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TRIMETHYLSILYL TRIFLATE-CATALYZED REACTION OF BIS(METHYLTHIOMETHYL)-AMINES WITH DIKETENE SILYL ACETALS. NOVEL CYCLIZATION LEADING TO FIVE- TO SEVEN-MEMBERED ALICYCLIC AMINES

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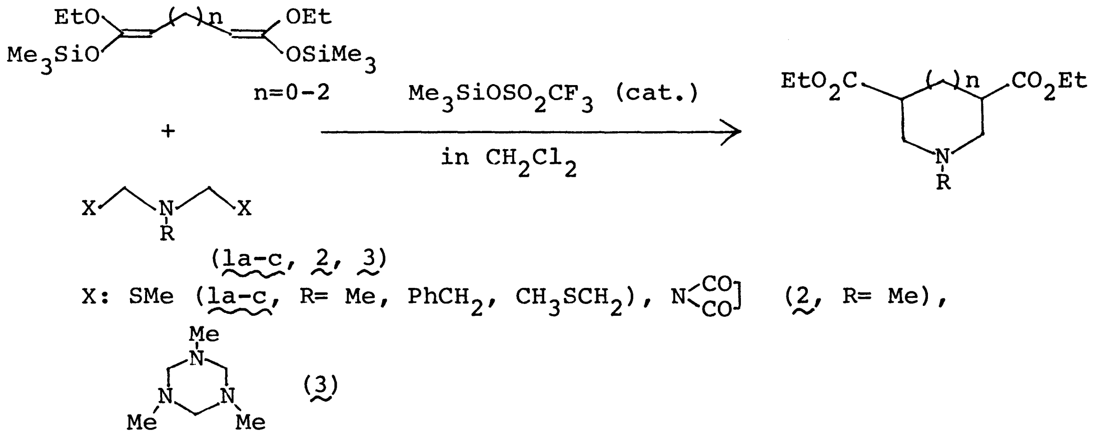
Bis(methylthiomethyl)amines have been shown to react with diketene silyl acetals in the presence of trimethylsilyl triflate catalyst to give five- to seven-membered alicyclic amines.

Susceptibility of silyl enol ethers and ketene silyl acetals to attack of electrophiles permits the formation of α-substituted carbonyl compounds and carboxylates, respectively.[1)] By this reaction recent papers reported the achievement of tertiary-aminomethylation of ketenes and secondary-aminomethylation of alkyl carboxylates utilizing dialkylaminomethyl ethers[2)] and 1,3,5-trialkyl-hexahydro-1,3,5-triazines,[3)] as electrophiles, in the presence of trimethylsilyl triflate catalyst.

The construction of alicyclic amines, five- to seven-membered rings in particular, is an important theme in organic synthesis, because the countless numbers of natural products and physiologically active compounds that contain these rings system have been known. We wish to describe here a novel synthesis of alicyclic amines through a double carbon-carbon closure. We have found that tertiary amines (1a-c, 2, and 3)[4)] possessing two functionalized methylenes, which can function as electrophilic centers, react with diketene silyl acetals (n=0-2)[5)] in the presence of trimethylsilyl triflate catalyst to afford dialkoxycarbonyl-substituted alicyclic amines.

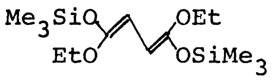
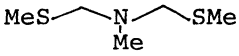
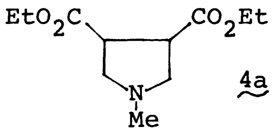
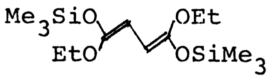
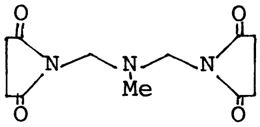
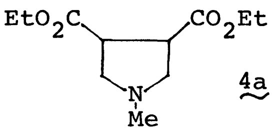
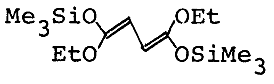
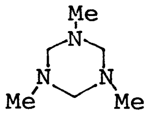
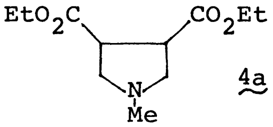
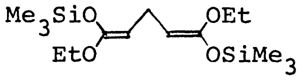
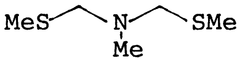
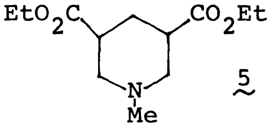
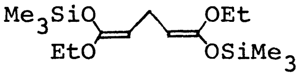
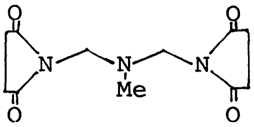
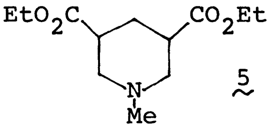
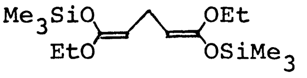
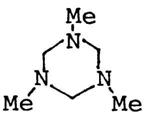
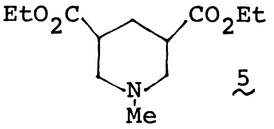
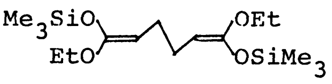
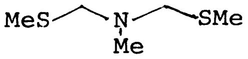
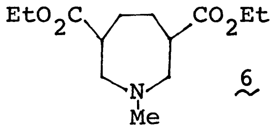
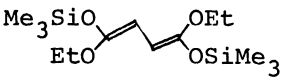
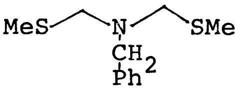
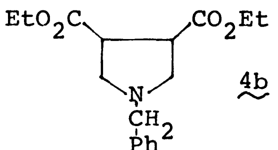
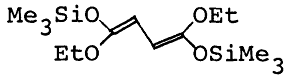
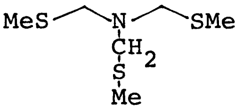
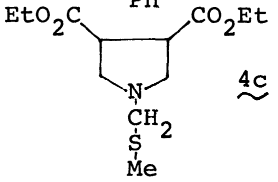


The conditions and the results of several examples of this reaction of **1a-c**, **2**, and **3** are summarized in Table 1. In every run, the reaction proceeded smoothly in dichloromethane at room temperature in the presence of 0.1 molar equivalent of trimethylsilyl triflate. Bis(methylthiomethyl)methylamines, **1a**, gave better yields of the products relative to the other, **2** and **3**.

A typical experiment (entry 1 in Table 1) is as follows. To a solution of **1a** (5 mmol) and 1,4-bis(trimethylsiloxy)-1,4-diethoxy-1,3-butadiene (5 mmol) in 15 ml of dichloromethane trimethylsilyl triflate (0.5 mmol) was added dropwise on cooling. The whole was stirred at room temperature for 3 h. The reaction mixture was then washed with 10% potassium hydrogen carbonate solution and dried over anhydrous magnesium sulfate. After removal of the solvent, the resulting residue was submitted to distillation to afford diethyl *N*-methylpyrrolidine-3,4-dicarboxylate in 95% yield.$^{6)}$ A liquid; bp 95 °C (0.4 mmHg); IR(film) 1740 cm^{-1} (ester C=O); ^{1}H NMR (CDCl$_3$) δ= 1.76 (t, J= 7.0 Hz, $CH_2C\underline{H}_3$), 2.32 (s, NCH$_3$), 2.59-2.99 (m, NCH$_2$), 3.21-3.69 (m, CH), 4.17 (q, J= 7.0 Hz, $C\underline{H}_2CH_3$); ^{13}C NMR (CDCl$_3$) δ= 14.2 (q), 41.6 (q), 46.2 (d), 59.1 (t), 61.0 (t), 173.4 (s).

The pyrrolidine derivatives (**4a-c**) were obtained as stereochemically pure forms, presumably thermodynamically stable 3,4-*trans*-configuration. In contrast, the piperidine and hexahydroazepine derivatives (**5** and **6**) were obtained as a mixture of two stereoisomers with respect to their 3,5- and 3,6-disubstituents, respectively.

Table 1. Synthesis of Alicyclic Amines[a]

Entry	Diketene silyl[b] acetal	Reagent	Conditions	Product[c]	Yield %
1			r.t., 3 h	 4a	95
2			r.t., 5 h	 4a	67
3			r.t., 5 h	 4a	75
4			r.t., 5 h	 5	56
5			r.t., 30 h	 5	31
6			r.t., 30 h	 5	35
7			r.t., 5 h	 6	63
8			30 °C, 5 h	 4b	68
9			30 °C, 5 h	 4c	51

a) All the reactions were carried out using a diketene silyl acetal (5 mmol), a reagent (5 mmol), and trimethylsilyl trifrate (0.5 mmol) in 15 ml of dichloromethane.

b) Mixture of geometrical isomers.

c) The products gave satisfactory elemental analyses and spectral data consistent with their structures.

N-Benzyl- and *N*-methylthiomethylpyrrolidines, **4b** and **4c**, obtained from **1b** and **1c**, were easily converted into the corresponding *N*-unsubstituted ones$^{7)}$ by catalytic hydrogenation over palladium-on-charcoal and by treatment with ethanolic hydrogen chloride, respectively.

Thus, bis(methylthiomethyl)amines (**1**) have been found to be potent reagents, of which two methylenes function as efficient electrophilic centers. The above reaction has paved a new convenient method for synthesizing five- to seven-membered alicyclic amines, i.e. pyrrolidines, piperidines, and hexahydroazepines in fair yields.

References

1) P.Brownbridge, Synthesis, **1983**, 1 and 85.
2) A.Hosomi, S.Iijima, and H.Sakurai, Tetrahedron Lett., **23**, 547 (1982).
3) K.Ikeda, K.Achiwa, and M.Sekiya, Tetrahedron Lett., **24**, 913 (1983).
4) Synthesis of **1a** and **1c**; W.P.Webb, U.S.Patent 2823515 (1958) (Chem. Abstr., **52**, 7656e (1958));
   1b; bp 110 °C (0.7 mmHg), Newly prepared from benzylamine, formalin, and methylsulfide;
   2; mp 173-174 °C, Newly prepared from methylamine, formalin, and succinimide;
   3; K.Ikeda, T.Morimoto, and M.Sekiya, Chem. Pharm. Bull., **28**, 1178 (1980).
5) (n=0); N.R.Long and M.W.Rathke, Synth. Commun., **11**, 687 (1981);
   (n=1 and 2); Similarly prepared from the corresponding diesters.
6) Satisfactory analytical and spectral data were obtained for this compound.
7) Diethyl pyrrolidine-3,4-dicarboxylate was obtained by flash bulb-to-bulb distillation (bp 110 °C (0.03 mmHg)). IR(film) 1728 cm^{-1}(ester C=O), 3300 cm^{-1} (NH); ^1H NMR($CDCl_3$) δ = 1.27(t, J= 7.1 Hz, $CH_2C\underline{H}_3$), 2.10(s, NH), 2.71-2.96(m, CH), 3.14-3.33(m, NCH_2), 4.16(q, J= 7.1 Hz, $C\underline{H}_2CH_3$).

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