Fluorinative Beckmann Fragmentation: Fluorinative α-Cleavage of Cyclic Ketoximes by Diethylaminosulfur Trifluoride

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Diethylaminosulfur trifluoride reacted with cyclic ketoximes bearing substituent(s) that can stabilize a carbocation to cause fluorinative fragmentation, affording fluorinated carbonitrile. Ketoximes lacking such substituents afforded complex mixtures. However, the introduction of a sulfur functionality, which can stabilize a carbocation and can be easily removed from the reaction products, into the ketoxime was effective for producing the fluorinative fragmentation.

Key words fluorinative Beckmann fragmentation; fluorination; diethylaminosulfur trifluoride

Beckmann rearrangement, the acid-mediated isomerization of oximes to amides, is one of the most famous and useful reactions in organic synthesis.[1)] However, a fragmentation reaction occurs if one of the oxime substituents can produce a relatively stable carbocation. This type of reaction is also known as Beckmann fragmentation (abnormal Beckmann rearrangement), and is widely utilized to synthesize ω-nitriles.[1)] Because the carbocation intermediates in this fragmentation are very active electrophiles, carbon nucleophiles react with these intermediates to provide a new carbon–carbon bond formation (Chart 1).[2)]

We assumed that Beckmann fragmentation in the presence of fluoride ion would afford fluorinated carbonitriles, and found that the treatment of cyclic ketoximes with diethylaminosulfur trifluoride (DAST)[3,4)] caused a ring fragmentation resulting in the formation of the desired compounds. We reported this result in a preliminary communication.[5)] We now report the full details of this reaction.

Results and Discussion

We first examined the reaction of camphor oxime (**1a**), which is a typical substrate for the Beckmann fragmentation, with several nucleophilic fluorinating agents. These results are summarized in Table 1. Hydrogen fluoride–pyridine, tetrabutylammonium fluoride, and tetrabutylammonium dihydrogentrifluoride were inert toward **1a** (runs 1—7). The reaction of **1a** (R=H) with Ishikawa's reagent (*N*,*N*-diethyl-1,1,2,3,3,3-hexafluoropropylamine)[6)] afforded the desired fluorinated carbonitrile (**2a**) in low yield (run 8) along with the olefin (**2a′**) as the major product. For the reaction with DAST, **2a** could be obtained in high yield (run 9).

These results correspond to the fluorination of a hydroxy group using the above fluorinating reagents. DAST is a more powerful reagent than other reagents used for the replacement of the hydroxy group with fluorine, and dehydration (elimination) appears to be less of a problem with DAST than with others.[3)] Middleton reported that cyclooctanol reacts with DAST to give a 70 : 30 ratio of cyclooctyl fluoride to cyclooctene, whereas Ishikawa's reagent reacts to give only cyclooctene.[3)]

We then examined the reaction of DAST toward several cyclic ketoximes (**1**). These results are summarized in Table 2. The presence of a substituent(s) capable of strongly stabilizing a carbocation at position α to the oximino carbon is essential for obtaining the fluorinated carbonitriles. Oximes lacking such substituents (**1f**, **1g**) afforded complex mixtures. In the case of **1e**, the product was a 1 : 1 mixture of stereoisomers.

The reaction mechanism is depicted in Chart 2. The first step is nucleophilic displacement of a fluorine in DAST by the oxygen of the oximino substrate **1** with the subsequent elimination of hydrogen fluoride. Next, the elimination of diethylaminosulfino fluoride from intermediate A causes bond cleavage and produces the carbocation intermediate B. Finally, the fluoride ion attacks B to afford the fluorinated carbonitrile **2** (path a). In the case of compounds lacking substituents to stabilize the α-carbocation, the reaction proceeds through a mechanism similar to that of the "normal" Beckmann rearrangement. The carbon–carbon bond *anti* to the oximino leaving group in intermediate A migrates to the nitro-

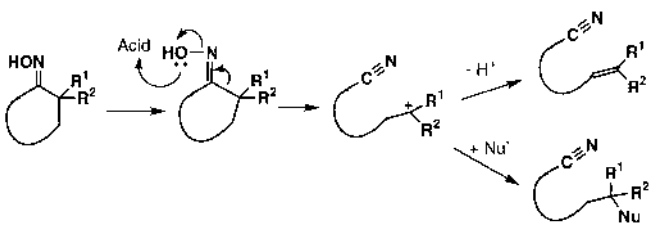
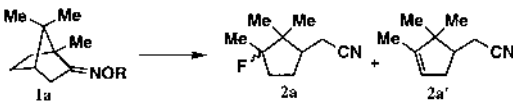


Chart 1. Beckmann Fragmentation

Table 1



Run	1a	Reaction conditions	2a	2a′
1	R=H	*n*-Bu_4NF, THF, reflux	N.R.	
2	R=H	70% HF/pyridine, THF, r.t.	N.R.	
3	R=Ts	*n*-Bu_4NF, THF, reflux	N.R.	
4	R=Ts	*n*-$Bu_4NH_2F_3$, THF, reflux	N.R.	
5	R=Tf	*n*-Bu_4NF, THF, reflux	N.R.	
6	R=Tf	*n*-$Bu_4NH_2F_3$, THF, reflux	N.R.	
7	R=Tf	70% HF/pyridine, THF, r.t.	N.R.	
8	R=H	$CF_3CHFCF_2NEt_2$ (Ishikawa's reagent), THF, reflux	11%	48%
9	R=H	Et_2NSF_3, CH_2Cl_2, −78 °C	69%	31%

THF=tetrahydrofuran. N.R.=no reaction.

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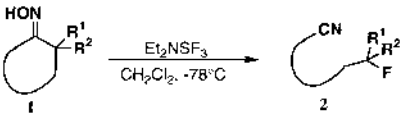
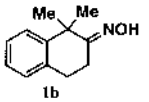
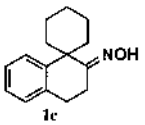
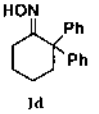
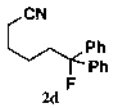
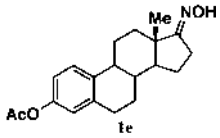
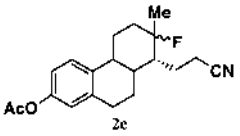
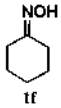
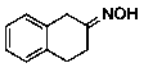
Table 2



Entry	Starting material	Product	Yield (%)
1	 1b	 2b	77
2	 1c	 2c	91
3	 1d	 2d	75
4	 1e	 2e	63[a]
5	 1f	Complex mixture	—
6	 1g	Complex mixture	—

a) A 1 : 1 mixture of stereoisomers.

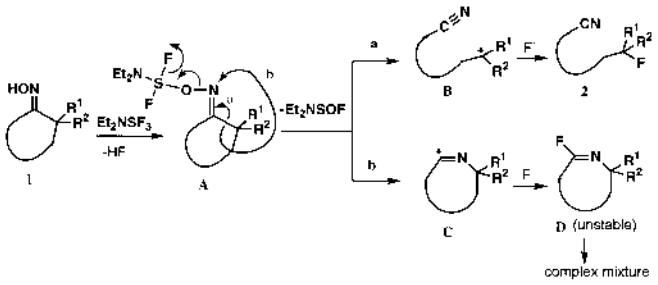


Chart 2

gen atom to afford the carbocation C. The fluoride ion attacks C to give an unstable compound D, which leads to a complex mixture (path b).

As described above, the starting cyclic ketoximes (**1**) must have substituent(s) that can strongly stabilize a carbocation at position α to the oximino carbon in order to cause the fluorinative fragmentation. Next, we introduced a sulfur functionality, which can stabilize a carbocation and can be easily removed from the reaction products, into the cyclic ketoximes to overcome this limitation. Ketoximes bearing a phenylthio group at position α to the oximino carbon (**3**) efficiently reacted with DAST to cause the fluorinative fragmentation leading to the desired α-fluoro sulfides (**4**). Since the α-fluoro sulfides (**4**) were not stable, they were subjected, without purification, to oxidation with *m*-chloroperbenzoic acid (*m*-CPBA). The resulting sulfoxides (**5**) were heated in a sealed tube at 160 °C to afford fluoroalkenes (**6**) in high yields (Chart 3).

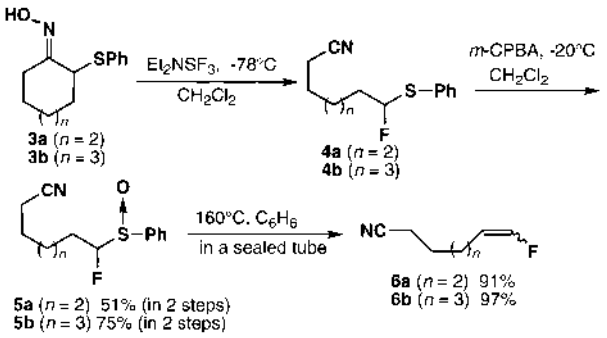


Chart 3

Experimental

Infrared spectra (IR) were measured using a Perkin-Elmer 1600 series FT-IR spectrophotometer. ^{1}H- and ^{19}F-NMR spectra were performed on a JEOL GX270, Varian Gemini 300 or Varian UNITY plus 500 instrument with tetramethylsilane (for ^{1}H) and chlorotrifluoromethane (for ^{19}F) as the internal standards. Mass spectra (MS) and high-resolution mass spectra (HR-MS) were measured on a JEOL JMS D-200 spectrometer. Column chromatography was performed on silica gel (Merck Kieselgel 60).

General Procedure for the Fluorinative Fragmentation of Cyclic Ketoximes To a solution of the oxime (**1**) (1.0 mmol) in dichloromethane (3 ml) was added DAST (1.0 mmol) at −78 °C under an inert atmosphere, and the reaction mixture was then stirred for 30 min. A saturated sodium bicarbonate solution was added to the reaction mixture, and the resulting mixture was extracted with dichloromethane. The extract was dried over anhydrous sodium sulfate, filtered, and evaporated to afford the crude product. Purification by chromatography (silica gel/ hexane dichloromethane) gave the pure sample.

2-(3-Fluoro-2,2,3-trimethylcyclopentyl)ethanenitrile (**2a**): A 1 : 1 mixture of stereoisomers. A part of the mixture was separated into two stereoisomers by chromatography. A less polar isomer; A colorless oil: IR (neat) cm^{-1}: 2246. ^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, s), 0.97 (3H, d, J=1.9 Hz), 1.28 (3H, d, J=22.6 Hz), 1.60—1.67 (1H, m), 1.78—1.92 (1H, m), 1.99—2.16 (3H, m), 2.33—2.46 (2H, m). ^{19}F-NMR ($CDCl_3$) δ: −142.4—−142.8 (m). *Anal*. Calcd for $C_{10}H_{16}FN$: C, 70.97; H, 9.53; N, 8.28. Found: C, 71.18; H, 9.39; N, 8.17. A more polar isomer; A colorless oil: IR (neat) cm^{-1}: 2304. ^{1}H-NMR ($CDCl_3$) δ: 0.69 (3H, s), 1.00 (3H, d, J=1.5 Hz), 1.29 (3H, d, J=22.2 Hz), 1.36—1.44 (1H, m), 1.78—2.04 (2H, m), 2.09—2.23 (2H, m), 2.34—2.39 (2H, m). ^{19}F-NMR ($CDCl_3$) δ: −143.3—−143.8 (m). *Anal*. Calcd for $C_{10}H_{16}FN$: C, 70.97; H, 9.53; N, 8.28. Found: C, 70.79; H, 9.60; N, 8.33.

2-(2,2,3-Trimethylcyclopent-3-enyl)ethanenitrile (**2a′**): The spectral data for this sample were identical with those in the literature.[7]

3-[2-(1-Fluoro-1-methylethyl)phenyl]propanenitrile (**2b**): A colorless oil: IR (neat) cm^{-1}: 2245; ^{1}H-NMR ($CDCl_3$) δ: 1.76 (6H, d, J=22.0 Hz), 2.46 (2H, t, J=7.5 Hz), 3.17 (2H, td, J=7.5, 3.0 Hz), 7.21—7.29 (4H, m); ^{19}F-NMR ($CDCl_3$) δ: −134.6 (septet, J=22.0 Hz). MS *m/z* 191 (M^+), 172 (M^+−F). HR-MS Calcd for $C_{12}H_{14}FN$: 191.1110. Found: 191.1137.

3-[2-(1-Fluorocyclohexyl)phenyl]propanemitrile (**2c**): A colorless oil: IR (neat) cm^{-1}: 2245. ^{1}H-NMR ($CDCl_3$) δ: 1.70—1.85 (10H, m), 2.64 (2H, t, J=3.5 Hz), 3.15—3.18 (2H, m), 7.21—7.27 (4H, m). ^{19}F-NMR ($CDCl_3$) δ: −158.2 (t, J=40.6 Hz). MS *m/z* 231 (M^+), 211 (M^+−HF). HR-MS Calcd for $C_{15}H_{18}FN$: 231.1424. Found: 231.1418.

6-Fluoro-6,6-diphenylhexanenitrile (**2d**): A colorless oil: IR (neat) cm^{-1}: 2246. ^{1}H-NMR ($CDCl_3$) δ: 1.50—1.55 (2H, m), 1.70 (2H, quintet, J=7.6 Hz), 2.31 (2H, t, J=7.6 Hz), 2.36—2.44 (2H, m), 7.27—7.38 (10H, m); ^{19}F-NMR ($CDCl_3$) δ: −150.6 (t, J=23.4 Hz). MS *m/z* 267 (M^+), 247 (M^+−HF). HR-MS Calcd for $C_{18}H_{18}FN$: 267.1423. Found: 267.1409.

(14*R*)-3-Acetoxy-13-fluoro-13,17-secoestra-1,3,5(10)-trienonitrile (**2e**): An inseparable 1 : 1 mixture of stereoisomers. A colorless oil: IR (neat) cm^{-1}: 2245, 1761. ^{1}H-NMR ($CDCl_3$) δ: 1.22—2.18 (14H, m), 2.29 (3H, s), 2.31—2.64 (4H, m), 6.80—7.30 (3H, m). ^{19}F-NMR ($CDCl_3$) δ: −130.5—−130.9 (1/2F, m), −160.0—−160.2 (1/2F, m). MS *m/z* 329 (M^+), 309

(M^+-HF). HR-MS Calcd for $C_{20}H_{24}FNO_2$: 329.1791. Found: 329.1786.

Representative Procedure for the Fluorinative Fragmentation of 2-Phenylthiocycloalkanone Oxime and the Successive Oxidation To a solution of 2-phenylthiocycloheptanone oxime (**3a**) (513 mg, 2.18 mmol) in dichloromethane (6 ml) was added DAST (346 μl, 2.62 mmol) at −78 °C under an inert atmosphere, then the reaction mixture was stirred for 15 min. A saturated sodium bicarbonate solution was added to the reaction mixture, and the resulting mixture was extracted with dichloromethane (50 ml×2). The extract was dried over anhydrous sodium sulfate, filtered, and evaporated to afford the crude α-fluorosulfide (**4a**). The crude product was dissolved in dichloromethane (15 ml) and cooled to −20 °C under an inert atmosphere. A dichloromethane (15 ml) solution of *m*-CPBA (376 mg, 2.18 mmol) was added dropwise to the mixture and stirred for 5 min. Saturated sodium bicarbonate (15 ml) was added and the resulting mixture was extracted with chloroform (50 ml×2). The extract was dried over anhydrous magnesium sulfate, filtered, and evaporated to afford the crude product. Purification by chromatography (silica gel/hexane : ethyl acetate=3 : 1) gave **5a** (281 mg, 51%) as a 1 : 1 mixture of diastereoisomers.

7-Fluoro-7-(phenylsulfinyl)heptanenitrile (**5a**): A part of the mixture was separated into the two stereoisomers. Less polar isomer; A colorless oil: IR (neat) cm^{-1}: 2245, 1048. ^{1}H-NMR ($CDCl_3$) δ: 1.50—1.59 (4H, m), 1.60—1.72 (4H, m), 2.35 (2H, t, J=7.0 Hz), 4.93 (1H, ddd, J=49.2, 8.5, 3.3 Hz) 7.40—7.60 (3H, m), 7.61—7.70 (2H, m). ^{19}F-NMR ($CDCl_3$) δ: −179.7—−180.1 (m). MS *m/z* 253 (M^+). HR-MS Calcd for $C_{13}H_{16}FNOS$: 253.0858. Found: 253.0863. More polar isomer; A colorless oil: IR (neat) cm^{-1}: 2245, 1049. ^{1}H-NMR ($CDCl_3$) δ: 1.53—2.25 (8H, m), 2.34 (2H, t, J=6.9 Hz), 5.10 (1H, ddd, J=48.1, 9.2, 3.9 Hz) 7.53—7.60 (3H, m), 7.61—7.70 (2H, m). ^{19}F-NMR ($CDCl_3$) δ: −185.7 (ddd, J=48.1, 34.5, 14.7 Hz). MS *m/z* 253 (M^+). HR-MS Calcd for $C_{13}H_{16}FNOS$: 253.0858. Found: 253.0901.

8-Fluoro-8-(phenylsulfinyl)octanenitrile (**5b**): A part of the mixture was separated into the two stereoisomers. Less polar isomer; A colorless oil: IR (neat) cm^{-1}: 2245, 1049. ^{1}H-NMR ($CDCl_3$) δ: 1.35—1.52 (4H, m), 1.59—1.68 (4H, m), 1.99—2.12 (2H, m), 2.34 (2H, t, J=7.1 Hz), 4.91 (1H, ddd, J=49.3, 8.7, 2.8 Hz) 7.56—7.58 (3H, m), 7.66—7.68 (2H, m). ^{19}F-NMR ($CDCl_3$) δ: −179.8 (ddd, J=49.3, 32.0, 19.7 Hz). MS *m/z* 267 (M^+). HR-MS Calcd for $C_{14}H_{18}FNOS$: 267.1078. Found: 267.1099. More polar isomer; A colorless oil: IR (neat) cm^{-1}: 2244, 1049. ^{1}H-NMR ($CDCl_3$) δ: 1.25—1.58 (4H, m), 1.62—1.78 (4H, m), 1.89—2.05 (2H, m), 2.33 (2H, t, J=7.1 Hz), 5.08 (1H, ddd, J=49.2, 9.1, 3.6 Hz) 7.56—7.58 (3H, m), 7.64—7.67 (2H, m). ^{19}F-NMR ($CDCl_3$) δ: −185.7 (ddd, J=49.2, 34.5, 14.8 Hz). MS *m/z* 267 (M^+). HR-MS Calcd for $C_{14}H_{18}FNOS$: 267.1078. Found: 267.1089.

Representative Procedure for the Desulfurization of α-Fluorosulfoxides A benzene (3 ml) solution of **5a** (100 mg, 0.422 mmol) was heated in a sealed tube at 160 °C for 10 h. The reaction mixture was evaporated, and the resulting residue was subjected to chromatography (silica gel/hexane : ethyl acetate=20 : 1) to give **6a** (49 mg, 91%) as a 1 : 1 mixture of stereoisomers.

7-Fluorohept-6-enenitrile (**6a**): A colorless oil: IR (neat) cm^{-1}: 2246. ^{1}H-NMR ($CDCl_3$) δ: 1.51—1.58 (2H, m), 1.65—1.72 (2H, m), 1.95—2.00 (1H, m), 2.14—2.20 (1H, m), 2.35 (2H, t, J=7.1 Hz), 2.37 (2H, t, J=7.1 Hz), 4.72 (0.5H, dtd, J=41.7, 7.7, 4.7 Hz) 5.28—5.37 (0.5H, m), 6.49 (0.5H, ddt, J=85.5, 4.8, 1.4 Hz), 6.52 (0.5H, ddt, J=85.5, 11.1, 1.3 Hz),. ^{19}F-NMR ($CDCl_3$) δ: −129.7 (0.5F, dd, J=85.5, 18.5 Hz), −130.57 (0.5F, dd, J=85.5, 41.7 Hz). MS *m/z* 128 (M^++H). HR-MS Calcd for $C_7H_{11}FN$ (M^++H): 128.0936. Found: 128.0867.

8-Fluorooct-7-enenitrile (**6b**): A 1 : 1 mixture of stereoisomers; a colorless oil: IR (neat) cm^{-1}: 2246. ^{1}H-NMR ($CDCl_3$) δ: 1.36—1.51 (4H, m), 1.64—1.71 (2H, m), 1.91—1.96 (1H, m), 2.12—2.18 (1H, m), 2.35 (2H, t, J=7.1 Hz), 4.72 (0.5H, dtd, J=43.2, 7.7, 4.7 Hz), 5.28—5.37 (0.5H, m), 6.47 (0.5H, ddt, J=85.5, 4.7, 1.5 Hz), 6.51 (0.5H, ddt, J=85.7, 11.1, 1.4 Hz), ^{19}F-NMR ($CDCl_3$) δ: −130.5 (0.5F, dd, J=86.1, 19.7 Hz), −130.14 (0.5F, dd, J=86.1, 44.3 Hz). MS *m/z* 142 (M^++H). HR-MS Calcd for $C_8H_{13}FN$ (M^++H): 142.0973. Found: 142.1042.

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