Pergamon

Tetrahedron Letters 42 (2001) 8181–8183

TETRAHEDRON LETTERS

Trifluoromethylation of heterocumulenes with trimethyl(trifluoromethyl)silane in the presence of fluoride ions: synthesis of trifluoroacetamides and trifluorothioacetamides from isocyanates and isothiocyanates

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Received 15 June 2001; revised 18 September 2001; accepted 19 September 2001

Abstract—Trimethyl(trifluoromethyl)silane reacts in the presence of fluoride ions with isocyanates and isothiocyanates under mild conditions to give corresponding trifluoroacetamides and trifluorothioacetamides in high yields. © 2001 Published by Elsevier Science Ltd.

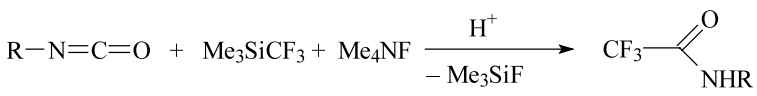
Trimethyl(trifluoromethyl)silane, Me_3SiCF_3, at present time is the most easily accessible and convenient source of the trifluoromethyl anion.[1,2] The importance of this reagent in fluorine chemistry might be compared with that of Grignard reagents introduced in organic chemistry about 150 years ago. Good storage and hydrolytic stability, ease in dosation and usability over a wide range of reaction conditions (in polar and nonpolar solvents, at different temperatures) exhibit great interest in this compound as a potential trifluoromethylating agent.[1,2]

The feasibility of the formal addition of the trifluoromethyl anion to the carbonyl bond was confirmed on a variety of organic substrates[3], however no examples of the addition of the 'anion', i.e. $[Me_3Si(CF_3)_2]^-$,[4] generated from trimethyl(trifluoromethyl)silane in the presence of fluoride ions, to heterocumulenes has been reported so far.

We have started on a systematic study of reactions of equivalents of trifluoromethyl, other perfluoroalkyl or pentafluorophenyl anions with heterocumulenes of the type R–X=Y=Z, where X=N, S; Y=C, S; Z=O, S in different combinations (isocyanates, isothiocyanates, sulfinylamines and so on).

In the present work, we used commercially available compounds with heterocumulene bonds, isocyanates and isothiocyanates, as substrates for the addition of the trifluoromethyl anion.

It has to be noted that nucleophilic addition of organometallic (magnesium and lithium) compounds to



1

a : R = c-C_6H_{11}
b : R = 1-Ad
c : R = 4-FC_6H_4

2

Scheme 1.

Keywords: iso(thio)cyanates; trifluoro(thio)acetamides; trifluoromethylation.
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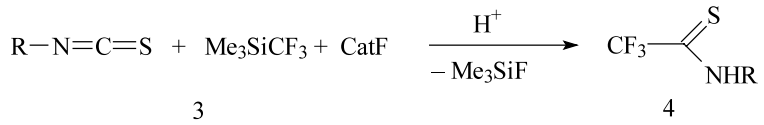
PII: S0040-4039(01)01764-6



3 4

Cat = Me_4N, Cs

a : R = Me
b : R = Et
c : R = Ph
d : R = 4-$NO_2C_6H_4$
e : R = 4-FC_6H_4

Scheme 2.

Table 1. Reactions of isocyanates and isothiocyanates with Me_3SiCF_3 and Me_4NF

Product	R	Reagents (mmol)			Monoglyme (mL)	Purification[a]	Isolated yield (%)	Mp (°C), bp (°C/Torr)
		RNCO(S)	Me_4NF	Me_3SiCF_3				
2a	*c*-C_6H_{11}	2.40	2.40	2.52	3	c[b]	91	98 (94–95[9])
2b	1-Ad	1.48	1.49	1.56	3	c[c]	94	95–96 (271–274[10])
2c	4-FC_6H_4	1.82	1.83	1.92	4	c[d]	89	112 (111–112.5[11])
4a	Me	2.39	2.39	2.51	5	v.d.	95	44/30
4b	Et	2.30	2.30	2.42	4	v.d.	92	65/12
4c	Ph	1.80	1.80	1.89	3	c[c]	90	28 (27.5–28.5[8])
						v.d.		72/0.4
4d	4-$NO_2C_6H_4$	1.72	1.72	1.81	3	c[e]	88	107
4e	4-FC_6H_4	2.90	2.90	3.05	6	v.d.	90	56–57/0.5

[a] Crystallization (c), vacuum distillation (v.d.).
[b] From *n*-pentane.
[c] From *n*-hexane.
[d] From diethyl ether *n*-pentane.
[e] From diethyl ether.

bonds –N=C=O and –N=C=S was investigated comprehensively[5,6] whereas, to the best of our knowledge, there are no reports on the interaction of perfluoroalkylating reagents with these groups.

We found out that the reaction of isocyanates **1a–c** with Me_3SiCF_3 in the presence of tetramethylammonium fluoride in THF or monoglyme, at −60 to +20°C, followed by protolysis with hydrochloric acid, gives *N*-substituted trifluoroacetamides **2a–c** in 85–95% yield (Scheme 1).[7]

In contrast to trifluoroacetamides, which can be obtained by other simple methods from readily available starting compounds, the synthesis of trifluorothioacetamides usually entails considerable difficulties.[8]

Isothiocyanates **3a–e** react with trimethyl(trifluoromethyl)silane in the presence of fluoride ions, under conditions similar to those used in the trifluoromethylation reactions of isocyanates, to give trifluorothioacetamides **4a–e** in 80–90% yield (Scheme 2).[7] Besides tetramethylammonium fluoride, dry cesium fluoride can be used in these reactions as a fluoride source; whereas potassium fluoride remains unreactive under the chosen conditions (THF solution).

Reaction conditions, yields and physical properties of amides **2a–c** and thioamides **4a–e** are summarized in Table 1. Analytic data of new or so far not fully characterized compounds are given in Ref. 7.

Acknowledgements

The generous financial support of this work by the DFG (grant 436 UKR 113) is gratefully acknowledged.

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7. *General procedure:* To a solution of appropriate isocyanate (isothiocyanate) in monoglyme (or THF) at −60°C, tetramethylammonium fluoride and trimethyl(trifluoromethyl)silane were added. The mixtures were stirred for 1 h at −40°C and for 1 h at room temperature. A 0.1 M aqueous solution of HCl was added and the product was extracted with diethyl ether. The extract was washed with water, dried ($MgSO_4$), and purified by crystallization or vacuum distillation.
All compounds reported here were characterized on the basis of analytical and spectroscopic data. Selected data: **2b**: ^{1}H NMR (200.1 MHz, $CDCl_3$): δ 1.65 (broad s, 6H, -Ad), 3.67 (broad s, 6H, -Ad), 2.07 (broad s, 3H, -Ad), 6.03 (broad s, 1H, -NH); ^{19}F NMR (188.3 MHz, $CDCl_3$): δ −76.7 (s); ^{13}C{^{1}H} NMR (50.3 MHz, $CDCl_3$): δ 29.2 (-CH, adamantyl), 35.9 (-CH_2, adamantyl), 40.7 (-CH_2, adamantyl), 53.3 (1C, adamantyl), 115.5 (q, -CF_3, $^1J_{CF}$ = 289.6 Hz), 155.6 (q, C(O), $^2J_{CF}$ = 35.5 Hz). MS (EI, 15 eV, 40°C) m/z: 247 (M^+). Anal. calcd for $C_{12}H_{16}F_3NO$: C, 58.29; H, 6.52; N, 5.66; F, 23.05. Found: C, 58.43; H, 6.18; N, 5.46; F, 23.31. Compound **4a**: ^{1}H NMR (200.1 MHz, CD_2Cl_2): δ 3.17 (d, 3H, $^3J_{HH}$ = 3.4 Hz), 8.29 (broad s, 1H, -NH); ^{19}F NMR (188.3 MHz, CD_2Cl_2): δ −70.3 (s). MS (EI, 15 eV, 25°C) m/z: 143 (M^+). Anal. calcd for $C_3H_4F_3NS$: C, 25.17; H, 2.82; N, 9.79; F, 39.82. Found: C, 25.43; H, 3.04; N, 10.02; F, 40.12. Compound **4b**: ^{1}H NMR (200.1 MHz, $CDCl_3$): δ 1.28 (t, 3H, $^3J_{HH}$ = 6.6 Hz), 3.67 (q, 2H, $^3J_{HH}$ = 6.6 Hz), 8.15 (broad s, 1H, -NH); ^{19}F NMR (188.3 MHz, $CDCl_3$): δ –70.4 (s); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 14.3 (q, -CH_3, $^1J_{CH}$ = 128.1 Hz), 42.7 (t, -CH_2, $^1J_{CH}$ = 141.1 Hz), 119.2 (q, -CF_3, $^1J_{CF}$ = 279.5 Hz), 184.8 (q, C(S), $^2J_{CF}$ = 35.4 Hz). MS (EI, 15 eV, 25°C) m/z: 157 (M^+). Anal. calcd for $C_4H_6F_3NS$: C, 30.57; H, 3.58; N, 8.91; F, 25.54. Found: C, 30.15; H, 3.85; N, 8.71; F, 25.29. Compound **4d**: ^{1}H NMR (200.1 MHz, CD_3CN): δ 8.29 (d, 2H, $^3J_{HH}$ = 9.3 Hz), 8.04 (d, 2H, $^3J_{HH}$ = 9.3 Hz), 10.75 (broad s, 1H, -NH); ^{19}F NMR (188.3 MHz, CD_3CN): δ −68.5 (s). MS (EI, 15 eV, 75°C) m/z: 250 (M^+). Anal. calcd for $C_8H_5F_3N_2O_2S$: C, 38.40; H, 2.01; N, 11.20; F, 22.78. Found: C, 38.07; H, 1.92; N, 10.88; F, 22.53. Compound **4e**: ^{1}H NMR (200.1 MHz, $CDCl_3$): δ 7.12 (t, 2H, $^3J_{HH}$ = 9 Hz), 7.69 (dd, 2H, $^3J_{HH}$ = 9 Hz, $^4J_{HF}$ = 4.8 Hz), 9.35 (broad s, 1H, -NH); ^{19}F NMR (188.3 MHz, $CDCl_3$): δ −70.1 (s, 3F, -CF_3), −112.2 (t, 1F, $^3J_{FH}$ = 8.5 Hz); ^{13}C{^{1}H} NMR (50.3 MHz, $CDCl_3$): δ 116.2 (d, 2C, phenyl, $^2J_{CF}$ = 23 Hz), 117.3 (q, -CF_3, $^1J_{CF}$ = 280.4 Hz), 125.4 (d, 2C, phenyl, $^3J_{CF}$ = 2.3 Hz), 132.3 (1C, phenyl), 161.3 (d, 1C, phenyl, $^1J_{CF}$ = 248.9 Hz), 180.9 (q, C(S), $^2J_{CF}$ = 35.1 Hz). MS (EI, 15 eV, 30°C) m/z: 223 (M^+). Anal. calcd for $C_8H_5F_4NS$: C, 43.05; H, 2.26; N, 6.28; F, 34.05. Found: C, 42.79; H, 1.98; N, 6.02; F, 33.87.
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