Regio- and Stereoselectivity of Cycloadditions of Trifluoromethylated Azomethine Ylide

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Synopsis. Trifluoromethylated azomethine ylide **1**, generated in situ by the conrotatory ring opening of *cis*-2-benzoyl-1-methyl-3-trifluoromethylaziridine, cycloadded with both electron-deficient and -rich monosubstituted olefins to give exclusively the corresponding 3-substituted pyrrolidines. This high regioselectivity is discussed in connection with the interaction between **1**-LUMO and olefin-HOMO.

Azomethine ylides are classified as allyl-type 1,3-dipolar compounds,[1] and their cycloadditions with olefins have been proved to be useful for the construction of pyrrolidines. Azomethine ylide cycloadditions are accelerated by electron-deficient olefins and this has been rationalized by the explanation that azomethine ylide-HOMO, lying at a rather high energy level, controls the reaction process.[2] We have been discovering effects of a trifluoromethyl group on the 1,3-dipolar cycloadditions of trifluoromethylated acetonitrile imines, -oxide, -ylides, and nitrones.[3] In this continuing study, we have demonstrated an ability of the trifluoromethyl group to lower both HOMO and LUMO energy levels of 1,3-dipolar compounds, which sometimes brings about an unusual behavior. Therefore it is of interest to investigate the reactivity of trifluoromethylated azomethine ylides. We now wish to report regio- and stereoselectivity and limitations of trifluoromethylated azomethine ylide cycloadditions.[4]

Azomethine ylide was generated in situ by heating *cis*-2-benzoyl-1-methyl-3-trifluoromethylaziridine (**2**) in a sealed cylinder. Refluxing a mixture of **2** and excess *N*-methylmaleimide in xylene for 20 h afforded a 46/54 mixture of *trans*-4,6-disubstituted cycloadducts **3** and **4** in 58% total yield (Scheme 1). The 4,3a- and 6,6a-configuration of these cycloadducts was identified on the basis of the coupling constants between 4- and 3a-protons and 6- and 6a-protons, respectively, in the ^{1}H NMR spectra and the smaller coupling constants are assigned to *trans*-configuration.[5] The ^{1}H NMR analyses support the *t*-4,*r*-3a,*c*-6a,*c*-6-configuration for **3** and the *c*-4, *r*-3a,*c*-6a,*t*-6-configuration for **4**. Interconversion between **3** and **4** was not found under these reaction conditions, pointing out these cycloadducts are primary products. These experimental results support the configuration of azomethine ylide to be *anti*-form **1** or **1′**, which is generated by the conrotatory ring opening of *cis*-aziridine **2**.[6] From consideration of the 1,5-dipolar interaction between azomethine-carbon and carbonyl-oxygen, *anti*-form **1** is more likely than **1′**.[7]

Great regioselectivity is recognized in the reactions with monosubstituted olefins. Cycloaddition with styrene gave exclusively 3-phenylpyrrolidine **5a** with the *r*-2,*c*-3,*t*-5-configuration. Stereochemistry of 2,5-substituents is assumed to be *trans*-configuration, as mentioned above. Cycloadditions with electron-deficient olefins such as methyl acrylate and acrylonitrile proceeded smoothly to give the corresponding 3-substituted pyrrolidines **5b** and **6c**, together with the dehydrogenated pyrroline **5b′** in the case with methyl acrylate. Those with 1-octene and norbornene resulted in sluggish reaction, giving a trace of cycloadducts. However electron-rich olefins such as butoxyethene afforded diastereoisomers, 3-butoxypyrrolidines **5d** and **6d**, in fairly good yield. Yields and stereochemistry of the products are collected in Table 1. This high regioselectivity was relaxed with methyl propiolate, giving 3-substituted *trans*-3-pyrroline **7**[8] and dehydrogenated pyrrole **8** along with its regioisomer **9** in the ratio of 4/1/2 (Scheme 2). 3-Pyrroline **7** was found to be converted to pyrrole **8** in refluxing xylene.

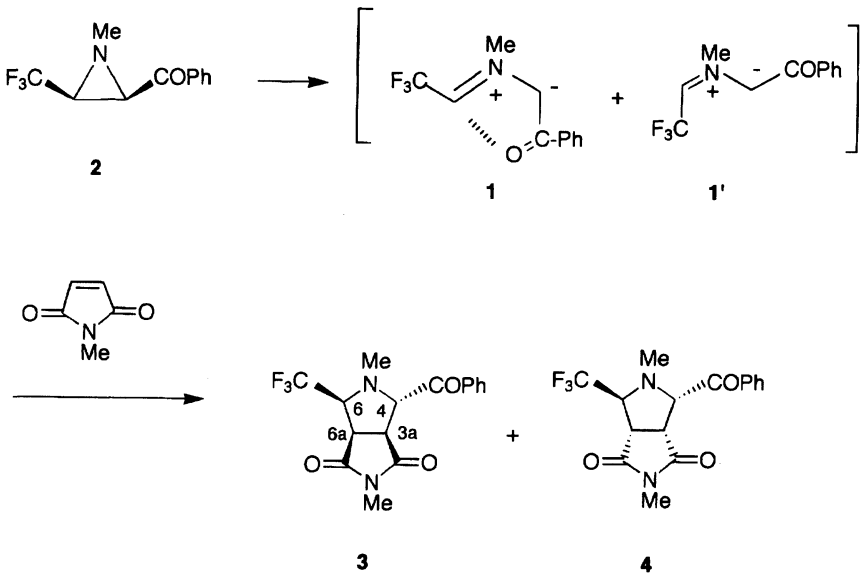
As was anticipated from the results of *C*-(trifluoromethyl)nitrone,[4] high regioselectivity in the cycloadditions of **1** with monosubstituted olefins may be explained by a **1**-LUMO control process, leading to the exclusive formation of 3-substituted pyrrolidines.[2] This is supported by the adequate reactivity toward electron-rich olefin. **1**-LUMO control is weakened with methyl propiolate because of its HOMO lying at a low energy level, resulting in relaxation of regioselectivity.

The exclusive formation of 3-phenylpyrrolidine **5a** with *r*-2,*c*-3-configuration is interpreted by the contribution of secondary orbital interaction between the styrene-phenyl group and the **1**-benzoyl group in a transition state. Similar interaction between methyl acrylate-ester group and **1**-benzoyl group is expected.

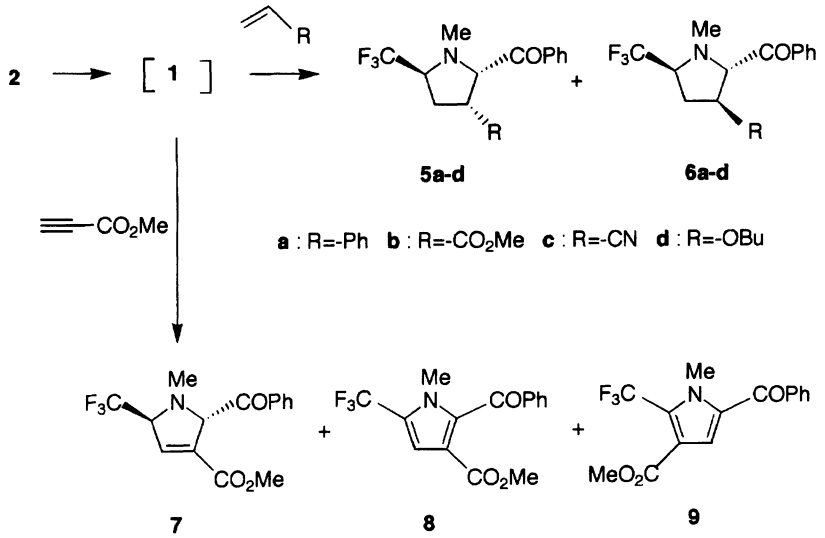
Table 1. Cycloadditions of Azomethine Ylide **1** with Monosubstituted Olefins

Olefin	Product	Yield/%	Ratio **5**/**6**[a]
	**5a**	81	100/0
	**5b**	39[b]	100/0
	**6c**	83	0/100
	5d and **6d**	89[c]	47/53

a) Determined by ^{1}H NMR analysis. b) Pyrroline **5b′** was isolated in 34% yield other than **5b**. c) Total yield.



Scheme 1.



Scheme 2.

Experimental

Infrared spectra were recorded on a JUSCO Report-100 spectrophotometer and samples were run as film or potassium bromide pellets. ^{1}H NMR spectra were taken on a JEOL-JNM-GX270 (270 MHz) spectrometer, using TMS as an internal standard. The chemical shifts (δ) were given in deuteriochloroform unless otherwise noted. The MS spectra were obtained on a Finnigan 4023 GC-MS DS spectrometer. The elemental analyses were measured with a Yanako MT-3 equipment. Aziridine **2** was prepared by the methods reported in our previous paper.[9]

Cycloaddition of Azomethine Ylide 1 with Olefins or Methyl Propiolate. General Procedure. A solution of **2** (0.50 g, 2.18 mmol) and 10.9 mmol of olefin or methyl propiolate in 10 cm^3 of xylene was added to a stainless cylinder (100 cm^3). The sealed cylinder was kept at 140—150 °C for 20 h. After removal of the solvent, the residue was chromatographed on silica gel with hexane–ethyl acetate–diethyl ether to give each product, which was further purified by preparative GLC or recrystallization. The analytical data of thus obtained products were as follows.

4-Benzoyl-4,5,6,6a-tetrahydro-2,5-dimethyl-6-trifluoromethylpyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione (3): Mp 172—174 °C (recrystallized from methanol); ^{1}H NMR (deuteriochloroform–DMSO-d_6) δ=2.55 (3H, s), 3.07 (3H, s), 3.28 (1H, d, J=8.3 Hz, 3a-H), 3.58 (1H, dd, J=8.3 and 8.3 Hz, 6a-H), 4.39 (1H, dq, J=8.3 and 7.3 Hz, 6-H), 5.28 (1H, s, 4-H), 7.5—8.2 (5H, m); IR 1710 (C=O), 1660 (C=O), 1150, 1140 cm^{-1} (CF_3).

Found: C, 56.44; H, 4.52; N, 8.21%. Calcd for $C_{16}H_{15}N_2F_3O_3$: C, 56.47; H, 4.44; N, 8.23%.

4-Benzoyl-4,5,6,6a-tetrahydro-2,5-dimethyl-6-trifluoromethylpyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione (4): Viscous oil; ^{1}H NMR δ=2.50 (3H, s), 2.91 (3H, s), 3.47 (1H, dd, J=8.8 and 1.8 Hz, 6a-H), 3.80 (1H, dd, J=8.8 and 8.8 Hz, 3a-H), 4.15 (1H, dq, J=1.8 and 7.9 Hz, 6-H), 5.05 (1H, d, J=8.8 Hz, 4-H), 7.5—8.1 (5H, m); IR 1710

(C=O), 1660 (C=O), 1160, 1110 cm^{-1} (CF_3).

Found: C, 56.58; H, 4.71; N, 8.24%. Calcd for $C_{16}H_{15}N_2F_3O_3$: C, 56.47; H, 4.44; N, 8.23%.

***r*-2-Benzoyl-1-methyl-*c*-3-phenyl-*t*-5-trifluoromethylpyrrolidine (5a):** Mp 92—94 °C (recrystallized from hexane–ethyl acetate–diethyl ether); ^1H NMR δ=2.22 (1H, ddd, J=12.7, 6.8, and 1.4 Hz, 4-H), 2.57 (3H, s), 2.93 (1H, ddd, J=12.7, 12.7, and 9.8 Hz, 4-H), 3.8—4.3 (2H, m, 3-H and 5-H), 5.13 (1H, d, J=7.6 Hz, 2-H), 7.0—7.5 (10H, m); IR 1660 (C=O), 1130, 1100 cm^{-1} (CF_3).

Found: C, 68.47; H, 5.44; N, 4.47%. Calcd for $C_{19}H_{18}NF_3O$: C, 68.46; H, 5.44; N, 4.20%.

Methyl *r*-2-Benzoyl-1-methyl-*t*-5-trifluoromethyl-*c*-3-pyrrolidinecarboxylate (5b): Mp 60—62 °C (recrystallized from hexane–ethanol); ^1H NMR δ=2.19 (1H, ddd, J=13.8, 7.5, and 2.5 Hz, 4-H), 2.50 (3H, s), 2.83 (1H, ddd, J=13.8, 12.5, and 7.5 Hz, 4-H), 3.27 (3H, s), 3.55 (1H, ddd, J=12.5, 7.5, and 7.5 Hz, 3-H), 3.73 (1H, m, 5-H), 5.16 (1H, d, J=7.5 Hz, 2-H), 7.5—8.0 (5H, m); IR 1720 (C=O), 1670 (C=O), 1160, 1140 cm^{-1} (CF_3).

Found: C, 57.28; H, 4.83; N, 4.07%. Calcd for $C_{15}H_{16}NF_3O_3$: C, 57.14; H, 5.11; N, 4.44%.

Methyl 2-Benzoyl-1-methyl-5-trifluoromethyl-2-pyrroline-3-carboxylate (5b′): Viscous oil; ^1H NMR δ=2.80 (3H, s), 3.05 (1H, dd, J=16.1 and 7.3 Hz, 4-H), 3.28 (1H, dd, J=16.1 and 12.2 Hz, 4-H), 3.50 (3H, s), 4.11 (1H, ddq, J=12.2, 7.3, and 7.3 Hz, 5-H), 7.5—8.0 (5H, m); IR 1710 (C=O), 1670 (C=O), 1160, 1120 cm^{-1} (CF_3).

Found: C, 57.31; H, 4.47; N, 4.24%. Calcd for $C_{15}H_{14}NF_3O_3$: C, 57.51; H, 4.50; N, 4.47%.

***r*-2-Benzoyl-*c*-3-cyano-1-methyl-*t*-5-trifluoromethylpyrrolidine (6c):** Mp 100—102 °C (recrystallized from chloroform); ^1H NMR δ=2.33 (1H, ddd, J=14.6, 3.0, and 2.2 Hz, 4-H), 2.59 (3H, s), 2.66 (1H, ddd, J=14.6, 9.2, and 9.2 Hz, 4-H), 3.13 (1H, ddd, J=9.2, 2.2, and 2.2 Hz, 3-H), 3.84 (1H, ddq, J=3.0, 9.2, and 6.0 Hz, 5-H), 5.09 (1H, d, J=2.2 Hz, 2-H), 7.5—8.0 (5H, m); IR 2215 (C≡N), 1660 (C=O), 1100 cm^{-1} (CF_3).

Found: C, 59.53; H, 4.47; N, 10.01%. Calcd for $C_{14}H_{13}N_2F_3O$: C, 59.57; H, 4.64; N, 9.92%.

***r*-2-Benzoyl-*c*-3-butoxy-1-methyl-*t*-5-trifluoromethylpyrrolidine (5d):** Yellow viscous oil; ^1H NMR δ=0.70 (3H, t, J=7.0 Hz), 0.9—1.3 (4H, m), 2.2—2.4 (2H, m, 4-H), 2.53 (3H, s), 3.20 (1H, dt, J=8.4 and 5.9 Hz), 3.34 (1H, dt, J=8.4 and 5.9 Hz), 3.8—3.9 (1H, m, 5-H), 4.39 (1H, ddd, J=9.1, 7.0, and 7.0 Hz, 3-H), 5.02 (1H, d, J=7.0 Hz, 2-H), 7.5—8.0 (5H, m); IR 1680 (C=O), 1140, 1110 cm^{-1} (CF_3).

Found: C, 62.08; H, 6.85; N, 4.15%. Calcd for $C_{17}H_{22}NF_3O_2$: C, 61.99; H, 6.73; N, 4.25%.

***r*-2-Benzoyl-*t*-3-butoxy-1-methyl-*t*-5-trifluoromethylpyrrolidine (6d):** Yellow viscous oil; ^1H NMR δ=0.90 (3H, t, J=7.0 Hz), 1.3—1.6 (4H, m), 2.35—2.5 (2H, m, 4-H), 2.60 (3H, s), 3.38 (1H, dt, J=8.6 and 6.4 Hz), 3.46 (1H, dt, J=8.6 and 6.4 Hz), 3.75—3.85 (2H, m, 3-H and 5-H), 5.01 (1H, s, 2-H), 7.4—8.1 (5H, m); IR 1680 (C=O), 1135, 1110 cm^{-1} (CF_3).

Found: C, 61.68; H, 6.38; N, 4.12%. Calcd for $C_{17}H_{22}NF_3O_2$: C, 61.99; H, 6.73; N, 4.25%.

Methyl *trans*-2-Benzoyl-1-methyl-5-trifluoromethyl-3-pyrroline-3-carboxylate (7): Yellow viscous oil; ^1H NMR δ=2.48 (3H, s), 3.64 (3H, s), 4.55 (1H, ddq, J=6.5, 2.2, and 6.5 Hz, 5-H), 5.91 (dd, J=6.5 and 1.8 Hz, 2-H), 6.81 (1H, dd, J=2.2 and 1.8 Hz, 4-H), 7.4—8.1 (5H, m); MS (CI, m/z) 314 $(M+H)^+$, 342 $(M+C_2H_5)^+$, 282 $(M-MeO)^+$.

Satisfactory analytical data could not be obtained because of it's instability during purification by preparative GLC.

Methyl 2-Benzoyl-1-methyl-5-trifluoromethyl-3-pyrrolecarboxylate (8): Yellow viscous oil; ^1H NMR δ=3.46 (3H, s), 3.68 (3H, q, J=0.8 Hz), 7.07 (1H, q, J=0.8 Hz, 4-H), 7.4—7.9 (5H, m); IR 1715 (C=O), 1660 (C=O), 1160, 1110 cm^{-1} (CF_3); MS (CI, m/z) 312 $(M+H)^+$, 340 $(M+C_2H_5)^+$.

Methyl 5-Benzoyl-1-methyl-2-trifluoromethyl-3-pyrrolecarboxylate (9): Yellow viscous oil; ^1H NMR δ=3.84 (3H, s), 4.11 (3H, q, J=2.7 Hz), 7.03 (1H, q, J=0.4 Hz, 3-H), 7.5—7.9 (5H, m); IR 1725 (C=O), 1640 (C=O), 1180, 1120 cm^{-1} (CF_3); MS (CI, m/z) 312 $(M+H)^+$, 340 $(M+C_2H_5)^+$.

Found: C, 57.68; H, 3.68; N, 4.52%. Calcd for $C_{15}H_{12}NF_3O_3$: C, 57.88; H, 3.89; N, 4.50% (for a mixture of **8** and **9**).

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