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Exo/Endo Stereoselectivity in 1,3-Dipolar Cycloaddition of Trifluoroacetonitrile Oxide and -nitrilimine with Bicyclic Olefins[1)]

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Trifluoroacetonitrile oxide and *N*-phenyl-*C*-(trifluoromethyl)nitrilimine cycloadded with norbornenes, resulting in the exclusive formation of the exo-adducts, while the concomitant formation of the endo-adducts was observed in their cycloadditions with norbornadienes. The nitrile oxide was subjected to the cycloaddition with 2,3-disubstituted norbornadienes to evaluate the effect of the substituents on the exo/endo stereoselectivity. The electron-withdrawing substituents tend to favor the formation of the exo-adducts.

Remarkable stereoselectivity has been observed in 1,3-dipolar cycloadditions with bicyclic systems,[2)] and indeed, that with norbornenes proceeds exclusively on the exo face.[3)] In norbornadiene system, however, the stereospecificity is released. Cycloadditions of benzonitrile oxide and *C,N*-diphenylnitrilimine with norbornadiene itself, for example, afford a small amount of the endo-adducts together with the exo-adducts as the major products.[4,5)] Imoto and his coworkers have reported that the substituents attached to the unsaturated carbon in norbornadiene system affect the exo/endo product ratios. The amount of the endo-adduct, in the cycloadditions of phenylglyoxylonitrile oxide, increases with the electron-withdrawing substituents.[5)] These interesting results prompted us to investigate the exo/endo stereoselectivity in 1,3-dipolar cycloadditions of trifluoroacetonitrile oxide (**2**), which could be comparable to phenylglyoxylonitrile oxide in point of its electronic effect, with norbornenes and norbornadienes. The stereoselectivity of *N*-phenyl-*C*-(trifluoromethyl)nitrilimine (**10**) is also described.

The nitrile oxide **2**, generated in situ from trifluoroacetohydroximoyl bromide etherate (**1**) with triethylamine, cycloadded with norbornene in toluene, resulting in the exclusive formation of the exo-adduct, 5-trifluoromethyl-3-oxa-4-azatricyclo[5.2.1.$0^{2,6exo}$]dec-4-ene (**3a**), in a good yield (Table 1). Its configuration was determined on the basis of the absence of the coupling between the 2-proton and the vicinal bridgehead

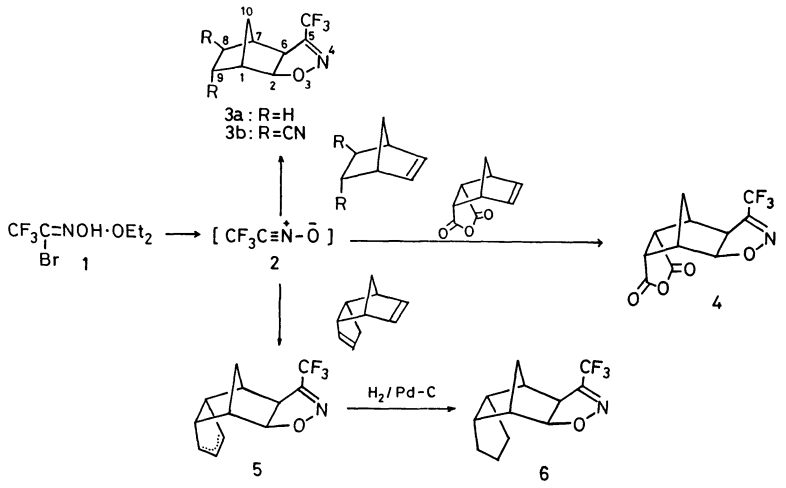
Table 1. Preparation of 5-Trifluoromethyl-3-oxa-4-azatricyclo[5.2.1.0]dec-4-enes and -deca-4,8-dienes

Compound	Yield %	Mp(θ_m/°C)[a)] [Bp(θ_b/°C/mmHg)]	Formula	Calcd(Found)/% C	H	N	IR ν/cm^{-1}
3a	68	[88—89/9]	$C_9H_{10}F_3NO$	52.69 (52.40)	4.91 (4.83)	6.83 (6.75)	1618(C=N)
3b	31	203—204[b)]	$C_{11}H_8F_3N_3O$	51.77 (52.08)	3.16 (3.15)	16.47 (16.43)	1614(C=N), 2215(C≡N)
4	56	183—184[c)]	$C_{11}H_8F_3NO_4$	48.01 (48.01)	2.93 (2.72)	5.09 (5.19)	1621(C=N), 1851, 1776(C=O)
5	72	[108—110/4][d)]	$C_{12}H_{12}F_3NO$	59.26 (59.21)	4.97 (4.93)	5.76 (5.93)	—
6	78[e)]	[100—101/4]	$C_{12}H_{14}F_3NO$	58.77 (58.71)	5.75 (5.82)	5.71 (5.85)	1617(C=N)
7a	77	Colorless oil	$C_9H_8F_3NO$	53.21 (53.05)	3.97 (3.93)	6.89 (6.86)	1617(C=N)
7'a		Colorless oil[f)]	$C_9H_8F_3NO$			6.89 (6.86)	1612(C=N)
7b	82	[140—141/3]	$C_{13}H_{12}F_3NO_5$	48.91 (48.76)	3.79 (3.98)	4.39 (4.25)	1620(C=N, C=C), 1730(C=O)
7'b		101—102	$C_{13}H_{12}F_3NO_5$	48.91 (48.91)	3.79 (3.84)	4.39 (4.44)	1615(C=N), 1635(C=C), 1740, 1718(C=O)
7c	75	115—116	$C_{11}H_6F_3N_3O$	52.18 (52.22)	2.39 (2.29)	16.60 (16.61)	1615(C=N), 2218(C≡N)
7'c		94—95	$C_{11}H_6F_3N_3O$	52.18 (52.22)	2.39 (2.35)	16.60 (16.58)	1610(C=N), 2225(C≡N)
7d	42	60—61	$C_{11}H_6F_9NO$			4.13 (3.90)	1616(C=N), 1681(C=C)

a) Recrystallized from hexane–chloroform unless otherwise noted. b) Recrystallized from ethanol. c) Recrystallized from chloroform–methanol. d) Boiling range. e) Yield from **5**. f) MS (CI, m/z) 204(M+1)$^+$, 138(M+1−C_5H_6)$^+$, 67(C_5H_6+1)$^+$. 1 mmHg=133.322 Pa.

proton and that between the 6- and 7-protons in ^{1}H NMR spectrum.[6] In the cycloaddition with 2,3-dicyanonorbornene, the product was isolated as the sole exo-adduct **3b** and, however, its absolute configuration around the carbon atom bearing the cyano group was ambiguous. The similar high stereospecificity was observed in the cases with endo-bicyclo-[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride and dicyclopentadiene to afford the exo-adducts **4** and **5**, respectively. The adduct **5** was a mixture consisting of two isomers, having the carbon-carbon double bond at different position. And their double bonds were selectively saturated by hydrogen using palladium-carbon catalyst to give the same product **6**.

In the cases with norbornadienes, the high stereospecificity was relaxed. The nitrile oxide **2** was first subjected to the reaction with norbornadiene in toluene at room temperature to afford a mixture of the exo-adduct, *5-trifluoromethyl-3-oxa-4-azatricyclo*-[5.2.1.$0^{2,6exo}$]deca-4,8-diene (**7a**), and its endo-isomer **7'a** in the ratio of 79/21 (Scheme 2). In ^{1}H NMR spectrum of the latter, both 2- and 6-protons couple with their adjacent bridgehead protons in 4 Hz (Table 2).[5] Although being stable at room temperature, both isomers were found to undergo the retro Diels-Alder reaction into 3-trifluoromethylisoxazole (**8**) under more drastic conditions.[7] ^{1}H NMR analysis of their breakdown with lapse of time reveals that the exo-adduct **7a** is much more stable than the endo-adduct **7'a**. After heating at 130 °C for 1 h, **7'a** was completely disappeared to form **8** in a 93% yield, whereas 33% of **7a** was found to survive even after 4 h, accompanied by the formation of 65% of **8**. These results support that **7'a** does not isomerize to the stable isomer **7a** on heating, indicating **7a** and **7'a** to be both primary products of the cycloaddition. The effect of the substituents, attached to the unsaturated carbon atom in the norbornadiene system, on the exo/endo stereoselectivity was next investigated. The reactions were carried out in toluene at room temperature and the results are summarized in Table 3. The electron-withdrawing substituents such as methoxycarbonyl and cyano groups



Scheme 1.

Table 2. ^{1}H NMR Data of 5-Trifluoromethyl-3-oxa-4-azatricyclo[5.2.1.0]dec-4-enes and -deca-4,8-dienes

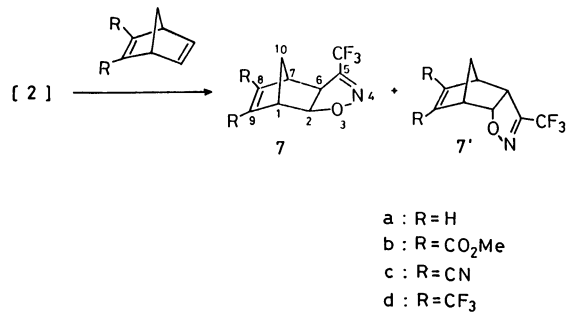
Compound	Chemical Shift/δ[a]	Coupling Constant/Hz		
		$J_{2,6}$	$J_{1,2}$	$J_{6,7}$
3a	1.0—1.8(m, 6H), 2.4—2.7(m, 2H), 3.19(d, 1H), 4.64(d, 1H)	9	—	—
3b	1.3—1.9(m, 2H), 2.8—3.8(m, 4H), 4.02(d, 1H), 5.12(d, 1H)[b]	8	—	—
4	1.4—2.0(m, 2H), 2.9—3.2(m, 2H), 3.6—3.8(m, 2H), 4.0—4.5(m, 1H), 4.94(d, 1H)[b]	9	—	—
6	1.4—1.8(m, 8H), 2.3—2.7(m, 4H), 3.48(d, 1H), 4.85(d, 1H)	8	—	—
7a	1.5—1.9(m, 2H), 3.1—3.3(m, 2H), 3.46(d, 1H), 5.00(d, 1H), 6.05(dd, 1H), 6.30(dd, 1H)[c]	8	—	—
7'a	1.2—1.7(m, 2H), 3.1—3.5(m, 2H), 3.81(dd, 1H), 5.41(dd, 1H), 5.9—6.2 (m, 2H)[c]	10	4	4
7b	1.5—2.1(m, 2H), 3.5—3.9(m, 3H), 3.80(s, 6H), 5.27(d, 1H)	8	—	—
7'b	1.5—2.1(m, 2H), 3.6—4.2(m, 3H), 3.80(s, 6H), 5.72(dd, 1H)	10	4	—[d]
7c	1.8—2.3(m, 2H), 3.6—4.0(m, 3H), 5.33(d, 1H)	8	—	—
7'c	1.6—2.2(m, 2H), 3.6—4.0(m, 2H), 4.20(dd, 1H), 5.80(dd, 1H)	10	4	4
7d	1.6—2.3(m, 2H), 3.5—4.0(m, 3H), 5.33(d, 1H)	8	—	—

a) Measured in $CDCl_3$ unless otherwise noted. b) Measured in $CDCl_3$-DMSO-d_6. c) Measured in CCl_4. d) Could not be evaluated because of the joint of the peaks of 6-H with other complex multiplet.

Table 3. Exo/Endo Stereoselectivity in the Cycloadditions of Trifluoroacetonitrile Oxide to Norbornadienes

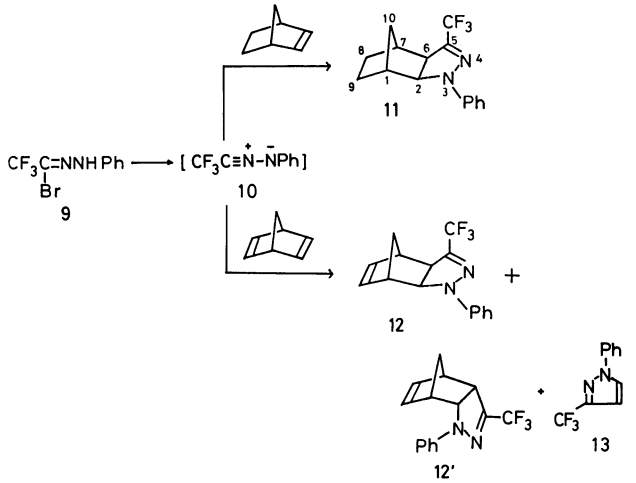
2,3-Disubstituted (R) Norbornadiene	Exo/Endo Ratio[a]	Reaction Conditions (Solvent, Temp.)
R=H	79/21	(Toluene, r.t.)
	72/28	(THF, r.t.)
	71/29	(THF, 0°C) [81/19 (THF, 0°C)][b]
R=CO_2Me	88/12	(Toluene, r.t.)
	88/12	(THF, r.t.)
	92/8	(THF, 0°C) [75/25 (THF, 0°C)][b]
R=CN	83/17	(Toluene, r.t.)
	92/8	(THF, r.t.) [68/32 (THF, 0°C)][b]
R=CF_3	100/0	(Toluene, r.t.)

a) Determined by ^{1}H NMR analysis of the reaction mixture. b) Outcome from the cycloaddition of phenylglyoxylonitrile oxide; see Ref. 5.



a : R=H
b : R=CO_2Me
c : R=CN
d : R=CF_3

Scheme 2.



Scheme 3.

were found to favor slightly the formation of the exo-adducts, compared with that in unsubstituted norbornadiene itself. And, in the case of trifluoromethyl group as the substituent, the exo-adduct was exclusively formed, accompanying no endo-adduct any longer. The temperature dependence of the exo/endo stereoselectivity is not apparently observed whereas the appreciable solvent effect between toluene and tetrahydrofuran is detected in the cases of norbornadiene and 2,3-dicyanonorbornadiene, as shown in Table 3.[8] However, in any case, the tendency of the electron-withdrawing substituents in favor of the exo-adducts is always consistent. This tendency is in sharp contrast to that of phenylglyoxylonitrile oxide, where the electron-withdrawing substituents increase the formation of the endo-adducts reversely (Table 3).[5] Although the reason why the tendency of **2** in the exo/endo stereoselectivity is different from that of phenylglyoxylonitrile oxide is not definite, it is suggested that the selectivity could be controlled by not only the electronic status of the substituted norbornadienes but also the interactions between the norbornadienes and the 1,3-dipolar compounds.

The stereoselectivity was next investigated with regard to the nitrilimine **10**, derived in situ from *N*-phenyltrifluoroacetohydrazonoyl bromide (**9**) in the presence of triethylamine. It was allowed to cycloadd with norbornene in toluene, giving rise to only the exo-adduct, 3-phenyl-5-trifluoromethyl-3,4-diazatricyclo-[5.2.1.$0^{2,6exo}$]dec-4-ene (**11**), in a moderate yield. With norbornadiene, the concomitant formation of the endo-adduct was again observed. 3-Phenyl-5-trifluoromethyl-3,4-diazatricyclo[5.2.1.$0^{2,6exo}$]deca-4,8-diene (**12**) and its endo-isomer **12'** as well as 1-phenyl-3-trifluoromethylpyrazole (**13**) were obtained in 45, 18, and 7% yields, respectively. The endo-adduct **12'** was found to undergo the breakdown rather easily even at room temperature into the pyrazole **13**.[9]

Experimental

All melting and boiling points are uncorrected. The IR spectra were recorded on a JASCO A-100 spectrometer. Samples were run as potassium bromide pellets for crystals or as film for oil. The ^{1}H NMR spectra were measured with a JEOL JNM-PMX 60 spectrometer using tetramethylsilane as an internal standard, the chemical shifts being given in δ ppm downfield. The MS spectra were obtained on a Finnigan 4023 GC-MS DS spectrometer. The bromides **1** and **9** were prepared by the methods reported in our previous papers.[10]

Cycloaddition of 2 with Norbornenes. General Procedures. A solution of triethylamine (20.0 mmol) in 10 cm^3 of toluene was added dropwise to a solution of **1** (10.0 mmol) and the corresponding norbornene derivative (30.0 mmol) in

20 cm^3 of toluene. After stirring at room temperature for 3 h, excess of hexane was added to the reaction mixture. The formed solid was filtered off and the filtrate was washed with water and brine, dried over magnesium sulfate, and evaporated to leave a residue. The resulting residue was (a) distilled under reduced pressure to give **3a** and **5**, respectively, (b) recrystallized from ethanol to give **3b**. On the other hand, **4** was isolated from the formed solid as follows. The solid consisting of **4** and triethylammonium bromide was extracted with acetone. Removal of the solvent left a solid which was recrystallized from chloroform–methanol to give **4**.

Hydrogenation of 5. A mixture of **5** (0.70 g, 2.88 mmol) and 5% palladium-carbon (40 mg) in 20 cm^3 of methanol was stirred at room temperature under an atmosphere of hydrogen. When an equivalent of hydrogen was consumed, the reaction was stopped. The catalyst was filtered off and, after the solvent was removed, the resulting oil was distilled to give 0.55 g (78%) of **6**.

Cycloaddition of 2 with Norbornadienes. General Procedures. To a solution of **1** (13.0 mmol) and the corresponding norbornadiene derivative (39.0 mmol for norbornadiene itself or 13.0 mmol for other substituted norbornadienes) in 20 cm^3 of toluene or tetrahydrofuran was added dropwise a solution of triethylamine (16.9 mmol) in 10 cm^3 of toluene or tetrahydrofuran at the temperature shown in Table 3. After the reaction mixture was stirred at the same temperature for 2 h, excess diethyl ether was added to the mixture and the resulting triethylammonium bromide was removed by filtration. The filtrate was washed with water and brine, dried over magnesium sulfate, and evaporated to leave a residue. Thus obtained residue was chromatographed on silica gel to separate the corresponding exo- and endo-adducts, respectively. Each adduct was further purified by distillation or recrystallization.

Retro Diels–Alder Reaction of 7'a. The endo-adduct **7'a** (100 mg) was heated at 130 °C in a sealed tube. After 1 h of heating, the mixture was cooled. ^1H NMR analysis of the mixture showed **8** in a 93% yield and dicyclopentadiene. The isoxazole **8** was purified by preparative GLC, ^1H NMR ($CDCl_3$) δ=6.64 (d, J=2.3 Hz, 1H), 8.59 (br.s, 1H), IR 3160, 3140 (CH), 1190, 1150 cm^{-1} (CF_3).

Found: C, 34.83; H, 1.21; N, 10.18%. Calcd for $C_4H_2F_3NO$: C, 35.05; H; 1.47; N, 10.22%.

Cycloaddition of 10 with Norbornadiene. Triethylamine (4 ml) was added dropwise to a solution of **9** (2.00 g, 7.5 mmol) and norbornadiene (2.07 g, 22.5 mmol) in 20 cm^3 of toluene. After 20 h of stirring at room temperature, 100 cm^3 of diethyl ether was added. The mixture was washed with water and brine, dried over magnesium sulfate, and evaporated under reduced pressure to leave a residue which was placed on a column (silica gel) and eluted with hexane–chloroform (10:1) to give 0.94 g (45%) of **12**, 0.37 g (18%) of **12'**, and 0.11 g (7%) of **13**, respectively. The exo-adduct **12** was further purified by recrystallization from hexane, mp 75—77 °C, ^1H NMR (CCl_4) δ=1.61 (br.s, 2H), 3.2—3.8 (m, 3H), 4.47 (d, J=10 Hz, 1H), 6.14 (dd, 1H), 6.32 (dd, 1H), 6.5—7.5 (m, 5H), IR 1604 (C=N), 1180, 1165 cm^{-1} (CF_3).

Found: C, 64.87; H, 4.54; N, 10.33%. Calcd for $C_{15}H_{13}F_3N_2$: C, 64.74; H, 4.71; N, 10.07%.

12': Pale yellow oil, ^1H NMR (CCl_4) δ=1.2—1.7 (m, 2H), 3.2—3.7 (m, 2H), 3.85 (ddq, J=11, 4, and 2 Hz, 1H), 4.83 (dd, J=11 and 4 Hz, 1H), 5.83 (dd, 1H), 6.06 (dd, 1H), 6.5—7.5 (m, 5H). IR 1602 (C=N), 1180, 1150 cm^{-1} (CF_3). The reliable elemental analysis could not be performed because of its easy breakdown.

Spectral data of thus obtained pyrazole **13** are consistent with those of our authentic sample.[11]

The exo-adduct **11** was similarly obtained in a 67% yield from the reaction of **9** with norbornene, mp 78.5—79.5 °C (lit,[12] 78.5—79.5 °C).

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