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Trimethylsilyl Triflate-Catalyzed 1,3-Dipolar Cycloaddition Leading to *N*-Unsubstituted Pyrrolidines

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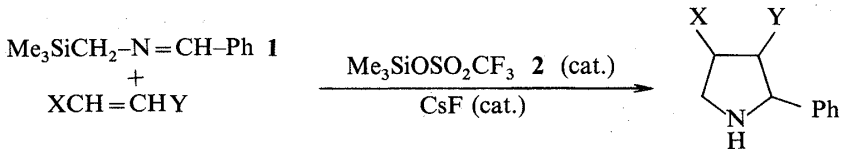
Dipolar cycloaddition of an intermediary *N*-trimethylsilyltrimethylsilylmethyliminium salt formed from *N*-(benzylidene)trimethylsilylmethylamine by the catalytical action of trimethylsilyl triflate to conjugated alkene or alkyne gave *N*-unsubstituted pyrrolidines. The stereochemistry of all the products was determined.

Keywords——*N*-trimethylsilyltrimethylsilylmethyliminium salt; *N*-trimethylsilylmethyleneiminium ylide; 1,3-dipolar cycloaddition; *N*-unsubstituted pyrrolidine; trimethylsilylmethylamine; *N*-(benzylidene)trimethylsilylmethylamine

As a part of our studies on 1,3-dipolar cycloaddition[1–3] involving an intermediary *N*-trimethylsilylmethyliminium ylide, we briefly described the trimethylsilyl triflate-catalyzed 1,3-dipolar cycloaddition of *N*-(benzylidene)trimethylsilylmethylamine (**1**) with dipolarophiles leading to *N*-unsubstituted pyrrolidines.[2] The details of this new reaction are the subject of this paper.



Although trimethylsilyl triflate (**2**) is known to catalyze carbon–carbon bond forming reactions, the generation of the carbanion by fission of the silicon–carbon bond in the course of such reactions has been reported only in the case of allyltrimethylsilanes.[4] The present reaction involves the cycloaddition of an ylide (**3**) formed from the intermediary *N*-trimethylsilylmethyliminium salt (**11**), which is derived from **1** in the presence of a catalytic amount of trimethylsilyl triflate (**2**). With olefinic (**4**) and acetylenic (**5**) dipolarophiles the reaction leads to the formation of *N*-trimethylsilyl-substituted pyrrolidine and 2,5-dihydropyrrole, which are easily transformed into *N*-unsubstituted compounds (**6**—**10**). The catalytic process, which is shown in Chart 1, involves a new fission of the silicon–carbon bond of the *N*-trimethylsilylmethyliminium salt (**11**). The reaction is further accelerated catalytically by addition of cesium fluoride (**12**), which aids in the fission of the silicon–carbon bond, as already known.[5]

Preliminary experiments were carried out to determine the efficiencies of several solvents for this cycloaddition. Using dimethyl fumarate as a dipolarophile, the results are summarized in Table I. Efficiencies of the solvents tested were in the order: hexamethylphosphoramide (HMPA), dimethylformamide (DMF) $\gg$ dimethoxyethane (DME) $>$ tetrahydrofuran (THF) $\gg$ acetonitrile $>$ benzene $>$ dichloromethane. Thus, HMPA was selected as the most suitable for this reaction. Although DMF was also highly efficient, the *N*-formyl pyrrolidine

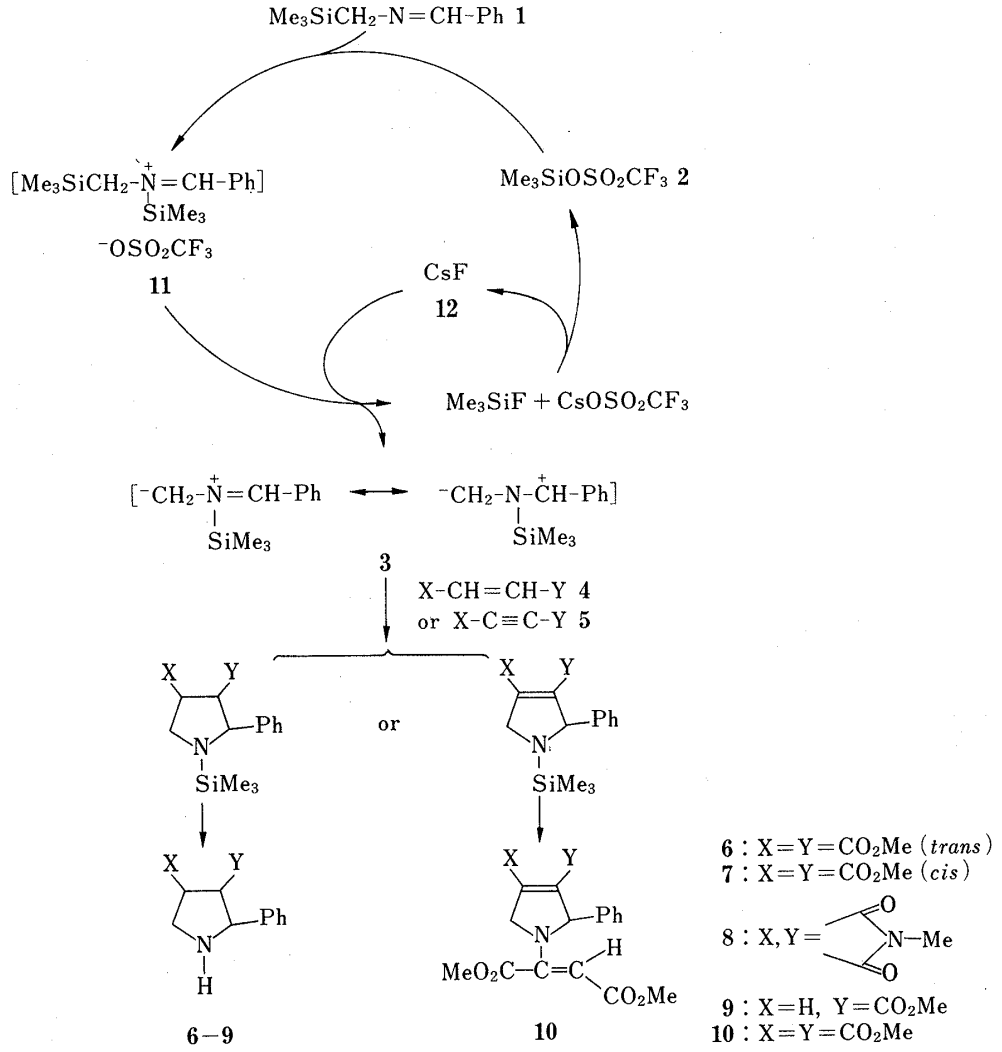


Chart 1

TABLE I. Solvent Effect on the 1,3-Dipolar Cycloaddition with Dimethyl Fumarate[a]

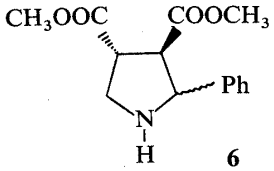
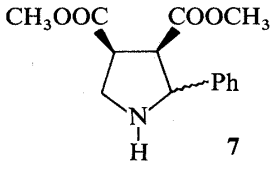
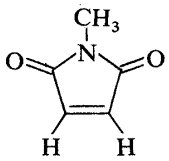
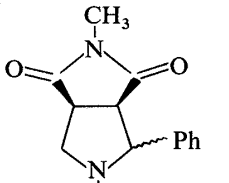
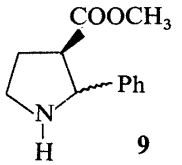
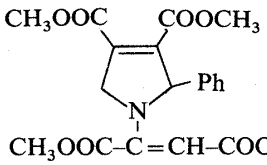
Solvent	Conversion (%)[b]
Hexamethylphosphoramide	100
Dimethylformamide	100[c]
Dimethoxyethane	85
Tetrahydrofuran	66
Acetonitrile	30
Benzene	17
Methylene chloride[d]	3

a) All reactions were carried out with Schiff base (**1**) (2.5 mmol), dimethyl fumarate (2.5 mmol), trimethylsilyl triflate (**2**) (0.5 mmol) and cesium fluoride (0.5 mmol) in 10 ml of solvent at 60—65 °C for 20 h unless otherwise indicated. *b*) Calculated from the disappearance of the Schiff base as determined by GLC (10% SE-30 on Chromosorb-W). *c*) The *N*-formylated product was obtained as a by-product in 10—20% yield. *d*) At reflux.

derivative was obtained as a by-product.

As dipolarophiles, dimethyl fumarate, dimethyl maleate, *N*-methylmaleimide, methyl acrylate and dimethyl acetylenedicarboxylate were employed, and the results of these

TABLE II. Synthesis of Pyrrolidines by 1,3-Dipolar Cycloaddition[a]

X–CH=CH–Y or X–C≡C–Y	Product	Yield (%)	2-Phenyl and 3-CO- *cis* : *trans*[b]
CH_3OOC, H, $C=C$, H, $COOCH_3$	 **6**	91	5:4
CH_3OOC, H, $C=C$, $COOCH_3$, H	 **7**	83	2:3
	 **8**	85	1:2
$CH_2=CH–COOCH_3$	 **9**	83	5:4
$CH_3OOC–C\equiv C–COOCH_3$[c]	 **10**	92	—

a) All the reactions were carried out as described in Experimental. *b*) The diastereomeric ratios were determined by ^{1}H-NMR measurement. *c*) In this run, 10 mmol of dimethyl acetylenedicarboxylate was used, since two mol eq consumed in the reaction to give the *N*-substituted product, as indicated.

extensive experiments are summarized in Table II. In every run the reaction proceeded smoothly at 60—65 °C for 20 h in HMPA.

The products **6**, **7**, **8** and **9** in Table II were obtained as mixtures of geometric isomers. The stereochemistry of **6**, **7** and **9** was confirmed by converting these products to the corresponding *N*-benzoyl derivatives, **15a**, **b**, **16a**, **b** and **18a**, **b**, respectively, whose structures were established in the previous paper[1] from this laboratory.

The relative stereochemistry between C_2-Ph and C_3–CO–N< of **17a**, and **17b** derived from **8** is assigned as *cis* for **17a** and *trans* for **17b**, based on their proton nuclear magnetic resonance (^{1}H-NMR) spectra, in which the *N*-methyl signal of the *cis*-C_2, C_3-substituted compound (**17a**) is shifted to higher field by the shielding effect of the 2-phenyl group.

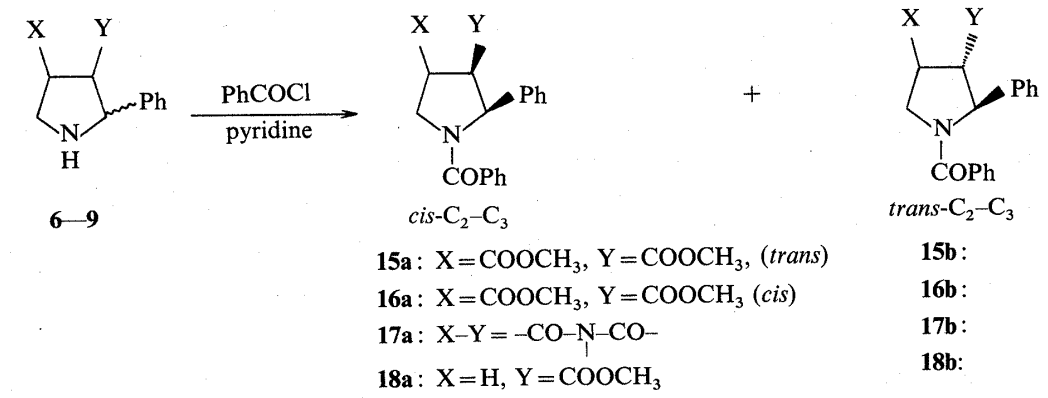
The structure of **10** was confirmed by converting it to the known *N*-benzoyl derivative, **20**,[1] by treatment with methanolic hydrogen chloride followed by *N*-benzoylation with benzoyl chloride in pyridine.

The stereochemistry of all the products is listed in Table II. In contrast to the previously reported cycloaddition of the *N*-acyliminium intermediate,[1] the present reaction *via* the *N*-

TABLE III. ^{1}H-NMR Data[a] for Pyrrolidine and 2,5-Dihydropyrrole Derivatives

Compd. No.	NH	3-$COOCH_3$	4-$COOCH_3$	2-H	3H 4H 5H	Others
6	2.32 (1H, s)	3.17 (s), 3.65 (s) (3H)	3.71 (s), 3.72 (s) (3H)	4.52 (d, $J_{2,3}=8.1$), 4.29 (d, $J_{2,3}=8.1$) (1H)	3.1—4.0 (4H, m)	7.1—7.4 (5H, m, Ph)
7	2.44 (1H, s)	3.22 (s), 3.65 (s) (3H)	3.63 (s), 3.65 (s) (3H)	4.41 (d, $J_{2,3}=6.1$), 4.62 (d, $J_{2,3}=6.1$) (1H)	3.1—4.0 (4H, m)	7.1—7.4 (5H, m, Ph)
8	1.99 (1H, s)	—	—	4.37 (d, $J_{2,3}=7.6$), 4.65 (br, $J_{2,3}<4$) (1H)	2.9—3.8 (4H, m)	7.1—7.4 (5H, m, Ph) 2.89, 3.02 (3H, s, $\geq$N–CH_3)
9	2.15 (1H, s)	3.20 (s), 3.67 (s) (3H)	—	4.34 (d, $J_{2,3}=7.6$), 4.37 (d, $J_{2,3}=7.1$) (1H)	2.0—3.8 (5H, m)	7.1—7.4 (5H, m, Ph)
10	—	3.62 (s), 3.49 (s) (3H)	3.79 (s), 3.82 (s) (3H)	5.74 (1H, br)	4.0—5.2 (2H, m)	3.18, 3.49 (3H, s, 2′-$COOCH_3$) 3.58 (3H, s, 1′-$COOCH_3$) 7.1—7.4 (5H, m, Ph)
17a	—	—	—	3.98 (1H, d, $J_{2,3}=7.6$)	2.9—3.9 (4H, m)	3.04 (3H, s, $\geq$N–CH_3) 7.1—7.4 (10H, m, Ph)

a) δ (ppm), J (Hz), number of protons and nature of the signal are shown.



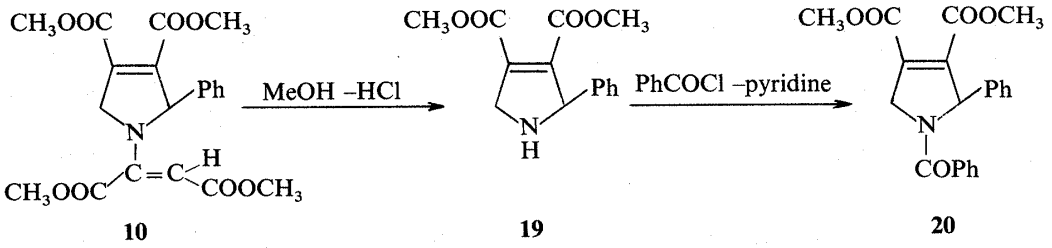
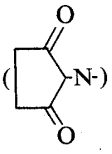
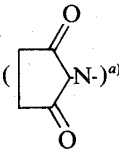


TABLE IV. 2,5-Dihydropyrrole and Pyrrolidines

Compd. No.	bp °C (mmHg)	Appearance	Formula	Analysis (%) Calcd (Found)			IR ν_{max}^{cap} cm^{-1}		
				C	H	N	(>NH)	(–COOCH$_3$)	
6	240 (0.2)	Oil	$C_{14}H_{17}NO_4$	63.86 (64.09	6.51 6.58	5.32 5.28)	3345	1735 1745	—
7	240 (0.2)	Oil	$C_{14}H_{17}NO_4$	63.86 (63.95	6.51 6.65	5.32 5.48)	3370	1730 1747	—
8	250 (0.2)	Oil	$C_{13}H_{14}N_2O_2$	67.81 (67.75	6.13 6.15	12.17 12.10)	3340	—	1779 1730 () 1684
9	200 (0.2)	Oil	$C_{12}H_{15}NO_2$	70.22 (69.92	7.37 7.03	6.82 6.80)	3340	1736	—
10	260—265 (0.2)	Oil	$C_{20}H_{21}NO_8$	59.55 (60.00	5.25 5.26	3.49 3.53)	—	1700 1743	1600 (>C=C<)
11	mp 151—152 °C (ethanol)[b]	Pillar	$C_{20}H_{18}N_2O_3$	71.84 (71.71	5.43 5.31	8.38 8.34)	—	—	1768 1743 ()[a] 1630 (>N–COPh)

a) IR ν_{max}^{KBr} cm^{-1}. *b*) Recrystallization solvent.

trimethylsilyliminium ylide showed the reverse stereochemistry, which is *trans* at the C_2–C_3 configuration only when dimethyl maleate and *N*-methylmaleimide are used as dipolarophiles. Although the reason for this selectivity is not clear, it is conceivable that the *N*-substituent of the ylide plays an important role in determining the stereochemistry of the products. The physical data for all the products are listed in Tables III and IV.

In summary, the trimethylsilyl triflate-catalyzed 1,3-dipolar cycloaddition has provided a new method for synthesizing *N*-unsubstituted pyrrolidines in good yields.

Experimental

All melting and boiling points are uncorrected. Infrared (IR) spectra were measured with a Hitachi EPI-G2 infrared spectrometer. ^{1}H-NMR spectra were taken on a JEOL JNM 90Q spectrometer (90 MHz) and all chemical shifts are given downfield from tetramethylsilane (TMS).

Solvent Effect on Cycloaddition of 1 with Dimethyl Fumarate——General Procedure: Trimethylsilyl triflate (0.5 mmol) was added to a solution of *N*-(benzylidene)trimethylsilylmethylamine (**1**, 2.5 mmol), dimethyl fumarate (2.5 mmol), cesium fluoride (0.5 mmol) in 10 ml of the solvent indicated in Table I, and the whole was stirred at 60—65 °C for 20 h, except for the use of dichloromethane as a solvent, when the reaction was carried out under reflux. Work-up of the reaction mixture in HMPA, DMF, benzene or dichloromethane was carried out by treatment with benzene (50 ml), saturated brine (50 ml) and 10% potassium bicarbonate solution (10 ml). On the other hand, in the case of DME and THF, the solvent was evaporated off, and the residue was treated with benzene, brine and potassium bicarbonate solution. The benzene layer was then separated, dried over magnesium sulfate and submitted to gas liquid chromatography (GLC) analysis (10% SE-30 on Chromosorb-W, 1 m). The solvent efficiency in this reaction was assessed in terms of the conversion percentage, which was calculated based on the disappearance of the starting material (**1**) and the product yield obtained by GLC analysis. These data are listed in Table I.

Pyrrolidines (6—9)——General Procedure: A solution of dipolarophile (5 mmol) and *N*-(benzylidene)-trimethylsilylmethylamine (**1**, 5 mmol) in 10 ml of HMPA was added to a stirred mixture of trimethylsilyl triflate (1 mmol), cesium fluoride (1 mmol) in 10 ml of HMPA. The whole was then heated at 60—65 °C with stirring for 20 h. The mixture was treated with potassium bicarbonate solution, and then extracted with benzene. The extract was dried over magnesium sulfate and evaporated, and the residual oil was subjected to column chromatography on silica-gel with benzene (200 ml), ether (200 ml) and then 10% methanol–ether as eluents. The product fractions were collected to give the corresponding product, **6**, **7**, **8** or **9** after removal of the solvent. The physical data are collected in Tables III and IV.

2,5-Dihydropyrrole Derivative (10)——This reaction was carried out as above using trimethylsilyl triflate (**2**) (1 mmol), cesium fluoride (1 mmol), dimethyl acetylenedicarboxylate (10 mmol), *N*-(benzylidene)trimethylsilyl-methylamine (**1**, 5 mmol) and 20 ml of HMPA. After the same work-up as above, the residual oil was purified by alumina column chromatography with benzene and benzene–ether as eluents. The physical data for **10** are listed in Tables II, III, and IV.

Synthesis of *N*-Benzoylpyrrolidines (15a, b, 16a, b, 17a, b, and 18a, b)——General Procedure: *N*-Benzoylation of pyrrolidine derivatives (**6**—**9**) was carried out with benzoyl chloride (1.5 eq) in pyridine at room temperature for 20 h. Each reaction mixture was then treated with dichloromethane and 10% hydrogen chloride solution. The dichloromethane solution was washed with water, dried over magnesium sulfate and concentrated to give the corresponding *N*-benzoyl derivative in almost quantitative yields. From **6**, **15a** and **15b** were obtained as a mixture. From **7**, **16a**, mp 88—89 °C, and **16b**, mp 131—132 °C, were obtained after preparative thin-layer chromatography (TLC) on silica-gel with isopropyl ether (IPE) as a developing solvent. From **9**, **18a**, mp 88—90 °C and **18b**, bp 250 °C (0.5 mmHg) were isolated by preparative TLC on silica-gel with IPE as a developing solvent. From **8**, **17a** mp 151—152 °C was obtained by recrystallization of the isomeric mixture (**17a** and **17b**) from ethanol, but **17b** could not be purified.

N-Benzoylpyrrolidines, **15a**, **b**, **16a**, **b**, and **18a**, **b**, thus obtained were identical with the previously reported compounds. The physical data for the new compound, **17a** are listed in Tables III and IV.

Synthesis of *N*-Benzoyl-2,5-dihydropyrrole Derivative (20)——A solution of **10** (1.8 g) in 33% hydrogen chloride in methanol (30 ml) was stirred at room temperature for 20 h. Then, after removal of the solvent, the residue was treated with benzene and potassium bicarbonate solution. The benzene layer was dried over magnesium sulfate, concentrated and then subjected to column chromatography on alumina with 10% ether–benzene as an eluent to give dimethyl 2-phenyl-2,5-dihydropyrrole-3,4-dicarboxylate, bp 228 °C (0.2 mmHg), 0.35 g (30% yield), which was then benzoylated with benzoyl chloride in pyridine to afford the *N*-benzoyl derivative (**20**), mp 181—182 °C, identified by comparison with the previously synthesized product.[1)]

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