One Flask Preparation of Trifluoromethylated Amides from Ketones and Trifluoromethyltrimethylsilane *via* Ritter Reaction with Nitriles[1]

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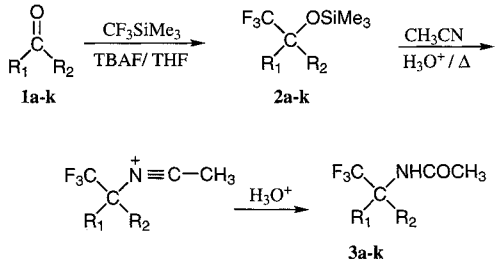
Abstract: Trifluoromethylated amides are prepared in a simple one-flask reaction *via* the Ritter reaction of the corresponding trifluoromethylated silyl ethers, which themselves are readily obtained from the starting ketones and trifluoromethyltrimethylsilane. The yields are good to average.

Fluorine can have profound and often unexpected effects on the activity of organic and bio-organic compounds.[2] Since the anticarcinogenic therapeutic effect of 2-[3] and 5-fluorouracil[4] derivatives and fluorosteroids[5] were discovered in the 1950's, interest in new methods for obtaining fluoro compounds with potential biological activities has continued. Partially fluorinated organic compounds have found diverse applications in materials science, agro, and pharmaceutical industry.[6] The effectiveness and utility of fluorine as a substituent is generally attributed to the high electronegativity of the fluorine atom, and the closeness in its van der Waal's radius (1.35 Å) with hydrogen (1.20 Å). Fluorine also imparts increased oxidative and thermal stability, due to the high carbon-fluorine bond strength (108 kcal/ mol).

In recent years, (trifluoromethyl)trimethylsilane, CF_3SiMe_3 **1**, and other perfluoroalkyl(trialkyl)silanes have become very useful perfluoroalkylation reagents.[7] The initial report of Prakash et al., on the trifluoromethylating properties of **1** with a variety of aldehydes and ketones[8] provides an easy route to the corresponding trifluoromethylated compounds. Although there are numerous examples of trifluoromethylated alcohols,[9] there are few trifluoromethylated amides reported.[10] We now describe an easy synthesis of trifluoromethylated amides **3a-3k**, *via* the Ritter reaction[11] of the corresponding trifluoromethylated silyl ethers **2a-2k** (Scheme 1). Addition of nitriles to alkenes or alcohols in the presence of a strong protic acid such as concentrated sulfuric acid and subsequent hydrolysis results in the formation of the corresponding amides. The mechanism is assumed to involve the protolytic formation of a carbocation (an α-trifluormethyl substituted carbocation in the present case) which adds to the nitrile, followed by hydrolysis of the nitrilium ion to the amide.



Scheme 1

A typical procedure is as follows. To a solution of ketone **1a-1k** (1.25 mmol) in THF (2.5 mL) was added CF_3SiMe_3 (0.25 mL, 1.5 mmol) and a catalytic amount of tetrabutylammonium fluoride (0.0625 mL, 0.0625 mmol). Conversion to the trifluoromethylated silyl ethers **2a-2k** is usually complete within several hours. The solvent THF is then vacuum evaporated, replaced with CH_3CN (10 - 20 mL), followed by addition of excess sulfuric acid/acetic acid (see Table 1) (0.5 - 3.0 mL), and the reaction mixture set to reflux. Only low conversion of the alcohol to the amide can be achieved at room temperature. Reaction times and reaction conditions differ slightly depending on the substrate (Table 1). Once the reaction is complete as indicated by ^{19}F NMR, the reaction mixture is carefully neutralized with aqueous $NaHCO_3$, and extracted several times with dichloromethane. Evaporation of the solvent gives the crude trifluoromethylated amide **3a-3k**, which is further purified through column chromatography.

Table 1. Reaction Times and Conditions

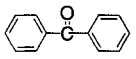
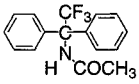
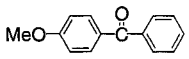
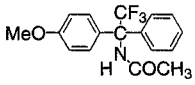
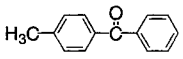
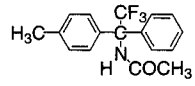
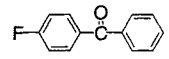
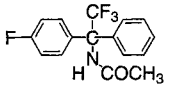
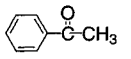
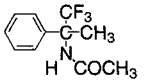
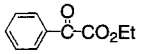
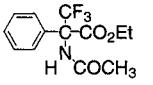
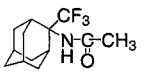
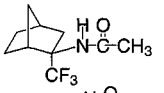
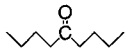
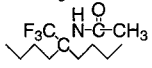
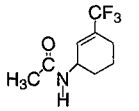
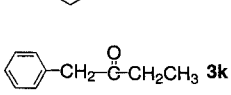
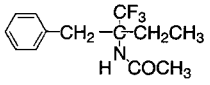
Entry	Product	Reaction Time	Ritter Conditions
1a	**3a**	5h	0.25 mL H_2SO_4/ 0.25 mL AcOH
1b	**3b**	5h	0.25 mL H_2SO_4/ 0.25 mL AcOH
1c	**3c**	5h	0.25 mL H_2SO_4/ 0.25 mL AcOH
1d	**3d**	5h	0.25 mL H_2SO_4/ 0.25 mL AcOH
1e	**3e**	3h	0.5 mL/ H_2SO_4
1f	**3f**	48h	1.5 mL H_2SO_4/ 1.5 mL AcOH
1g	**3g**	24h	0.5 mL H_2SO_4/ 0.5 mL AcOH
1h	**3h**	24h	1.0 mL H_2SO_4/ 1.0 mL AcOH
1i	**3i**	24h	1.0 mL H_2SO_4/ 1.0 mL AcOH
1j	**3j**	3h	0.5 mL H_2SO_4
1k	**3k**	15h	0.25 mL H_2SO_4/ 0.25 mL AcOH

The Ritter reaction for the synthesis of trifluoromethylated amides was investigated for aromatic (**3a-3f**), aliphatic (**3g-3i**) and α,β-unsaturated ketone (**3j**). Amidation for **3j** occurs at the carbon-carbon double bond, rather than the alcohol. Ritter conditions were also applied to trifluoromethylated silyl ether of 1-phenyl-2-butanone (**1k**), which contains acidic benzylic protons. Finally, the Ritter method was investigated in the case of secondary trifluoromethylated alcohol derived from benzaldehye. However, in this case the reaction did not proceed cleanly and gave multiple products, as shown by GC/MS analysis. Amidation was also attempted using excess trimethylsilyl cyanide as the nitrile in sulfuric acid, as reported by Chen et al.,[12] but only the unreacted trifluoromethylated alcohol was isolated. The obtained yields are summarized in Table 2.

In summary, we report a simple and practical method for the preparation of tertiary trifluoromethylated amides, by a one-flask procedure starting from readily available ketones. Work is in progress to utilize the trifluoromethylated amides in the preparation of the corresponding amines and related derivatives.

^1H and ^{13}C NMR spectra were taken in $CDCl_3$ solutions on a Varian unity 300 (300 MHz) instrument; ^{19}F NMR spectra were taken on a Varian 200 (200 MHz) instrument. GC/MS data were obtained from a Hewlett Packard 5890 series. HRMS data were taking using chemical or electron ionization, and performed by the Southern California Mass

Table 2. Preparation of Trifluormethylated Amides

Entry	Starting Ketone	Product	M.p./ °C[a]	Yield[b] (%)
1a		3a 	187-188	68
1b		3b 	130	66
1c		3c 	161-162	81
1d		3d 	180	57
1e		3e 	128	54
1f		3f 		59
1g		3g 	152	40
1h		3h 		32
1i		3i 		32
1j		3j 	73	54
1k		3k 		49

[a]melting points are uncorrected [b]isolated yields

Spectroscopy Facility at University of California Riverside. Elemental analyses were done at Galbraith Laboratories. All starting ketones were commercially available, and used without further purification. All products were isolated as white powders, except for **3f**, **3h**, **3i**, and **3k** which were isolated as pale yellow oils.

***N*-(1,1-diphenyl-2,2,2-trifluoroethyl)acetamide 3a.**
Purified through silica gel with 200:1 dichloromethane/ methanol as eluent. ^{1}H NMR (δ): 2.05 (3H, s); 6.37 (1H, s); 7.36 (10H, b). ^{13}C NMR (δ): 24.2 ($NHCOCH_3$); 68.7 (C-CF_3, q, $J_{C\text{-}C\text{-}F}$ = 27 Hz); 125.5 (CF_3, q, $J_{C\text{-}F}$ = 288 Hz); 128.0 (CH); 128.1 (CH); 128.2 (CH); 128.5 (CH); 136.9 ($C_{quat.}$); 168.4 (CO). ^{19}F NMR (δ): -67.9. Mass spectra, *m/z*: 293 (M^+, 23); 182 (100); 165 (24); 77 (21). Anal. for $C_{16}H_{14}F_3NO$: Calc. C, 65.52; H, 4.81; N, 4.78. Found C, 64.80; H, 4.91; N, 4.68. HRMS, *m/z*: Calc. 294.110 (MH^+). Found 294.111 (MH^+).

***N*-(1-(4-methoxyphenyl)-1-phenyl-2,2,2-trifluoroethyl) acetamide 3b.**
Purified through silica gel with 200:1 dichloromethane/ methanol as eluent. ^{1}H NMR (δ): 2.05 (3H, s); 3.81 (3H, s); 6.32 (1H, s); 6.87 (2H, d, J=9 Hz); 7.27 (2H, d, J=8 Hz); 7.37 (5H, s). ^{13}C NMR (δ): 24.4 ($NHCOCH_3$); 55.2 (CH_3); 68.7 (C-CF_3, q, $J_{C\text{-}C\text{-}F}$ = 27 Hz); 113.5 (CH); 125.5 (CF_3, q, $J_{C\text{-}F}$ = 286 Hz); 128.0 (CH); 128.2 (CH); 128.4 (CH); 128.9 (CH); 129.4 (CH); 136.9 ($C_{quat.}$); 159.4 ($C_{quat.}$); 168.3 (CO). ^{19}F NMR (δ): -68.4. Mass spectra, *m/z*: 323 (M^+, 15); 254 (16); 212 (100); 77 (9). Anal. for $C_{17}H_{16}F_3NO_2$: Calc. C, 63.15; H, 4.99; N, 4.33; F 17.63. Found C, 63.39; H, 5.07; N, 4.19; F, 17.28. HRMS, *m/z*: Calc. 324.121 (MH^+). Found 324.120 (MH^+).

***N*-(1-(4-methylphenyl)-1-phenyl-2,2,2-trifluoroethyl)acetamide 3c.**
Purified through silica gel with 200:1 dichloromethane/ methanol as eluent. ^{1}H NMR (δ): 2.06 (3H, s); 2.36 (3H, s); 6.31 (1H, s); 7.19 (4H, q, J=8 Hz); 7.36 (4H, s). ^{13}C NMR (δ): 20.9 (CH_3); 24.3 ($NHCOCH_3$); 68.8 (C-CF_3, q, $J_{C\text{-}C\text{-}F}$ = 27 Hz); 125.5 (CF_3, q, $J_{C\text{-}F}$ = 288 Hz); 127.9 (CH); 128.0 (CH); 128.2 (CH); 128.4 (CH); 128.9 (CH); 133.9 ($C_{quat.}$); 136.9 ($C_{quat.}$); 138.4 ($C_{quat.}$); 168.3 (CO). ^{19}F NMR (δ): -68.1. Mass spectra, *m/z*: 307 (M^+, 17); 196 (100); 91 (9); 77 (11). Anal. for $C_{17}H_{16}F_3NO$: Calc. C, 66.44; H, 5.25; N, 4.56; F 18.55. Found C 66.36; H, 5.31; N, 4.35; F, 18.93. HRMS, *m/z*: Calc. 308.126 (MH^+). Found 308.125 (MH^+).

***N*-(1-(4-fluorophenyl)-1-phenyl-2,2,2-trifluoroethyl)acetamide 3d.**
Purified through silica gel with 200:1 dichloromethane/ methanol as eluent. ^{1}H NMR (δ): 2.06 (3H, s); 6.28 (1H, s); 7.03 (2H, t, J=8Hz); 7.35 (7H, s). ^{13}C NMR (δ): 24.3 ($NHCOCH_3$); 68.7 (C-CF_3, q, $J_{C\text{-}C\text{-}F}$ = 27 Hz); 114.9 (CH); 115.2 (CH); 125.4 (CF_3, q, $J_{C\text{-}F}$ = 287 Hz); 128.1 (CH); 128.3 (CH); 128.7 (CH); 130.2 (CH); 130.3 (CH); 132.4 ($C_{quat.}$); 136.6 ($C_{quat.}$); 162.5 (d, $J_{C\text{-}F}$ = 247 Hz); 168.5 (CO). ^{19}F NMR (δ): -68.8; -113.8. Mass spectra, *m/z*: 311 (M^+, 17); 200 (100); 95 (7); 77 (11). Anal. for $C_{16}H_{13}F_4NO$: Calc. C, 61.74; H, 4.21; N, 4.50. Found C, 61.40; H, 4.44; N, 4.40. HRMS, *m/z*: Calc. 312.101 (MH^+). Found 312.102 (MH^+).

***N*-(1-methyl-1-phenyl-2,2,2-trifluoroethyl)acetamide 3e.**
Purified through silica gel with 200:1 dichloromethane/ methanol as eluent. ^{1}H NMR (δ): 1.95 (3H, s); 2.03 (3H, s); 6.55 (1H, s); 7.29-7.43 (5H, m). ^{13}C NMR (δ): 19.6 (CH_3); 23.8 ($NHCOCH_3$); 62.2 (C-CF_3, q, $J_{C\text{-}C\text{-}F}$ = 27 Hz); 125.6 (CF_3, q, $J_{C\text{-}F}$ = 284 Hz); 126.7 (CH); 128.2 (CH); 136.4 ($C_{quat.}$); 169.2 (CO). ^{19}F NMR (δ): -79.2. Mass spectra, *m/z*: 231 (M^+, 44); 211 (21); 172 (69); 120 (100). Anal. for $C_{11}H_{12}F_3NO$: Calc. C, 57.14; H, 5.23; N, 6.06; F, 24.65. Found C, 57.63; H, 5.43; N, 5.95; F, 25.14. HRMS, *m/z*: Calc. 232.095 (MH^+). Found 232.095 (MH^+).

***N*-(1-phenyl-1-carboethoxy-2,2,2-trifluoroethyl)acetamide 3f.**
Purified through silica gel with 2:1 dichlomethane/ hexanes as eluent. ^{1}H NMR (δ): 1.27 (3H, t, J=7 Hz); 2.28 (3H, s); 4.32 (2H, dq, J_d=1 Hz); 5.50-6.50 (1H, very broad s); 7.41-7.44 (3H, m); 7.63-7.66 (2H, m). ^{13}C NMR (δ): 13.6 (CH_3); 20.5 ($NHCOCH_3$); 62.7 (CO_2CH_2); 80.9 (C-CF_3, q, $J_{C\text{-}C\text{-}F}$ = 30 Hz); 122.1 (CF_3, q, $J_{C\text{-}F}$ = 286 Hz); 126.6 (CH); 128.2 (CH); 129.5 (CH); 130.9 ($C_{quat.}$); 164.3 ($COCH_3$); 167.6 (CO). ^{19}F NMR (δ): -74.3 (CF_3). Mass spectra, *m/z*: 290 (M+1, 14); 198 (79); 176 (46); 156 (76); 105 (100). HRMS, *m/z*: Calc. 290.100 (MH^+). Found 290.083 (MH^+).

***N*-(2-trifluoromethyl-2-adamantyl)acetamide 3g.** Purified through silica gel with 80:1 dichloromethane/ methanol as eluent. ^{1}H NMR (δ): 1.34-2.39 (16H, m); 4.56 (1H, t, J=8 Hz); 6.06 (1H, s). ^{13}C NMR (δ): 23.5 ($NHCOCH_3$); 26.5 (CH); 32.4 (CH_2); 33.9 (CH); 34.9 (CH); 36.9 (CH_2); 38.5 (CH_2); 38.9 (CH_2); 41.5 (CH_2); 46.1 (CH); 51.7 (C-CF_3, q, $J_{C\text{-}C\text{-}F}$ = 23 Hz); 128.9 (CF_3, q, $J_{C\text{-}F}$ = 282 Hz); 168.9 (CO). ^{19}F NMR

(δ): -72.6. Mass spectra, *m/z*: 261 (M^+, 100); 202 (84); 160 (37); 60 (7). Anal. for $C_{13}H_{18}F_3NO$: Calc. C, 59.76; H, 6.94; N, 5.36; F 21.81. Found C, 59.95; H, 6.98; N, 5.37; F, 21.90. HRMS, *m/z*: Calc. 262.142 (MH^+). Found 262.141 (MH^+).

***N*-(2-*endo*-trifluoromethyl-2-norbornyl)acetamide 3h.**
Purified through silica gel with 80:1 dichloromethane/ methanol as eluent. ^1H NMR (δ): 1.24-2.15 (11H, m); 2.29 (1H, s); 3.11 (1H, s). ^{13}C NMR (δ): 21.5 ($NHCOCH_3$); 23.7 (CH_2); 27.5 (CH_2); 37.7 (CH_2); 34.9 (CH); 39.8 (CH_2); 42.7 (CH); 86.9 (C-CF_3, q, J_{C-C-F} = 27 Hz); 125.4 (CF_3, q, J_{C-F} = 284 Hz); 169.1 (CO). ^{19}F NMR (δ): -74.5. Mass spectra, *m/z*: 222 (M+1, 1); 207 (8); 134 (100); 111 (90); 93 (30). HRMS, *m/z*: Calc. 222.111 (MH^+). Found 222.110 (MH^+).

***N*-(1,1-dibutyl-2,2,2-trifluoroethyl)acetamide 3i.**
Purified through silica gel with 80:1 dichloromethane/ methanol as eluent. ^1H NMR (δ): 0.86-0.94 (6H, m); 1.24-1.38 (8H, m); 2.01-2.18 (8H, m). ^{13}C NMR (δ): 13.8 (CH_3); 21.8 ($NHCOCH_3$); 22.9 (CH_2); 25.3 (CH_2); 32.9 (CH_2); 84.8 (C-CF_3, q, J_{C-C-F} = 27 Hz); 125.2 (CF_3, q, J_{C-F} = 286 Hz); 168.8 (CO). ^{19}F NMR (δ): -74.5. Mass spectra, *m/z*: 194 (M-59, 6); 174 (57); 132 (39); 61 (100); 56 (76). HRMS, *m/z*: Calc. 254.173 (MH^+). Found 254.174 (MH^+).

***N*-(3-trifluoromethyl-1-cyclohexenyl)acetamide 3j.**
Purified through silica gel with 80:1 dichloromethane/ methanol as eluent. ^1H NMR (δ): 1.44-2.16 (9H, m); 4.59-4.67 (1H, broad m); 5.77-5.804 (1H, broad m); 6.18 (1H, s). ^{13}C NMR (δ): 19.3 (CH_2); 21.7 (CH_2); 22.9 ($NHCOCH_3$); 28.2 (CH_2); 44.1 (CH); 123.3 (CF_3, q, J_{C-F} = 272 Hz); 130.7 (CH, q, $J_{C-C-C-F}$ = 6 Hz); 131.2 (C-CF_3, q, J_{C-C-F} = 30 Hz); 169.7 (CO). ^{19}F NMR (δ): -70.4. Mass spectra, *m/z*: 207 (M^+, 44); 137 (97); 96 (100). HRMS, *m/z*: Calc. 208.095 (MH^+). Found 208.094 (MH^+).

***N*-(1-ethyl-1-benzyl-2,2,2-trifluoroethyl)acetamide 3k.**
Purified through silica gel with 80:1 dichloromethane/ methanol as eluent. ^1H NMR (δ): 1.00 (3H, dt, J=7Hz); 2.00-2.14 (5H, s overlapping q); 2.38-2.44 (1H, broad m); 3.44 (2H, s); 7.20-7.33 (5H, m). ^{13}C NMR (δ): 7.9 (CH_3); 21.9 ($NHCOCH_3$); 25.9 (CH_2); 38.3 (CH_2); 84.9 (C-CF_3, q, J_{C-C-F} = 26 Hz); 124.9 (CF_3, q, J_{C-F} = 287 Hz); 127.0 (CH); 128.1 (CH); 130.6 (CH); 134.4 (C_{quat}); 169.2 (CO). ^{19}F NMR (δ): -73.7. Mass spectra, *m/z*: 200 (M-59, 99); 185 (100); 131 (32); 91 (64).

Acknowledgment

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