Cycloadditions of Trifluoroacetonitrile Oxide with Olefins and Acetylenes

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The regio- and stereoselectivity of the cycloadditions of trifluoroacetonitrile oxide (**1**) with olefins and acetylenes were described. The oxide **1**, generated *in situ* from trifluoroacetohydroximoyl bromide etherate in the presence of triethylamine, reacted with various monosubstituted olefins and acetylenes to give exclusively 5-substituted 3-trifluoromethyl-2-isoxazolines and -isoxazoles, respectively, whereas **1** cyclized with 1,2-disubstituted olefins and acetylenes to result in the formation of a mixture of two regioisomeric products. On the other hand, the cycloaddition of **1** with (*Z*)-β-methylstyrene afforded a mixture consisting of two regioisomeric isoxazolines retaining *Z*-configuration and one diastereoisomeric isoxazoline.

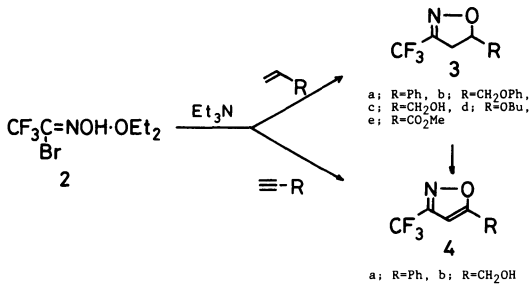
A number of heterocyclic compounds bearing a fluorine or trifluoromethyl group are known to be effective pharmaceutically and agrochemically,[1] but the introduction of such a fluorine group into heterocyclic rings has been limited.[2] As a part of research on applications of the fluorinated 1,3-dipolar compounds as building blocks of heterocycles with fluorine groups,[3] we remarked trifluoroacetonitrile oxide (**1**). Although only one report described the cycloadditions of the nitrile oxide **1**, liberated from trifluoroacetohydroximoyl chloride, the dipolarophiles employed were limited to the reactive ones such as acetylenic and enol ethers.[4] In the present paper, we wish to report that the oxide **1**, generated from trifluoroacetohydroximoyl bromide etherate (**2**), cyclizes with various olefins and acetylenes to give the corresponding 3-trifluoromethyl-2-isoxazolines and -isoxazoles,[5] and also to describe the regio- and stereoselectivity of the cycloadditions.

$$CF_3C \equiv N \rightarrow O$$

1

The bromide **2** was prepared by bromination of trifluoroacetaldehyde oxime[6] which was readily obtained from trifluoroacetaldehyde hydrate and hydroxylamine hydrochloride.

The reactions of **2** with monosubstituted olefins such as styrene, allyloxybenzene, allyl alcohol, and butoxyethylene proceeded smoothly in the presence of triethylamine at room temperature to afford exclusively 5-substituted 3-trifluoromethyl-2-isoxazolines **3** in good yields. Similarly, **2** was allowed to react with methyl acrylate, an olefin bearing electron-withdrawing group, to give only 5-methoxycarbonylisoxazoline in appreciable yield (Table 1). The structure of these 3-trifluoromethyl-2-isoxazolines was determined on the basis of the comparable chemical shifts of 5-methine and 4-methylene protons to those of 3-phenyl analogues reported in the literatures[7] and the existence of the H–F couplings between 4-methylene protons and trifluoromethyl group. Similarly, the oxide **1** readily underwent the cycloadditions with monosubstituted acetylenes. The reaction of **2** with phenylacetylene gave exclusively 5-phenyl-3-trifluoromethylisoxazole (**4a**) in excellent yield, where the alternative 1,3-addition product described in the reaction of benzonitrile oxide[8] was not detected at all. A similar reaction with 2-propyn-1-ol also gave **4b** in moderate yield and, however, that with methyl propiolate resulted in a tar-like matter. Dehydrogenation of **3a** with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) was so sluggish that only 12% of **4a** was obtained (Scheme 1).



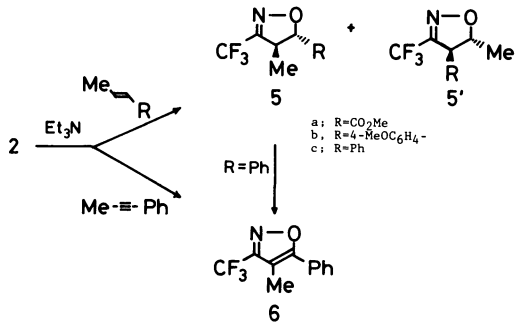
Scheme 1.

TABLE 1. PREPARATIONS OF ISOXAZOLINES **3** AND ISOXAZOLES **4**

3 or 4	Yield[a] %	Bp(°C/mmHg)[Mp(°C)](lit)	IR $\tilde{\nu}$/cm^{-1} C=N	Formula	Calcd(Found)/% C	H	N
3a	84[b]	85—87/3.5	1628	$C_{10}H_8NOF_3$	55.82 (55.78)	3.75 (3.41)	6.51 (6.41)
3b	80	[48.5—49.5]	1620	$C_{11}H_{10}NO_2F_3$	53.88 (54.01)	4.11 (4.15)	5.71 (5.71)
3c	60	82—83/6	1635	$C_5H_6NO_2F_3$			8.28 (8.25)
3d	89	45—46/2(78—80/10)[c]	1625	—		—	
3e	82	76—77/6(64—66/3)[c]	1635	—		—	
4a	93	[44—45.5]	1610	$C_{10}H_6NOF_3$	56.35 (56.56)	2.84 (2.38)	6.57 (6.83)
4b	38	75—77/6	1603	$C_5H_4NO_2F_3$			8.38 (8.33)

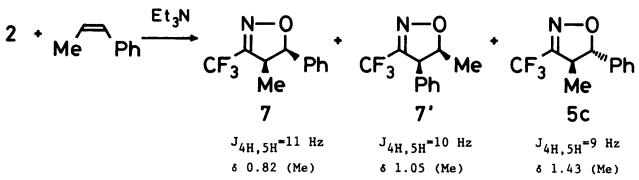
a) Isolated yield. b) Besides **3a**, a trace of 1,1,1-trifluoro-4-phenyl-3-buten-2-one oxime was obtained. c) See ref. 4).

On the other hand, the cycloadditions of **1** with 1,2-disubstituted olefins under the similar conditions produced a mixture of regioisomeric products. The reaction with methyl crotonate gave a mixture of 4-methylisoxazoline **5a** and 5-methyl isomer **5a'** in 39% yield (**5a**/**5a'** ratio of 43/57). The cycloaddition with 1-methoxy-4-(1-propenyl)benzene proceeded more easily to give a mixture of **5b** and **5b'** in 87% yield (**5b**/**5b'** ratio of 93/7). Similarly, from the reaction with (*E*)-*β*-methylstyrene, 66% yield of a mixture of **5c** and **5c'** was obtained (**5c**/**5c'** ratio of 86/14). The cycloaddition with 1,2-disubstituted acetylene such as 1-phenyl-1-propyne, however, proceeded regioselectively to afford only **6** in 23% yield. The formation of its regioisomer was not observed at all. The structure of **6** is supported by the fact that dehydrogenation of **5c** with chromium trioxide gave **6** in 47% yield (Scheme 2).



Scheme 2.

The stereoselectivity of the cycloaddition of **1** was next investigated. Since (*Z*)-stilbene and dimethyl maleate usually employed for such a purpose were both unreactive toward **1**, the reaction with (*Z*)-*β*-methylstyrene including 3% of its *E*-isomer was carried out, giving a mixture of two regioisomers with retention of *Z*-configuration, **7** and **7'**, and diastereoisomer of **7**, **5c**, in 30% yield (**7**/**7'**/**5c** ratio of 10/5/3). The stereochemical assignments are based on ^{1}H NMR spectra. The *Z*-configuration of **7** and **7'** is supported by both the more shielded methyl protons[9] and the bigger coupling constants between 4- and 5-methine protons[7b] in **7** and **7'** as compared to **5c** (Scheme 3). In the reaction mixture, 3% of (*E*)-*β*-methylstyrene was still present and, on further treatment of the reaction products with triethylamine, the ratio of **7**/**7'**/**5c** was found to be unchanged. These results indicate that **5c** may be directly led from (*Z*)-*β*-methylstyrene.



Scheme 3.

As a conclusion, the regioselectivity of the cycloadditions of **1** toward monosubstituted olefins and acetylenes, affording exclusively 5-substituted isoxazolines and isoxazoles, is similar to that of benzonitrile oxide,[7] whereas the tendency toward 1,2-disubstituted olefins is somewhat different. Summarized for comparison are the regioselective results of benzonitrile oxide,[7b,10] cyanogen *N*-oxide,[10] and benzenesulfonyl cyanide *N*-oxide[11] (Table 2). Trifluoromethyl group favors the formation of 4-methylisoxazolines **5**, compared with benzonitrile oxide, and its effect on the regioselectivity seems to be almost equal to that of cyano group. It also turns out that the regioselectivity depends on the configuration of the olefins used, namely, (*E*)-*β*-methylstyrene is more regioselective than (*Z*)-*β*-methylstyrene. It is also found that the cycloaddition proceeds with high stereoselectivity. However, the formation of the diastereoisomer **5c** in the case of (*Z*)-*β*-methylstyrene suggests that the partial inversion of the *Z*-configuration takes place during course of the cycloaddition, pointing out the possibility of the partial lack of the concerted process.

Experimental

All melting and boiling points are uncorrected. The IR spectra were recorded on a JASCO IRA-1 spectrometer. The ^{1}H and ^{19}F NMR spectra were measured with a JEOL JNM-PMX 60 spectrometer and a Hitachi R-24F spectrometer using an internal tetramethylsilane (TMS) and an external trifluoroacetic acid as a standard, respectively, the chemical shifts being given in δ ppm downfield. The MS spectra were obtained on a Finnigan 3300E GC-MS spectrometer operating at 120 eV.

Preparation of **2**. The previously reported procedures were modified for the preparations of trifluoroacetaldehyde hydrate and its oxime.[12] To a suspension of 7.6 g (0.20 mol) of lithium aluminium hydride in 500 ml of diethyl ether, dried over calcium chloride, was added dropwise a solution of 30.0 g (0.26 mol) of trifluoroacetic acid in 400 ml of diethyl ether holding the temperature below 5 °C. The mixture was stirred at 0 °C for an additional 1 h. To the mixture were added 18 ml of methanol, 16 ml of water, and 32 ml of concd

Table 2. Regioselectivity of nitrile oxides (R–C≡N→O)

R–C≡N→O R	Olefin or Acetylene	Ratio 4-Methyl product/5-Methyl product
CF_3–	(*E*)-CH_3CH=$CHCO_2Me$	43/57[a]
Ph–		34/66[b]
NC–		44.5/55.5[b]
PhO_2S–		62/38[c]
CF_3–	(*E*)-CH_3CH=CHC_6H_4OMe-4	93/7[a]
Ph–		78/22[d]
CF_3–	(*E*)-CH_3CH=$CHPh$	86/14[a]
CF_3–	$CH_3C{\equiv}CPh$	100/0

a) Determined by ^{19}F NMR and/or GLC analysis. b) See Ref. 9). c) See Ref. 10). d) See Ref. 7b).

sulfuric acid and then diethyl ether layer was separated. Water was added to the residual mixture and the mixture was extracted twice with diethyl ether. The combined ethereal extracts were washed with brine, dried over magnesium sulfate, and evaporated under reduced pressure to leave 33.9 g of crude trifluoroacetaldehyde hydrate.

To a mixture of 33.9 g of thus-obtained crude trifluoroacetaldehyde hydrate, 50 ml of methanol, 50 ml of water, 50 g of ice, and 20.3 g of hydroxylamine hydrochloride, was added dropwise 44 g of 50% aqueous sodium hydroxide. Then the temperature of the mixture was maintained below 35 °C. After stirring at room temperature for 10 h, the mixture was washed with diethyl ether, acidified to pH 6 with concd hydrochloric acid, and extracted twice with diethyl ether. The extracts were washed with water and brine, dried over magnesium sulfate, and distilled to give 28.3 g of trifluoroacetaldehyde oxime including small amount of diethyl ether (boiling range 78—79 °C).

Holding the temperature below 40 °C, a solution of 44.6 g of *N*-bromosuccinimide in 125 ml of *N,N*-dimethylformamide (DMF) was added dropwise to a solution of 28.3 g of trifluoroacetaldehyde oxime in 50 ml of DMF. After stirring at room temperature for 3 h, the mixture was poured into 400 ml of cold water and extracted with diethyl ether. The extracts were washed with water and brine, dried over magnesium sulfate, and distilled to afford 29.9 g of **2**; bp 115 °C (lit, bp 52—55 °C/72 mmHg (1 mmHg≈133.322 Pa))[13], 43% yield based on trifluoroacetic acid, ^{19}F NMR ($CDCl_3$) δ= 10.5 (s) and 10.3 (s), MS (*m/z*) 191 and 193 (M^+-Et_2O), 171 and 173 ($M^+-Et_2O\cdot HF$), and 111 (CF_3CNO^+).

Reactions of 2 with Monosubstituted Olefins. Triethylamine (4.89 g, 48.4 mmol) diluted with 20 ml of toluene was added to a solution of 6.45 g (24.2 mmol) of **2** and 7.55 g (72.6 mmol) of styrene in 50 ml of toluene over a period of 1 h and the mixture was stirred at room temperature for additional 10 h. After excess hexane ws added to the reaction mixture, the resulting salt (4.51 g) was collected on a filter. The filtrate was washed with water and brine, dried over magnesium sulfate, and evaporated to leave crude **3a** which was purified by distillation under reduced pressure to give 4.35 g (84%) of pure **3a**, ^{1}H NMR ($CDCl_3$) δ=3.07 (ddq, 1H), 3.57 (ddq, 1H), 5.76 (dd, 1H), and 7.30 (m, 5H).

Similarly, **3c**, **3d**, and **3e** were obtained and their ^{1}H NMR data are as follows; **3c**, ($CDCl_3$) δ=2.83 (br.s, 1H), 3.07 (m, 1H), 3.25 (m, 1H), 3.58 (dd, 1H), 3.90 (dd, 1H), and 4.93 (tdd, 1H), **3d**, (CCl_4) δ=0.95 (t, 3H), 1.15—1.80 (m, 4H), 2.85 (dm, 1H), 3.25 (dm, 1H), 3.30—4.05 (m, 2H), and 5.66 (dd, 1H), **3e**, (CCl_4) δ=3.33 (m, 1H), 3.50 (m, 1H), 3.77 (s, 3H), and 5.17 (dd, 1H).

The isoxazoline **3b** was also obtained from the reaction of **2** with 1.5 equiv of allyloxybenzene and the successive isolation by column chromatography (silica gel, hexane–ethyl acetate, 9:1). Thus-obtained **3b** was further recrystallized from hexane to give the white needles **3b**, ^{1}H NMR (CCl_4) δ=3.10 (m, 1H), 3.27 (m, 1H), 3.97 (d, 2H), 5.02 (tt, 1H), and 6.85—7.27 (m, 5H).

Reactions of 2 with Monosubstituted Acetylenes. In a similar manner, crude **4a** was obtained and purified by column chromatography (silica gel, hexane) followed by recrystallization from hexane, ^{1}H NMR (CCl_4) δ=6.67 (s, 1H) and 7.28—7.90 (m, 5H), whereas **4b** was purified by distillation under reduced pressure, ^{1}H NMR ($CDCl_3$) δ= 3.67 (br.s, 1H), 4.85 (s, 2H), and 6.56 (s, 1H).

Dehydrogenation of 3a to 4a. A solution of 1.00 g (4.65 mmol) of **3a** and 1.06 g (4.65 mmol) of DDQ in 10 ml of toluene was refluxed for 2 d. Diethyl ether was added to the reaction mixture and the resulting mixture was washed with water and brine, dried over magnesium sulfate, and evaporated under reduced pressure to leave oily matter which was submitted to short column chromatography (silica gel, hexane) to give 0.84 g of a mixture of **3a** and **4a** in the ratio of 86/14, according to ^{1}H NMR analysis. The isoxazole **4a** was separated by preparative GLC and its IR and ^{1}H NMR data are consistent with those obtained above.

Reactions of 2 with 1,2-Disubstituted Olefins. To a solution of 1.81 g (6.8 mmol) of **2** and 2.04 g (20.4 mmol) of methyl crotonate in 15 ml of toluene, was added dropwise a solution of 1.37 g (13.6 mmol) of triethylamine in 5 ml of toluene over a 75 min period and the mixture was stirred at room temperature for additional 15 h. The similar procedure described above gave 1.03 g of the white salt and the oily matter which was submitted to distillation (boiling range, 73—75 °C/5 mmHg) to produce 0.42 g (29%) of a mixture of **5a** and **5a′** in the ratio of 43/57 (^{19}F NMR analysis). The isoxazolines **5a** and **5a′** were isolated by preparative GLC, **5a** ^{1}H NMR (CCl_4) δ=1.43 (d, 3H), 3.70 (dq, 1H), 3.82 (s, 3H), and 4.67 (d, 1H), ^{19}F NMR (CCl_4) δ=14.3, **5a′**, ^{1}H NMR (CCl_4) δ=1.47 (d, 3H), 3.73 (dq, 1H), 3.78 (s, 3H), and 5.07 (dq, 1H), ^{19}F NMR (CCl_4) δ=14.7.

Found: N, 6.58%. Calcd for $C_7H_8NO_3F_3$: N, 6.63% (for a mixture of **5a** and **5a′**).

Similarly, a mixture of **5b** and **5b′** in the ratio of 93/7 was collected by distillation (boiling range. 115—119 °C/1 mmHg) and each isomer was isolated by preparative GLC, **5b**, ^{1}H NMR (CCl_4) δ=1.40 (d, J=7 Hz, 3H), 3.38 (dqm, 1H). 3.78 (s, 3H), 5.10 (d, J=9 Hz, 1H), and 6.7—7.2 (A_2X_2, 4H), IR (film) 1610 cm^{-1} (C≡N), **5b′**, ^{1}H NMR (CCl_4) δ=1.40 (d, J=7 Hz, 3H), 3.77 (s, 3H), 3.90 (dm, J=7 Hz, 1H), 4.67 (dq, 1H), 6.8—7.1 (A_2X_2, 4H), IR (film) 1610 cm^{-1} (C=N).

Found: N, 5.36%. Calcd for $C_{12}H_{12}NO_2F_3$: N, 5.40% (for a mixture of **5b** and **5b′**).

A mixture of **5c** and **5c′** in the ratio of 86/14 was also collected by distillation (boiling range, 87—92 °C/4 mmHg) in 66% yield, **5c**, ^{1}H NMR (CCl_4) δ=1.43 (d, J=7 Hz, 3H), 3.40 (dqm, 1H), 5.17 (d, J=9 Hz, 1H), and 7.3 (s, 5H), IR (film) 1620 cm^{-1} (C=N), **5c′**, ^{1}H NMR (CCl_4) δ=1.43 (d, J=7 Hz, 3H), 3.90 (dm, J=6 Hz, 1H), 4.67 (dq, 1H), and 6.9—7.3 (m, 5H), IR (film) 1610 cm^{-1} (C=N).

Found: N, 6.12%. Calcd for $C_{11}H_{10}NOF_3$: N, 6.11% (for a mixture of **5c** and **5c′**).

Reaction of 2 with 1-Phenyl-1-propyne. In a similar manner to the above, crude **6** was obtained and purified by column chromatography (silica gel, hexane) followed by recrystallization from hexane, mp, 69—69.5 °C, ^{1}H NMR ($CDCl_3$) δ=2.30 (s, 3H) and 7.4—7.8 (m, 5H), IR (KBr) 1615 cm^{-1} (C=N).

Found: C, 57.91; H, 3.45; N, 6.07%. Calcd for $C_{11}H_8NOF_3$: C, 58.16; H, 3.55; N, 6.17%.

Dehydrogenation of 5c to 6. A solution of 430 mg (1.88 mmol) of **5c**, 500 mg of chromium trioxide, and 3 drops of concd sulfuric acid in 10 ml of acetic acid was refluxed for 40 min and evaporated under reduced pressure. The resulting mixture was extracted with diethyl ether and extracts were washed with water and brine, dried over magnesium sulfate, and evaporated under reduced pressure to leave crude **6** which was purified by column chromatography (silica gel, hexane–ethyl acetate, 10:1) to give 200 mg (47%) of the white solid **6**, mp, 67.5—69.5 °C.

Reaction of 2 with (Z)-β-Methylstyrene. (*Z*)-β-Methylstyrene was obtained by hydrogenation with Lindlar catalyst according to the previously reported procedure.[14] The reaction of **2** with 1.3 equiv of (*Z*)-β-methylstyrene was carried out in a similar manner and a mixture of **7**, **7′**, and **5c** in the ratio of 10/5/3 (^{1}H NMR analysis) was collected in 30% yield by column chromatography (silica gel, hexane–ethyl acetate, 3:1). Each isomer was separated by preparative GLC, **7**, ^{1}H NMR (CCl_4) δ=0.82 (d, J=8 Hz, 3H), 3.60 (dqm, 1H), 5.73 (d, J=11 Hz, 1H), and 7.1—7.4 (m, 5H), IR (film)

1618 cm^{-1} (C=N), **7'**, ^1H NMR (CCl_4) δ=1.05 (d, J=6 Hz, 3H), 4.22 (d, J=10 Hz, 1H), 4.90 (dq, 1H), and 6.9—7.7 (m, 5H), IR (film) 1610 cm^{-1} (C=N). Spectral data of **5c** are consistent with those obtained above.

Found: N, 5.83%. Calcd for $C_{11}H_{10}NOF_3$: N, 6.11% (for a mixture of **7** and **7'**).

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