57772-74-4; allyl octylcyanoacetate, 122846-13-3; decanenitrile, 1975-78-6; diethyl malonate, 105-53-3; monoethyl malonate, 1071-46-1; allyl ethyl malonate, 15973-34-9; benzyl chloride, 100-44-7; allyl ethyl 2-((ethoxycarbonyl)methyl)-2-[6-(2-(trimethylsilyl)-2-dioxolanyl)hexyl]malonate, 122846-09-7; diethyl [6-(2-(trimethylsilyl)-2-dioxolanyl)hexyl]succinate, 122846-11-1.

Supplementary Material Available: ^{13}C and ^{1}H NMR spectra of the starting allylic esters and the reaction products (34 pages). Ordering information is given on any current masthead page.

Preparation of β-Amino Esters from Ethyl Azidoformate and 1-Alkoxy-1-siloxycyclopropanes

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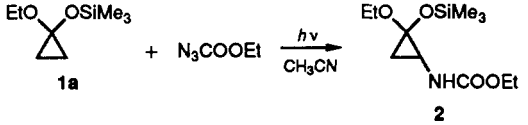
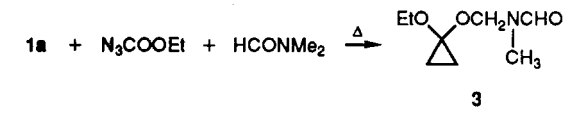
Nitrenes have been known to perform electrophilic reactions such as addition to a carbon–carbon double bond and insertion into a carbon–hydrogen bond. Cyclopropane ring systems possess π-character to some degree and have been well-known to undergo electrophilic attack by proton or Lewis acids to bring about ring-opening. However, the ring-opening of cyclopropane derivatives by nitrene has been relatively unknown except for an intramolecular reaction in a conjugate position to afford an azetine derivative.[1] Limited examples have been reported as to an analogous reaction of a cyclopropane with a carbene.[2] A silyl acetal functionality possesses a highly electron donating character and is easily transformed to an ester group. Indeed, a variety of reactions of the silyl acetal derivatives for preparation of ester derivatives have been reported,[3] including the reaction of ketene silyl acetals with nitrenes to give α-amino esters.[4] Thus, we thought that cyclopropanes with their electron density enhanced by the silyl acetal substituents would react with a nitrene to yield β-amino esters.

Photolysis of a CH_3CN solution containing ethyl azidoformate and 1-ethoxy-1-(trimethylsiloxy)cyclopropane (**1a**) at room temperature for 48 h[4a] gave a product **2**, which was derived from insertion of (ethoxycarbonyl)nitrene into a cyclopropyl C–H bond of **1a** to maintain the cyclopropane ring intact.



1a **2**

Thermolysis of **1a** in DMF did not apparently afford a product due to a reaction of the nitrene with **1a**, but instead gave a product assigned as **3**. The mechanism of formation of **3** is unclear at this time.



3

However, thermolysis of **1a** in DMSO realized opening of the cyclopropane ring by the nitrene. Thus, a solution composed of ethyl azidoformate (2 mmol), **1a** (5 mmol), and DMSO (10 mL) was heated at 120 °C until 2 mmol of N_2 had been evolved (3 h). Then, the reaction mixture was poured into water and extracted with ether. After evaporation of the ether, the residue was subjected to silica gel column chromatography ($CCl_4 \rightarrow CCl_4/Et_2O$) to afford 3-aminopropionate **4a** in 69% yield. ^{1}H and ^{13}C NMR, IR, and mass spectra were in accordance with the assigned structure. As to the mechanism of the formation of **4a**, we thought that two pathways may be possible candidates as shown in Scheme I. One includes insertion of the nitrene into a C–C bond of the cyclopropane ring to form an azetidine intermediate **5** (path A),[5] and the other involves electrophilic attack of the nitrene upon the σ-bond of the ring to induce ring-opening followed by immediate elimination of the electrofugal silyl group (path B).[6] At this stage, we do not have sufficient evidence to prove which of the two pathways operates preferentially. However, path A may be less likely since intermolecular insertion reactions of nitrenes into the C–C bond of the cyclopropane ring have not been reported. Furthermore, Kuwajima et al. have shown that upon reacting 1-alkoxy-1-siloxycyclopropanes with $TiCl_4$, electrophilic attack of the metal on the ring brings about ring cleavage followed by desilylation to generate the titanium homoenolate.[7] DMSO has been known to be an effective trap of nitrenes to result in the formation of sulfoximines,[8] although (ethoxycarbonyl)nitrene has been reported to perform an oxygen transfer from the sulfoxide.[8c] Thus, although we tentatively assumed in Scheme I that the reaction proceeds via attack of the free nitrene upon **1a**, the actual species for the reaction with **1a** might be an intermediate generated from the reaction of the nitrene with DMSO. It might be attributable to intervention of this intermediate that the production of **4a** was attained in DMSO but not in CH_3CN or DMF. The intermediate would not be *N*-(ethoxycarbonyl)dimethylsulfoximine because a nucleophilic character of the sulfoximines[9] seems to be inconsistent with attack on the electron-rich cyclopropane ring of **1a** and, in the reaction with 2-methyl-1-methoxy-1-(trimethylsiloxy)cyclopropane (**1b**), preferential attack upon C-2 with an electron donating substituent over C-3

(1) Szeimies, G.; Siefken, U.; Rinck, R. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 161.
(2) (a) Doering, W. E.; Coburn, J. F., Jr. *Tetrahedron Lett.* **1965**, 991. (b) Shiue, G.-H.; Misslitz, U.; Ding, X.-t.; Jones, M., Jr. *Tetrahedron Lett.* **1985**, *26*, 5399.
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(6) A route in which a zwitterion intermediate **6** generated in path B affords **5** by bond-forming between negative and positive charge centers may not be excluded. Its possibility, however, seems to be diminished since loss of the silyl group from a siloxycarbinyl cation is anticipated to be very rapid: Tu, C. L.; Mariano, P. S. *J. Am. Chem. Soc.* **1987**, *109*, 5287.
(7) (a) Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1977**, *99*, 7360. (b) Nakamura, E.; Oshino, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1986**, *108*, 3745.
(8) (a) *Nitrenes*; Lwowski, W., Ed.; Wiley-Interscience: New York, 1970; p 216. (b) Banks, R. E.; Prakash, A. *Tetrahedron Lett.* **1973**, 99. (c) Lwowski, W.; Rao, O. S. *Tetrahedron Lett.* **1980**, *21*, 727. (d) Hutchins, M. G. K.; Swern, D. *Tetrahedron Lett.* **1981**, *22*, 4599.
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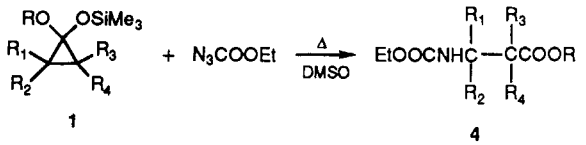
0022-3263/89/1954-5397$01.50/0

Table I



1 4

	R	R_1	R_2	R_3	R_4	yield of 4, %
a	Et	H	H	H	H	69
b	Me	Me	H	H	H	68
c	Me	H	H	Me	Me	71
d	Me	H	H	Ph	H	60
e		$-(CH_2)_2-$	H	H	H	67
f	Et	$CH(Me)OSiMe_3$	H	H	H	46
g	Et	H	H	Me	$CH(Me)OSiMe_3$	51
h	Et	Me	H	Me	H	68

(vide infra), but a loose complex of (ethoxycarbonyl)nitrene with DMSO.[10] The results of thermoreactions of ethyl azidoformate with various 1-alkoxy-1-siloxycyclopropanes in DMSO are shown in Table I.

As to regiochemistry in the formation of β-amino esters from unsymmetrically substituted cyclopropanes **1b–g**, some interesting results were obtained. Regioselective formation of the 3-aminobutanoate **4b** from **1b** can probably be rationalized by electrophilic attack of the nitrene complex predominantly upon C-2 due to the electron-donating effect of the methyl substituent superior to its steric effect, although, in the case of 2,2-dimethylcyclopropane **1c**, the nitrene complex attacks the unsubstituted carbon of the cyclopropane ring due to the enhanced steric factor, to afford 2,2-dimethyl-3-aminopropionate **4c**. The reaction of **1e** and **1f** may also be regiocontrolled by the same rationale as for **4b** from **1b**. On the other hand, production of 3-amino-2-phenylpropionate **4d** from 2-phenylcyclopropane **1d** may be explained by a rationale in which attack of the nitrene complex upon the cyclopropane ring is controlled preferentially by a steric factor owing to the diminished electron-donating effect of the phenyl group compared to that of the alkyl group. These regiochemical consequences of the nitrene complex attack upon 2-substituted 1-alkoxy-1-siloxycyclopropanes are in sharp contrast with the ring-opening reactions promoted by metal salts in which the methyl group effects ring cleavage preferentially at a less substituted position and the phenyl group does the opposite.[7b,11]

The stereochemistry in the formation of the β-amino ester **4h** from 2,3-dimethylcyclopropane **1h** might shed some light on the reaction mechanism in Scheme I. Compound **4h** was formed as a 1:1 mixture of diastereomers. Cyclopropyl silyl ketal **1h**, however, was composed of a 1:1 mixture of cis and trans isomers, and thus any suggestion as to a direction of attack of the nitrene complex upon the cyclopropane ring was not afforded from reaction of **1h**.

From the above-mentioned results with 1-alkoxy-1-siloxycyclopropanes, the reaction of the nitrene complex with a siloxycyclopropane might be expected to give a β-amino ketone. Thus, a DMSO solution containing ethyl azidoformate and 1-phenyl-1-(trimethylsiloxy)cyclopropane or 1-(trimethylsiloxy)norcarane was subjected to thermoreaction at 120 °C. However, the expected β-amino ketones were not produced. Therefore, high activation of the cyclopropane ring by the two electron-donating groups (i.e., alkoxy and siloxy) seems to facilitate electrophilic attack of the nitrene complex to afford β-amino esters.

In summary, thermoreactions of ethyl azidoformate with 1-alkoxy-1-(trimethylsiloxy)cyclopropanes in DMSO effect a direct preparation of β-amino esters, and photolysis in CH_3CN affords an insertion product of the nitrene into a cyclopropyl C–H bond, which may be readily converted to a β-amino ester. This investigation presents a novel method for the preparation of β-amino esters and a new class of reaction of the nitrene embodying attack upon a σ C–C bond.

Experimental Section

^1H and ^{13}C NMR spectra were recorded in $CCl_4/CDCl_4$ (4:1) at 60 MHz and 15 MHz on a JEOL FX60E spectrometer with chemical shifts in δ, parts per milion (ppm), downfield from tetramethylsilane. IR spectra were recorded on a Hitachi EPI-G3 spectrometer. Mass spectra were recorded on a Hitachi M-80B spectrometer using direct and/or gas chromatography inlets. Column chromatography was carried out on silica gel (Wakogel C-300).

Preparation of 1-Alkoxy-1-(trimethylsiloxy)cyclopropanes. 1a, 1b, and **1h** were prepared by reductive silylation of ethyl 3-chloropropionate, methyl 3-bromobutanoate, and ethyl 2-methyl-3-bromobutanoate, respectively, according to the method of Ruhlman.[12] **1c–g** were prepared by cyclopropanation of the corresponding ketene silyl acetals[13] with diiodomethane and zinc–silver couple according to the modified Simmons–Smith reaction by Conia et al.[14]

Synthesis of the β-Amino Esters by the Thermoreaction of Ethyl Azidoformate with the 1-Alkoxy-1-(trimethylsiloxy)cyclopropanes in DMSO. A solution of ethyl azidoformate (2 mmol) and 1 (5 mmol) in DMSO (10 mL) was placed in a three-necked flask and purged by nitrogen with ice cooling. Then the flask was put into a bath maintained at 120 °C. Nitrogen gas evolution started immediately and ceased after 3 h. The reaction mixture was poured into water (100 mL) and extracted with ether (40 mL × 2). The combined extracts were dried over $MgSO_4$ and concentrated. The residue was chromatographed on a silica gel column, eluting with CCl_4 and then a CCl_4/ether system (1:2), to give **4**.

Ethyl 3-[(ethoxycarbonyl)amino]propionate (4a): a colorless oil; IR (neat) 3340, 1730, 1675 cm^{-1}; ^1H NMR δ 1.29 (t, 3 H), 1.31 (t, 3 H), 2.56 (t, 2 H), 3.51 (q, 2 H), 4.17 (q, 2 H), 4.23 (q, 2 H), 5.20 (br s, 1 H); ^{13}C NMR δ 14.13, 14.52, 34.25, 36.20, 60.08, 60.32; low-resolution MS *m/e* 189 (M^+), 160, 144, 116, 102; high-resolution MS calcd for $C_8H_{15}NO_4$ 189.1000, found 189.1005.

Methyl 3-[(ethoxycarbonyl)amino]butanoate (4b): a colorless oil; IR (neat) 3345, 1730, 1680 cm^{-1}; ^1H NMR δ 1.28 (d,

(10) As a loose complex of (ethoxycarbonyl)nitrene with 1,4-dioxane has been reported to perform electrophilic reactions, it may be reasonably anticipated that the loose complex of the nitrene with DMSO performs electrophilic attack upon the cyclopropane ring: Takeuchi, H.; Nishiyama, T.; Mitani, M.; Tsuchida, T.; Koyama, K. *J. Chem. Soc., Perkin Trans. 2* **1979**, 839.

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(13) Ainsworth, C.; Chen, F.; Kuo, Y.-N. *J. Organometal. Chem.* **1972**, *46*, 59.

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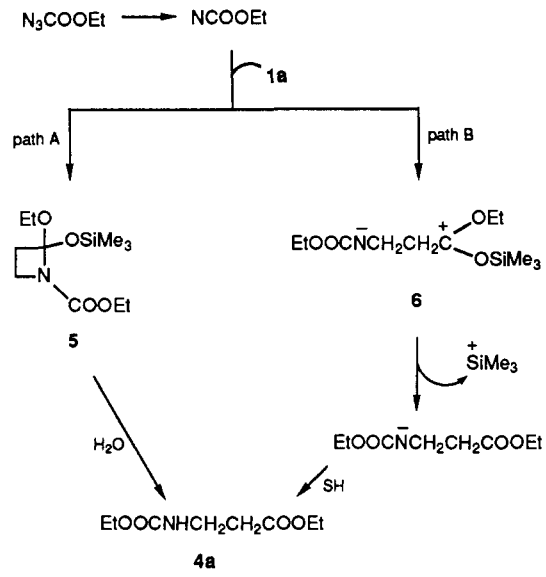
Scheme I



3 H), 1.31 (t, 3 H), 2.56 (d, 1 H), 2.67 (d, 1 H), 3.74 (s, 3 H), 3.63–4.14 (m, 1 H), 4.28 (q, 2 H), 6.26 (br s, 1 H); ^{13}C NMR δ 14.23, 14.43, 34.30, 38.50, 51.47, 60.34; low-resolution MS m/e 189 (M^+), 174, 158, 130, 116; high-resolution MS calcd for $C_8H_{15}NO_4$ 189.1000, found 189.1008.

Methyl 2,2-dimethyl-3-[(ethoxycarbonyl)amino]-propionate (4c): a colorless oil; IR (neat) 3360, 1725, 1680 cm^{-1}; ^{1}H NMR δ 1.28 (s, 6 H), 1.30 (t, 3 H), 3.48 (d, 2 H), 3.78 (s, 3 H), 4.24 (q, 2 H), 5.80 (br s, 1 H); ^{13}C NMR δ 13.88, 14.54, 36.33, 54.70, 60.34; low-resolution MS m/e 203 (M^+), 188, 172, 144, 102; high-resolution MS calcd for $C_9H_{17}NO_4$ 203.1157, found 203.1154.

Methyl 2-phenyl-3-[(ethoxycarbonyl)amino]propionate (4d): a colorless oil; IR (neat) 3365, 3025, 1740, 1685, 770, 700 cm^{-1}; ^{1}H NMR δ 1.32 (t, 3 H), 3.76 (s, 3 H), 3.48–4.00 (m, 3 H), 4.25 (q, 2 H), 6.18 (br s, 1 H), 7.39 (s, 5 H); ^{13}C NMR δ 14.61, 35.31, 36.62, 56.22, 60.41, 126.50, 127.78, 129.56; low-resolution MS m/e 251 (M^+), 236, 220, 192, 102; high-resolution MS calcd for $C_{13}H_{17}NO_4$ 251.1157, found 251.1152.

4-[(Ethoxycarbonyl)amino]tetrahydro-2*H*-pyran-2-one (4e): a colorless oil; IR (neat) 3365, 1735, 1680 cm^{-1}; ^{1}H NMR δ 1.38 (t, 3 H), 1.86–2.26 (m, 2 H), 2.68 (t, 2 H), 3.70–4.21 (m, 1 H), 4.21 (t, 2 H), 4.25 (q, 2 H), 6.23 (br s, 1 H); ^{13}C NMR δ 14.54, 24.58, 35.28, 46.15, 60.41, 61.95; low-resolution MS m/e 187 (M^+), 157, 143, 115; high-resolution MS calcd for $C_8H_{13}NO_4$ 187.0844, found 187.0843.

Ethyl 3-[(ethoxycarbonyl)amino]-4-(trimethylsiloxy)-pentanoate (4f): a colorless oil; IR (neat) 3460, 1760, 1685 cm^{-1}; ^{1}H NMR δ 0.18 (s, 9 H), 1.26 (d, 3 H), 1.30 (t, 3 H), 1.34 (t, 3 H), 2.58 (d, 1 H), 2.66 (d, 1 H), 3.58–4.15 (m, 2 H), 4.18 (q, 2 H), 4.30 (q, 2 H), 5.95 (br s, 1 H); ^{13}C NMR δ 0.72, 14.09, 14.72, 17.23, 34.72, 36.57, 60.11, 60.68, 63.28; low-resolution MS m/e 305 (M^+), 290, 276, 260, 232, 218, 117, 73; high-resolution MS calcd for $C_{13}C_{27}NO_5Si$ 305.1657, foun 305.1660.

Ethyl 2-methyl-2-[[(ethoxycarbonyl)amino]methyl]-3-(trimethylsiloxy)butanoate (4g): a colorless oil; IR (neat) 3460, 1760, 1680 cm^{-1}; ^{1}H NMR δ 0.18 (s, 9 H), 1.24 (d, 3 H), 1.30 (t, 3 H), 1.32 (t, 3 H), 1.36 (s, 3 H), 3.55 (s, 2 H), 3.78 (q, 1 H), 4.19 (q, 2 H), 4.24 (q, 2 H), 6.00 (br s, 1 H); ^{13}C NMR δ 0.74, 14.20, 14.55, 14.92, 17.10, 36.31, 60.12, 60.30, 63.30; low-resolution MS m/e 319 (M^+), 304, 290, 274, 246, 117, 102, 73; high-resolution MS calcd for $C_{14}H_{29}NO_5Si$ 319.1813, found 319.1810.

Ethyl 2-Methyl-3-[(ethoxycarbonyl)amino]butanoate (4h). This product was obtained as a colorless oil and shown to be a 1:1 mixture of diastereomers by GC–MS and ^{13}C NMR: IR (neat) 3350, 1730, 1680 cm^{-1}; ^{1}H NMR δ 1.09–1.52 (m, 12 H), 2.53–3.10 (m, 1 H), 3.40–4.15 (m, 1 H), 4.19 (q, 2 H), 4.25 (q, 2 H), 5.85 (br s, 1 H); ^{13}C NMR δ 10.92, 13.71, 14.03, 14.18, 14.53, 16.71, 36.28, 37.19, 38.43, 39.52, 60.06, 60.38; low-resolution MS m/e 217 (M^+), 188, 172, 144, 116; high-resolution MS calcd for $C_{10}H_{19}NO_4$ 217.1313, found 217.1310.

Regioselective Addition Reactions of Organometallic Reagents with 3-Benzylidene Heterocyclic Imines Leading to the Synthesis of Pyrrolizidines

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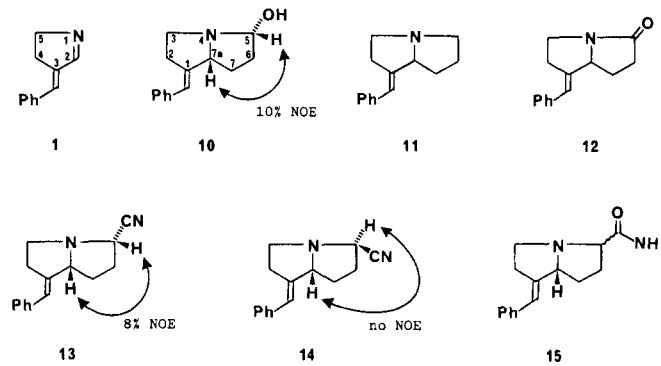
The pyrrolizidine alkaloids, an important class of natural product, have been the subject of many synthetic, pharmacological, and biological studies.[1] During our studies of the construction of functionalized pyrrolizidines, we have investigated addition reactions of organometallic reagents with 3-benzylidene heterocyclic imines, which are ambident electrophiles. Herein we report the regioselective addition of organomagnesium and organolithium reagents with 3-benzylidene-1-pyrroline (**1**)[2] and the subsequent cyclization to pyrrolizidines.

Some addition reactions of imines[3] and α,β-unsaturated aldimines[4] have been reported. We now find that the ambident electrophile **1** undergoes exclusively 1,2-addition with organomagnesium and organolithium reagents. The results are summarized in Table I. The general procedure for these reactions consists of treating enimine **1** with 1.2 equiv of the organomagnesium reagent in THF at −30 °C for 30 min and 25 °C for 1 to 3 h, or with 1.2 equiv of the organolithium reagent in THF at −78 °C for 1 h. The organomagnesium reagents chelate with the nitrogen of **1** at −30 °C to 0 °C and precipitate as brown solids. At 25 °C, these complexes then react to form the 1,2-adduct, which is indicated by the dissolution of the solids. No 1,4-adducts were detected in any case. Thus the reaction path is suggested to consist of the chelation of metal of the reagents with the nitrogen of the imine followed by the nucleophilic attack of the R group at the carbon of the C=N bond.[3b]



Adduct amine **9** underwent stereoselective ring closure with 1 N HCl[5] in ethanol at 25 °C for 24 h, forming pyrrolizidinol **10** (a single diastereomer) in 90% yield. The stereochemistry was established by ^{1}H NMR spectroscopy (nuclear Overhauser enhancement difference). Irradiation of the 5-H showed 10% enhancement of the 7a-H. The amine intramolecularly attacks the aldehyde from the pro-*R* face. Reduction of **10** with lithium aluminum hydride in THF at 25 °C gave pyrrolizidine **11** in 89% yield. Alternatively, oxidation of **10** with pyridinium chlorochromate (PCC)[6] in CH_2Cl_2 provided lactam **12**[4f] in 86% yield.

Cyclization of **9** was also successfully carried out in 1 N HCl–KCN–CH_2Cl_2 as previously suggested;[1d] at 25 °C for

† Fellow of the Alfred P. Sloan Foundation, 1989–1991.

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