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Regioselective addition of trimethylsilyl cyanide to *E*-1,1,1-trifluoro-4-ethoxybut-3-en-2-one

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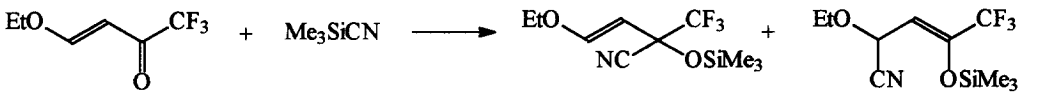
Abstract: The 1,2- and 1,4-addition reactions of trimethylsilyl cyanide to 1,1,1-trifluoro-4-ethoxybut-3-en-2-one were studied. The regioselectivity of this reaction depends on the temperature, the nature of solvent and the catalyst: low temperatures or basic catalysts direct in favour of 1,2-addition while high temperatures or acidic catalysts direct in favour of 1,4-addition.

Keywords: Addition, Trimethylsilyl cyanide, α,β-Unsaturated Ketone, Catalysis

The introduction of the trifluoromethyl group into organic molecules often confers significant and useful changes in their chemical and physical properties and therefore methods for the synthesis of trifluoromethylated compounds have received considerable interest in recent years.[1] Though direct trifluoromethylation is the most attractive and powerful new tool for constructing trifluoromethylated compounds, trifluoromethyl-containing synthons are often used as accessible and convenient starting reagents.[2] *E*-1,1,1-Trifluoro-4-ethoxybut-3-en-2-one **1** is an accessible trifluoromethyl-containing synthon for the synthesis of various fluorine-containing substances: dyes, heterocycles, enaminones, drugs and for use as a protective reagent for amino groups in peptide synthesis.[3] Generally, nucleophiles attack the β-carbon atom of the carbon-carbon double bond of **1** with elimination of ethanol. Until now, few cases of 1,2-addition to the C=O group using organozinc or lithium reagents were known.[4] During our investigation of new fluorinated synthons, we expected that the reaction of TMSCN and enone **1** would be useful for the construction of new polyfunctional trifluoromethyl-containing compounds because **1** is an α,β-unsaturated ketone and the addition reaction of TMSCN could yield both 1,2- and 1,4-adducts with CF_3- and CN-groups.

Scheme 1



1 **2** **3** **4**

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The first attempts to carry out conjugate additions of TMSCN to α,β-unsaturated ketones were unsuccessful.[5] Utimoto and his co-workers[6] could obtain the products of 1,4-cyanosilylation of cyclohexenones by the combined use of TMSCN and Lewis acids, such as Et_3Al, ZnI_2 and $AlCl_3$. Recently Onaka and his co-workers[7] reported that TMSCN 1,4-adducts of enones were produced in the presence of strong solid acids, such as Fe^{3+} and Sn^{4+} ion-exchanged Montmorillonites, while 1,2-adducts were produced in the presence of solid bases, such as CaO, MgO. In this letter we describe the results of our study on TMSCN addition reactions to enone **1**.

We found that reaction of TMSCN and enone **1** (**Scheme 1**) takes place readily at room temperature without solvent and is complete within 1 day to give the 1,2-adduct **3** in quantitative yield (entry 1, Table 1). An increase in reaction temperature results in the formation of the 1,4-adduct **4** as a new product and conjugated cyanosilylation becomes dominant above 100°C. The optimum temperature for the formation of the adduct **4** is 145°C as further increase of reaction temperature leads to decomposition of reaction products (entry 3, Table 1). Satisfactory analytical data (NMR ^1H, ^{19}F, ^{13}C spectra and elemental analyses) were obtained for the adducts **3** and **4**.[8] The double bond of the product **3** retains the *E* configuration: $^3J_{HH}$ 12.5 Hz. Theoretically the adduct **4** can exist in two isomeric forms *E*- or *Z*- but we observed only a single isomer of the product **4** in the reaction mixture. The *Z*-configuration of the trisubstituted double bond in **4** was assigned by ^{13}C NMR spectroscopy: the $^3J_{CF}$ (4 Hz)[8] value for the carbon atom at position 3 confirms the *cis*-orientation between the CF_3 group and the olefinic proton according to the rule which was proposed by Bégué and his co-workers.[9]

Table 1. The influence of temperature.[a]

Entry	Temperature, °C	Time, h	Yield, %	Ratio	
				3	**4**
1	20	24	>99	95	5
2	70	20	97	45	55
3	145	3	85	18	82

a) 0.6g (6.06mM) of **2** was added to 0.8g (4.76mM) of **1** in a sealed micro vial with GLC monitoring of the reaction mixture; the product ratio was analyzed by ^{19}F and ^1H NMR spectroscopy.

Table 2. The influence of solvent.[a]

Entry	Solvent	ε	Time,	Ratio, %			
			Day	**1**	**3**	**4**	Others
1	Hexane	1.89	1	91	6	0	3
2	CCl_4	2.23	1	84	14	1	1
3	PhMe	2.38	1	97	3	0	0
4	$CHCl_3$	4.7	1	87	11	1	1
5	$CHCl_3$	4.7	3	77	21	1	1
6	CH_2Cl_2	8.9	1	71	28	1	0
7	CH_2Cl_2	8.9	3	28	59	9	4
8	Et_2O	4.34	1	38	37	16	9
9	$MeCO_2Et$	6.02	1	40	48	9	3
10	THF	7.32	1	0	50	47	3
11	MeCN	36.2	1	0	93	2	5
12	DMF	36.7	30 min	0	0	0	100
13	DMSO	49	30 min	0	0	0	100
14	$(Me_2N)_2CO$		30 min	0	0	0	100

a) to the solution of 0.6g (6.06mM) of **2** in 5 mL of the corresponding solvent, 0.8g (4.76mM) of **1** was added at rt with GLC monitoring of the reaction mixture; the product ratio was analyzed by ^{19}F and ^1H NMR spectroscopy.

The influence of temperature on the regioselectivity of trimethylsilylcyanation of α,β-unsaturated ketones has not been observed before. It is possible to assume that **4** is formed by an isomerisation of **3** as was

determined by Onaka and his co-workers[7] in case of nonfluorinated α,β-unsaturated ketones. We have tried to carry out an isomerisation of **3** to **4** under various conditions: **3** (with or without 2 eq of TMSCN) under heating (3 days at 145°C) or in the presence of catalysts (ZnI_2, I_2, CF_3SO_3TMS; 1 week at room temperature) but all our attempts were unsuccessful. We observed only slow decomposition of **3** without formation of any quantity of **4**, indicating on absence or restriction of the equilibrium between **1** and **3**.

The effects of solvents on the reaction between **1** and **2** have also been studied but the choice of solvent has many restrictions. The use of hydroxyl-containing solvents is impossible due to silylation by **2**.[10] In highly polar aprotic solvents such as DMF, DMSO, tetramethylurea, complex mixtures of unidentified products (10-30 peaks in ^{19}F NMR spectra between 70-85 ppm) were obtained without the signals due to **3** and **4** (entries 12-14, Table 2). However, these data allow us to make the following conclusion: an increase of solvent polarity results in not only in an increase of reaction rate, but an increase of amount of **4** in the final reaction mixture (entries 1-7, Table 2). This effect becomes even more appreciable when oxygen or nitrogen atoms are present in the solvent (entries 8-11, Table 2). Earlier we observed[11] an increase in the rate of reaction between **1** and amines with increasing solvent polarity.

The effects of catalysts were also studied (Table 3). Nucleophilic catalysts such as amines (entries 2-5, Table 3) afford adduct **3** very rapidly with high yields and purity; electrophilic catalysts (entries 7-13, Table 3) afford adduct **4**, whereas LiBr affords a mixture of the products **3** and **4** (entry 6, Table 3). It is very interesting and not quite clear how $Hg(OOCCF_3)_2$ causes inhibition of the reaction (compare entries 1 and 14, Table 3). It is necessary to emphasize that catalytic reactions in table 3 were carried out without solvent. Use of solvents (CH_2Cl_2, $CHCl_3$, Et_2O) resulted in a decrease of the reaction rate and an increase of by-product formation.

Table 3. The influence of catalyst.[a]

Entry	Catalyst	Time, min	Yield, %	Ratio	
				3	**4**
1	-	24h	>99	95	5
2[b]	Et_3N	<1	95	100	0
3[b]	$(i\text{-}Pr)_2NEt$	<1	95	100	0
4[b]	DMAP	<1	95	100	0
5	(+)-N-Methylephedrine	3	93	100	0
6	LiBr	5	94	71	29
7[b]	$TiCl_4$	<1	95	<1	>99
8[b]	$Et_2O{\cdot}BF_3$	<1	95	<1	>99
9	$(i\text{-}PrO)_4Ti$	20	89	8	92
10[b]	CF_3SO_3TMS	<1	>97	0	100
11[b]	I_2	<1	>97	0	100
12[b]	ZnI_2	<1	95	0	100
13	$LiClO_4$	<1	>97	0	100
14	$Hg(CF_3COO)_2$	24 h	28[c]	95	5

a) 0.2mM of corresponding catalyst was added to 0.6g (6.06mM) of **2** under stirring at rt and then 0.8g (4.76mM) of **1** was added with GLC monitoring of the reaction mixture; the product ratio was analyzed by ^{19}F and ^{1}H NMR spectroscopy; b) warming of the reaction mixture was observed; c) the rest is 72% of **1**.

In summary, we have found and developed the regioselective trimethylsilylcyanation reaction of **1** which is very sensitive to reaction conditions: temperature, solvents and catalysts afford the two highly functionalized trifluoromethyl-containing adducts **3** and **4**. These fluorinated substances may be utilized as practical building blocks for effective synthesis of bioactive fluorinated compounds.

Experimental procedures for the preparation of:

***E*-4-Ethoxy-2-trifluoromethyl-2-trimethylsilyloxybut-3-enenitrile (3).**

a) A mixture of **2** (6.0 g, 60.6 mmol) and **1** (8.0 g, 47.6 mmol) was stood for 24 h at 20°C. Excess **2** was removed using a water aspirator vacuum. The yield of **3** was 12.7 g (100% with 95% purity).

b) To a mixture of **2** (6.0 g, 60.6 mmol) and Et_3N (250 mg, 2.5 mmol) was added **1** (8.0 g, 47.6 mmol) under stirring and at 0-5°C. Then the mixture was stirred for 30 min at 20°C. The excess of **2** and NEt_3 were removed *in vacuo* and 12.6 g of **2** was obtained in 100% yield and 97% purity. Additional purification of **3** can be performed by vacuum distillation.

***Z*-2-Ethoxy-5,5,5-trifluoro-4-trimethylsilyloxypent-3-enenitrile (4).**

To a suspension of $LiClO_4$ (250 mg) in **2** (6.0 g, 60.6 mmol) was added **1** (8.0 g, 47.6 mmol) with stirring. The reaction mixture warmed up to 60°C. The reaction mixture was stirred for 20 min and distilled. The yield of **4** was 12.1 g (95%).

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References and Notes

1. a) Welch, J.T., Eswarakrishnan, S., Eds.; *Fluorine in Bioorganic Chemistry*; John Wiley & Sons, New York, 1991. b) Filler, R., Kobayashi, Y., Eds.; *Biochemical Aspects of Fluorine Chemistry*; Elsevier Biomedical Press and Kodansha LTD; 1982.

2. Percy, J.M., *Top. Curr. Chem.*, **1997**, *193*, 131.

3. Gerus, I.I., Gorbunova, M.G., Kukhar, V.P., *J. Fluorine Chem.*, **1994**, *69*, 195.

4. a) Gorbunova, M.G., Gerus, I.I., Kukhar, V.P., *J. Fluorine Chem.*, **1993**, *65*, 25. b) Bravo P., Bruche L., Farina A., Gerus I.I., Kolycheva M.T., Kukhar V.P., Meille S.V., Viani F., *J. Chem. Soc., Perkin Trans.* 1, **1995**, 1667-1671.

5. Evans, D.A., Carole, G.L., Truesdale, L.K., *J. Org. Chem.*, **1974**, *39*, 914.

6. a) Utimoto, K., Obayashi, M., Shishiyama, Y., Inoue, M., Nozaki, H., *Tetrahedron Lett.*, **1980**, *21*, 3389. b) Utimoto, K., Wakabayashi, Y., Horiie, T., Inoue, M., Shishiyama, Y., Obayashi, M., Nozaki, H., *Tetrahedron*, **1983**, *39*, 967.

7. Higuchi, K., Onaka, M., Izumi, Y., *Bull. Chem. Soc. Jpn.*, **1993**, *66*, 2016.

8. **3:** bp 84-85 °C /14 mmHg; ^1H NMR ($CDCl_3$) δ: 0.26 (s, 9 H), 1.32 (t, 3 H, J = 7.1 Hz), 3.85 (q, 2 H, J=7.1 Hz), 4.83 (d, 1 H, J = 12.5 Hz), 6.98 (d, 1 H, J = 12.5 Hz); ^{19}F NMR ($CDCl_3$) δ: -82.0 (s); ^{13}C NMR ($CDCl_3$) δ: 0.78 (s), 14.26 (s), 66.27 (s), 72.51 (q, J = 35 Hz), 96.96 (s), 114.82 (s), 121.88 (q, J = 285 Hz), 157.96 (s).
Anal. Calcd for $C_{10}H_{16}F_3NO_2Si$: C, 44.93; H, 5.98; N, 5.24. Found: C, 45.02; H, 6.05; N, 5.06.
4: bp 87-89 °C /9 mmHg; ^1H NMR ($CDCl_3$) δ: 0.29 (s, 9 H), 1.27 (t, 3 H, J = 7.0 Hz), 3.55 (dq, 1 H, J = 8.7 Hz, J = 7.0 Hz), 3.81 (dq, 1 H, J = 8.7 Hz, J = 7.0 Hz), 4.86 (d, 1 H, J = 8.4 Hz), 5.57 (d, 1 H, J = 8.4 Hz); ^{19}F NMR ($CDCl_3$) δ: -72.66 (s); ^{13}C NMR ($CDCl_3$) δ: -0.22 (s), 14.48 (s), 62.20 (s), 65.62 (s), 107.50 (q, J = 4 Hz), 116.29 (s), 119.54 (q, J = 275 Hz), 143.25 (q, J = 35 Hz).
Anal. Calcd for $C_{10}H_{16}F_3NO_2Si$: C, 44.93; H, 5.98; N, 5.24. Found: C, 44.98; H, 6.08; N, 5.17.

9. Bégué, J.-P., Bonnet-Delpon, D., Mesureur, D., Ourevitch, M., *Magnetic Resonance in Chemistry*, **1991**, *29*, 675.

10. Mai, K., Patil, G., *J. Org. Chem.*, **1986**, *51*, 3345.

11. a) Kukhar, V.P., Vdovenko, S.I., Gerus, I.I., Gorbunova, M.G., Pit, G.L., *Dokl. Akad. Nauk Ukr.*, **1991**, 129. b)Vdovenko, S.I., Gerus, I.I., Gorbunova, M.G., *J. Fluorine Chem.*, **1997**, *82*, 167. c) Vdovenko, S.I., Gerus, I.I., Wojcik, J., *Molecular Spectr.*, **1999**, in press.