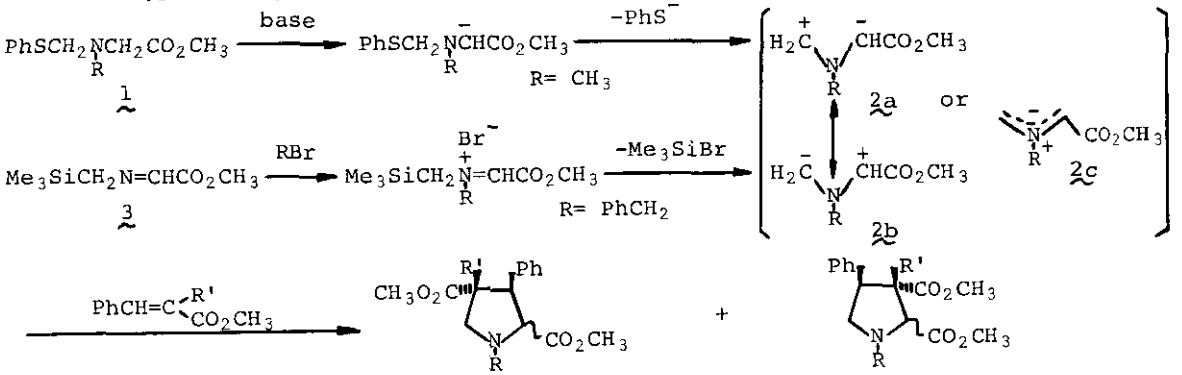
A NEW SYNTHETIC METHOD FOR PROLINE DERIVATIVES VIA THE AZOMETHINE YLIDE INTERMEDIATE GENERATED FROM METHYL N-(TRIMETHYLSILYLMETHYL)IMINOACETATE

Nobuyuki Imai, Yoshiyasu Terao, and Kazuo Achiwa*

Shizuoka College of Pharmacy, 2-2-1 Oshika, Shizuoka 422, Japan

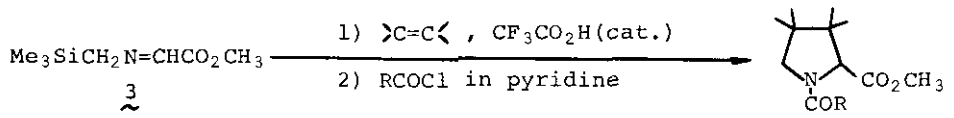
Abstract —— Proline derivatives were found to be synthesized by the 1,3-dipolar cycloaddition of the azomethine ylide, produced from methyl N-(trimethylsilylmethyl)iminoacetate and benzyl bromide or a catalytic amount of trifluoroacetic acid, to conjugated olefins.

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 ⟷ 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 ⟷ 2b or 2c) as indicated in Scheme 1.



Scheme 1

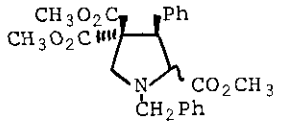
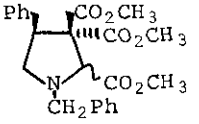
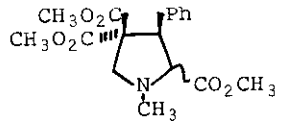
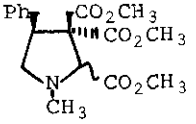
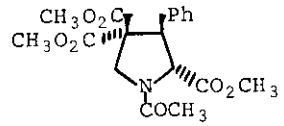
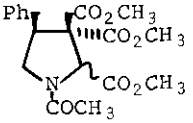
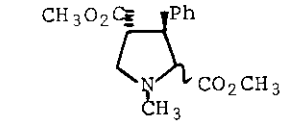
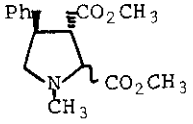
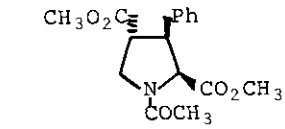
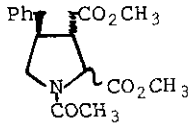
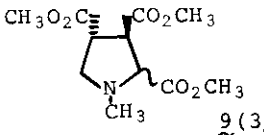
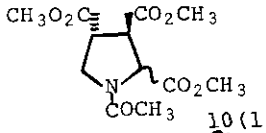
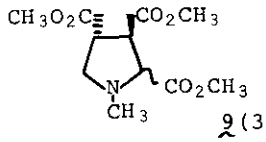
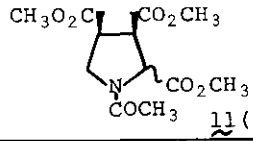
Together with such mechanistic interests, it was noticeable that this reaction provided a new method for the synthesis of proline derivatives by 1,3-dipolar cycloaddition involving silicon-carbon bond cleavage.[2] Further investigations revealed that the reaction proceeded also in the presence of a catalytic 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-pyrrolidinetricarboxylate (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	$PhCH=C(CO_2CH_3)_2$ $PhCH_2Br$	 4a(trans: 1.2) 4a'(cis: 2.6)	 4b(1)	51
2[d]	1	$PhCH=C(CO_2CH_3)_2$ NaH	 5a(trans: 1.2) 5a'(cis: 1.3)	 5b(1)	71
3	3	$PhCH=C(CO_2CH_3)_2$ CF_3CO_2H, CH_3COCl	 6a(1.1)	 6b(1)	62
4[d]	1	$PhCH=CHCO_2CH_3$ NaH	 7a(trans: 0.2) 7a'(cis: 1.4)	 7b(1)	84
5	3	$PhCH=CHCO_2CH_3$ CF_3CO_2H, CH_3COCl	 8a'(4)	 8b(1)	49
6[e]	1	$CH_3O_2CCH=CHCO_2CH_3$ (trans) NaH	 9(3/1)[f]		70
7	3	$CH_3O_2CCH=CHCO_2CH_3$ (trans) CF_3CO_2H, CH_3COCl	 10(1.8/1)[f]		49
8[e]	1	$CH_3O_2CCH=CHCO_2CH_3$ (cis) NaH	 9(3/1)[f]		16
9	3	$CH_3O_2CCH=CHCO_2CH_3$ (cis) CF_3CO_2H, CH_3COCl	 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/$PhCH_2Br$/$PhCH=C(CO_2CH_3)_2$= 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.

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

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