

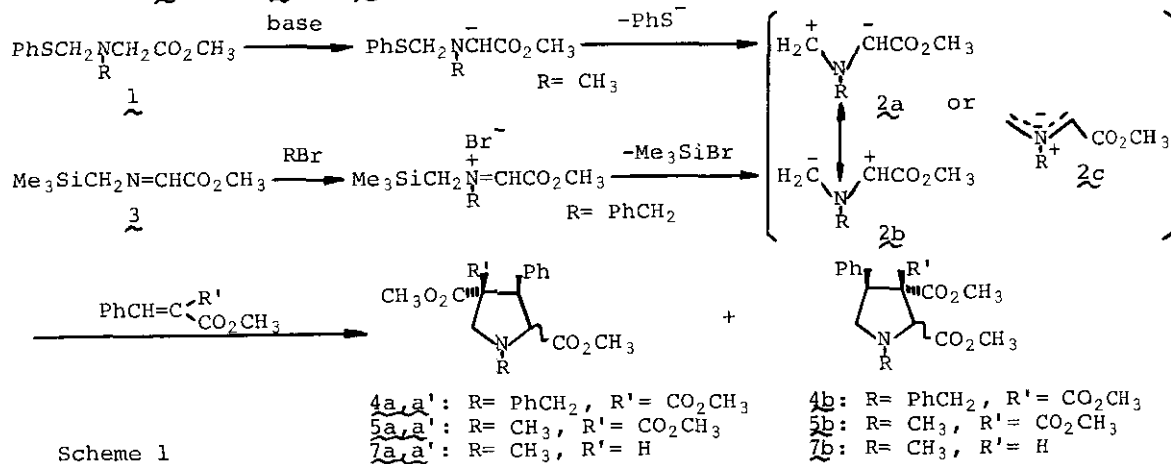
A NEW SYNTHETIC METHOD FOR PROLINE DERIVATIVES VIA THE AZOMETHINE YLIDE
INTERMEDIATE GENERATED FROM METHYL N-(TRIMETHYLSILYLMETHYL) IMINOACETATE

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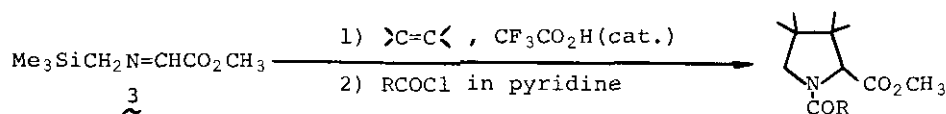
Abstract — Proline derivatives were found to be synthesized by the 1,3-dipolar cycloaddition of the azomethine ylide, produced from methyl N-(trimethylsilylmethyl)iminoacetate and benzyl bromide or a catalytic amount of trifluoroacetic acid, to conjugated olefins.

The base-promoted 1,3-dipolar cycloaddition of N-(phenylthiomethyl)amino acid methyl ester (1) to conjugated olefinic dipolarophiles has been shown to give the corresponding proline derivatives with low regioselectivity.¹ This fact may be due to the ambivalence of the 1,3-dipole termini and indicate 2a $\longleftrightarrow$ 2b (or 2c) as the structures of the intermediary azomethine ylides in this 1,3-dipolar cycloaddition. We wish to describe here that a new 1,3-dipolar cycloaddition of methyl N-(trimethylsilylmethyl)iminoacetate (3) and benzyl bromide as the synthon 2b gave almost the same regioselectivity of the products as the base-promoted 1,3-dipolar cycloaddition of 1 as the synthon 2a. This result indicates that both of the 1,3-dipolar cycloadditions proceed via the common ambivalent azomethine ylide intermediates (2a $\longleftrightarrow$ 2b or 2c) as indicated in Scheme 1.



Scheme 1

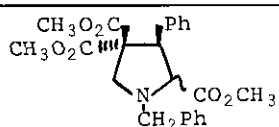
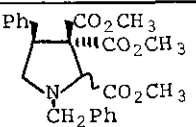
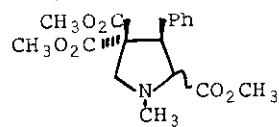
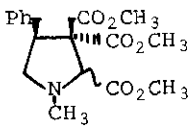
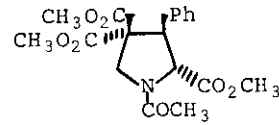
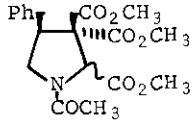
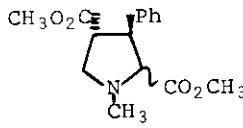
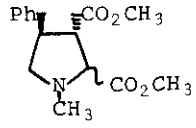
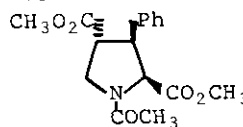
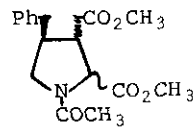
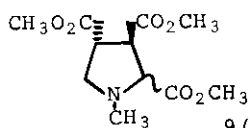
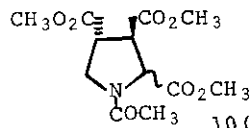
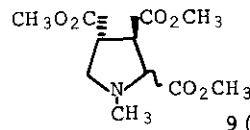
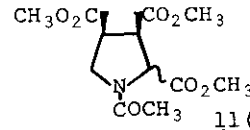
Together with such mechanistic interests, it was noticeable that this reaction provided a new method for the synthesis of proline derivatives by 1,3-dipolar cycloaddition involving silicon-carbon bond cleavage.² Further investigations revealed that the reaction proceeded also in the presence of a catalytic amount of trifluoroacetic acid^{2b} instead of benzyl bromide to give N-unsubstituted proline derivatives, which were purified after N-acylation because of their instability.



A typical experiment using 3, dimethyl benzylidenemalonate, and trifluoroacetic acid is shown below. To a stirred suspension of methyl α -hydroxy- α -methoxyacetate (12 mmol) and MgSO_4 in dried ether (10 ml) trimethylsilylmethylamine (13.2 mmol) was added dropwise on ice-cooling. The mixture was stirred at r.t. for 30 min and filtered off. The filtrate was added dropwise to an ice-cooling solution of dimethyl benzylidenemalonate (2 mmol) and trifluoroacetic acid (0.2 mmol) in hexamethylphosphoramide (HMPA) (20 ml) with stirring. The whole was stirred for 1.5 h at the temperature under nitrogen atmosphere. The reaction mixture was diluted with benzene and washed with sat. aq. NaCl -10% aq. KHCO_3 and sat. aq. NaCl , and dried over MgSO_4 . After removal of benzene, acetyl chloride (13.2 mmol) was added dropwise to a solution of the resulted residue in pyridine (5 ml) on ice-cooling. The mixture was stirred for 1.5 h under nitrogen atmosphere and diluted with dichloromethane. The solution was washed with 15% aq. HCl , sat. aq. NaCl -10% KHCO_3 , and sat. aq. NaCl , and then dried over MgSO_4 . After removal of dichloromethane, the residual oil was submitted to silica gel chromatography using hexane-ethyl acetate (1 : 3) as an eluent. Trimethyl N-acetyl-3-phenyl-2,4,4-pyrrolidinetricarboxylate (6a) and trimethyl N-acetyl-4-phenyl-2,3,3-pyrrolidine-tricarboxylate (6b) were obtained.³ Results of extensive experiments with the other dipolarophiles are collected in Table 1. Table 1 clearly indicates that the present reaction is superior to the base-promoted one in regard to the product stereoselection, because no epimerization of the products is observed (entries 5 and 9).

Its further application to the synthesis of natural proline derivatives is under investigation.

Table 1. Synthesis of Proline Derivatives^a

Entry	Substrate	Dipolarophile Reagents	Product ^b	Total yield (%)	
1 ^c	3	PhCH=C(CO ₂ CH ₃) ₂ PhCH ₂ Br	 4a (trans: 1.2) 4a' (cis: 2.6)	 4b (1)	51
2 ^d	1	PhCH=C(CO ₂ CH ₃) ₂ NaH	 5a (trans: 1.2) 5a' (cis: 1.3)	 5b (1)	71
3	3	PhCH=C(CO ₂ CH ₃) ₂ CF ₃ CO ₂ H, CH ₃ COC1	 6a (1.1)	 6b (1)	62
4 ^d	1	PhCH=CHCO ₂ CH ₃ NaH	 7a (trans: 0.2) 7a' (cis: 1.4)	 7b (1)	84
5	3	PhCH=CHCO ₂ CH ₃ CF ₃ CO ₂ H, CH ₃ COC1	 8a' (4)	 8b (1)	49
6 ^e	1	CH ₃ O ₂ CCH=CHCO ₂ CH ₃ (trans) NaH	 9 (3/1) ^f		70
7	3	CH ₃ O ₂ CCH=CHCO ₂ CH ₃ (trans) CF ₃ CO ₂ H, CH ₃ COC1	 10 (1.8/1) ^f		49
8 ^e	1	CH ₃ O ₂ CCH=CHCO ₂ CH ₃ (cis) NaH	 9 (3/1) ^f		16
9	3	CH ₃ O ₂ CCH=CHCO ₂ CH ₃ (cis) CF ₃ CO ₂ H, CH ₃ COC1	 11 (6.6/1) ^f		27

- a. All reactions were carried out as described in the text unless otherwise noted.
- b. Ratio of the isomers is described in parentheses.
- c. Reaction conditions: molar ratio, $3/\text{PhCH}_2\text{Br}/\text{PhCH}=\text{C}(\text{CO}_2\text{CH}_3)_2 = 6/1.1/1$; solvent, HMPA; temp, 0 °C; time, 1.5 h.
- d. See the reference 1.
- e. This run shows the result obtained by the base-promoted cycloaddition in the similar manner as described in the previous paper (ref. 1).
- f. Ratio of the stereoisomers at the 2-position was estimated on the basis of the NMR spectrum.

REFERENCES AND NOTES

1. N. Imai, Y. Terao, K. Achiwa, and M. Sekiya, Tetrahedron Lett., 1984, 25, 1579.
2. a. E. Vedejs and G. R. Martinez, J. Am. Chem. Soc., 1979, 101, 6452; E. Vedejs and G. R. Martinez, ibid., 1980, 102, 7993; K. Achiwa and M. Sekiya, Chem. Lett., 1981, 1213; K. Achiwa and M. Sekiya, Tetrahedron Lett., 1982, 23, 2589; Y. Terao, N. Imai, K. Achiwa, and M. Sekiya, Chem. Pharm. Bull., 1982, 30, 3167; T. Livinghouse and R. Smith, J. Chem. Soc., Chem. Commun., 1983, 210; R. Smith and T. Livinghouse, J. Org. Chem., 1983, 48, 1554; K. Achiwa, T. Motoyama, and M. Sekiya, Chem. Pharm. Bull., 1983, 31, 3939; E. Vedejs and F. G. West, J. Org. Chem., 1983, 48, 4773; A. Padwa and Y. -Y. Chen, Tetrahedron Lett., 1983, 24, 3447; O. Tsuge, S. Kanemasa, S. Kuraoka, and S. Takenaka, Chem. Lett., 1984, 279; O. Tsuge, S. Kanemasa, A. Hatada, and K. Matsuda, ibid., 1984, 801; K. Achiwa, N. Imai, T. Inaoka, and M. Sekiya, Chem. Pharm. Bull., 1984, 32, 2878; A. Hosomi, Y. Sakata, and H. Sakurai, Chem. Lett., 1984, 1117; K. Achiwa, N. Imai, T. Motoyama, and M. Sekiya, ibid., 1984, 2041; A. Padwa, G. Haffmanns, and M. Tomas, J. Org. Chem., 1984, 49, 3314; K. Achiwa, K. Sugiyama, and M. Sekiya, Chem. Pharm. Bull., in press; b. Y. Terao, H. Kotaki, N. Imai, and K. Achiwa, ibid., in press.
3. Satisfactory analytical and spectral data were obtained for these compounds.

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