Communications to the Editor

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1,3-DIPOLAR CYCLOADDITION LEADING TO N-ALKYLPYRROLIDINES

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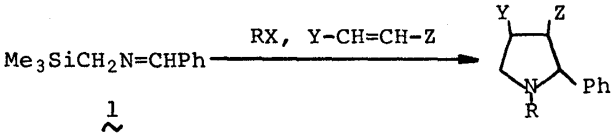
1,3-Dipolar cycloaddition of an intermediary methyleneiminium ylide formed from N-(benzylidene)trimethylsilylmethylamine and alkyl halide to conjugated olefinic dipolarophiles has been found to give N-alkylpyrrolidines.

KEYWORDS——— N-alkylpyrrolidine; N-unsubstituted pyrrolidine; 1,3-dipolar cycloaddition; N-alkyltrimethylsilylmethyliminium salt; methyleneiminium ylide

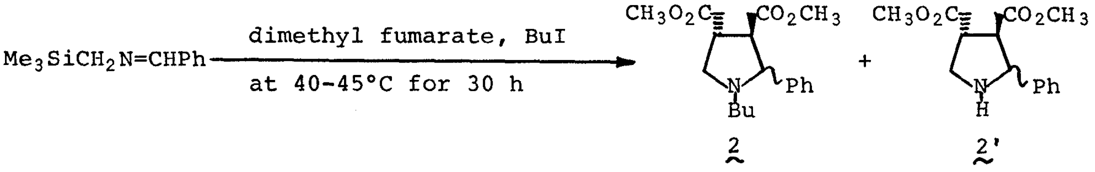
In previous work in the field of 1,3-dipolar cycloaddition,[1-2] we described N-acylated pyrrolidine synthesis by the reaction among a Schiff's base of trimethylsilylmethylamine, acyl halides and olefins.[1] In continuation we developed a general synthesis of N-alkylpyrrolidines by 1,3-dipolar cycloaddition using alkyl halides and tosylate in place of the acyl halides.



RX: alkyl halides or tosylate

Preliminary experiments included examination of solvent effect (Table I) and relative reactivities (Table II) of butyl halides and tosylate using N-(benzylidene)trimethylsilylmethylamine (1) and dimethyl fumarate. The reaction with butyl iodide proceeded smoothly in the solvents indicated in Table I to give the corresponding N-alkylpyrrolidine (2) with the minor formation of an N-unsubstituted one (2').

Table I. Solvent Effect[a)]



Solvent	Yield (%)	Molar proportion 2	Molar proportion 2'
Hexamethylphosphoramide (HMPA)	100	99	1
Tetramethylurea	90	70	30
Dimethylformamide	70	65	35
Acetonitrile	20	70	30

a) Yield and molar proportion are determined by VPC analysis.

Table II. Relative Reactivities of Butyl Halides and Tosylate[a)]

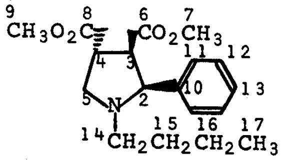
$$Me_3SiCH_2N{=}CHPh \xrightarrow[\text{in HMPA at 40-45°C}]{\text{dimethyl fumarate, BuX}} 2 + 2'$$

BuX	Total yield (%)	Molar proportion 2	 2'
BuI	100	99	1
BuBr	100	63	37
BuCl	66	—	100
BuOTs	79	50	50

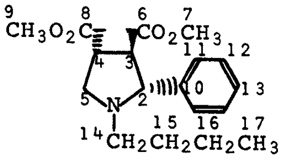
a) Yield and molar proportion are determined by VPC analysis.

Interestingly, marked differences among butyl halides and tosylate were observed as shown in Table II. Butyl iodide gave 2 exclusively, in which the reaction proceeded faster, whereas butyl chloride gave 2'.

A typical experiment using 1, butyl iodide and dimethyl fumarate is as follows. To a stirred mixture of 1 (5 mmol), butyl iodide (5 mmol) and HMPA (20 ml) dimethyl fumarate (6 mmol) was added. The whole was then heated at 80-85°C with stirring for 2 h under nitrogen atmosphere. After cooling the mixture was triturated with benzene (100 ml). The benzene solution was washed with sat. aq. NaCl-10% aq. $KHCO_3$ (50 ml + 25 ml) and sat. aq. NaCl (75 ml) and dried over magnesium sulfate. After removal of benzene the residual oil was submitted to silica gel chromatography using benzene as an eluent. Dimethyl N-butyl-2-phenyl-3,4-pyrrolidinedicarboxylates (2a and 2b) were obtained.[3)] 2a: oil, yield 49%, bp 110-111°C/0.2 mmHg, IR(neat); 1740 cm^{-1} (CO), ^{1}H-NMR δ ($CDCl_3$); 0.60-1.04(3H, m, $CH_2C\underline{H}_3$), 1.04-1.70(4H, m, CH_2CH_2), 1.79-2.81(4H, m, $N(CH_2)_2$), 3.03(3H, s, 3-CO_2CH_3, cis to 2-phenyl[4)]), 3.29-4.01(3H, m, 2-CH, 3-CH, 4-CH), 3.65(3H, s, 4-CO_2CH_3), 7.20(5H, s, C_6H_5), ^{13}C-NMR δ ($CDCl_3$); 13.9(q, 17-C), 20.4(t, 16-C), 30.5(t, 15-C), 44.4(d, 4-C), 51.1(t, 14-C), 51.9(q, OCH_3), 52.3(q, OCH_3), 53.4(d, 3-C), 55.4(t, 5-C), 71.6(d, 2-C), 127.5, 127.9, 128.5, 139.4(d, d, d, s, C_6H_5), 171.9(s, CO), 173.4(s, CO), 2b: oil, yield 33%, bp 111-112°C/0.2 mmHg, IR(neat); 1740 cm^{-1} (CO), ^{1}H-NMR δ ($CDCl_3$); 0.56-1.03(3H, m, $CH_2C\underline{H}_3$), 1.03-1.60(4H, m, CH_2CH_2), 1.60-2.80 (4H, m, $N(CH_2)_2$), 3.14-4.10(3H, m, 2-CH, 3-CH, 4-CH), 3.55(3H, s, 3-CO_2CH_3, trans to 2-phenyl), 3.67(3H, s, 4-CO_2CH_3), 7.21(5H, s, C_6H_5), ^{13}C-NMR δ ($CDCl_3$); 13.9(q, 17-C), 20.3(t, 16-C), 30.3(t, 15-C), 45.1(d, 4-C), 51.8(q, OCH_3), 52.2(q, OCH_3), 52.8(t, 14-C), 55.0(d, 3-C), 55.3(t, 5-C), 73.5(d, 2-C), 127.7, 128.0, 128.4, 141.1(d, d, d, s, C_6H_5), 173.6(s, CO), 173.9(s, CO).



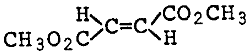
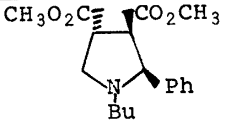
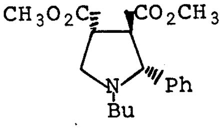
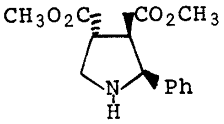
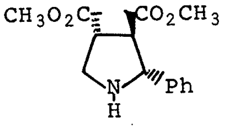
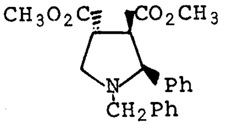
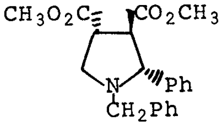
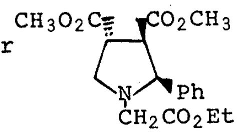
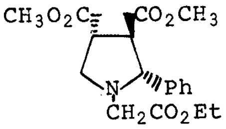
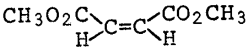
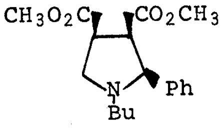
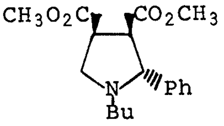
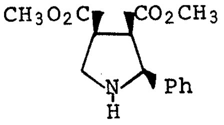
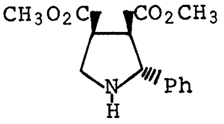
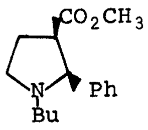
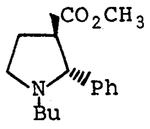
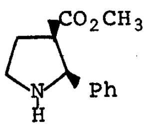
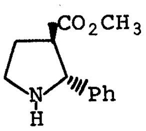
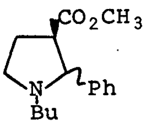
2a



2b

Mechanistically, the formation of N-unsubstituted pyrrolidine 2' is rationalized as shown in Chart 1, which proceeds through intermediary N-trimethylsilylmethyleneiminium salt formed by a catalytic action of a small amount of trimethylsilyl halides or tosylate produced in the course of the reaction.

Table III. Synthesis of N-Alkylpyrrolidines and N-Unsubstituted Pyrrolidines

Olefin	RX	Product^a)	Total yield (%)
 $\mathrm{CH_3O_2C(H)C{=}C(H)CO_2CH_3}$	BuI	 2a(3)  2b(2)	82
	BuCl	 2'a(1)  2'b(1.2)	76
	$PhCH_2Br$	 3a(1.2)  3b(1)	79
	EtO_2CCH_2Br	 4a(1.1)  4b(1)	74
 $\mathrm{CH_3O_2C(H)C{=}C(H)CO_2CH_3}$	BuI	 5a(1)  5b(2)	61
	BuCl	 5'a(3)  5'b(7)	76
$H_2C{=}CHCO_2CH_3$	BuI	 6a(3)  6b(2)	45
	BuCl	 6'a(5.4)  6'b(4)  6a,b(1)	65

a) Ratio of the diastereomers is described in parentheses.

b) Reaction conditions: molar ratio, $Me_3SiCH_2N{=}CHPh/RX/Y{-}CH{=}CH{-}CO_2CH_3$= 1/1/1.2; solvent, HMPA; temp, 80-85°C; time, 2 h.

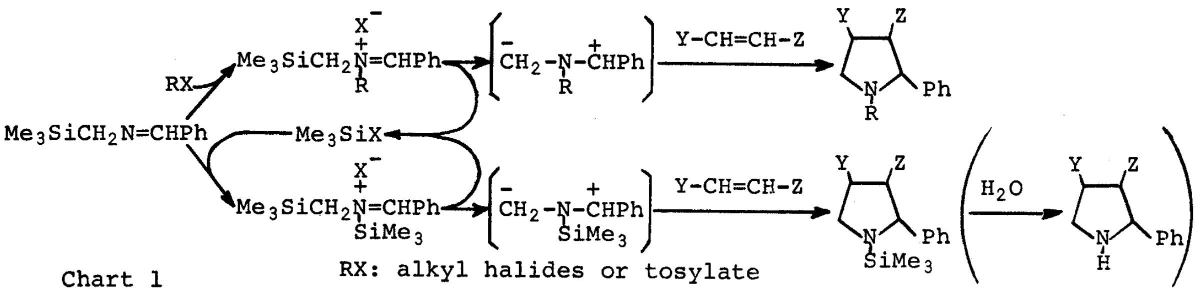
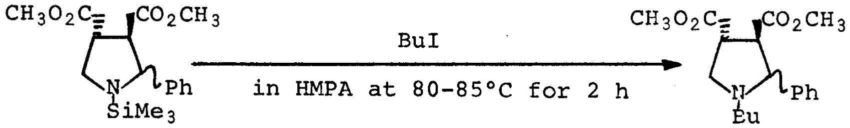


Chart 1

RX: alkyl halides or tosylate

Virtually 2' was obtained by the reaction of 1 and dimethyl fumarate in the presence of a catalytic amount of trimethylsilyl iodide under the same conditions. In addition it should be noted that after the end of this reaction, further reaction with the addition of butyl iodide gave N-butylsubstituted pyrrolidine 2 in considerable yield. From this it appears that the replacement of N-trimethylsilyl by N-butyl can be involved in part in the course of the formation 2 in the foresaid cycloaddition reaction as follows.



Results of extensive experiments are summerized in Table III.

It should be noted that the present 1,3-dipolar cycloaddition involving heterolysis of the silicon-carbon bond of the intermediary N-alkyltrimethylsilylmethyliminium salt is convenient for the simple synthesis of N-alkylpyrrolidines.

Further investigations along this line are under way.

REFERENCES AND NOTES

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2) K. Achiwa and M. Sekiya, Tetrahedron Lett., 23, 2589(1982); Y. Terao, N. Imai, K. Achiwa, and M. Sekiya, Chem. Pharm. Bull., 30, 3167(1982); R. Smith and T. Livinghouse, J. Org. Chem., 48, 1554(1983); idem, J. Chem. Soc., Chem. Commun., 1983, 210; A. Padwa and Y. Y. Chen, Tetrahedron Lett., 24, 3447(1983); A. Padwa, G. Haffmanns, and M. Tomas, ibid., 24, 4303(1983); E. Vedejs and F. G. West, J. Org. Chem., 48, 4773(1983) and references cited therein; T. Motoyama, K. Achiwa, and M. Sekiya, Abstracts of Papers, the 103 rd Annual Meeting of the Pharmacentical Society of Japan, Tokyo, April 1983, p. 132; O. Tsuge, S. Kanemasa, S. Kuraoka, and S. Takenaka, Chem. Lett., 1984, 279.

3) Satisfactory analytical and spectral data were obtained for these compounds.

4) ^{1}H-NMR signals of methyl esters oriented cis to the phenyl group on the 5-membered ring usually shift to near 3.1 ppm due to the shielding effect of the phenyl group. M. Joucla, D. Gree, and J. Hamelin, Tetrahedron, 29, 2315(1973).

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