis was carried out at room temperature with 6 N HCl for 3 h to form *trans*-1,1,1-trifluoro-2,4-diphenyl-3-buten-2-ol (**3a**)[12] in 96% isolated yield. However, since at room temperature the reaction proceeded smoothly in ethylene glycol dimethyl ether over 3 h followed by acid hydrolysis to give the same product (**3a**) in 96% isolated yields, all further reactions were carried out at 25 °C. Using the same reaction conditions, *trans*-enones **1b**−**e** were reacted with TMS-CF_3 in the presence of catalytic amounts of CsF to give the corresponding α-trifluoromethyl silyl ethers **2b**−**e**. Hydrolysis of the silyl ethers with 6 N HCl at room temperature formed the α-trifluoromethyl allylic alcohols **3b**−**e** (Scheme 1) in >90% isolated yield (Table 1). We also found that cyclic enones, such as 2-cyclohexen-1-one (**1f**), reacted in an identical fashion with TMS-CF_3 and 6 N HCl to give the trifluoromethylated allylic alcohol (**3f**).

Table 1. Trifluoromethylation of Enones with TMS-CF_3

Substrate	Intermediate	Yield (%)[b]	Product	Yield (%)[b]
 **1a**	 **2a**	99	 **3a**	96
 **1b**	 **2b**	98	 **3b**	96
 **1c**	 **2c**	98	 **3c**	95
 **1d**	 **2d**	97	 **3d**	91
 **1e**	 **2e**	98	 **3e**	95
 **1f**	 **2f**	96	 **3f**	92

[a] All reactions were carried out with 5 mmol of substrate, 5.25 mmol of TMS-CF_3, and 0.1 mmol of CsF in 5 mL of ethylene glycol dimethyl ether. [b] Isolated.

The nucleophilic reaction mechanism for the trifluoromethylation of these *trans*-enones with TMS-CF_3 is most likely the same as that reported for ketones.[13]

The *trans*-α-trifluoromethyl allylic alcohols that we have prepared (Table 1) are liquids. They are soluble in common organic solvents and very stable to air and moisture. The liquid-phase infrared spectra of **3a**−**f** showed a broad peak in the region 3300−3600 cm^{-1} due to the ν(OH) vibration and a sharp peak in the region 1630−1690 cm^{-1} arising from the (C=C) stretching vibration. In the ^{19}F NMR spectra, a single peak was observed in all cases in the range from δ −83 to −77 for the CF_3 moiety. ^1H NMR spectra for **3a**−**f** clearly showed the presence of the hydroxyl proton. This resonance disappeared upon addition of D_2O. In the ^{13}C NMR spectra, the α-C=O peak that appeared at δ 199 in **1a** shifted upfield to δ 77.7 in **3a**. This resonance appears as a quartet

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(8) Singh, R. P.; Cao, G.; Kirchmeier, R. L.; Shreeve, J. M. *J. Org. Chem.* **1999**, *64*, 2873.
(9) Singh, R. P.; Vij, A.; Kirchmeier, R. L.; Shreeve, J. M. *J. Fluorine. Chem.* **1999**, in press.
(10) Singh, R. P.; Vij, A.; Kirchmeier, R. L.; Shreeve, J. M. *Inorg. Chem.* Submitted.
(11) Spectral data for **2a**: IR (neat) 1650 (s, C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.19 (s, 9H), 6.04 (d, 1H, J = 16.3 Hz), 6.84 (d, 1H, J = 16.3 Hz), 7.40 (m, 8H), 7.64 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 2.0, 80.1 (q, J_{C-C-F} = 28.8 Hz), 125.2 (q, J_{C-F} = 286.4 Hz), 126.9, 127.0, 128.0, 128.6, 128.7, 128.9, 135.4, 135.8, 138.1; ^{19}F NMR ($CDCl_3$) δ −77.5 (s); MS (EI) *m*/*z* (species, rel int) 350 (M^+, 30), 281 ($M^+ - CF_3$, 98), 260 ($M^+ - Me_3SiOH$, 100), 73 ($SiMe_3$, 43).
(12) Spectral data for **3a**: IR (neat) 3545 (b, OH), 1651 (s, C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.03 (s, broad, 1H), 6.82 (d, 1H, J = 16.1 Hz), 6.98 (d, 1H, J = 16.1 Hz), 7.44 (m, 8H), 7.75 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 77.7 (q, J_{C-C-F} = 29 Hz), 125.6 (q, J_{C-F} = 283 Hz), 126.5, 126.9, 127.0, 128.4, 128.7, 128.8, 128.9, 133.7, 135.6, 137.5; ^{19}F NMR ($CDCl_3$) δ −78.7 (s); MS (EI) *m*/*z* (species, rel int) 278 (M^+, 10), 260 ($M^+ - H_2O$, 3), 209 ($M^+ - CF_3$, 100), 103 (PhCH=CH, 36), 77 (Ph, 7); HRMS calcd for $C_{16}H_{13}F_3O$ 278.0918, found 278.0898. Anal. Calcd for $C_{16}H_{13}F_3O$: C, 69.06; H, 4.71. Found: C, 69.02; H, 4.69.
(13) Krishnamurti, R.; Bellew, D. R.; Prakash, G. K. S. *J. Org. Chem.* **1991**, *56*, 984.

with $J_{C-C-F} = 29$ Hz. This upfield shift resulted from the formation of the OH group and introduction of the CF_3 moiety. The CF_3 carbon appeared as a quartet at about δ 125.6 for **3a** with $J_{C-F} = 283$ Hz. Similar results were observed in the ^{13}C NMR spectra of **3b**−**f**.

In summary, we have developed a very efficient method for the synthesis of *trans*-α-trifluoromethyl allylic alcohols via the direct nucleophilic trifluoromethylation of *trans*-enones with TMS-CF_3. The reaction is very selective. Reaction conditions are very mild, and the isolated yields are excellent.

Acknowledgment. This work was supported by the National Science Foundation (Grant No. CHE-9720365). We would like to thank Dr. Gary Knerr for obtaining HRMS.

Supporting Information Available: Experimental procedure and characterization data for compounds **2b**−**f** and **3b**−**f**; IR, NMR (^1H, ^{13}C and ^{19}F), MS. High-resolution mass spectroscopic (HRMS) data for **2e**, **3b, 3c,** and **3e**.

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