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New α,β-Didehydroamino Acid Derivatives as Precursors in the Synthesis of 1-Aminocyclopropanecarboxylic Acids

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Abstract: The reaction of *N*-(diphenylmethylene)didehydroalanine methyl ester and *N*-[bis(methylthio)methylene]didehydroalanine methyl ester with diazoalkanes or ylides gives the corresponding cyclopropane derivatives in high yields. The *cis/trans* ratio of these compounds was dependent on substrate, reagent and reaction temperature. From stereochemically homogeneous compounds the corresponding 1-aminocyclopropanecarboxylic acids were easily obtained by acid hydrolysis.

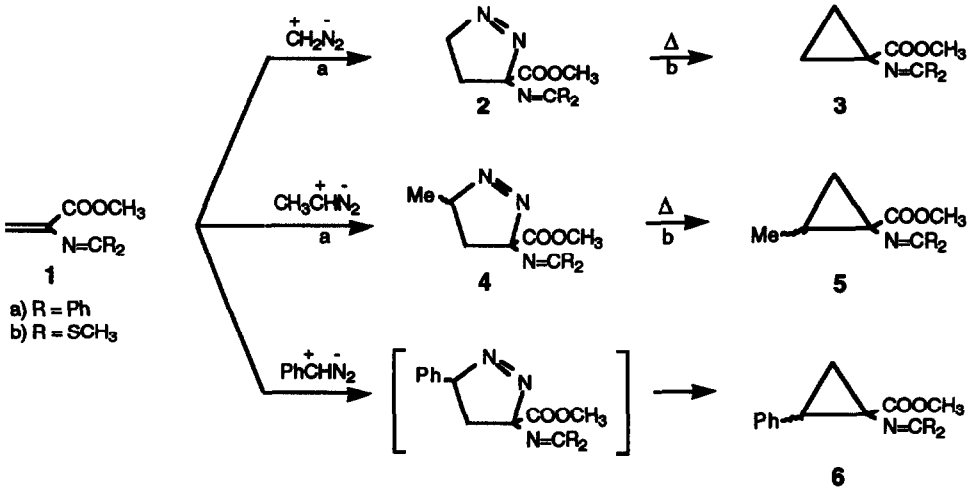
Since the first report of the isolation[1] and identification of 1-aminocyclopropanecarboxylic acid (ACC) as an intermediate in the biosynthesis of ethylene, the phytohormone which initiates and regulates many aspects of the plant growth[2] including germination and ripening of fruits, the synthesis of this compound and its derivatives has attracted special interest[3] because of their biological activity[4] and potential use in conformationally restricted peptides.[5]

In this context we have now studied the behaviour of *N*-(diphenylmethylene)didehydroalanine methyl ester **1a** and *N*-[bis(methylthio)methylene]didehydroalanine methyl ester **1b** which are α,β-didehydroamino acid derivatives with easily removable protecting groups, as intermediates in the synthesis of 1-aminocyclopropanecarboxylic acid ACC and 2-substituted derivatives. These compounds can obviate the drawbacks of some methodologies described previously such as lengthy sequences and hydrolysis or deprotection in strong conditions that make it difficult to retain the cyclopropane ring.

Among the various strategies for the synthesis of ACC and its derivatives involving α,β-didehydroamino acid derivatives we can choose either cyclopropanation with diazoalkanes[6] followed by extrusion of nitrogen gas or addition of sulphoxonium ylides.[7]

Firstly we examined diazoalkanes as cyclopropanating reagents (Scheme 1) and we observed that when compounds **1a** and **1b** were treated with a solution of diazomethane in ethyl acetate for 5 hours at 0 °C followed by heating at 70 °C during 10 minutes in order to achieve thermolysis of the intermediates Δ^1-pyrazolines **2a** and **2b**, quantitative yields of cyclopropanes **3a** and **3b** were obtained as we have previously communicated.[8,9]

In a similar fashion, when compounds **1a** and **1b** were treated with a solution of diazoethane in ethyl acetate for 35 minutes at 0 °C non-separable mixtures of *cis* and *trans* Δ^1-pyrazolines **4a** and **4b** in ratios of 1:1 and 3:1 respectively were obtained. The mixtures were submitted to thermolysis to afford non-separable mixtures of *cis* and *trans* cyclopropanes **5a** and **5b** with a ratio 1.5:1 in both cases.



Scheme 1

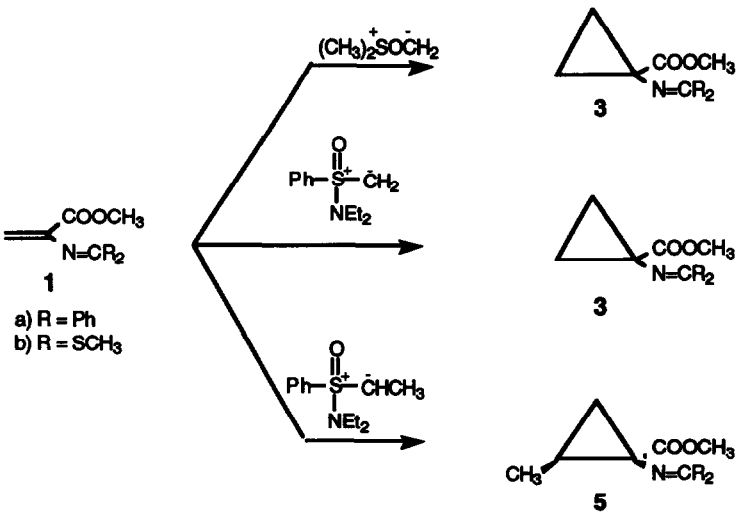
Table 1. Diazoalkanes as Cyclopropanating Agents

R	Reagent	step	temp [°C]	t	Yield [%]	cis:trans[a]
Ph	CH_2N_2	a	0	5 h	≈ 100	-
		b	70	10 m	≈ 100	-
Ph	CH_3CHN_2	a	0	35 m	≈ 100	1:1
		b	70	15 m	≈ 100	1.5:1
Ph	$PhCHN_2$		r.t.	72 h	96	1.2:1
SCH_3	CH_2N_2	a	0	5 h	≈ 100	-
		b	70	10 m	≈ 100	-
SCH_3	CH_3CHN_2	a	0	35 m	≈ 100	3:1
		b	70	15 m	≈ 100	1.5:1
SCH_3	$PhCHN_2$		r.t.	72 h	≈ 100	1:1.1

[a] Determined by integration of the crude reaction ^{1}H-NMR spectra.

When a solution of phenyldiazomethane in toluene was added to compounds **1a** and **1b** and the resulting solution was stirred at room temperature for 3 days, the corresponding 2-phenyl derivatives were obtained in almost quantitative yields as mixtures of *cis* and *trans* cyclopropanes **6a** and **6b** in a ratio 1.2:1 and 1:1.1 respectively, which were easily separated by MPLC. The *cis/trans* stereochemistries of compounds ***cis*-6a**, ***trans*-6a**, ***cis*-6b**, and ***trans*-6b** were unequivocally determined on the basis of NOE difference ^{1}H NMR experiments. Thus, in compounds having a *cis* stereochemistry, the signal due to the benzylic proton showed significant NOE enhancement when the signal due to the carbomethoxy group was selectively irradiated. This stereochemical assignment was later confirmed on the basis of the known stereochemistries of the corresponding hydrolysis products.

Subsequently we examined oxosulfonium ylides as cyclopropanating reagents (Scheme 2). The first of such reagents assessed in this endeavour was the Corey ylide, dimethyloxosulfonium methylide.[10] Upon treatment of **1a** and **1b** with 1.2 molar equiv. of the NaH-derived ylide, cyclopropanation products **3a** and **3b** were obtained in high yields. In a similar fashion, when compounds **1a** and **1b** were treated with 1.2 molar equiv. of the ylide derived from (diethylamino)methylphenyloxosulfonium tetrafluoroborate,[11] cyclopropanation products **3a** and **3b** were obtained also in high yields.



Scheme 2

The excellent behaviour of our substrates towards oxosulfonium ylides prompted us to try this methodology to obtain 2-methylcyclopropane derivatives. Upon treatment of **1a** and **1b** at room temperature with 1.2 molar equiv. of the ylide derived from (diethylamino)ethylphenyloxosulfonium tetrafluoroborate,[11] cyclopropanation products **5a** and **5b** were obtained in very high yields and with a good *cis* selectivity.

When the reaction was carried out at low temperature (-20 °C) there was a decrease in the reaction rate but in both cases the *cis* selectivity of the reaction was increased. An additional decrease in the temperature (-55 °C) further diminished the reaction rate but increased once again the reaction selectivity so that *cis* derivatives of **5a** and **5b** were obtained in very high yields and with almost total *cis* selectivity. The stereochemistries of compounds ***cis*-5a** and ***cis*-5b** were unequivocally determined on the basis of that of their hydrolysis products.

In contrast, the addition of dimethyloxosulfonium methylide or (diethylamino)phenyloxosulfonium methylide to *Z* or *E* methyl *N*-(diphenylmethylene)-2-aminocrotonate and *Z* or *E* *N*-[bis(methylthio)methylene]-2-aminocrotonate was not stereospecific and we obtained *cis/trans* mixtures of compounds **5a** and **5b.**

(Diethylamino)benzylphenyloxosulfonium tetrafluoroborate could not be obtained by the standard procedure used for the synthesis of (diethylamino)ethylphenyloxosulfonium tetrafluoroborate. Moreover, the reaction of **1a** and **1b** with benzylidenetriphenylphosphorane, generated by treatment of benzyltriphenylphosphonium iodide in benzene with a hexane solution of *n*-butyllithium according to the method of Najera,[12] did not work at all. Indeed all further attempts to obtain other similar benzylides were unsuccessful and so 2-phenylcyclopropane derivatives **6a** and **6b** could not be obtained by this methodology.

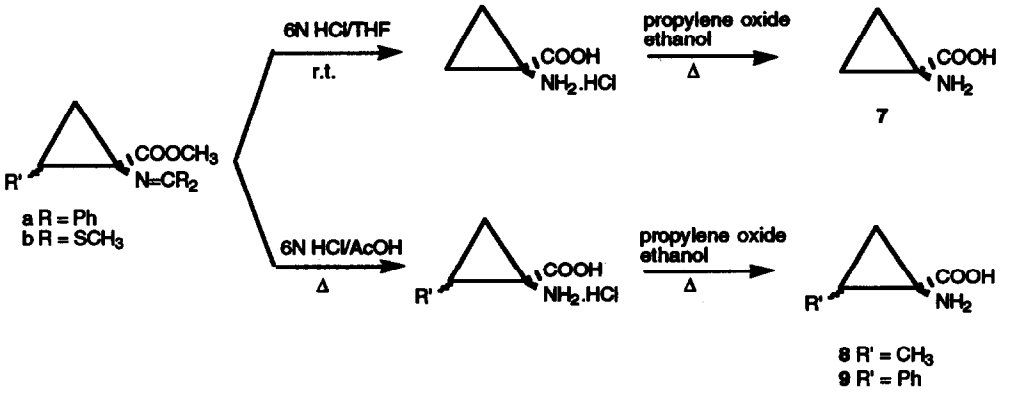
Table 2. Oxosulfonium Ylides as Cyclopropanating Reagents

R	Reagent	temp [°C]	t	Yield [%]	cis:trans[a]
Ph	$(CH_3)_2SOCH_2$	r.t.	15 m	90	-
Ph	$Ph(NEt)_2SOCH_2$	r.t.	12 h	75	-
Ph	$Ph(NEt)_2SOCHCH_3$	r.t.	2 h	96	95:5
Ph	$Ph(NEt)_2SOCHCH_3$	-20	24 h	95	98:2
Ph	$Ph(NEt)_2SOCHCH_3$	-55	5 d	93	>98:2
SCH_3	$(CH_3)_2SOCH_2$	r.t.	15 m	70	-
SCH_3	$Ph(NEt)_2SOCH_2$	r.t.	15 h	80	-
SCH_3	$Ph(NEt)_2SOCHCH_3$	r.t.	4 h	92	83:17
SCH_3	$Ph(NEt)_2SOCHCH_3$	-20	3 d	85	92:8
SCH_3	$Ph(NEt)_2SOCHCH_3$	-55	5 d	70	96:4

[a] Determined by integration of the crude reaction ^{1}H-NMR spectra.

Final deprotection of unsubstituted derivatives, using 6N hydrochloric acid in THF at room temperature, gave the cyclopropylamino acid hydrochloride in nearly quantitative yield. However, hydrolysis of 2-methyl and 2-phenyl derivatives ***cis*-5a**, ***cis*-5b**, ***cis*-6a**, ***cis*-6b**, ***trans*-6a** and ***trans*-6b** under the same conditions afforded the corresponding methyl ester hydrochlorides. Nevertheless, when these

compounds were refluxed with 6N hydrochloric acid in glacial acetic the corresponding cyclopropylamino acid hydrochlorides were obtained in nearly quantitative yield. Amino acid hydrochlorides were then converted into free amino acids **7**, ***cis*-8**, ***cis*-9**, and ***trans*-9** by refluxing the salt in ethanol with an excess of propylene oxide. Purification of the free amino acids was accomplished by eluting an aqueous solution of the appropiate amino acid through a sep-pak C_{18} cartridge (Scheme 3). This procedure works extremely well and enables us to obtain ACC and 2-substituted compounds as free amino acids in more than 90% overall yield from the corresponding cyclopropyl derivatives **3**, **5** and **6**, avoiding the need for ion exchange-chromatography.



Scheme 3

In conclusion, we have developed new synthetic approaches to valuable cyclopropyl amino acids from readily available starting materials, which allow the synthesis of these compounds under mild conditions with excellent yields and, in some cases, very high stereoselectivity.

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EXPERIMENTAL

Apparatus: ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian Unity-300 spectrometer in deuteriochloroform or deuterium oxide using the solvent signal as internal standard, chemical shifts (δ) are expressed in parts per million and the coupling constants (J) are given in hertz. IR spectra were recorded on a Perkin-Elmer 1600 FTIR infrared spectrophotometer. Melting points were determined on a Büchi 510 capillary melting point apparatus and are uncorrected. Microanalyses were carried out using a Perkin-Elmer 2400 C,H,N,S element analyzer.

Chemicals: All reactions were carried out under an atmosphere of argon with magnetic stirring. Solvents were dried prior to use. *N*-(Diphenylmethylene)didehydroalanine methyl ester[13] **1a** and *N*-[bis(methylthio)methylene]didehydroalanine methyl ester[14] **1b** were prepared following the literature procedures. *N*-Methyl-*N'*-nitro-*N*-nitrosoguanidine and sodium hydride were purchased from the Aldrich Chemical Co. TLC was performed on Merck precoated silica-gel plates which were visualised using UV light and iodine. Medium Pressure Chromatography was performed using 230-400 mesh (Merck) silica-gel. Sep-Pak C18 (reverse phase) cartridges were purchased from Waters.

General procedure for diazomethane cycloaddition and subsequent nitrogen extrusion
A typical experiment was carried out as follows: A solution of compound **1a** or **1b** (1 mmol) in ethyl acetate (10 mL) was treated with a solution of diazomethane in ethyl acetate (generated from 1.0 g of *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine) in a stoppered flask, protected-from-light at 0°C for about 5 h until completion (TLC, hexane/ethyl acetate = 9:1). The solution was treated with anhydrous $CaCl_2$ to destroy the excess diazomethane and after filtration the solution was heated under reflux for about 10 min until completion (TLC, hexane/ethyl acetate = 9:1). The solution was then cooled and concentrated *in vacuo* to afford a quantitative yield of pure **3a** or **3b**.

Methyl *N*-(diphenylmethylene)-1-aminocyclopropanecarboxylate 3a
Oil (Lit.,[9] oil); IR(Nujol) 1725, 1610 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.16 (dd, 2H, J = 7.5 Hz, J = - 4.5 Hz); 1.48 (dd, 2H, J = 7.5 Hz, J = - 4.5 Hz); 3.49 (s, 3H); 7.18-7.82 (m, 10H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.3, 45.2, 51.8, 127.9, 128.0, 128.1, 128.7, 128.8, 130.4, 137.7, 139.9, 172.9, 174.2.

Methyl *N*-[bis(methylthio)methylene]-1-aminocyclopropanecarboxylate 3b
Oil (Lit.,[8] oil); IR(Nujol) 1725 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.22 (dd, 2H, J = 7.5 Hz, J = - 4.5 Hz); 1.58 (dd, 2H, J = 7.5 Hz, J = - 4.5 Hz); 2.41 (s, 3H), 2.55 (s, 3H), 3.68 (S, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.8, 15.0, 18.9, 43.8, 52.2, 169.6, 171.4.

General procedure for diazoethane cycloaddition and subsequent nitrogen extrusion
A typical experiment was carried out as follows: A solution of compound **1a** or **1b** (1 mmol) in ethyl acetate (10 mL) was treated with a solution of diazoethane in ethyl acetate (generated from 0.4 g of *N*-nitrosoethylurea) in a stoppered flask, protected-from-light at 0°C for about 35 m until completion (TLC, hexane/ethyl acetate = 9:1). The solution was treated with anhydrous $CaCl_2$ to destroy the excess diazoethane and after filtration the solution was heated under reflux for about 15 min until completion (TLC, hexane/ethyl acetate = 9:1). The solution was then cooled and concentrated *in vacuo* to afford a quantitative yield of **5a** or **5b** as a mixture of diastereoisomers which were not isolated.

General procedure for phenyldiazomethane cycloaddition
A typical experiment was carried out as follows: A solution of compound **1a** or **1b** (1 mmol) in toluene (10 mL) was treated with a solution of phenyldiazomethane (1.5 mmol) in toluene (10 mL), in a stoppered flask, protected-from-light at room temperature for about 3 days until completion (TLC, hexane/ethyl acetate = 9:1). The solution was treated with anhydrous $CaCl_2$ to destroy the excess of phenyldiazomethane and after filtration the solution was concentrated *in vacuo* to afford **6a** or **6b** as a mixture of diastereoisomers from

which *cis* and *trans* stereoisomers were isolated by medium pressure chromatography eluting with hexane/ethyl acetate 9:1.

***Cis*-Methyl *N*-(diphenylmethylene)-1-amino-2-phenylcyclopropanecarboxylate *cis*-6a**
Oil ; IR(Nujol) 1725, 1595 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.30 (dd, 1H, J = 7.6 Hz, J = - 5.6 Hz); 1.88 (dd, 1H, J = 9.6 Hz, J = - 5.6 Hz); 3.06 (dd, 1H, J = 9.6 Hz, J = 7.6 Hz); 3.66 (s, 3H); 6.80-7.70 (m, 15H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.2, 35.5, 50.4, 52.1, 126.3, 127.2, 127.3, 127.7, 127.9, 128.0, 128.7, 128.8, 130.3, 135.7, 137.5, 139.8, 172.5, 174.4. Anal. Calcd. for $C_{24}H_{21}NO_2$: C, 81.10; H, 5.96; N, 3.94. Found C, 81.20; H, 5.82; N, 4.12.

***Trans*-Methyl *N*-(diphenylmethylene)-1-amino-2-phenylcyclopropanecarboxylate *trans*-6a**
Oil; IR(Nujol) 1725, 1595 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.60 (dd, 1H, J = 9.0 Hz, J = - 5.5 Hz); 2.26 (dd, 1H, J = 8.7 Hz, J = - 5.5 Hz); 3.04 (s, 3H); 3.08 (dd, 1H, J = 9.0 Hz, J = 8.7 Hz); 7.10-7.83 (m, 15H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.4, 37.9, 51.1, 53.9, 126.5, 127.6, 128.0, 128.1, 128.4, 128.8, 128.9, 129.9, 130.4, 135.8, 137.7, 139.9, 168.8, 172.8. Anal. Calcd. for $C_{24}H_{21}NO_2$: C, 81.10; H, 5.96; N, 3.94. Found C, 81.01; H, 6.07; N, 3.92.

***Cis*-Methyl *N*-[bis(methylthio)methylene]-1-amino-2-phenylcyclopropanecarboxylate *cis*-6b**
Oil; IR(Nujol) 1727, 1602 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.45 (dd, 1H, J = 8.6 Hz, J = - 5.4 Hz); 2.26 (dd, 1H, J = 8.6 Hz, J = - 5.4 Hz); 2.45 (s, 3H); 2.56 (s, 3H); 2.86 (dd, 1H, J = 8.6 Hz, J = 8.6 Hz); 3.36 (s, 3H); 7.15-7.40 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.6, 15.3, 22.7, 34.6, 52.4, 126.3, 127.4, 128.8, 136.0, 170.2, 171.8. Anal. Calcd. for $C_{14}H_{17}NO_2S_2$: C, 56.92; H, 5.80; N, 4.74; S, 21.70. Found C, 56.75; H, 5.63; N, 4.58; S, 21.63.

***Trans*-Methyl *N*-[bis(methylthio)methylene]-1-amino-2-phenylcyclopropanecarboxylate *trans*-6b**
Oil; IR(Nujol) 1718, 1603 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.56 (dd, 1H, J = 7.7 Hz, J = - 5.4 Hz); 2.09 (s, 3H), 2.12 (dd, 1H, J = 9.75 Hz, J = - 5.4 Hz); 2.33 (s, 3H), 3.06 (dd, 1H, J = 9.7 Hz, J = 7.7 Hz); 3.70 (s, 3H); 7.05-7.24 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.1, 15.4, 20.5, 36.1, 51.7, 51.8, 126.6, 127.8, 129.2, 136.0, 169.1, 169.9. Anal. Calcd. for $C_{14}H_{17}NO_2S_2$: C, 56.92; H, 5.80; N, 4.74; S, 21.70. Found C, 57.08; H, 5.71; N, 4.85; S, 21.85.

General procedure for dimethyloxosulphonium methylide addition
A typical experiment was carried out as follows: A mixture of trimethyloxosulphonium iodide (264 mg, 1.2 mmol) and 95 % sodium hydride (30.3 mg, 1.2 mmol) in dry dimethylformamide (3 mL) was stirred at room temperature for several minutes. When the evolution of gas had ceased, the freshly prepared ylide was added *via* cannula to a solution of compound **1a** or **1b** (1 mmol) in dimethylformamide (5 mL). The solution was stirred at room temperature for about 15 m. To the mixture was added brine (3 mL) followed by extraction with ethyl acetate (3 x 10 mL). The organic fractions were combined, washed with water (3 x 10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford pure **3a** or **3b** whose physical and spectroscopic data are given above.

General procedure for (diethylamino)phenyloxosulphonium methylide addition

A typical experiment was carried out as follows: A mixture of (diethylamino)methylphenyloxosulphonium tetrafluoroborate (359 mg, 1.2 mmol) and 95 % sodium hydride (30.3 mg, 1.2 mmol) in dry dimethylformamide (3 mL) was stirred at room temperature for several minutes. When the evolution of gas had ceased the freshly prepared ylide was added *via* cannula to a solution of compound **1a** or **1b** (1 mmol) in dimethylformamide (5 mL). The solution was stirred at room temperature for about 15 h. To the mixture was added brine (3 mL) followed by extraction with ethyl acetate (3 x 10 mL). The organic fractions were combined, washed with water (3 x 10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography eluting with hexane/ethyl acetate 8:2 afforded pure **3a** or **3b** whose physical and spectroscopic data are given above.

General procedure for (diethylamino)phenyloxosulphonium ethylide addition

A typical experiment was carried out as follows: A mixture of (diethylamino)ethylphenyloxosulphonium tetrafluoroborate (376 mg, 1.2 mmol) and 95 % sodium hydride (30.3 mg, 1.2 mmol) in dry dimethylformamide (3 mL) was stirred at room temperature for several minutes. When the evolution of gas had ceased the freshly prepared ylide was added *via* cannula to a solution of compound **1a** or **1b** (1 mmol) in dimethylformamide (5 mL). The solution was stirred at the appropiate temperature for the time indicated in table 2. To the mixture was added brine (3 mL) followed by extraction with ethyl acetate (3 x 10 mL). The organic fractions were combined, washed with water (3 x 10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography eluting with hexane/ethyl acetate 8:2 afforded pure ***cis*-5a** or ***cis*-5b**.

***Cis*-Methyl *N*-(diphenylmethylene)-1-amino-2-methylcyclopropanecarboxylate *cis*-5a**

Oil; IR(Nujol) 1725, 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.46 (dd, 1H, J = 7 Hz, J = - 4.9 Hz); 1.23 (d, 3H, J = 6 Hz); 1.49 (dd, 1H, J = 9 Hz, J = - 4.9 Hz); 1.64-1.76 (m, 1H); 3.50 (s, 3H); 7.15-7.20 (m, 2H); 7.30-7.40 (m, 6H); 7.65-7.70 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.9, 25.7, 25.8, 29.7, 48.0, 51.8, 127.9, 128.0, 128.1, 128.7, 128.9, 130.4, 137.9, 140.1, 173.4, 174.4. Anal. Calcd. for $C_{14}H_{17}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found C, 77.55; H, 6.61; N, 4.91.

***Cis*-Methyl *N*-[bis(methylthio)methylene]-1-amino-2-methylcyclopropanecarboxylate *cis*-5b**

Oil, IR(Nujol) 1725 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.63 (dd, 1H, J = 5.7 Hz, J = - 3 Hz); 1.11 (d, 3H, J = 5.7 Hz); 1.70-1.80 (m, 2H); 2.42 (s, 3H), 2.52 (s, 3H), 3.64 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.0, 14.9, 15.0, 24.6, 24.8, 47.2, 52.2, 169.7, 172.8. Anal. Calcd. for $C_{14}H_{17}NO_2S_2$: C, 46.32; H, 6.48; N, 6.00; S, 27.48. Found C, 46.51 H, 6.53; N, 5.87; S, 27.23.

General procedure for unsubstituted derivatives hydrolysis

A typical experiment was carried out as follows: To a solution of compound **3a** or **3b** (1 mmol) in THF was added 6N HCl (5 mL). The mixture was stirred at room temperature for 6 h. The solution was extracted with ether and the aqueous layer was evaporated *in vacuo*. To the crystalline residue was added anhydrous ethanol (10 mL) and a large excess of propylene oxide (3 mL) and the mixture was refluxed for 20 min. After removal of the ethanol, the white residue was dissolved in distilled water (2 mL) and eluted through a C_{18} reverse-

phase Sep-pak cartridge which, after removal of water, gave 1-aminocyclopropanecarboxylic acid in nearly quantitative yield.

1-Aminocyclopropanecarboxylic acid 7

M.p. 229 ° C dec (Lit.,[6c] m.p. 229-231 ° C dec); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 0.78 (dd, 2H, J = 7.5 Hz, J = - 4.5 Hz); 1.00 (dd, 2H, J = 7.5 Hz, J = - 4.5 Hz). ^{13}C-NMR (D_2O/DMSO-d_6) δ 12.7, 36.4, 176.1.

General procedure for 2-substituted derivatives hydrolysis

A typical experiment was carried out as follows: To a solution of either compound **5** or **6** (1 mmol) in glacial acetic acid (10 mL) was added 6N HCl (10 mL) and the mixture was refluxed for 24 h. The solution was extracted with ether and the aqueous layer was evaporated *in vacuo*. To the crystalline residue was added anhydrous ethanol (10 mL) and a large excess of propylene oxide (3 mL) and the mixture was refluxed for 20 min. After removal of the ethanol, the white residue was dissolved in distilled water (2 mL) and eluted through a C_{18} reverse-phase Sep-pak cartridge which, after removal of water, gave 2-substituted 1-aminocyclopropanecarboxylic acids in nearly quantitative yield.

***Cis*-1-Amino-2-methylcyclopropanecarboxylic acid *cis*-8**

M.p. 210 ° C dec. (Lit.,[15] m.p. 213-214 ° C dec.); ^{1}H NMR (D_2O, 300 MHz) δ 0.77 (dd, 1H, J = 7.2 Hz, J = - 6.3); 1.08 (d, 3H, J = 6.6 Hz); 1.32 (dd, 1H, J = 9.6 Hz, J = - 6.3 Hz); 1.48-1.58 (m, 1H). ^{13}C-NMR (D_2O/CD_3COCD_3) δ 11.5, 18.1, 18.9, 39.7, 175.8.

***Cis*-1-Amino-2-phenylcyclopropanecarboxylic acid *cis*-9**

M.p. 154 ° C dec. (Lit.,[6e] m.p. 156-157 ° C dec.);^{1}H NMR (D_2O, 300 MHz) δ 1.60 (dd, 1H, J = 7.8 Hz, J = - 6.9); 1.72 (dd, 1H, J = 9.6 Hz, J = - 6.9); 3.28 (dd, 1H, J = 9.6 Hz, J = 7.8 Hz); 7.20-7.40 (m, 5H). ^{13}C-NMR (D_2O) δ 15.5, 28.2, 40.3, 128.1, 129.0, 129.5, 132.7, 172.4.

***Trans*-1-Amino-2-phenylcyclopropanecarboxylic acid *trans*-9**

M.p. 229 ° C dec. , m. p. ***trans*-9.HCl** 205 ° C (Lit.,[6h] m.p. 208-209 ° C); ^{1}H NMR (D_2O, 300 MHz) δ 1.53 (dd, 1H, J = 10.5 Hz, J = - 7.0); 1.79 (dd, 1H, J = 8.7 Hz, J = - 7.0); 2.75 (dd, 1H, J = 10.5 Hz, J = 8.7 Hz); 7.05-7.40 (m, 5H). ^{13}C-NMR (D_2O) δ 15.2, 28.9, 41.3, 127.0, 128.2, 128.8, 1335.1, 172.1.

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