[Chem. Pharm. Bull. 33(7)2762—2766(1985)]

Trifluoroacetic Acid-Catalyzed 1,3-Cycloaddition of the Simplest Iminium Ylide Leading to 3- or 3,4-Substituted Pyrrolidines and 2,5-Dihydropyrroles

YOSHIYASU TERAO, HIROMI KOTAKI, NOBUYUKI IMAI, and KAZUO ACHIWA*

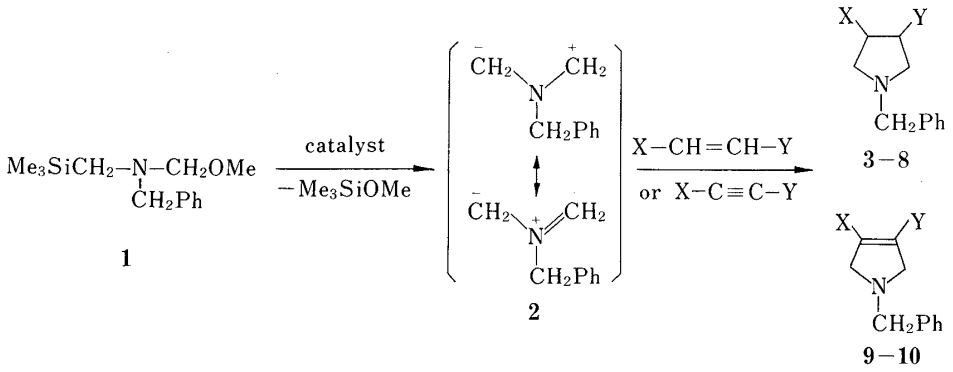
Shizuoka College of Pharmacy, 2–2–1 Oshika, Shizuoka 422, Japan

(Received October 15, 1984)

The 1,3-dipolar cycloaddition of an intermediary iminium ylide formed from *N*-benzyl-*N*-(methoxymethyl)trimethylsilylmethylamine to conjugated olefinic and acetylenic dipolarophiles in the presence of a catalytic amount of trifluoroacetic acid has been found to give 3- or 3,4-substituted pyrrolidines and 2,5-dihydropyrroles.

Keywords——1,3-dipolar cycloaddition; iminium ylide; 3,4-substituted pyrrolidine; 2,5-dihydropyrrole; *N*-benzyl-*N*-(methoxymethyl)trimethylsilylmethylamine

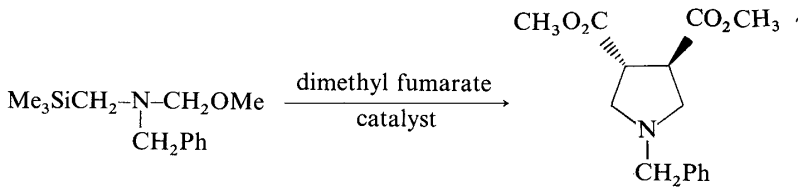
Previously we have exploited interesting new aspects of the chemistry of non-stabilized iminium ylides[1] and developed new synthetic methods for 2,3,4-, 2,3- or 2,4-substituted pyrrolidine and 2,5-dihydropyrrole derivatives.[1a–d] As a part of our continuing attempt to develop a general synthesis of 3,4- or 3-substituted pyrrolidines[1h,2] and 2,5-dihydropyrroles, the former of which are potentially useful in the field of azaprostacycline synthesis,[3] we have selected *N*-benzyl-*N*-(methoxymethyl)trimethylsilylmethylamine (**1**) as a synthon for the simplest iminium ylide (**2**) which is expected to undergo 1,3-cycloaddition to conjugated olefinic and acetylenic dipolarophiles in the presence of a catalyst to afford the corresponding pyrrolidines (**3**—**8**) and 2,5-dihydropyrroles (**9**—**10**) as shown below.



Preliminary experiments included an examination of the relative activities of several catalysts using **1** and dimethyl fumarate in dichloromethane at room temperature (Table I). The table indicates that this reaction proceeded almost quantitatively in the presence of 10 mol% trifluoroacetic acid at room temperature for 3 h when 1.2 molar equivalent of **1** was used to compensate for its instability resulting bis(*N*-benzyl-*N*-trimethylsilylmethylamino)methane.[4]

The results of extensive experiments with the other dipolarophiles are listed in Table II.

TABLE I. Effectiveness of Various Catalysts[a]



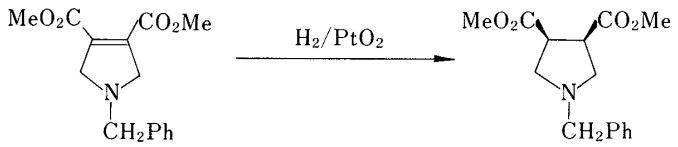
1 3

Catalyst[b]	Time (h)	Yield (%)
CF_3CO_2H[c]	3	97
CF_3CO_2H	3	76
CH_3CO_2H	3	71
$TiCl_4$	5	49
CF_3SO_3H	24	49
$CF_3SO_3SiMe_3$	24	44

a) Reaction conditions: solvent, CH_2Cl_2; temp., r.t. *b*) Molar ratio, **1**: dimethyl fumarate: catalyst = 1:1:0.1. *c*) Molar ratio, **1**: dimethyl fumarate: catalyst = 1.2:1:0.1.

Table II shows clearly that all the reactions proceeded smoothly to give the corresponding pyrrolidines (**3**—**8**) and 2,5-dihydropyrroles (**9**—**10**) in good to excellent yields.

The spectral and analytical data of the products (Table III) are consistent with the proposed structures. Compounds **3**, **4**, and **5** were concluded to retain the configurations of the olefinic dipolarophiles (3,4-*trans* for **3**, 3,4-*cis* for **4**, and 3,4-*trans* for **5**) on the basis of the following results. The similarity of the proton nuclear magnetic resonance (^{1}H-NMR) and carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectra of **3** and **4** suggests that they are in a stereoisomeric relationship. The ^{1}H-NMR spectrum of the compound obtained by catalytic hydrogenation of the product (**9**), which is generally regarded as involving *cis* addition of hydrogen, was in good agreement with that of **4**.



9 **4**

The methoxycarbonyl group of **5** was confirmed to be *trans* to the phenyl group from its ^{1}H-NMR spectrum, in which the signal of an ester methyl appears at 3.60 ppm without any shielding effect of the adjacent phenyl group.[5]

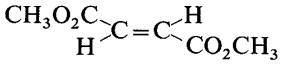
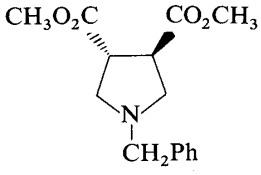
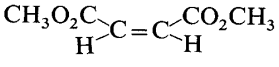
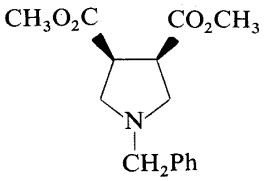
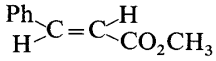
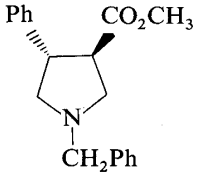
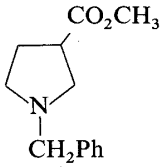
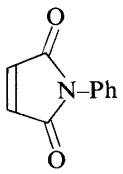
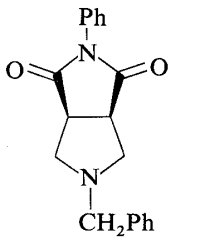
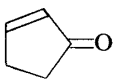
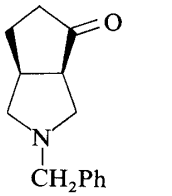
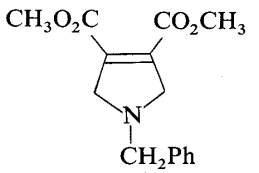
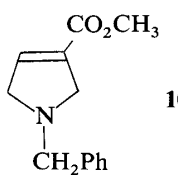
In summary, this trifluoroacetic acid-catalyzed 1,3-dipolar cycloaddition of the simplest iminium ylide is admirably suited for synthesizing 3-, or 3,4-substituted pyrrolidines and also 2,5-dihydropyrroles in good to excellent yields under mild conditions, in contrast to the recently reported silver fluoride-promoted cycloaddition of *N*-benzyl-*N*-(cyanomethyl)trimethylsilylmethylamine[1h] and the trimethylsilyl triflate- or trimethylsilyl iodide-fluoride catalyzed cycloaddition of **1** and related compounds[2] to olefinic dipolarophiles.

Further investigation in this area is under way.

Experimental

All boiling and melting points are uncorrected. The infrared (IR) spectra were recorded on a JASCO IRA-2

TABLE II. Synthesis of 3- or 3,4-Substituted Pyrrolidines and 2,5-Dihydropyrroles[a)]

Dipolarophile	Product	Compound No.	bp or mp (°C)	Yield (%)
		**3**	138—139 (0.4 mmHg)	97
		**4**	129—130 (0.5 mmHg)	94
		**5**	159—160 (0.1 mmHg)	87
$H_2C=CHCO_2CH_3$		**6**	104—105 (4 mmHg)	89
		**7**	125—127	86
		**8**	117—118 (0.5 mmHg)	66
$CH_3O_2CC\equiv CCO_2CH_3$		**9**	146—148 (0.6 mmHg)	66
$HC\equiv CCO_2CH_3$		**10**	116—117 (2 mmHg)	58

a) Reaction conditions: molar ratio, $Me_3SiCH_2N(CH_2Ph)CH_2OMe$: olefin : $CF_3COOH = 1.2 : 1 : 0.1$; solvent, CH_2Cl_2; temp, r.t.; time, 3 h.

TABLE III. Spectral Data for the Products

Compound No.	IR ν_{max}^{neat} cm^{-1}	^{1}H-NMR δ ($CDCl_3$)[a]	^{13}C-NMR δ ($CDCl_3$)[a]	Formula	Analysis (%) Calcd (Found)		
					C	H	N
3	1739 (C=O)	2.73—3.30 (4H, m), 3.25—3.54 (2H, m), 3.59 (2H, s), 3.68 (6H, s), 7.27 (5H, s)	45.5 (d, 2×C), 52.0 (q, 2×C), 56.6 (t, 2×C), 59.3 (t), 128.1 (d), 128.2 (d, 2×C), 128.6 (d, 2×C), 138.4 (s), 173.8 (s, 2×C)	$C_{15}H_{19}NO_4$	64.96 (64.96	6.91 7.16	5.05 5.29)
4	1739 (C=O)	2.65—2.81 (2H, m), 3.03—3.40 (4H, m), 3.65 (8H, s), 7.28 (5H, s)	46.3 (d, 2×C), 56.6 (q, 2×C), 56.9 (t, 2×C), 60.7 (t), 128.0 (d), 129.2 (d, 2×C), 129.5 (d, 2×C), 139.6 (s), 173.7 (s, 2×C)	$C_{15}H_{19}NO_4$	64.96 (65.06	6.91 6.89	5.05 5.13)
5	1735 (C=O)	2.63—3.14 (6H, m), 3.60 (3H, s), 3.64 (2H, s), 7.30—7.40 (10H, m)	47.0 (d), 51.7 (q, d, 2×C), 57.4 (t), 59.9 (t), 61.7 (t), 126.5 (d), 127.0 (d), 127.4 (d, 2×C), 128.2 (d, 2×C), 128.5 (d, 2×C), 128.6 (d, 2×C), 138.9 (s), 144.2 (s), 174.4 (s)	$C_{19}H_{21}NO_2$	77.26 (76.99	7.17 7.31	4.74 4.74)
6	1731 (C=O)	1.71—2.20 (2H, m), 2.31—3.05 (5H, m), 3.46 (2H, s), 3.50 (3H, s), 7.11 (5H, s)	27.7 (t), 42.1 (d), 51.7 (q), 53.7 (t), 56.7 (t), 60.1 (t), 126.9 (d), 128.2 (d, 2×C), 128.7 (d, 2×C), 139.0 (s), 175.3 (s)	$C_{13}H_{17}NO_2$	71.20 (70.96	7.82 7.75	6.39 6.26)
7	1780 1708 (C=O)	2.27—2.56 (2H, m), 3.30—3.45 (4H, m), 3.57 (2H, s), 7.21—7.37 (10H, m)	44.5 (d, 2×C), 56.6 (t, 2×C), 58.2 (t), 126.5 (d, 2×C), 127.2 (d, 2×C), 128.2 (d, 2×C), 128.4 (d, 2×C), 129.0 (d, 2×C), 132.3 (s), 137.8 (s), 178.2 (s, 2×C)	$C_{19}H_{18}N_2O_2$	74.49 (74.39	5.92 6.10	9.15 9.04)
8	1741 (C=O)	1.94—3.06 (10H, m), 3.51 (1H, d, J=13 Hz), 3.53 (1H, d, J=13 Hz), 7.13 (5H, s)	27.4 (t), 38.6 (t), 39.0 (d), 50.6 (d), 58.0 (t), 59.5 (t), 61.4 (t), 126.9 (d), 128.2 (d, 2×C), 128.5 (d, 2×C), 138.9 (s), 193.0 (s)	$C_{14}H_{17}NO$	78.10 (77.81	7.96 7.96	6.51 6.44)
9	1728 (C=O) 1661 (C=C)	3.74 (6H, s), 3.77 (2H, s), 3.81 (4H, s), 7.30 (5H, s)	51.9 (q, 2×C), 59.6 (t), 60.6 (t, 2×C), 128.1 (d), 128.3 (d, 4×C), 137.0 (s, 2×C), 138.4 (s), 163.7 (s, 2×C)	$C_{15}H_{17}NO_4$	65.44 (65.16	6.22 6.32	5.09 5.16)
10	1724 (C=O) 1671 (C=C)	3.65 (2H, s), 3.70 (3H, s), 3.76 (2H, br), 3.79 (2H, br), 6.73 (1H, br), 7.30 (5H, s)	51.4 (q), 58.4 (t), 60.0 (t), 60.2 (t), 127.1 (d), 128.4 (d, 2×C), 128.5 (d, 2×C), 139.0 (s), 139.4 (d), 152.7 (s), 163.8 (s)	$C_{13}H_{15}NO_2$	71.86 (71.59	6.96 6.96	6.45 6.44)

a) s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad.

spectrophotometer. The ^{1}H-NMR and ^{13}C-NMR spectra were measured on a JEOL FX-90-Q spectrometer.

***N*-Benzyl-*N*-(methoxymethyl)trimethylsilylmethylamine (1)**——A solution of methoxymethyl chloride (1.61 g, 20 mmol) in tetrahydrofuran (THF 3 ml) was added to a stirred solution of lithium *N*-benzyltrimethylsilylmethylamide [freshly prepared from *N*-benzyltrimethylsilylmethylamine (3.82 g, 20 mmol) and a 1.55 M hexane solution of butyllithium (12.9 ml) in THF (50 ml)] at −70 °C. The solution was stirred for a further 3 h at the same temperature, then THF was removed under reduced pressure and the residue was extracted with hexane. The product obtained by evaporation of the hexane was almost pure without further purification, yield 4.06 g (90%). ^{1}H-NMR δ ($CDCl_3$): 0.07 (9H, s, $Si(CH_3)_3$), 2.18 (2H, s, $SiCH_2N$), 3.20 (3H, s, OCH_3), 3.71 (2H, s, NCH_2Ph), 3.95 (2H, s, NCH_2O), 7.71 (5H, s, C_6H_5).

Reactions of *N*-Benzyl-*N*-(methoxymethyl)trimethylsilylmethylamine (1) with Conjugated Olefinic and Acetylenic Dipolarophiles——General Procedure: A 1 M solution of trifluoroacetic acid (0.5 ml) in CH_2Cl_2 was added at 0—5 °C to a stirred solution of **1** (1.42 g, 6 mmol) and dipolarophile (5 mmol) in CH_2Cl_2 (10 ml). After 3 h of stirring at room temperature, the solution was washed with saturated sodium bicarbonate and with brine, then dried over $MgSO_4$. After removal of the CH_2Cl_2, the residual oil was distilled under reduced pressure (**3**—**6**, **8**—**10**) or subjected to column chromatography on silica gel with benzene–THF (9 : 1) (**7**).

Yields and spectral and analytical data of the products are listed in Tables II and III.

Catalytic Hydrogenation of 9——A mixture of **9** (100 mg) and platinum (IV) oxide (10 mg) in methanol (2 ml) was stirred at room temperature under a hydrogen atmosphere. After 5 h of stirring, filtration of catalyst followed by evaporation of the solvent gave the product (**4**) in an almost quantitative yield. This product was identical with that obtained by direct 1,3-dipolar cycloaddition of **1** with dimethyl maleate.

References and Notes

1) *a*) K. Achiwa and M. Sekiya, *Chem. Lett.*, **1981**, 1213; *b*) *Idem, Tetrahedron Lett.*, **23**, 2589 (1982); *c*) Y. Terao, N. Imai, K. Achiwa, and M. Sekiya, *Chem. Pharm. Bull.*, **30**, 3167 (1982); *d*) K. Achiwa, T. Motoyama, and M. Sekiya, *ibid.*, **31**, 3939 (1983); *e*) E. Vedejs and G. R. Martinez, *J. Am. Chem. Soc.*, **101**, 6452 (1979); *f*) *Idem, ibid.*, **102**, 7993 (1980); *g*) E. Vedejs and F. G. West, *J. Org. Chem.*, **48**, 4773 (1983); *h*) A. Padwa and Y.-Y. Chen, *Tetrahedron Lett.*, **24**, 3447 (1983); *i*) A. Padwa, G. Hoffmann, and M. Tomas, *ibid.*, **24**, 4303 (1983); *j*) T. Livinghouse and R. Smith, *J. Chem. Soc., Chem. Commun.*, **1983**, 210; *k*) R. Smith and T. Livinghouse, *J. Org. Chem.*, **48**, 1554 (1983); *l*) S.-F. Chen, J. W. Ullrich, and P. S. Mariano, *J. Am. Chem. Soc.*, **105**, 6160 (1983); *m*) O. Tsuge, S. Kanemasa, S. Kuraoka, and S. Takenaka, *Chem. Lett.*, **1984**, 279; *n*) O. Tsuge, S. Kanamasa, A. Hatada, and K. Matsuda, *ibid.*, **1984**, 801.

2) After this work was completed, a communication on trimethylsilyl triflate- or trimethyl iodide-fluoride catalyzed cycloaddition of **1** appeared. *Cf.* A. Hosomi, Y. Sakata, and H. Sakurai, *Chem. Lett.*, **1984**, 1117.

3) *Cf.* N. Nakai, Y. Arai, N. Hamanaka, and M. Hayashi, *Tetrahedron Lett.*, **1979**, 805.

4) bp 110—112 °C (10 mmHg). ^{1}H-NMR δ ($CDCl_3$): 0.04 (18H, s, $2 \times Si(CH_3)_3$), 1.95 (4H, s, $2 \times SiCH_2N$), 2.88 (2H, s, NCH_2N), 3.62 (4H, s, $2 \times NCH_2Ph$), 7.21 (10H, s, $2 \times C_6H_5$).

5) The ^{1}H-NMR signal of ester methyl oriented *cis* to a phenyl group on a 5-membered ring is usually shifted to near 3.1 ppm due to the shielding effect of the phenyl group. M. Joucla, D. Gree, and J. Hamalin, *Tetrahedron*, **29**, 2315 (1973).