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1,3-Dipolar Cycloaddition Leading to *N*-Acylated Pyrrolidines and 2,5-Dihydropyrroles

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Dipolar cycloaddition of an intermediary *N*-acyltrimethylsilylmethyliminium salt formed from *N*-(benzylidene)trimethylsilylmethylamine and acyl chloride to conjugated alkenes or alkynes gave *N*-acylpyrrolidines or *N*-acyl-2,5-dihydropyrroles, respectively. The stereochemistry of all the products was established.

Keywords—*N*-acylpyrrolidine; *N*-acyl-2,5-dihydropyrrole; 1,3-dipolar cycloaddition; trimethylsilylmethylamine; trimethylsilylmethyliminium salt; methyleneiminium ylide

Following a recent communication dealing with the cycloaddition of the intermediary 1,3-dipole derived from *N*-(benzylidene)trimethylsilylmethylamine and acyl chloride, we now wish to present the details of our work in this area.¹⁾

N-(1-Chloroalkyl)amides are known to be formed in the reaction of Schiff's bases and acyl chlorides.²⁾ The finding is that their *N*-trimethylsilylmethyl derivatives, formed *in situ* from *N*-(benzylidene)trimethylsilylmethylamine³⁾ and acyl chlorides, function as methyleneiminium ylides, undergoing cycloaddition with olefinic or acetylenic dipolarophiles to give pyrrolidines or 2,5-dihydropyrroles, respectively. A previous paper has reported 1,3-dipolar cycloaddition of ylides derived by *in situ* desilylation of trimethylsilylmethyliminium triflate with cesium fluoride.⁴⁾ In contrast with this reaction, the present reaction, which may involve desilylation of analogous *N*-acylated trimethylsilylmethyliminium salts, proceeds smoothly in the absence of cesium fluoride.

The reaction is represented by the following general scheme and the results of experiments are summarized in Table I. All the reactions proceeded smoothly at 40—45 °C in tetrahydrofuran (THF).

Mechanistically, the intermediary *N*-acyliminium salt (**10**) initially formed from the starting compound (**1**) and acyl chloride undergoes 1,3-dipolar cycloaddition with olefinic or acetylenic dipolarophiles to give pyrrolidines or 2,5-dihydropyrroles, respectively. Presumably this cycloaddition proceeds through generation of intermediary methyleneiminium ylide or 1,3-dipole (**11**), which may be induced by chloride ion.

TABLE I. Synthesis of 2,5-Dihydropyrrole and Pyrrolidine Derivatives^{a)}

Entry	RCOCl	Y-C≡C-COOCH ₃ or Y-CH=CH-COOCH ₃	Yield (%)	Products	2-Ph and 3-COOCH ₃ (<i>cis/trans</i>) ^{b)}	
1	PhCOCl	CH ₃ OOC-C≡C-COOCH ₃	85		2	—
2	PhCH ₂ OCOC	CH ₃ OOC-C≡C-COOCH ₃	78		3	—
3	CH ₃ COC	CH ₃ OOC-C≡C-COOCH ₃	79		4	—
4	PhCOCl	HC≡C-COOCH ₃	26 ^{c)}		5	—
5	PhCOCl		81		6	1.5
6	PhCH ₂ OCOC		79		7	1.4
7	PhCOCl		68		8	2.0
8	PhCOCl	H ₂ C=CH-COOCH ₃	80		9	1.2

a) All reactions were carried out with Schiff's base (5 mmol), acyl chloride (5 mmol) and 1,3-dipolarophile (5.5 mmol) in THF (60 ml) at 40–45°C for 2 h.

b) The product ratios were determined by ¹H-NMR measurement.

c) Compound 12 was obtained as a by-product in 30% yield.

As described in entries 5, 6 and 7 of Table I, *cis*- and *trans*-configurations between C-3 and C-4 of the products show complete retention of those of the starting dimethyl fumarate and dimethyl maleate. This fact is suggestive of the cycloaddition of 11 rather than the alternative two-step ring formation from 10.

When dipolarophile was absent in the reaction, 1 itself functioned as a dipolarophile to give the imidazolidine derivative (12); when 1 and benzoyl chloride were allowed to react in THF at 40–45 °C a mixture of geometric isomers of 12 was obtained in 63% yield.

The side-formation of 12 in the experiments in Table I was effectively avoided by slow addition of 1 to a solution of acyl chloride and dipolarophile in THF. The reaction with methyl propiolate was exceptional, giving 12 in 30% yield as a by-product, presumably owing to its lower reactivity.

The product 8 in entry 7 consisted of two diastereomers which were separated into crystals, 8a, mp 88–89 °C, and 8b, mp 131–132 °C, by preparative thin-layer chromatography (TLC) on silica gel using isopropyl ether as a developing solvent. The existence of two diastereomers, which were different from 8a and 8b, in the product 6 in entry 5 was confirmed by gas liquid chromatography (GLC) and proton nuclear magnetic resonance (¹H-NMR) analysis, but separation proved difficult. Therefore, by working up the reaction mixture with benzyloxycarbonyl chloride, as shown in entry 6, a diastereomeric mixture of the *N*-benzyloxycarbonyl analogue 7 was obtained, and repeated recrystallization from isopropyl ether–methanol afforded a single isomer, 7a, mp 101–102 °C. Debenzyloxycarbonylation of 7a by catalytic hydrogenation followed by *N*-benzoylation gave a pure isomer identical with one of the two isomers of 6.

On the other hand, catalytic hydrogenation of the product 2 obtained in entry 1 over palladium-on-charcoal give a product identical with a mixture of 8a and 8b.

On the basis of the general predominantly *cis*-addition of hydrogen in catalytic hydrogenation, the C-3–C-4 configuration of the diastereomers 8a and 8b appears to be *cis*, retaining that of the starting maleate. Consequently, the product 6 is a mixture of *trans*

TABLE II. ¹H-NMR data^{a)} for 2,5-Dihydropyrroles and Pyrrolidines

Compd. No.	3-COOCH ₃	4-COOCH ₃	2-H	3-H	4-H	5-H	Others
2	3.59 (s) (3H) 3.67 (s) (3H)	3.78 (s) (3H) 3.83 (s) (3H)	5.75 (t, $J_{2,5}=4$) ^{b)} (1H) 6.38 (m) (1H)	—	—	4.3–5.0 (2H, m)	7.19 (5H, s, Ph) 6.9–7.6 (5H, m, Ph)
3	3.62 (3H, s)	3.81 (3H, s)	5.6–5.9 (1H, m)	—	—	4.8–5.2 (2H, m)	4.99 (2H, s, O-CH ₂ Ph) 7.21 (5H, s, Ph) 7.27 (5H, s, Ph)
4	3.65 (3H, s)	3.82 (3H, s)	5.74 (t, $J_{2,5}=4$) ^{b)} (1H) 5.99 (t, $J_{2,5}=4$) (1H)	—	—	4.70 (d, $J_{2,5}=4$) ^{b)} 4.73 (d, $J_{2,5}=4$) (2H)	1.78 (s) (3H, CH ₃ CON) 2.08 (s) (3H, CH ₃ CON) 7.22 (5H, s, Ph)
5	3.56 (s) (3H) 3.59 (s) (3H)	—	5.78 (t, $J_{2,5}=4$) ^{b)} (1H) 6.20 (m) (1H)	—	7.12 (1H, s)	4.1–4.8 (2H, m)	7.19 (5H, s, Ph) 6.9–7.6 (5H, m, Ph)
6a	3.38 (3H, s)	3.72 (3H, s)	5.18 (br) (1H) 5.76 (br) (1H)	3.0–3.7 (2H, m)	—	4.0–4.5 (2H, m)	7.26 (5H, s, Ph) 6.9–7.6 (5H, m, Ph)
6b	3.61 (3H, s)	3.72 (3H, s)	5.47 (br) (1H)	3.0–3.7 (2H, m)	—	4.0–4.5 (2H, m)	7.26 (5H, s, Ph) 6.7–7.6 (5H, m, Ph)
7a	3.39 (3H, s)	3.72 (3H, s)	5.34 (d, $J_{2,3}=8.1$) (1H)	3.1–4.0 (2H, m)	—	4.0–4.5 (2H, m)	5.00 (2H, s, O-CH ₂ Ph) 7.26 (5H, s, Ph) 6.7–7.6 (5H, m, Ph)
7b	3.61 (3H, s)	3.71 (3H, s)	5.10 (d, $J_{2,3}=4$) (1H)	3.1–4.2 (2H, m)	—	4.0–4.5 (2H, m)	5.00 (2H, s, O-CH ₂ Ph) 7.26 (5H, s, Ph) 6.9–7.6 (5H, m, Ph)
8a	3.11 (3H, s)	3.66 (3H, s)	5.62 (d, $J_{2,3}=8.3$) (1H)	3.0–3.7 (2H, m)	—	4.0–4.6 (2H, m)	7.26 (5H, s, Ph) 6.9–7.8 (5H, m, Ph)
8b	3.65 (s) (3H) 3.70 (s) (3H)	3.72 (s) (3H) 3.76 (s) (3H)	5.22 (d, $J_{2,3}=4$) (1H) 5.77 (d, $J_{2,3}=4$) (1H)	3.0–3.7 (2H, m)	—	3.7–4.7 (2H, m)	7.26 (5H, s, Ph) 6.9–7.8 (5H, m, Ph)
9a	3.38 (3H, s)	—	5.06 (d, $J_{2,3}=7.8$) (1H) 5.70 (d, $J_{2,3}=8.0$) (1H)	2.6–3.3 (1H, m)	2.0–2.5 (2H, m)	3.7–4.3 (2H, m)	7.26 (5H, s, Ph) 6.9–7.6 (5H, m, Ph)
9b	3.73 (3H, s)	—	5.22 (d, $J_{2,3}=1$) (1H) 5.77 (d, $J_{2,3}=4$) (1H)	2.6–3.3 (1H, m)	2.0–2.5 (2H, m)	3.7–4.2 (2H, m)	7.36 (5H, s, Ph) 6.9–7.6 (5H, m, Ph)

a) δ (ppm), J (cps), number of protons and appearance of the signal are shown.b) The long-range coupling constant values reported for compounds of this type (H-C-C=C-C-H) are $J_{1,4}=0.5-5.0$ Hz (N. F. Chamberlain, "The Practice of NMR Spectroscopy," Plenum Press, New York, 1974, p. 305).

TABLE III. 2,5-Dihydropyrroles and Pyrrolidines

Compd. No.	mp (°C) Recrystn. ^{a)} solvent	Appearance	Formula	Analysis (%)			IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1}		
				Calcd	Found		-COOCH ₃	>NCOR	>C=C<
2	181—182 (MeOH)	Needles	C ₂₁ H ₁₉ O ₅ N	69.03 (68.94)	5.24 (5.28)	3.83 (3.88)	1738 1719	1645	1656
3	116—117 (MeOH)	Needles	C ₂₂ H ₂₁ O ₆ N	66.82 (66.75)	5.35 (5.37)	3.54 (3.51)	1726	1703	1655
4	145—146 (MeOH)	Prisms	C ₁₆ H ₁₇ O ₅ N	63.36 (63.49)	5.65 (5.66)	4.62 (4.64)	1725	1664	1652
5	122—124 (MeOH-IPE)	Prisms	C ₁₉ H ₁₇ O ₃ N	74.25 (74.05)	5.58 (5.65)	5.56 (5.54)	1734	1627	1649
6a	140—141 (MeOH-IPE- n-Hex.)	Needles	C ₂₁ H ₂₁ O ₅ N	68.65 (68.67)	5.76 (5.76)	3.81 (3.84)	1741 1732	1632	—
7a	101—102 (MeOH-IPE)	Prisms	C ₂₂ H ₂₃ O ₆ N	66.49 (66.77)	5.83 (6.08)	3.52 (4.02)	1738	1700	—
8a	88—89 (IPE)	Prisms	C ₂₁ H ₂₁ O ₅ N	68.65 (68.82)	5.76 (5.93)	3.81 (3.70)	1740 1732	1640	—
8b	131—132 (IPE)	Needles	C ₂₁ H ₂₁ O ₅ N	68.65 (68.80)	5.76 (5.82)	3.81 (3.70)	1746 1732	1630	—
9a	88—90 (IPE)	Prisms	C ₁₉ H ₁₉ O ₃ N	73.76 (73.78)	6.19 (6.22)	4.53 (4.52)	1738	1634	—
9b	bp 250 (0.5 mmHg)	—	C ₁₉ H ₁₉ O ₃ N	73.76 (73.40)	6.19 (6.23)	4.45 (4.80)	1741	1640	—

a) IPE = isopropyl ether; Hex. = hexane.

diastereomers with respect to the C-3 and C-4 configurations.

The C-2—C-3 configurations of **6a**, **b**, **7a**, **b** and **8a**, **b** were assigned to be *cis* for **6a**, **7a** and **8a**, and *trans* for **6b**, **7b** and **8b** based on ¹H-NMR measurement, in which the chemical shifts of 3-COOCH₃ oriented *cis* to 2-phenyl on the pyrrolidine ring showed lower values (3.1—3.4 ppm) as compared with those (3.6—3.7 ppm) of the *trans* isomers due to the shielding effect of 2-phenyl.⁵⁾ The ratios of the two diastereomers of the products were calculated from the signal areas of the proton at the 2-position. These ¹H-NMR and physical data are listed in Tables II and III. As shown in Table I, the *cis* isomers were produced predominantly in all runs of the experiments.

The diastereomers of the product **9** (entry **8**) were separated in a pure state as crystals, **9a**, mp 88—89 °C, and a liquid, **9b**, bp 250 °C (0.5 mmHg). On the other hand, catalytic hydrogenation of the product **5** in entry **4** gave a mixture of two isomers identical with **9a** and **9b**.

As stated above, the lower chemical shift (3.38 ppm) of 3-COOCH₃ observed in the ¹H-NMR spectrum of **9a** was taken as indicating *cis*-COOCH₃ with respect to phenyl on the pyrrolidine ring. Accordingly, the higher value (3.73 ppm) in **9b** indicates *trans*-configurations. Thus, the

reaction was shown to proceed regioselectively to give the 3-carbomethoxy-substituted pyrrolidine or 2,5-dihydropyrrole.

As shown in Table II, $^1\text{H-NMR}$ spectra of the products, **2**, **5** and **8b**, exhibit two pairs of signals of 3- COOCH_3 and 4- COOCH_3 , presumably owing to the presence of conformational isomers of their *N*-benzoyl groups.

In summary, this 1,3-dipolar cycloaddition is admirably suited for synthesizing 2,5-dihydropyrrole and pyrrolidine derivatives in good yields by a simple procedure in contrast to the previously reported cycloaddition giving *N*-alkylpyrrolidines.⁴⁾ Easy removal of the *N*-acyl substituent of the products may extend the usefulness of this method to the synthesis of *N*-unsubstituted pyrrolidine derivatives.⁶⁾

Experimental

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

***N*-(Benzylidene)trimethylsilylmethylamine (1)**—A mixture of trimethylsilylmethylamine (10.8 g, 0.105 mol), benzaldehyde (10.6 g, 0.100 mol), Molecular Sieve 4A (15 g) and 150 ml of benzene was stirred at room temperature overnight, then filtered to remove the Molecular Sieve. Evaporation of the solvent gave a residue, which was subjected to distillation. *N*-(Benzylidene)trimethylsilylmethylamine (bp $75^\circ\text{C}/3\text{ mmHg}$, 15.3 g) was obtained as a colorless oil in 80% yield. IR_{max}^{cap} cm^{-1} : 1636 ($>\text{C}=\text{N}-$); $^1\text{H-NMR}$ (CDCl_3) δ : 0.07 (9H, s, Me_3Si), 3.41 (2H, s, SiCH_2-N), 7.2–7.9 (5H, m, aromatic proton), 8.11 (1H, s, $-\text{N}=\text{CH}-\text{Ph}$). Anal. Calcd for $\text{C}_{11}\text{H}_{17}\text{NSi}$: C, 69.04; H, 8.96; N, 7.32. Found C, 68.93; H, 8.85; N, 7.23.

1,5-Dihydropyrroles (2–5) and Pyrrolidines (6–9)—General Procedure: A solution of *N*-(benzylidene)trimethylsilylmethylamine (**1**) (5 mmol) in 20 ml of THF was added dropwise to a stirred solution of acyl chloride (5 mmol) and a conjugated acetylene or olefin (5.5 mmol) in 40 ml of THF at $40\text{--}45^\circ\text{C}$ for 1 h. Heating and stirring were continued for another 2 h. Removal of the solvent gave the crude products. Pure crystals, **2**, **3** and **4**, were obtained by recrystallization from the solvent indicated in Table III. Otherwise, the product **5** was purified by column chromatography of the residue on silica gel with methylene chloride–isopropyl ether (IPE) (9:1) as an eluate followed by recrystallization from the indicated solvent, and the by-product **12** was obtained from the more mobile fraction ($R_f=0.8$) in 30% yield.

The purified products, **6**, **7**, **8** and **9** were obtained as diastereomeric mixtures by column chromatography of the residue on silica gel with methylene chloride–IPE. Successive separation of the diastereomers, **8a**, **b** and **9a**, **b**, was carried out by preparative TLC on silica gel with IPE as a developing solvent. The pure product **7a** was obtained by repeated recrystallization of **7** from methanol–IPE. The physical data and recrystallization solvents are listed in Tables II and III.

1-Benzoyl-2,4-diphenyl-3-trimethylsilylmethylimidazolidine (12)—A solution of benzoyl chloride (703 mg, 5 mmol) and *N*-(benzylidene)trimethylsilylmethylamine (1.91 g, 10 mmol) in 60 ml of THF was stirred at $40\text{--}45^\circ\text{C}$ for 2 h. After removal of the solvent, the residue was subjected to bulb-to-bulb distillation. The product, **12**, was obtained in 60% yield. **12**; bp $240\text{--}250^\circ\text{C}$ (0.5 mmHg), viscous oil, Anal. Calcd for $\text{C}_{26}\text{H}_{30}\text{N}_2\text{OSi}$: C, 75.32; H, 7.29; N, 6.76. Found: C, 75.74; H, 7.04; N, 6.81. IR_{max}^{cap} cm^{-1} : 1640 ($>\text{N}-\text{COPh}$). Hydrogen carbonate, mp $188\text{--}189^\circ\text{C}$ (dec.). Anal. Calcd for $\text{C}_{26}\text{H}_{30}\text{N}_2\text{OSi} \cdot \text{H}_2\text{CO}_3$: C, 68.04; H, 6.77; N, 5.88. Found: C, 68.05; H, 6.86; N, 5.82.

Preparation of 6a from 7a—A mixture of **7a** (199 mg, 0.5 mmol), 10% palladium-on-charcoal (80 mg) and 8 ml of methanol was stirred under an atmosphere of hydrogen gas at room temperature. Filtration of the catalyst from the reaction mixture followed by removal of the solvent gave the debenzoyloxycarbonylated product in almost quantitative yield. Then benzoylation was carried out with benzoyl chloride (110 mg, 0.71 mmol) in pyridine (2 ml). The reaction mixture was treated with methylene chloride and 10% HCl solution. The methylene chloride solution was washed with water, dried and concentrated to give the *N*-benzoyl derivative, **6a**, in 80% yield. Physical data are listed in Tables II and III.

Catalytic Hydrogenation of 2. Synthesis of 8a and 8b—A solution of **2** (102 mg, 0.28 mmol) and 10% palladium-on-charcoal (20 mg) in methanol was stirred at room temperature under a hydrogen atmosphere. Filtration of catalyst followed by evaporation of the solvent *in vacuo* gave **8a** and **8b** in almost quantitative yield. GLC analysis of the mixture on 10% Silicon SE-30 (1 m) at 210°C indicated that the product ratio (**8a/8b**) is 1.9/1.

Preparative TLC on silica gel with IPE gave **8a** (59 mg) and **8b** (28 mg) in pure form. They were identical with the products of direct 1,3-dipolar cycloaddition of **1** with dimethyl maleate as a dipolarophile.

Catalytic Hydrogenation of 5. Synthesis of 9a and 9b—Catalytic hydrogenation of **5** (54.3 mg, 0.18 mmol) under the same conditions as used for hydrogenation of **2** gave **9a** and **9b** in almost quantitative yield in a ratio of 1.5/1.

Preparative TLC on silica gel with IPE gave **9a** (18.8 mg) and **9b** (16.8 mg) in pure form. These products were identical with those obtained by direct 1,3-dipolar cycloaddition of **1** with methyl acrylate as a dipolarophile.

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References and Notes

- 1) K. Achiwa and M. Sekiya, *Chem. Lett.*, **1981**, 1213.
- 2) E. Popowski, M. Böttcher, and H. Kelling, *Z. Chem.*, **15**, 353 (1975).
- 3) a) K. Ikeda, T. Morimoto, and M. Sekiya, *Chem. Pharm. Bull.*, **28**, 1178 (1980); b) K. Ikeda, Y. Terao, and M. Sekiya, *ibid.*, **29**, 1156 (1981), and references cited therein.
- 4) E. Vedejs and G. R. Martinez, *J. Am. Chem. Soc.*, **101**, 6452 (1979).
- 5) M. Joucla, D. Grée, and J. Hamelin, *Tetrahedron*, **29**, 2315 (1973).
- 6) a) J. J. Tufariello and G. E. Lee, *J. Am. Chem. Soc.*, **102**, 373 (1980); b) G. E. Keck and D. G. Nickell, *ibid.*, **102**, 3632 (1980), and references cited therein.