A Convenient Trifluoroacetylation Reagent: *N*-(Trifluoroacetyl)succinimide

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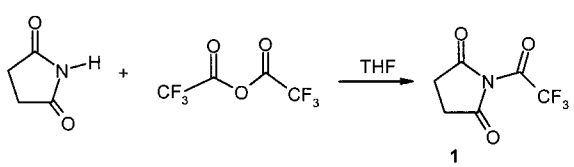
Abstract: *N*-(Trifluoroacetyl)succinimide, easily prepared from trifluoroacetic anhydride and succinimide forms a novel, convenient trifluoroacetylating reagent. It trifluoroacetylates alcohols, phenols and amines, to generate trifluoroacetate esters, and trifluoroacetamides in excellent yields with very efficient work up procedures.

Key words: *N*-(trifluoroacetyl)succinimide, trifluoroacetylating reagent, trifluoroacetate esters, trifluoroacetamides

Trifluoroacetylation has many uses in the protection and activation of functional groups.[1] Recently, we have reported trifluoroacetylbenzotriazole as a convenient novel trifluoroacetylation reagent for amines and alcohols.[2] Continuing our research work on this area, we found that *N*-(trifluoroacetyl)succinimide is an easily prepared, crystalline solid trifluoroacetylating reagent with a unique advantage: the byproduct of the reaction, succinimide is a solid sparingly soluble in most organic solvents and therefore easily removed from the reaction mixture.

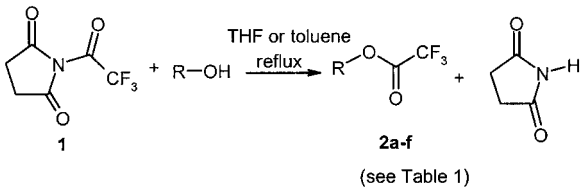
The only previous literature report of *N*-(trifluoroacetyl)succinimide[3] is its formation by oxidation of *N*-(trifluoroacetyl)pyrrolidine with ruthenium tetroxide. To the best of our knowledge, no one has prepared *N*-(trifluoroacetyl)succinimide by the simple reaction of succinimide and trifluoroacetic anhydride, and no one has used it as trifluoroacetylating reagent. Bergeron et al. protected primary amines using *N*-(trifluoroacetoxy)succinimide which is prepared from *N*-hydroxysuccinimide and trifluoroacetic anhydride; this reagent needs to be stored in benzene solution in a freezer.[4] We now report a simple procedure for *N*-(trifluoroacetyl)succinimide and its ability to trifluoroacetylate alcohols, phenols and amines.

N-(Trifluoroacetyl)succinimide **(1)** was obtained by reaction of trifluoroacetic anhydride with succinimide in dry tetrahydrofuran at room temperature overnight (Scheme 1). The succinimide gradually dissolved as the reaction took place. After the removal of the solvent and byproduct trifluoroacetic acid, a white solid was obtained which contains 10% succinimide as determined by ^{1}H NMR analysis. Attempts to obtain pure *N*-(trifluoroacetyl)-succinimide by adding excess trifluoroacetic anhydride to the reaction mixture or by recrystallization were unsuccessful. The crude crystalline product can be stored in a sealed bottle for several weeks at 5 °C without decomposition and used directly for trifluoroacetylations.



Scheme 1

Trifluoroacetylation of alcohols or phenols with *N*-(trifluoroacetyl)succinimide **(1)** was carried out at reflux in tetrahydrofuran or toluene. After the reaction was finished, the precipitated byproduct (succinimide) was filtered off, and solvent was then removed to give the trifluoroacetate esters **2a–f** in excellent yields. The trace of succinimide present in the products **2** can be removed by extracting with dry diethyl ether and evaporating the filtrate after removal of undissolved succinimide. The results are summarized in Scheme 2 and Table 1.

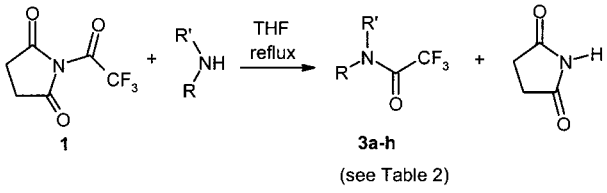


Scheme 2

Table 1 Synthesis of Trifluoroacetates **2**

Compound	R	Solvent	Time (h)	Yield (%)
2a	*n*-$C_{18}H_{37}$	THF	5	95
2b	menthyl	THF	10	86
2c	(1*S*)-*endo*-(–)-bornyl	THF	10	95
2d	3-pentadecylphenyl	THF	12	92
2e	1-naphthyl	toluene	5	99
2f	4-nitrophenyl	toluene	10	96

N-(Trifluoroacetyl)succinimide also reacts with amines to generate trifluoroacetamides **3** in excellent yields as shown in Scheme 3 and Table 2. The workup procedure is again very simple: direct filtration of the succinimide byproduct and removal of the solvent.



Scheme 3

Table 2 Synthesis of Trifluoroacetamides **3**

Compound	R	R'	Time (h)	Yield (%)
3a	2-phenylethyl	H	10	88
3b	4-methylbenzyl	H	12	83
3c	benzyl	benzyl	12	83
3d	1-piperidinyl		12	87
3e	*t*-Bu	H	12	91
3f	phenyl	ethyl	12	92
3g	phenyl	H	12	91
3h	4-nitrophenyl	H	12	86

We have already pointed out that *N*-(trifluoroacetyl)benzotriazole has significant advantages over previously available trifluoroacetylation reagents. *N*-(Trifluoroacetyl)succinimide **(1)** as a trifluoroacetylation reagent shares many of these advantages: (i) ease of preparation, as described above, reagent **1** can easily be prepared from succinimide and trifluoroacetic anhydride at room temperature; (ii) ease of handling, as solid **1** can be stored in a covered bottle for several weeks and weighted out in air; (iii) ease of workup, as the only byproduct, succinimide is precipitated and can be filtered off due to its low solubility in most of solvents; (iv) safe and unambiguous reaction: the only byproduct formed is unreactive; (v) when *N*-(trifluoroacetyl)benzotriazole is used for trifluoroacetylation, the byproduct benzotriazole is most conveniently removed by washing with aqueous sodium hydroxide. Our new reagent **1** is advantageous for the preparation of trifluoroacetate esters which are easily hydrolyzed in aqueous solution.

In a conclusion, *N*-(trifluoroacetyl)succinimide **(1)** is a convenient, practical, and useful trifluoroacetylation reagent due to its ease of preparation, handling and workup. Especially for the preparation of high molecular weight trifluoroacetate esters, *N*-(trifluoroacetyl)succinimide has unique advantages and should be widely applied in organic and bioorganic synthesis.

Mps were measured with a Koefler hot stage apparatus without correction. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini (300 MHz and 75 MHz respectively) spectrometer in $CDCl_3$ or DMSO-d_6 with TMS as the internal standard for ^{1}H and solvent as the internal standard for ^{13}C. Elemental analyses were performed using a Carlo Erba 1106 elemental analyzer. HRMS was measured on an AEI-30 mass spectrometer.

Preparation of *N*-(Trifluoroacetyl)succinimide (1)

To a solution of succinimide (9.8 g, 0.1 mol) in anhyd THF (100 mL) was added slowly trifluoroacetic anhydride (30.5 g, 0.15 mol) at rt under N_2. The mixture was stirred overnight until no solid was in the solution. After removal of the solvent, excess of anhydride and byproduct TFA, a white solid was obtained, which contained 10% succinimide as determined by ^{1}H NMR.

^{1}H NMR: δ = 2.95 (s, 4 H).

^{13}C NMR: δ = 172.3, 158.0 (q, *J* = 43.0 Hz), 114.0 (q, *J* = 285.3 Hz), 28.7.

Trifluoroacetylation of Alcohols or Phenols; General Procedure

A solution of alcohol or phenol (5 mmol) and *N*-(trifluoroacetyl)succinimide (8 mmol) in anhyd THF or toluene (20 mL) was stirred under reflux for several hours under N_2. After cooled down, the solid precipitated and was filtered off. Then, the solvent was removed, the product, trifluoroacetate ester **2** was obtained.

Octadecyl Trifluoroacetate (2a)

Colorless oil; yield: 1.74 g (95%).

^{1}H NMR: δ = 0.88 (t, *J* = 6.9 Hz, 3H), 1.15–1.40 (m, 30H), 1.69–1.78 (m, 2H), 4.34 (t, *J* = 6.3 Hz, 2H).

^{13}C NMR: δ = 14.0, 22.7, 25.5, 28.2, 29.1, 29.2, 29.4, 29.5, 29.7, 32.0, 68.3, 114.6 (q, *J* = 283.9 Hz), 157.6 (q, *J* = 41.7 Hz).

$C_{20}H_{37}O_2F_3$	calcd	C	65.52	H	10.18
(366.5)	found		65.16		10.16

Menthyl Trifluoroacetate (2b)

Colorless oil; yield: 1.08 g (86%).

^{1}H NMR: δ = 0.79 (d, *J* = 6.8 Hz, 3H), 0.92–0.95 (m, 6H), 1.04–1.21 (m, 2H), 1.49–1.58 (m, 2H), 1.70–1.77 (m, 2H), 1.80–1.88 (m, 1H), 2.02–2.08 (m, 1H), 4.88 (dt, *J* = 11.0 and 4.5 Hz, 1H).

^{13}C NMR: δ = 16.1, 20.4, 21.7, 23.5, 26.3, 31.4, 33.9, 40.1, 46.8, 79.3, 114.2 (q, *J* = 284.1 Hz), 157.1 (q, *J* = 41.3 Hz).

$C_{12}H_{19}O_2F_3$	calcd	C	57.11	H	7.59
(252.1)	found		56.55		7.66

(1*S*)-*endo*-(–)-Bornyl Trifluoroacetate (2c)

Colorless oil; yield: 1.19 g (95%).

^{1}H NMR: δ = 0.88 (s, 3H), 0.91 (s, 3H), 0.93 (s, 3H), 1.12 (dd, *J* = 14.0 and 3.2 Hz, 1H), 1.24–1.44 (m, 2H), 1.72–1.96 (m, 3H), 2.38–2.50 (m, 1H), 5.10 (dd, *J* = 9.6 and 2.3 Hz, 1H).

^{13}C NMR: δ = 13.2, 18.7, 19.6, 26.8, 27.8, 36.2, 44.8, 48.1, 49.2, 84.9, 114.6 (q, *J* = 285.9 Hz), 157.8 (q, *J* = 42.0 Hz).

HRMS (EI): *m/z* calcd for $C_{12}H_{17}O_2F_3$: 250.1181 (M^+). Found: 250.1183.

3-Pentadecylphenyl Trifluoroacetate (2d)

Colorless oil; yield: 1.84 g (92%).

^{1}H NMR: δ = 0.88 (t, *J* = 6.9 Hz, 3H), 1.15–1.40 (m, 24H), 1.55–1.68 (m, 2H), 2.63 (t, *J* = 7.7 Hz, 2H), 7.00–7.05 (m, 2H), 7.13 (d, *J* = 7.5 Hz, 1H), 7.30–7.38 (m, 1H).

^{13}C NMR: δ = 14.0, 22.7, 29.2, 29.4, 29.5, 29.6, 29.7, 31.1, 31.3, 32.0, 35.7, 35.9, 114.6 (q, *J* = 283.8 Hz), 117.6, 120.3, 127.3, 129.5, 145.4, 149.5, 155.8 (q, *J* = 42.7 Hz).

$C_{23}H_{35}O_2F_3$	calcd	C	68.96	H	8.81
(400.5)	found		69.29		8.95

1-Naphthyl Trifluoroacetate (2e)

Colorless oil; yield: 1.20 g (99%).

^{1}H NMR: δ = 7.31–7.36 (m, 1H), 7.37–7.44 (m, 1H), 7.48–7.54 (m, 2H), 7.72–7.78 (m, 1H), 7.79–7.87 (m, 2H).

^{13}C NMR: δ = 114.9 (q, *J* = 284.0 Hz), 117.2, 120.1, 125.1, 125.5, 127.0, 127.3, 127.4, 128.1, 134.7, 145.0, 155.9 (q, *J* = 43.1 Hz).

$C_{12}H_7O_2F_3$	calcd	C	59.99	H	2.94
(240.0)	found		59.82		3.41

4-Nitrophenyl Trifluoroacetate (2f)

Colorless oil;[2] yield: 1.13 g (96%).

^{1}H NMR: δ = 7.48 (d, *J* = 9.1 Hz, 2H), 8.35 (d, *J* = 9.1Hz, 2H).

^{13}C NMR: δ = 114.3 (q, *J* = 283.6 Hz), 121.7, 125.5, 146.4, 153.3, 154.9 (q, *J* = 44.5 Hz).

HRMS (EI): *m/z* calcd for $C_8H_4NO_4F_3$: 235.0092 (M^+). Found: 235.0085.

Trifluoroacetylation of Amines; General Procedure
A solution of amine (5 mmol) and *N*-(trifluoroacetyl)succinimide (8 mmol) in anhyd THF (20 mL) was stirred at reflux for 12 h under N_2. After cooled down, the solid was precipitated and filtered off. Then, the solvent was removed and the product, trifluoroacetamide **3** was obtained.

***N*-(2-Phenylethyl)trifluoroacetamide (3a)**
Solid; yield: 0.96 g (88%); mp 57–58 °C.

^{1}H NMR: δ = 2.87 (t, *J* = 7.0 Hz, 2H), 3.57 (q, *J* = 6.8 Hz, 2H), 6.81 (br s, 1H), 7.18 (d, *J* = 6.9 Hz, 2H), 7.21–7.36 (m, 3H).

^{13}C NMR: δ = 34.8, 41.0, 115.7 (q, *J* = 286.0 Hz), 126.7, 128.6, 128.8, 137.6, 157.3 (q, *J* = 37.7 Hz)

$C_{10}H_{10}NOF_3$	calcd	C	55.28	H	4.64	N	6.45
(217.2)	found		54.99		4.74		6.11

***N*-(4-Methylbenzyl)trifluoroacetamide (3b)**
White solid; yield: 0.96 g (83%); mp 99–100 °C (Lit.[2] mp 100–102 °C).

^{1}H NMR: δ = 2.36 (s, 3H), 4.49 (d, *J* = 5.8 Hz, 2H), 6.51 (br s, 1H), 7.19 (s, 4H).

^{13}C NMR: δ = 21.0, 43.6, 115.8 (q, *J* = 285.8 Hz), 127.9, 129.6, 132.9, 138.0, 157.2 (q, *J* = 34.6 Hz).

***N,N*-Dibenzyltrifluoroacetamide (3c)**
Oil; yield: 1.22 g (83%) (Lit.[5] bp 140–142 °C/0.4 Torr).

^{1}H NMR: δ = 4.52 (s, 4H), 7.15–7.23 (m, 4H), 7.32–7.42 (m, 6H).

^{13}C NMR: δ = 48.3, 49.6, 116.7 (q, *J* = 286.7 Hz), 127.3, 128.0, 128.2, 128.3, 128.8, 129.0, 133.9, 134.5, 157.9 (q, *J* = 36.3 Hz).

1-(Trifluoroacetyl)piperidine (3d)
Oil; yield: 0.79 g (87%) (Lit.[2] bp 77 °C/15 Torr).

^{1}H NMR: δ = 1.60–1.78 (m, 6H), 3.56–3.62 (m, 4H).

^{13}C NMR: δ = 23.8, 25.2, 26.2, 45.2, 47.2, 116.5 (q, *J* = 285.3 Hz), 156.0 (q, *J* = 35.3 Hz).

***N*-*tert*-Butyltrifluoroacetamide (3e)**
Yellow solid; yield: 0.77 g (91%); mp 45–47 °C (Lit.[2] mp 44 °C); a mixture of two isomers.

^{1}H NMR: δ = 1.38 (s, 9H), 6.25 (br s, 1H).

^{13}C NMR: δ = 27.8 [27.1], 53.4 [54.0], 115.6 (q, *J* = 286.4 Hz) [115.5 (q, *J* = 286.3 Hz)], 160.1 (q, *J* = 39.8 Hz) [157.1 (q, *J* = 36.1 Hz)].

***N*-Ethyl-*N*-phenyltrifluoroacetamide (3f)**
Oil; yield: 1.00 g (92%) (Lit.[2] bp 120 °C/11 Torr).

^{1}H NMR: δ = 1.18 (t, 3H, *J* = 7.1 Hz), 3.80 (q, 2H, *J* = 7.2 Hz), 7.20–7.23 (m, 2H), 7.42–7.44 (m, 3H).

^{13}C NMR: δ = 11.7, 47.3, 116.3 (q, *J* = 285.6 Hz), 128.1, 129.2, 129.4, 138.3, 157.8 (q, *J* = 37.0 Hz)

***N*-Phenyltrifluoroacetamide (3g)**
Solid; yield: 0.86 g (91%); mp 87–88 °C (Lit.[6] mp 88–89 °C).

^{1}H NMR: δ = 7.23 (t, *J* = 7.2 Hz, 1H), 7.37 (t, *J* = 7.9 Hz, 2H), 7.56 (d, *J* = 7.9 Hz, 2H).

^{13}C NMR: δ = 115.7 (q, *J* = 287.0 Hz), 120.6, 126.4, 129.3, 135.1, 155.0 (q, *J* = 37.0 Hz).

***N*-(4-Nitrophenyl)trifluoroacetamide (3h)**
Yellow solid; yield: 1.01 g (86%); mp 150–151 °C (Lit.[2] mp 151–152 °C).

^{1}H NMR (DMSO-d_6): δ = 7.97 (d, *J* = 9.3 Hz, 2H), 8.31 (d, *J* = 9.3 Hz, 2H), 11.8 (s, 1H).

^{13}C NMR (DMSO-d_6): δ = 115.5 (q, *J* = 286.7 Hz), 121.0, 124.8, 142.4, 144.0, 155.0 (q, *J* = 37.8 Hz).

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