TBAF-Catalyzed Direct Nucleophilic Trifluoromethylation of α-Keto Amides with Trimethyl(trifluoromethyl)silane

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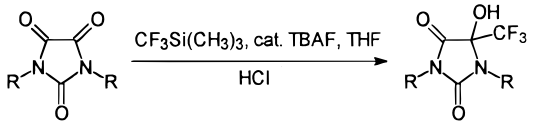
Introduction

Synthetic and structural aspects of organofluorine compounds derived directly from nonfluorinated precursors by using fluorinating agents have been the focal point of vigorous research.[1] Biological activity[2] and numerous commercial applications[3] of organofluorine compounds have also aroused interest. 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 the physical and chemical properties of the derived fluorinated compounds and also induces novel reactivities. These changes have been exploited in the fields of pharmaceutical, agrochemical, and polymer chemistry.[4]

α-Hydroxy α-trifluoromethylated amides are of particular interest due to their structural analogy to some of the antiandrogens which have found application in the treatment of prostate cancer in humans.[5] There are very few literature reports on fluorinated amides.[6] α-Hydroxy α-trifluoromethylated amides were earlier synthesized by J. C. Tatlow[7] by using the reaction of concentrated sulfuric acid with hydroxy trifluoromethylated cyanohydrin under drastic conditions but the yields were low. Recently, Prakash et al. have reported[8] the low yield preparation of some trifluoromethylated amides which involved the reaction of trifluoromethylated silyl ethers with acetonitrile (solvent) followed by the addition of excess sulfuric acid/acetic acid. Previously we have demonstrated[9] that TMS-CF_3 can be used to generate trifluoromethylated alcohols by trifluoromethylation of a variety of sulfur and carbon centers. We have now extended this chemistry to the study of the reactions of TMS-CF_3 with some α-keto amides. We report the synthesis of several α-hydroxy α-trifluoromethylated amides in excellent isolated yields.

Results and Discussion

Little is known about the trifluoromethylation of amides. It was reported that *N*-methylsuccinimide, an imide with an activated carbonyl group, reacted with TMS-CF_3 in the presence of a catalytic amount of TBAF to give the expected corresponding trifluoromethylated alcohol in almost quantitative yields after acid hydrolysis.[10] However, a similar system with a double bond in the ring, i.e., *N*-methylmaleimide,[11] reacted with TMS-CF_3 in the presence of TBAF to give the corresponding trifluoromethylated alcohol in only 40% yield. Imidazolidinetrione-based systems that contain an activated amide carbonyl were also reported[12] to react with TMS-CF_3 in THF in the presence of a catalytic amount of TBAF to produce trifluoromethylated derivatives in low yields as shown in the following equation:



R	yield (%)
CH_3	50
cyclohexyl	58
C_6H_5	25

These studies have shown clearly that the success of nucleophilic trifluoromethylation of amides is a function of the structure of the substrates.

Potassium fluoride has been used by us as an initiator for the reactions of TMS-CF_3 with many inorganic substrates.[9] Here we report that TBAF is an initiator at room temperature for organic substrates such as α-keto amides. The α-keto amides can be easily prepared by literature procedures either by palladium-catalyzed carbonylation reactions[13] or by converting the α-keto acids into the corresponding halides[14] followed by reaction with secondary amines.

Initially we studied the optimization of the reaction conditions (Scheme 1) by using $PhCOCONEt_2$ (**1a**) as a substrate. To avoid the formation of the addition products formed by reaction at both carbonyls, the reaction was run at 0 °C. Substrate (**1a**) and TMS-CF_3 were dissolved in THF and cooled to 0 °C, and a catalytic amount of TBAF in THF was added. The temperature was allowed to rise slowly to room temperature over 1 h. The reaction was monitored by ^{19}F NMR and was shown to be complete to give the silyl ether (**2a**) in 3 h. Hydrolysis

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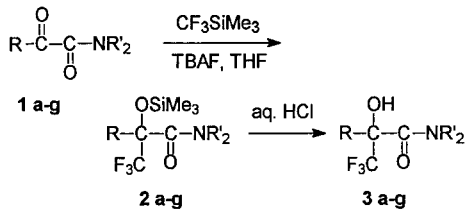
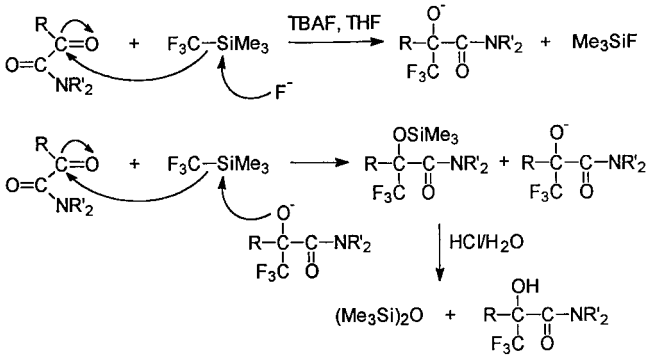
Scheme 1



a: R = Ph, NR'$_2$ = NEt$_2$ **b:** R = Ph, NR'$_2$ = C_4H_8NO
c: R = Ph, NR'$_2$ = $C_5H_{10}N$ **d:** R = CH_3, NR'$_2$ = NEt_2
e: R = CH_3, NR'2= $C_5H_{10}N$,
f: R = Ph, NR'$_2$ = $N[CH_2CH(CH_3)_2]_2$
g: R = CH_3, NR'$_2$ = $N[CH_2CH(CH_3)_2]_2$

Scheme 2



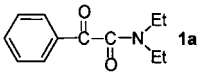
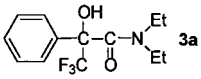
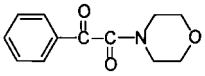
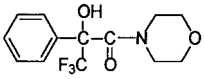
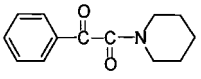
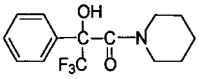
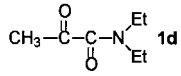
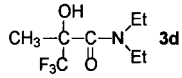
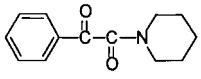
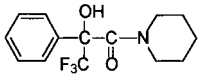
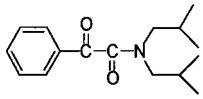
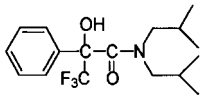
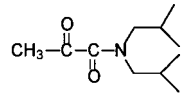
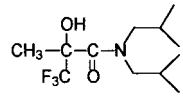
was carried out at room temperature with 4 N HCl for 2 h to give the corresponding α-hydroxy α-trifluoro-methylated derivative (**3a**) in 91% isolated yield. Under these conditions only the α-keto group was found to be reactive. No other products were isolated. At room temperature the same reaction in THF for 3 h followed by acid hydrolysis gave the same single product (**3a**) in 90% isolated yields. All of the α-keto amides (**1b**−**g**) were reacted with TMS-CF_3 in THF with addition of catalytic amounts of TBAF (THF solution) under identical reaction conditions to give the corresponding trifluoromethylated silyl ethers (**2b**−**g**). Hydrolysis of the silyl ethers with 4 N HCl at room temperature formed the α-hydroxy α-trifluoromethylated amides (**3b**−**g**).

Interestingly, we also found that for liquid substrates the reaction goes smoothly in the absence of solvent at room temperature. Thus, the reaction of **1a** or **1g** with TMS-CF_3 and a catalytic amount of TBAF led to the formation of the corresponding silyl ethers **2a** or **2g** in quantitative yields in 1.5 h. After acid hydrolysis, the products **3a** or **3g** were obtained. (Caution: the addition of TBAF should be done very slowly. The reaction is quite exothermic, and larger scale syntheses are not recommended.)

The nucleophilic reaction mechanism for the trifluoromethylation of these α-keto amides with TMS-CF_3 should be the same as that reported for ketones.[10] The reaction involves fluoride ion initiation to form trifluoromethylated oxyanions which catalyze subsequent reaction as shown in Scheme 2.

The α-hydroxy α-trifluoromethylated amides that we have synthesized (Table 1) are colorless solids with sharp melting points with the exception of **3e**, which is a viscous liquid. They are soluble in common organic solvents and very stable to air and moisture. They are easily crystallizable from a mixture of ether and pentane at room temperature or low temperature. The infrared spectra

Table 1. Trifluoromethylation[a] of α-Keto Amides with TMS-CF_3 Catalyzed by TBAF in THF at Room Temperature for 3 h

Entry	Substrate	Product	Yield (%) [b]
1	 **1a**	 **3a**	91
2	 **1b**	 **3b**	95
3	 **1c**	 **3c**	96
4	 **1d**	 **3d**	93
5	 **1e**	 **3e**	94
6	 **1f**	 **3f**	95
7	 **1g**	 **3g**	92

[a] All the reactions were carried out with 5.0 mmol of substrate, 6.0 mmol of TMS-CF_3, and 0.1 mmol of TBAF in 5 mL of THF. [b] Isolated.

of **3a**−**g** show a broad peak in the region 3295−3370 cm^{-1} due to the ν(OH) vibration and a sharp peak in the region 1620−1645 cm^{-1} arising from the (C═O) stretching vibration. In the ^{19}F NMR spectra a single peak was observed in all cases in the range of −72 to −79 ppm for the CF_3 moiety. ^1H NMR spectra (**1a**−**g**) clearly show 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 which appeared at 191.5 ppm in **1a** shifted upfield to 79 ppm in **3a**. It is a quartet with J_{C-C-F} = 28 Hz. This shift results from the formation of the OH group and introduction of the CF_3 moiety. The CF_3 carbon also appeared as a quartet at about 124 ppm in all of the trifluoromethylated products with J_{C-F} = about 283 Hz.

Conclusion

We have developed a very efficient method to prepare α-hydroxy α-trifluoromethylated amides via direct nucleophilic trifluoromethylation of α-keto amides with TMS-CF_3 in the presence of a catalytic amount of TBAF. The reaction is very selective. Only the α-keto group of the amides was found to be reactive, and no side reactions or byproducts were observed. The reaction conditions are very mild, and the isolated yields are excellent.

Experimental Section

General. ^1H, ^{13}C, and ^{19}F NMR spectra were recorded in $CDCl_3$ at 200, 50, and 188 MHz, respectively. Chemical shifts are reported in ppm relative to the standard: $CFCl_3$ for ^{19}F and tetramethylsilane for ^1H and ^{13}C NMR spectra. IR spectra were recorded using NaCl plates for neat liquid and KBr pellets for solids. Mass spectra were taken on an electron impact 70 eV spectrometer, and high-resolution mass spectra were obtained

using a suitable mass spectrometer. Elemental analyses were performed by Desert Analytics Laboratory, Tucson, AZ.

Materials. Trimethyl(trifluoromethyl)silane (TMS-CF_3) was prepared by the literature procedure.[15] Tetrabutylammonium fluoride (TBAF) (1 M solution in THF) was purchased from Aldrich. THF was dried rigorously by refluxing over sodium metal under nitrogen atmosphere. α-Keto amides were prepared by converting the α-keto acids into acid chlorides with α,α-dichloromethyl methyl ether[14] and reacting the acid chlorides with secondary amines in ether in the presence of triethylamine.

General Trifluoromethylation Procedure. In a typical reaction, α-keto amides (5 mM) and trimethyl(trifluoromethyl)-silane (6.0 mM) were dissolved in 5 mL of THF, and tetrabutylammonium fluoride (0.1 mM, 0.1 mL 1 M solution in THF) was added dropwise at room temperature. The reaction was exothermic, and the solution changed from colorless to yellowish brown. 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 product in excellent yields (Table 1).

***N,N*-Diethyl-α-hydroxy-α-(trifluoromethyl)benzeneacetamide (3a):** 91% yield; colorless solid, mp 130−131 °C; IR (KBr) 3370 (b, OH), 1645 (s, C═O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.62/1.16 (t, 6H, J = 7 Hz), 3.18/3.45 (q, 4H, J = 3 Hz), 5.74 (s, 1H), 7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 12.1, 40.5, 79.0 (q, J_{C-C-F} = 28 Hz), 124.0 (q, J_{C-F} = 282 Hz), 126.3, 128.7, 128.9, 135.4, 166.5; ^{19}F NMR ($CDCl_3$) δ −73.2 (s); MS (EI) m/z (species, rel int) 276 (M^+ + H, 100), 258 (M^+ − OH, 26), 100 ($CONEt_2^+$, 33); HRMS calcd for $C_{13}H_{17}F_3NO_2$ (M^+ + H) 276.1211, found 276.1210. Anal. Calcd for $C_{13}H_{16}F_3NO_2$: C, 56.72; H, 5.86; N, 5.09. Found: C, 56.81; H, 5.70; N, 5.05.

4-[2-Hydroxy-2-phenyl-2-(trifluoromethyl)acetyl]morpholine (3b): 95% yield; colorless solid, mp 150−151 °C; IR (KBr) 3295 (b, OH), 1644 (s, C═O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.45 (m, 8), 5.57 (s, broad, 1H), 7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 66.1, 78.9 (q, J_{C-C-F} = 28 Hz), 123.6 (q, J_{C-F} = 282 Hz), 126.2, 128.9, 129.3, 134.5, 166.2; ^{19}F NMR ($CDCl_3$) δ -74.4 (s); MS (EI) m/z (species, rel int) 289 (M^+, 38), 272 (M^+ − OH, 27), 114 ($CONC_4H_8O^+$, 100); HRMS calcd for $C_{13}H_{14}F_3NO_3$ (M^+) 289.0926, found 289.0937.

1-[2-Hydroxy-2-phenyl-2-(trifluoromethyl)acetyl]piperidine (3c): 96% yield; colorless solid; mp 116−117 °C; IR (KBr) 3321 (b, OH), 1634 (s, C═O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (m, 6H), 3.43 (m, 4H), 5.4 (s, broad, 1H), 7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 12.1, 40.5, 79.0 (q, J_{C-C-F} = 28.1 Hz), 124.4 (q, J_{C-F} = 282.2 Hz), 126.3, 128.7, 135.4, 165.7; ^{19}F NMR ($CDCl_3$) δ −72.9 (s); MS (EI) m/z (species, rel int) 288 (M^+ + H, 6), 269 (M^+ − H_2O, 3), 112 ($CONC_5H_{10}^+$, 100); HRMS calcd for $C_{14}H_{17}F_3NO_2$ (M^+ + H) 288.1211, found 288.1212. Anal. Calcd for $C_{14}H_{16}F_3NO_2$: C, 58.53; H, 5.61; N, 4.88. Found: C, 58.38; H, 5.83; N, 4.73.

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***N,N*-Diethyl-α-hydroxy-α-(trifluoromethyl)propanamide (3d):** 93% yield; colorless solid; mp 39−40 °C; IR (KBr) 3338 (b, OH), 1625 (s, C═O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.09 (t, 6H, J = 6 Hz), 1.58 (s, 3H), 3.46 (q, 4H, J = 4 Hz), 5.50 (s, broad, 1H); ^{13}C NMR ($CDCl_3$) δ 12.3, 20.4, 42.69, 75.2 (q, J_{C-C-F} = 28.9 Hz), 124.3 (q, J_{C-F} = 284.2 Hz); ^{19}F NMR ($CDCl_3$) δ −78.6 (s); MS (EI) m/z (species, rel int) 213 (M^+, 66), 196 (M^+ − OH, 10), 100 ($CONEt_2^+$, 57); HRMS calcd for $C_8H_{14}F_3NO_2$ (M^+) 213.0977, found 213.0993.

1-[2-Hydroxy-2-(trifluoromethyl)propionyl]piperidine (3e): 94% yield; colorless viscous liquid; IR (neat) 3335 (b, OH), 1628 (s, C═O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.57(m, 6H), 1.66 (s, 3H), 3.61 (m, 4H), 5.50 (s, broad, 1H); ^{13}C NMR ($CDCl_3$) δ 20.4, 24.2, 25.9, 47.2, 74.5 (q, J_{C-C-F} = 29.5 Hz), 124.3 (q, J_{C-F} = 283.7 Hz); ^{19}F NMR ($CDCl_3$) δ −78.6 (s); MS (EI) m/z (species, rel int) 225 (M^+, 35), 208 (M^+ − OH, 5), 112 ($CONC_5H_{10}^+$, 36); HRMS calcd for $C_9H_{14}F_3NO_2$ (M^+) 225.0977, found 225.0969.

α-Hydroxy-*N,N*-diisobutyl-α-(trifluoromethyl)benzeneacetamide (3f): 95%; colorless solid; mp 145−146 °C; IR (KBr) 3305 (b, OH), 1628 (s, C═O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.37 (d, 6H, J = 6.5 Hz), 0.86 (d, 6H, J = 6.5 Hz), 1.87 (m, 2), 2.85 (m, 2H), 2.97 (m, 2H), 5.82 (s, 1H), 7.37 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 18.7, 19.7, 25.5, 53.4, 76.0 (q, J_{C-C-F} = 28.2 Hz), 124.0 (q, J_{C-F} = 285.9 Hz), 126.8, 128.6, 128.9, 135.9, 167.8; ^{19}F NMR ($CDCl_3$) δ −72.6 (s); MS (EI) m/z (species, rel int) 332 (M^+ + H, 61), 315 (M^+ − OH, 41), 156 ($CON[CH_2CH(CH_3)_2]_2^+$, 20); 57 ($CH_2CH(CH_3)_2^+$, 100); HRMS calcd for $C_{17}H_{25}F_3NO_2$ (M + H) 332.1837, found 332.1856. Anal. Calcd for $C_{17}H_{24}F_3NO_2$: C, 61.62; H, 7.25; N, 4.23. Found: C, 61.40; H, 7.37; N, 4.35.

α-Hydroxy-*N,N*-diisobutyl-α-(trifluoromethyl)propanamide (3g): 92% yield; colorless solid, mp 64−65 °C; IR (KBr)) 3338 (b, OH), 1620 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (d, 6H, J = 6 Hz), 0.89 (d, 6H, J = 6 Hz), 1.68 (s, 3H), 2.00 (m, 2H), 3.09 (m, 2H), 3.45 (m, 2H), 5.49 (s, broad, 1H); ^{13}C NMR ($CDCl_3$) δ 19.26, 19.58, 19.81, 21.53, 26.35, 54.25, 74.69 (q, J_{C-C-F} = 29.3 Hz), 124.41 (q, J_{C-F} = 286.0 Hz); ^{19}F NMR ($CDCl_3$) δ −78.05 (s); MS (EI) m/z (species, rel int) 269 (M^+, 19), 252 (M^+ − OH, 4), 226 (M^+ − $CH(CH_3)_2$, 94), 156 ($CON[CH_2CH(CH_3)_2]_2^+$, 11); HRMS calcd for $C_{12}H_{22}F_3NO_2$ (M^+) 269.1598, found 269.1610. Anal. Calcd for $C_{12}H_{22}F_3NO_2$: C, 53.52; H, 8.18; N, 5.20. Found: C, 53.76; H, 8.33; N, 5.16.

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Supporting Information Available: Tables of crystal data and structure determination, displacement parameters for hydrogen and non-hydrogen atoms, anisotropic displacement parameters, and bond distances and angles for **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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