CHEMISTRY LETTERS, pp. 1213-1216, 1981.

NEW 1,3-DIPOLAR CYCLOADDITION
LEADING TO 2,5-DIHYDROPYRROLE AND PYRROLIDINE DERIVATIVES

Kazuo ACHIWA and Minoru SEKIYA
Shizuoka College of Pharmacy, 2-2-1 Oshika, Shizuoka 422

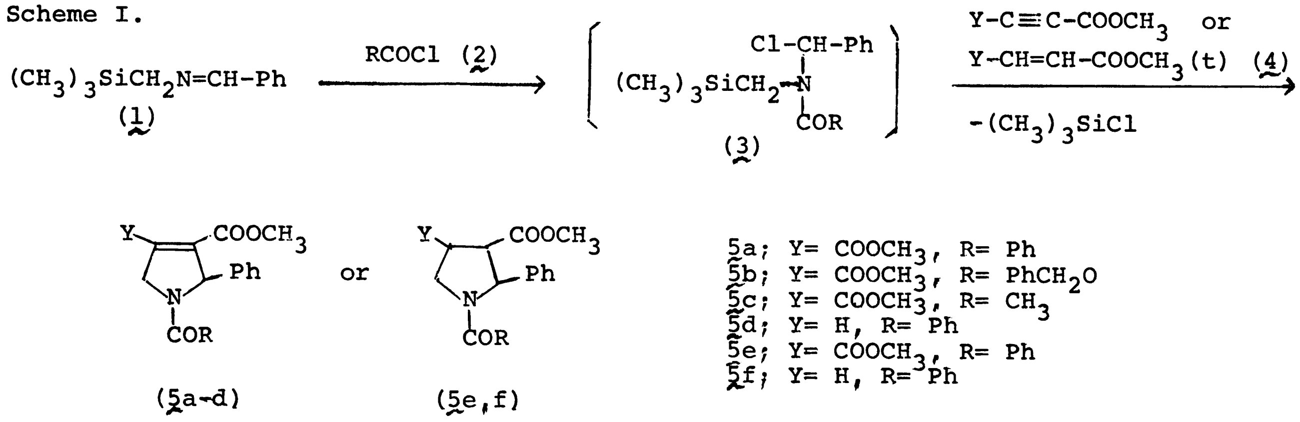
A novel 1,3-cycloaddition of intermediaries derived from N-(benzylidene)trimethylsilylmethylamine and acyl chlorides to conjugated olefins and acetylenes gave pyrrolidine and 2,5-dihydropyrrole derivatives, respectively.

Schiff bases and hexahydro-1,3,5-triazines have been known to give N-(1-chloroalkyl)amide by the reaction with acyl halides. Among them N-chloromethylamides have been recently reported to function as efficient nucleophiles in the N-alkylamidomethylation at the electron-rich carbons.[1)]

We have found that a Schiff base of trimethylsilylamine, i.e. N-(benzylidene)-trimethylsilylmethylamine (**1**)[2)] reacts with acyl halides in the presence of conjugated alkenes or alkynes to give pyrrolidines (**5e,f**) or 2,5-dihydropyrroles (**5a-d**) (See Scheme I).

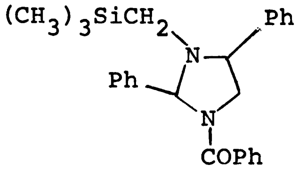
In a typical experiment, a solution of N-(benzylidene)trimethylsilylmethylamine (**1**) (5 mmol) in 20 ml of tetrahydrofuran (THF) was added dropwise to a stirred solution of acetyl chloride (5 mmol) and dimethyl acetylenedicarboxylate (5.5 mmol) in 40 ml of THF at 40-45°C over a period of 1 hr. Heating and stirring were continued for 2 hr. After removal of the solvent **5c** was obtained in 79% yield by recrystallization of the residure from methanol-isopropyl ether. **5c**: mp 145-146°C, IR_{max}^{KBr} (cm^{-1}): 1726 ($-COOCH_3$), 1664 ($>C=C<$), 1652 ($\geq N-COCH_3$); NMR δppm ($CDCl_3$); 1.78 (s), 2.04 (s) ($\geq N-CO\underline{CH_3}$, 3H), 3.59 (s) ($-COO\underline{CH_3}$, 3H), 3.78 (s) ($-COO\underline{CH_3}$, 3H), 4.70 (d, J=4 Hz), 4.73 (d, J=4 Hz) ($\genfrac{}{}{0pt}{}{H}{\underline{H}}\!>\!N\!<$, 2H), 5.74 (t, J=4 Hz), 5.99 (t, J=4 Hz) ($\geq N\!<\!\genfrac{}{}{0pt}{}{Ph}{\underline{H}}$, 1H), 7.22 (s, aromatic, 5H); Mass M^+: 303. The long range coupling constant values reported for this type of compounds ($\underline{H}-C-C=C-C-\underline{H}$) are J= 0.5-5 Hz.[3)]

Scheme I.



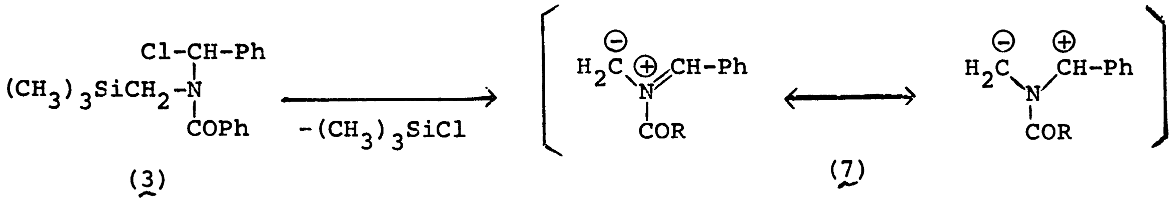
5a; Y= $COOCH_3$, R= Ph
5b; Y= $COOCH_3$, R= $PhCH_2O$
5c; Y= $COOCH_3$, R= CH_3
5d; Y= H, R= Ph
5e; Y= $COOCH_3$, R= Ph
5f; Y= H, R= Ph

When 4 was absent, 1 played a role of dipolarophile to give 6, as demonstrated by the following experiment. A solution of benzoyl chloride (5 mmol) was added slowly to a solution of N-(benzylidene)trimethylsilylmethylamine (1) (10 mmol) in 40 ml of THF at 40-45°C to give 6[4] as a mixture of its geometric isomers in 63% yield.



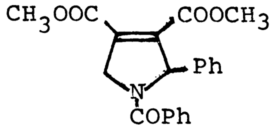
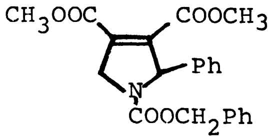
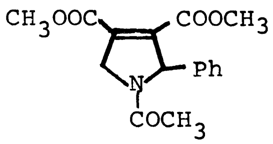
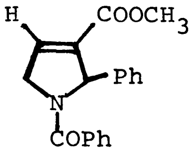
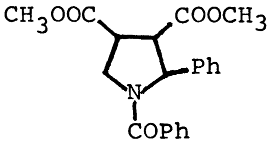
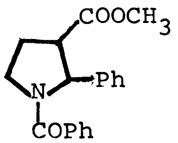
(6)

A recent paper[5d] has reported a 1,3-dipolar addition of ylides derived by desilylation of trimethylsilylmethyliminium triflate by cesium fluoride. The present reaction may involve a likely intermediate (7) derived from 3 by desilylation, surprisingly in the absence of cesium fluoride, which is virtually unknown in the literature.



Results of extensive experiments are summarized in Table I.

Table I. Synthesis[a)] of 2,5-Dihydropyrrole and Pyrrolidine Derivatives

R COCl	Y-C≡C-COOCH$_3$ or Y-CH=CH-COOCH$_3$	Product[b)] (yield %)
PhCOCl	CH$_3$OOC-C≡C-COOCH$_3$	 (85) (5a)
PhCH$_2$OCOCl	CH$_3$OOC-C≡C-COOCH$_3$	 (78) (5b)
CH$_3$COCl	CH$_3$OOC-C≡C-COOCH$_3$	 (79) (5c)
PhCOCl	H-C≡C-COOCH$_3$	 (26) (5d)[c)]
PhCOCl	CH$_3$OOC-CH=CH-COOCH$_3$ (t)	 (78) (5e)[d)]
PhCOCl	H$_2$C=CH-COOCH$_3$	 (65) (5f)[d)]

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

b) All the products gave satisfactory elemental analyses and spectral data (ir and nmr) consistent with their structures.

c) As a by-product, 6 was obtained in 30% yield.

d) The products, 5e and 5f, were obtained in a state of stereochemical purity, investigation of which is under way.

It is noted that this new 1,3-dipolar cycloaddition gave 2,5-dihydropyrrole and pyrrolidine derivatives in good yields by simple procedure and, in contrast to the previously reported cycloaddition5) giving N-alkylpyrrolidines, easy removal of the N-acyl-substituent of the products may increase its usefulness for synthesis of N-unsubstituted pyrrolidine derivatives.6)

Further active investigations along this line are under way.

REFERENCES

1) a) K. Ikeda, T Morimoto, and M. Sekiya, Chem. Pharm. Bull., 28, 1178 (1980).
   b) K. Ikeda, Y. Terao, and M. Sekiya, Chem. Pharm. Bull., 29, 1156 (1981).
2) E. Popowski, M. Böttcher, and H. Kelling, Z. Chem., 15, 353 (1975).
3) N. F. Chamberlain,"The Practice of NMR Spectroscopy," Plenum Press, New York, 1974, p 305.
4) 6: Colorless liquid, IR_{max}^{KBr} (cm^{-1}): 1640 (>N-COPh).
   Hydrogen carbonate, mp 188-189°C (decomp)
   Anal. Calcd for $C_{26}H_{30}N_2OSi \cdot CO_3H_2$: C, 68.04; H, 6.77; N, 5.88.
   Found: C, 68.05; H, 6.86; N, 5.82.
5) a) R. M. Kollog, Tetrahedron, 32, 2165 (1976).
   b) R. Huisgen, J. Org. Chem., 41, 403 (1976).
   c) H. Hermann, R. Huisgen, and H, Mader, J. Am. Chem. Soc., 93, 1779 (1971).
   d) E. Vedejs and G. R. Martinez, J. Am. Chem. Soc., 101, 6452 (1979), and references cited therein.
6) a) J. J. Tufariello and G. E. Lee, J. Am. Chem. Soc., 102, 373 (1980).
   b) G. E. Keck and D. G. Nickell, J. Am. Chem. Soc., 102, 3632 (1980), and references cited therein.

(Received May 18, 1981)