Synthesis of (*E*)- and (*Z*)-1-Amino-2-aryl(methyl)-cyclopropanecarboxylic Acids via Spirooxazolones

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We have earlier described the synthesis of (*Z*)-1-amino-2-arylcyclopropanecarboxylic acids via spirothiazolones[1]. Unfortunately, this method has up to date not proven suitable for the preparation of the stereoisomeric (*E*)-derivatives. Here we report a synthesis of both (*E*)- and (*Z*)-isomers of 2-substituted 1-aminocyclopropanecarboxylic acids.

The starting (*E*)- and (*Z*)-4-methylene-2-phenyl-5-(4*H*)-oxazolones (**1**) were prepared by known procedures[2,3]. Addition of diazomethane to these compounds was stereoselective[4,5,6] and produced acceptable yields of the corresponding spiro derivatives **2** (Table 1). However, (*Z*)-4-ethylidene-2-phenyl-5(4*H*)-oxazolone (**1g**) gave an equimolecular mixture of (*E*)- and (*Z*)-spiro derivatives (**2g**) and a third compound **6**; these products were separated by column chromatography.

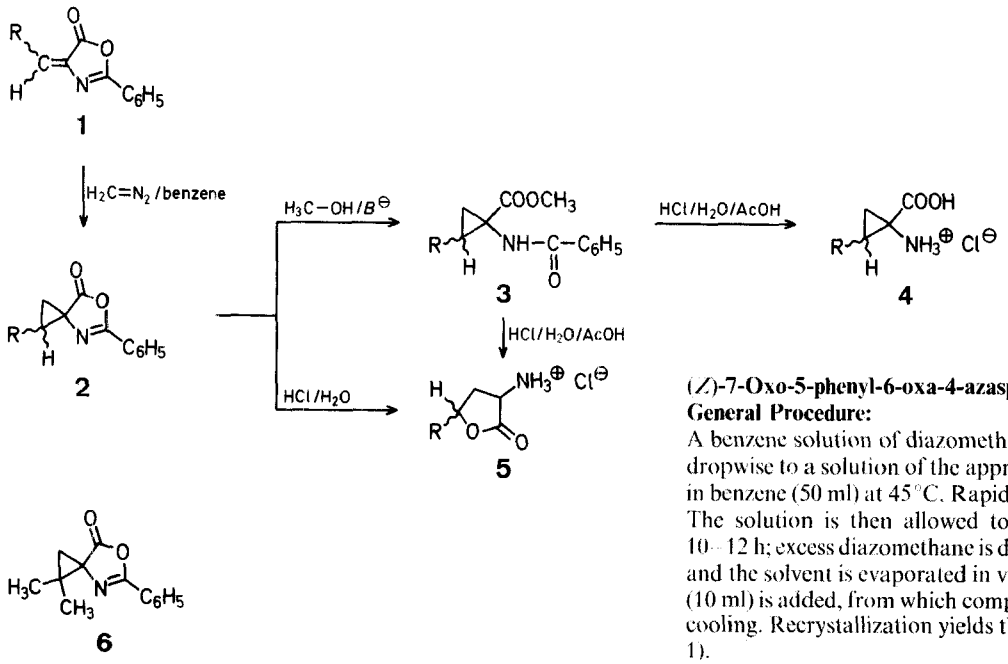
The attempted direct basic hydrolysis **2** → **4** led only to the corresponding 1-benzoylamino-2-aryl(methyl)-cyclopropanecarboxylic acids which resisted further basic treatments[4], while acidic hydrolysis caused cleavage of the cyclopropane ring, giving lactones **5**[4].

Spiro derivatives **2** were readily converted into the corresponding methyl esters **3** in high yields by treatment with absolute methanol containing catalytic amounts of sodium methoxide (Table 2). Hydrolysis of esters **3** with hydrochloric acid/acetic acid furnished the corresponding aminoacid hydrochlorides **4**. (*Z*)-Esters required refluxing times of 9–24 hours, and in most cases the resultant products (*Z*)-**4** contained varying amounts of the undesired lactones **5**, which lowered the yields. Several recrystallizations were necessary in order to obtain the pure aminoacid hydrochlorides. However, (*E*)-esters [and also aliphatic (*Z*)-**3g**] were hydrolyzed in 2–3 hours, producing very good yields of the corresponding hydrochlorides **4**.

The configuration of all compounds **2**, **3**, and **4** was established by ^{1}H-N.M.R. spectrometry. For spiro compounds **2**, we have deduced[7] that protons which are *syn* with respect to the C=N group give a signal at lower field than that of the *anti* protons. Cleavage of the oxazolone ring leads to an upfield shift of the signals of the *syn* protons (by 0.5–0.7 ppm) so that the situation is reversed (Tables 1 and 2). In the cyclopropanecarboxylic esters **3** having an aromatic substituent R, the signal of the methoxy group shows an upfield shift when the ester group is *syn* to the substituent R, probably due to the anisotropy of the aromatic ring.

Melting points were determined on a Kofler Thermopan Reichert apparatus and are uncorrected: ^{1}H-N.M.R. spectra were recorded on a Brucker WP-80 spectrometer. Analyses of the spectral data were performed with a PANIC program.

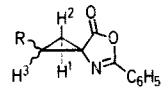
Compounds **1** are prepared as described previously[2].



(*Z*)-7-Oxo-5-phenyl-6-oxa-4-azaspiro[2.4]hept-4-enes [(*Z*)-2]; General Procedure:

A benzene solution of diazomethane (~ 50 mmol; 100 ml) is added dropwise to a solution of the appropiate (*Z*)-oxazolone **1** (20 mmol) in benzene (50 ml) at 45 °C. Rapid evolution of nitrogen takes place. The solution is then allowed to stand at room temperature for 10–12 h; excess diazomethane is destroyed with a few drops of acetic and the solvent is evaporated in vacuo to give a yellow syrup. Ether (10 ml) is added, from which compounds (*Z*)-**2** usually crystallize on cooling. Recrystallization yields the pure spiro derivative (see Table 1).

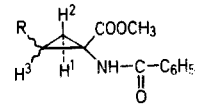
Table 1. Spiro Derivatives 2 prepared



Product	R	Yield[a] [%]	m.p. [°C][b]	Molecular Formula[c] or Lit. m.p. [°C]	^{1}H-N.M.R. ($CDCl_3$/TMS_{int}), significant parameters					
					δ [ppm]			J [Hz]		
					H^1	H^2	H^3	$J_{1,2}$	$J_{1,3}$	$J_{2,3}$
(*E*)-**2a**	C_6H_5	50	112°	112–113°[5]	2.38	2.36	3.52	−5.5	9.6	9.2
(*Z*)-**2a**	C_6H_5	45	141–142°	143–145°[5]	2.33	2.24	3.20	−5.3	8.7	9.7
(*E*)-**2b**	4-H_3C—C_6H_4	40	138–139°	$C_{18}H_{15}NO_2$ (277.3)	2.32	2.31	3.44	−5.4	9.8	8.6
(*Z*)-**2b**	4-H_3C—C_6H_4	60	147–148°	$C_{18}H_{15}NO_2$ (277.3)	2.32	2.23	3.17	−5.3	8.7	9.7
(*E*)-**2c**	4-H_3CO—C_6H_4	50	139–140°	$C_{18}H_{15}NO_3$ (293.3)	2.36	2.32	3.48	−5.5	9.6	9.1
(*Z*)-**2c**	4-H_3CO—C_6H_4	55	123–124°	$C_{18}H_{15}NO_3$ (293.3)	2.30	2.23	3.17	−5.3	8.7	9.8
(*E*)-**2d**	3-H_3CO—C_6H_4	30	78–80°	$C_{18}H_{15}NO_3$ (293.3)	2.36	2.34	3.49	−5.5	9.4	9.3
(*E*)-**2e**	4-Cl—C_6H_4	50	110–111°	$C_{17}H_{12}ClNO_2$ (297.7)	2.37	2.28	3.42	−5.5	9.8	8.6
(*Z*)-**2e**	4-Cl—C_6H_4	50	139–140°	$C_{17}H_{12}ClNO_2$ (297.7)	2.28	2.25	3.15	−5.5	8.5	9.8
(*E*)-**2f**	2-Cl—C_6H_4	50	165–166°	$C_{17}H_{12}ClNO_2$ (297.7)	2.42	2.28	3.47	−5.6	9.3	9.1
(*E*)-**2g**	CH_3	25	49–50°	$C_{12}H_{11}NO_2$ (201.2)	2.08	1.62	2.30	−4.9	9.2	8.6
(*Z*)-**2g**	CH_3	25	59–60°	$C_{12}H_{11}NO_2$ (201.2)	1.68	1.93	2.11	−4.7	8.3	9.3

[a] Yield of isolated product; not optimized.
[b] All products were recrystallized from ethyl acetate, except for (*E*)-**2g** and (*Z*)-**2g** which were recrystallized from aqueous methanol.
[c] The microanalyses were in satisfactory agreement with the calculated values: C ±0.25, H ±0.19, N ±0.21.

Table 2. Methyl Cyclopropanecarboxylates **(3)** prepared



Product	R	Yield[a] [%]	m.p. [°C][b]	Molecular Formula[c]	^{1}H-N.M.R. ($CDCl_3$/TMS_{int}), significant parameters						
					δ [ppm]				J [Hz]		
					H^1	H^2	H^3	OCH_3	$J_{1,2}$	$J_{1,3}$	$J_{2,3}$
(*E*)-**3a**	C_6H_5	90	195–196°	$C_{18}H_{17}NO_3$ (295.3)	1.71	2.31	2.96	3.34	−5.6	9.6	8.6
(*Z*)-**3a**	C_6H_5	90	164–165°	$C_{18}H_{17}NO_3$ (295.3)	1.86	2.29	3.05	3.70	−6.0	8.0	9.5
(*E*)-**3b**	4-H_3C—C_6H_4	90	219–220°	$C_{19}H_{19}NO_3$ (309.4)	1.70	2.30	2.91	3.34	−5.6	9.7	8.5
(*Z*)-**3b**	4-H_3C—C_6H_4	90	151–152°	$C_{19}H_{19}NO_3$ (309.4)	1.80	2.30	3.00	3.72	−5.9	8.0	9.6
(*E*)-**3c**	4-H_3CO—C_6H_4	96	188–189°	$C_{19}H_{19}NO_4$ (325.4)	1.66	2.26	2.90	3.34	−5.6	9.7	8.5
(*Z*)-**3c**	4-H_3CO—C_6H_4	95	174–175°	$C_{19}H_{19}NO_4$ (325.4)	1.78	2.29	2.98	3.71	−5.9	7.9	9.6
(*E*)-**3d**	3-H_3CO—C_6H_4	95	189–190°	$C_{19}H_{19}NO_4$ (325.4)	1.71	2.30	2.94	3.36	−5.5	9.8	8.5
(*E*)-**3e**	4-Cl—C_6H_4	80	199–200°	$C_{18}H_{16}ClNO_3$ (329.8)	1.70	2.23	2.93	3.37	−5.6	9.7	8.6
(*Z*)-**3e**	4-Cl—C_6H_4	85	165–166°	$C_{18}H_{16}ClNO_3$ (329.8)	1.82	2.24	3.03	3.70	−6.0	8.0	9.5
(*E*)-**3f**	2-Cl—C_6H_4	90	221–222°	$C_{18}H_{16}ClNO_3$ (329.8)	1.97	2.47	2.83	3.39	−6.0	9.7	8.5
(*E*)-**3g**	CH_3	85	154–155°	$C_{13}H_{15}NO_3$ (233.3)	~1.4	~1.6	~1.6[d]	3.75		[d]	
(*Z*)-**3g**	CH_3	85	158–159°	$C_{13}H_{15}NO_3$ (233.3)	0.96	1.81	1.93	3.71	−5.0	7.6	9.4

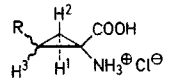
[a] Yield of isolated product; not optimized.
[b] All products were recrystallized from methanol.
[c] The microanalyses were in satisfactory agreement with the calculated values: C ±0.31, H ±0.24, N ±0.17.
[d] Compound (*E*)-**3g** could not be throughly analyzed.

The reaction of compound (*Z*)-**1g** gives a mixture of three spiro derivatives, namely (*Z*)-**2g**, (*E*)-**2g**, and a third compound which was characterized as 1,1-dimethyl-7-oxo-5-phenyl-6-oxa-4-azaspiro-[2.4]hept-4-ene **(6)**. Isolation of the individual compounds may be accomplished by column chromatography on silica gel using 1/7 benzene/hexane as eluent.

(*E*)-7-Oxo-5-phenyl-6-oxa-4-azaspiro[2.4]hept-4-enes [(*E*)-2]; General Procedure:

The (*E*)-oxazolone **1** (20 mmol) is added portionwise to an ice-cooled ethereal diazomethane solution (~ 50 mmol; 100 ml). The resultant mixture is stirred in the cold for 10 h, excess diazomethane is then destroyed with a few drops of acetic acid, and the solution is

Table 3. 1-Aminocyclopropanecarboxylic Acid Hydrochlorides (**4**) prepared



Product	R	Yield[a] [%]	m.p. [°C][b]	Molecular Formula[c] or Lit. m.p. [°C]	^{1}H-N.M.R. (D_2O/DSS$_{int}$)[d], significant parameters					
					δ [ppm]			J [Hz]		
					H^1	H^2	H^3	$J_{1,2}$	$J_{1,3}$	$J_{2,3}$
(*E*)-**4a**	C_6H_5	85	208–209°	208°[8]	1.95	2.20	3.18	−6.9	10.3	8.5
(*Z*)-**4a**	C_6H_5	60	218–220°	218–220°[1,8]	1.95	2.09	3.34	−7.1	8.2	10.1
(*E*)-**4b**	4-H_3C—C_6H_4	80	198–199°	$C_{11}H_{14}ClNO_2$ (227.7)	1.93	2.19	3.14	−7.0	10.5	8.9
(*Z*)-**4b**	4-H_3C—C_6H_4	55	191–192°	191–192°[1]	1.91	2.05	3.23	−7.0	8.3	10.0
(*Z*)-**4c**	4-H_3CO—C_6H_4	28	198–199°	198–199°[1]	1.90	2.06	3.22	−7.0	8.4	10.0
(*E*)-**4d**	3-H_3CO—C_6H_4	76	188–190°	$C_{11}H_{14}ClNO_3$ (243.7)	1.81	2.05	3.02	−7.0	10.4	8.8
(*E*)-**4e**	4-Cl—C_6H_4	82	230–232°	$C_{10}H_{11}Cl_2NO_2$ (248.1)	1.96	2.19	3.15	−7.1	10.5	8.8
(*Z*)-**4e**	4-Cl—C_6H_4	50	190–191°	190–191°[1]	1.89	2.07	3.25	−6.8	8.3	9.6
(*E*)-**4f**	2-Cl—C_6H_4	88	229–231°	$C_{10}H_{11}Cl_2NO_2$ (248.1)	2.02	2.19	3.10	−7.0	10.3	8.7
(*E*)-**4g**	CH_3	90	207–208°	$C_5H_{10}ClNO_2$ (151.6)	1.54	1.46	1.76	−6.1	10.3	8.9
(*Z*)-**4g**	CH_3	84	225–227°	$C_5H_{10}ClNO_2$ (151.6)	1.14	1.71	1.90	−6.5	7.4	9.4

[a] Yield of isolated product; not optimized.
[b] All products were recrystallized from absolute ethanol/ether and decomposed on melting.
[c] The microanalyses were in satisfactory agreement with the calculated values: C ±0.26, H ±0.17, N ±0.27.
[d] DSS = sodium 4,4-dimethyl-4-silapentanesulfonate.

filtered. The solvent is removed in vacuo; compounds (*E*)-**2** usually crystallize at this stage. Recrystallization affords the pure products (Table 1).

Methyl 1-Benzoylamino-2-aryl(methyl)-cyclopropanecarboxylates (3); General Procedure:

A solution of the (*E*)- or (*Z*)-spiro compound **2** (10 mmol) in absolute methanol (50 ml) containing a catalytic amount (~ 5%) of sodium methoxide is stirred until the starting material has disappeared (as evidenced by T. L. C.). Compounds **3** usually crystallize on cooling of the mixture. In some cases, removal of the solvent is vacuo is necessary to obtain the esters **3**.

1-Amino-2-aryl(methyl)-cyclopropanecarboxylic Acids (4); General Procedure:

A mixture of the appropriate ester **3** (5 mmol), glacial acetic acid (20 ml), and 12 normal hydrochloric acid (20 ml) is refluxed for 2–24 h. Esters (*E*)-**3** and (*Z*)-**3g** are hydrolyzed within 3 h, esters (*Z*)-**3a–d** require 9–12 h, and ester (*Z*)-**3f** requires 20–24 h for complete hydrolysis. The solvent is then removed in vacuo and the resultant solid recrystallized from absolute ethanol/ether. From the (*Z*)-esters, a mixture of hydrochlorides **4** and lactones **5** is obtained; several recrystallizations are necessary to obtain the pure products **4**.

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