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A Convenient Synthesis of Methyl (Z)-1-Carbamoyl-2-ethenylcyclopropanecarboxylate and (Z)-1-Carbamoyl-2-ethenylcyclopropanecarboxylic Acid

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SYNTHETIC COMMUNICATIONS, 24(17), 2477-2483 (1994)

A CONVENIENT SYNTHESIS OF METHYL (*Z*)-1-CARBAMOYL-2-ETHENYLCYCLOPROPANECARBOXYLATE AND (*Z*)-1-CARBAMOYL-2-ETHENYLCYCLOPROPANECARBOXYLIC ACID

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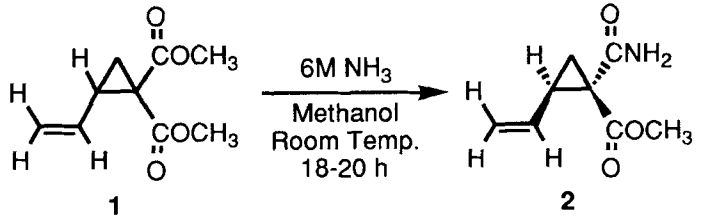
Abstract: *A simple method for the preparation of the title compounds via the reaction of dimethyl 2-ethenylcyclopropane-1,1-dicarboxylate with 6M ammonia in methanol is described.*

Highly stereoselective reactions are important in organic chemistry for the selective preparation of molecules of defined stereochemistry. We report herein a highly stereoselective reaction of dimethyl 2-ethenylcyclopropane-1,1-dicarboxylate (**1**)[2] with ammonia to give methyl (*Z*)-1-carbamoyl-2-ethenylcyclopropanecarboxylate (**2**).

Stirring a solution of **1** in 6M ammonia in methanol for 18 to 20 hours at room temperature afforded a 62-70% yield of **2** (eq 1). The other product of this reaction, 2-ethenylcyclopropane-1,1-dicarboxamide (**3**), is easily separated from



1 **2** (1)

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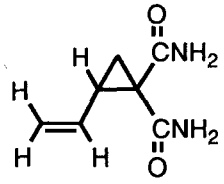
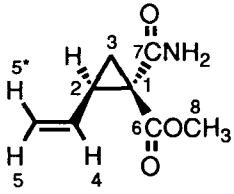
2 by dissolving the crude material in methylene chloride and filtering away **3**, which is insoluble.



3

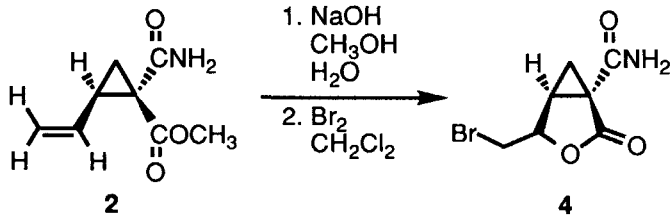
The structure of **2** was confirmed by ^{1}H and ^{13}C NMR spectrometry, and the spectral data are summarized in **Table 1.** The structure of **2** was further confirmed by chemical derivitization. Treatment of **2** with one equivalent of sodium hydroxide in aqueous methanol followed by one equivalent of bromine in methylene chloride afforded the bromolactone **4** which was isolated by concentrating the organic phase of the reaction (eq 2). Only a *cis* relationship

Table 1. NMR Spectral Parameters (DMSO-d6) for Methyl (*Z*)-1-Carbamoyl-2-ethenylcyclopropanecarboxylate (**2**).



Position	^{13}C (δ ppm)	^{1}H (δ ppm)	$\lvert {}^{n}J_{HH} \rvert$ (Hz)
1	35.8	----	
2	31.5	2.41	$^{3}J_{2,3} = 9.0$; $^{3}J_{2,3'} = 7.4$; $^{3}J_{2,4} = 9.0$
3,3'[a]	19.6	1.49, 1.55	$^{2}J_{3,3'} = 4.3$
4	133.9	5.43	$^{3}J_{4,5} = 10.1$; $^{3}J_{4,5*} = 17.1$
5,5*	118.5	5.08, 5.28	$^{2}J_{5,5*} = 2.0$
6	169.3[b]	----	
7	168.7[b]	----	
8	52.2	3.63	
NH_2	----	7.30, 7.53	

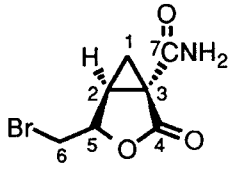
[a]Denotes non-equivalent methylene protons (the prime is assigned to the downfield proton). [b]These assignments may be reversed.



2 4 (2)

between the ethenyl and the carboxylate groups could give rise to the formation of **4**. The structure of **4** was confirmed by NMR spectrometry and the spectral data are summarized in **Table 2.**

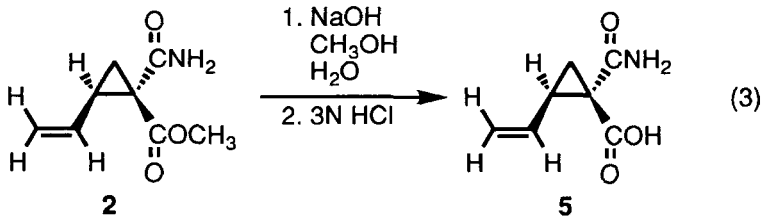
Table 2. NMR Spectral Parameters (CD_2Cl_2) for (1α,4α,5α)-4-(Bromomethyl)-2-oxo-3-oxabicyclo[3.1.0]hexane (**4**).



Position	^{13}C (δ ppm)	^{1}H (δ ppm)	$\lvert {}^{n}J_{HH} \rvert$ (Hz)
1,1'[a]	21.6	2.00, 2.73	$^{2}J_{1,1'} = 8.0$; $^{3}J_{1,2} = 5.3$
2	30.9	1.42	$^{3}J_{1,2} = 4.6$; $^{3}J_{2,5} \cong 0$
3	31.2	----	
4	174.1[b]	----	
5	77.1	4.60	$^{3}J_{5,6} = 4.4$; $^{3}J_{5,6} = 3.3$
6,6'[a]	35.2	3.63, 3.67[c]	$^{2}J_{6,6'} = 11.4$
7	167.1[b]	----	
NH_2	----	5.87, 7.50	

[a]Denotes non-equivalent methylene protons (the prime is assigned to the downfield proton). [b]Assignments may be reversed. [c]Analysis of the AB quartet formed by protons 6 and 6'.

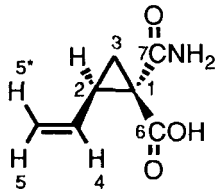
Hydrolysis of **2** with sodium hydroxide in methanol/water followed by neutralization with 3N hydrochloric acid afforded (*Z*)-1-carbamoyl-2-ethenylcylopropanecarboxylic acid (**5**) in 80% yield (eq 3). The structure of **5** was confirmed



2 5 (3)

by NMR spectrometry and the spectral data are summarized in **Table 3.**

Table 3. NMR Spectral Parameters (D_2O/CD_3OD) for (*Z*)-1-Carbamoyl-2-ethenylcyclopropanecarboxylic Acid, **5**.



Position	^{13}C (δ ppm)	^{1}H (δ ppm)	$\lvert {}^{n}J_{HH} \rvert$ (Hz)
1	36.2	-----	
2	36.0	2.51	$^{3}J_{2,3} = {}^{3}J_{2,3'} = {}^{3}J_{2,4} = 8.6$
3,3'[a]	21.8	1.82, 1.84[b]	$^{4}J_{2,5} = 0.7$; $^{4}J_{2,5*} = 0.6$
4	134.0	5.70	$^{3}J_{3,3'} = 5.0$
5,5*	120.0	5.22, 5.38	$^{3}J_{4,5} = 10.1$; $^{3}J_{4,5*} = 17.1$
6	174.4[c]	----	$^{2}J_{5,5*} = 0.6$
7	173.4[c]	----	

[a]Denotes non-equivalent methylene protons (the prime is assigned to the downfield proton). [b]Analysis of the AB quartet formed by protons 3 and 3'. [c]Assignments may be reversed.

Experimental Section

General. All melting points and boiling points are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded with a Bruker ACE 300 spectrometer. The HPLC analyses are reported as area percents and were performed using the following conditions:

Pump	Hitachi; L-420 UV-VIS Detector
Mobile Phase	Isocratic; 4% acetonitrile/96% 0.01 M $NH_4H_2PO_4$ in nanopure water
Flowrate	1.5 mL/min.
Column	Alltech, Adsorbosphere SCX 5μm, #228001
Length	25cm
Diameter	4.6mm
Packing Diameter	5μm
Auto sampler/Valve	AS-2000 Hitachi
Injection Volume	20μL
Detector	ABI, 759 A, SN 9202671
Wavelength	205nm
AU	0.1 V/AU
Filter	O.1 sec.
Integrator	Hitachi D-2500 Chromo-Integrator

Methyl (*Z*)-1-Carbamoyl-2-ethenylcyclopropanecarboxylate (2). A 2-L, Morton flask with an air-driven, mechanical stirrer and nitrogen purge was charged with 1040 mL of HPLC grade methanol and 111.8 g (6.11 moles) of ammonia gas was dissolved. To the resulting solution, 40.0 g (0.217 mol) of dimethyl 2-ethenylcyclopropane-1,1-dicarboxylate (1) was added. Samples were taken for HPLC analysis at 18, 19, and 20 hours during the reaction. A decrease in **2** between 19 and 20 hours was detected. The reaction was stopped and worked up after the 20 hour analysis. The reaction mixture was concentrated on a rotary evaporator. The residue was stirred with 150 mL of diethyl ether for ten min. The solid which separated was collected on a Buchner funnel while being washed with 100 mL of diethyl ether. The chromatogram for this fine crystalline solid showed that it contained 6.23% **3** and 93.77% **2**. The filter cake was added to 350 mL of methylene chloride. After stirring for 10 min., a solid (0.93 g) was collected by filtration. HPLC analysis showed 94.53% **3** and 4.0% of **2** present. The mother liquor was concentrated on a rotary evaporator and 22.82 g (62.2% yield) of **2** was collected. HPLC analysis showed 98.19% **2** and 1.18% **3**. A sample of **2** was further purified by preparative HPLC for analysis , mp 98-100 ^{o}C.

Analysis. Calc'd for $C_8H_{11}NO_3$: C, 56.79; H, 6.60; N, 8.32. Found: C, 56.74; H, 6.62; N, 8.21.

(1α,4α,5α)-4-(Bromomethyl)-2-oxo-3-oxabicyclo[3.1.0]hexane (4). A solution of 1.015 g (6 mmol) of 2 in 10 mL of methanol was treated at room

temperarure with 2 mL of aqueous sodium hydroxide (0.125 g/mL = 0.250 g; 6 mmol). The mixture was heated at reflux for 2 h, cooled, and concentrated with a rotary evaporator. The residue was dissolved in 10 mL of water and concentrated to approximately one-half the volume to remove any residual methanol. The solution was then diluted to 10 mL with water. After washing once with methylene chloride, the solution was cooled in an ice bath and treated in 5 to 6 portions with a solution of 0.984 g (6.2 mmol) of bromine in 10 mL of methylene chloride. The layers were separated and the aqueous layer extracted with three 5-mL portions of methylene chloride. The combined organic layers were washed with 4 mL of 1M sodium bisulfite solution and then with 5 mL of saturated sodium bicarbonate solution. After drying the organic layer over magnesium sulfate, it was concentrated with a rotary evaporator and the residue (549 mg; 39% yield) was treated with 1 mL of isopropyl acetate. The solution was warmed and then stored over night under refrigeration to give an analytical sample of **4** as a fine, white crystalline solid.

Analysis. Calculated for $C_7H_8BrNO_3$: C, 35.92; H, 3.45; N, 5.98. Found: C, 35.50; H, 3.34; N, 5.78.

(*Z*)-1-Carbamoyl-2-ethenylcyclopropanecarboxylic Acid (5). A 500-mL, 3-neck, round-bottom flask equipped with a condenser, a nitrogen purge, a heating mantle, and a West 3100 Timer/Temperature control apparatus was charged with 5.7g (0.143 mol) of sodium hydroxide pellets dissolved in 45.6 mL (2.53 mol) of deionized water. To this solution, 228 mL (7.12 mol) of methanol and 22.82 g (0.135 mol) of **2** were added. The reaction mixture was refluxed for 2 h, cooled, and concentrated on a rotary evaporator. After purging with nitrogen gas overnight, the residue was dissolved in 114 mL (6.33 mol) of water and then acidified with approximately 45 mL of 5N hydrochloric acid to a pH of <2. The resulting white solid was collected on a Buchner funnel, washed with cold deionized water, and air dried to give 16.84 g (80.5% yield) of **5** as a white solid. This material was further purified by dissolving it in aqueous sodium bicarbonate solution, extracting the solution with methylene chloride, and neutralization with 3N hydrochloric acid to give, after drying *in vacuo* at 60 °C, 13.84 g of 5 as a white solid, mp 160-161 °C (dec).

Analysis. Calc'd for $C_7H_9NO_3$: C, 54.19; H, 5.85; N, 9.03. Found: C, 54.14; H, 5.61; N, 8.96.

References and Notes

1. Deceased June, 1992. This paper is dedicated to his memory.

2. (a) Stewart, J.M.; Pagenkopf, G.K. *J. Org. Chem.* **1969**, *34*, 7. (b) Fayter, Jr., R.G.; White, J.F.; Harris, E.G. U.S. Patent 4 252 739, 1981. (c) Fayter, Jr., R.G. U.S. Patent 4 713 478, 1987. (d) Clark, Jr., C.E.; Fayter, Jr., R.G. U.S. Patent 4 713 479, 1987.

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