Russian Journal of General Chemistry, Vol. 72, No. 1, 2002, pp. 86–90. Translated from Zhurnal Obshchei Khimii, Vol. 72, No. 1, 2002, pp. 93–97.

Hydrolysis of Cyclopropane Derivatives of Aspartic and Adipic Acids

N. A. Anisimova, G. A. Berkova, and L. I. Deiko

Mountain Altai State University, Mountain Altai, Russia
Gertsen State Pedagogical University, St. Petersburg, Russia

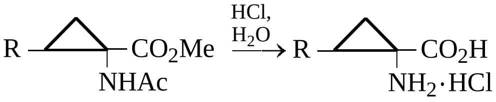
Received July 20, 1998

Abstract—Hydrolysis of substituted cyclopropane amino acids was performed. Free and partially substituted *Z* and *E* isomers of cyclopropane analogs of aspartic and adipic acids were obtained.

The intensive recent development of the chemistry of cyclopropane amino acids is associated with their wide natural occurrence and diverse physiological activity [1, 2]. The interest of synthetic chemists and pharmacologists has been attracted to neuroreceptors activated by *L*-glutamic and aspartic acids which are known as exciting amino acids. These acids strongly affect neurons of the central nervous system of mammals and neuromuscular synapses of insects [3, 4]. For studies on glutamate receptors of interest are rigid structural analogs of exciting amino acids, containing a three-carbon ring [5, 6]. In this connection the search for effective exciting amino acids and their antagonists among cyclopropane amino acids is a topical problem, since in this series one can reveal both new drugs and selective insecticides.

It is known that hydrolysis of precursors of cyclopropane amino acids involves some difficulties and is not infrequently accompanied by cleavage of the three-membered ring or elimination of functional groups. The yield of free cyclopropane amino acids in the hydrolysis is much affected by the number and positions of ring substituents [7].

Thus, the authors of [8, 9] could hydrolyze esters of cyclopropane *N*-(acetyl)amino acids **I** and **II** under rigid conditions (6 N HCl, boiling, 6 h) with preservation of the three-membered ring to obtain 1-aminocyclopropanecarboxylic acid hydrochloride (**III**) in an yield of 70%. Phenyl substituion in the three-membered ring reduces the yield of hydrochloride **IV** to 50% as a result of partial ring cleavage and formation of unsaturated hydrolysis products [9]. We used milder conditions of acid hydrolysis (3 N HCl, boiling, 15–20 min) for esters **I** and **II** and thus improved the yields of hydrochlorides **III** and **IV** to 90 and 70%, respectively.



I, II **III, IV**

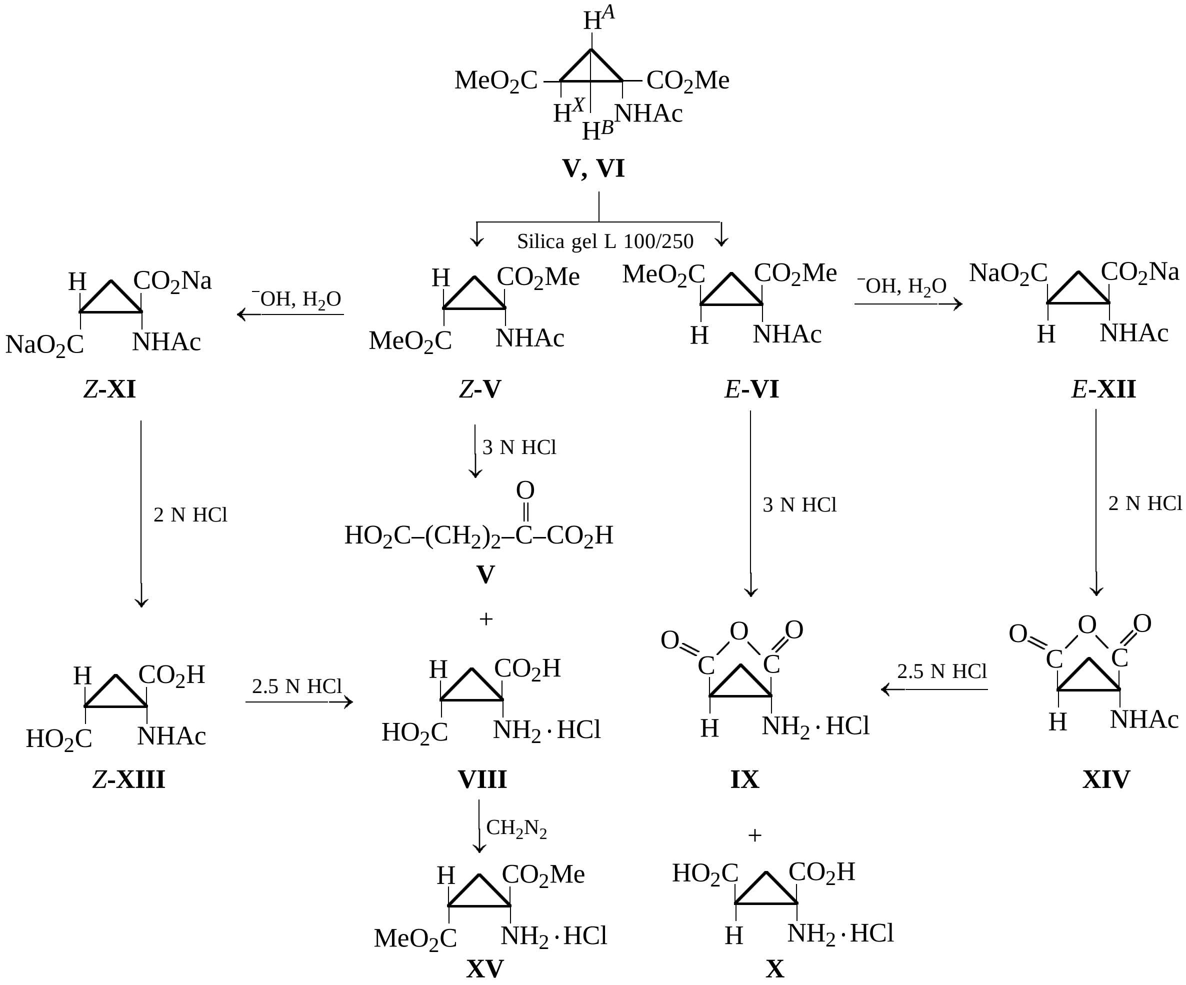
R = H (**I, III**), Ph (**II, IV**).

Cyclopropanedicarboxylic amino acids, cyclic analogs of glutamic and aspartic acids, are of particular interest for assessment of the effect of the conformation of exciting amino acids on receptor activity. In [6, 10, 11], only cyclic analogs of glutamic acid could be obtained. Attempted preparation of the cyclopropane analog of aspartic acid failed [7]. Using stereohomogeneous isomers of dimethyl ester of 1-(acetylamino)cyclopropane-1,2-dicarboxylic acid (*Z*-**V** and *E*-**VI**), as well as milder hydrolysis conditions allowed us to preserve the three-membered ring and to isolate for the first time and identify its hydrochlorides. It was shown that hydrochloric acid hydrolysis of substituted isomers **V** and **VI** is not unidirectional. Thus, hydrolysis of ester *Z*-**V** gives rise to 2-oxoglutaric acid (**VII**) (yield 60%) and hydrochloride *Z*-**VIII** (yield 8%). Isomer *E*-**VI** under the same conditions gives primarily a more stable anhydride hydrochloride **IX** and hydrochloride *E*-**X** in yields of 60 and 6%, respectively.

Consecutive elimination of the *C*- and *N*-protective groups allowed the yield of hydrochloride *Z*-**VIII** to be raised to 15%. Studies on the behavior of esters **V** and **VI** under base hydrolysis conditions showed that treatment of the latter with an equimolar amount of 1 N aqueous sodium hydroxide results in formation of *N*-substituted disodium salts *Z*-**XI** and *E*-**XII**. Acidification of these salts to pH 5–6 gives rise to *N*-substituted 1-aminocyclopropane-1,2-dicarboxylic acid *Z*-

XIII and its anhydride **XIV**. On further acidification to pH 2 and heating, an acyclic reaction product **VII** and hydrochloride *Z*-**VIII** are formed; anhydride hydrochloride **IX** is a single hydrolysis product of isomer *E*-**VI** under similar conditions.

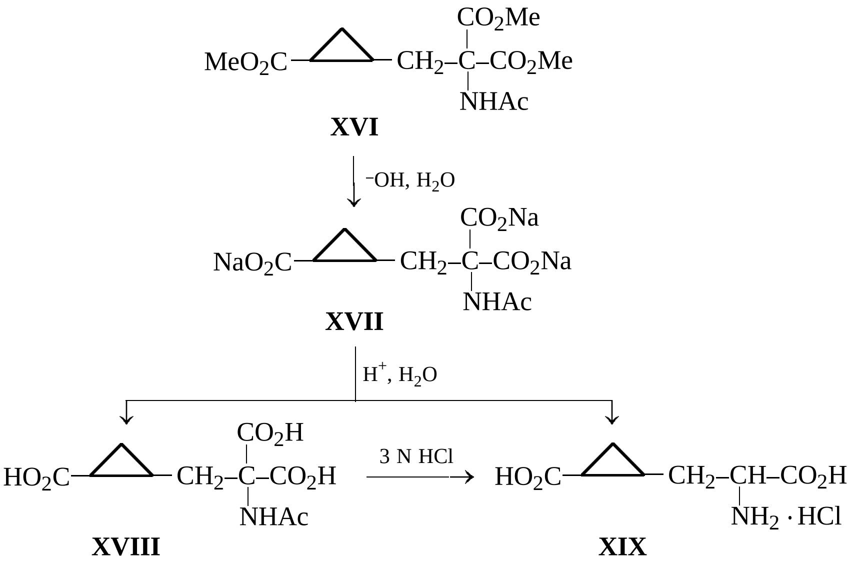
Hydrochloride *Z*-**XV** was obtained by alkylation of hydrochloride *Z*-**VIII** with diazomethane.



Hydrolysis of 2-(acetylamino)-2-(methoxycarbonyl)-3-(2-methoxycarbonylcyclopropyl)propanoic acid (**XVI**) involves no three-membered ring cleavage.

Base hydrolysis of ester **XVI** occurs at room temperature and yields trisodium salt **XVII** whose acidification in the cold makes possible preservation of the three carboxy groups and isolation of 2-(acetylamino)-2-carboxy-3-(2-carboxycyclopropyl)propanoic acid (**XVIII**) (yield 90%). Subsequent acidification of the latter with 3 N HCl (boiling, 30 min) gives 2-amino-3-(2-carboxycyclopropyl)propanoic acid hydrochloride (**XIX**) (yield 90%). It should be noted that acidification of trisodium salt **XVII** under heating (boiling, 1 h), as would be expected, results in removal of one of the COOH group and decreases the yield of hydrochloride **XIX** to 60%.

The structures of the first prepared compounds, amino acids **VIII**, **X**, and **XIX**, their derivatives **IX**, **XIII**–**XV**, and **XVIII**, and salts **XI**, **XII**, and **XVII**, were established from a comparison with specially prepared model compounds **III** and **IV** [8, 9, 12]. The mutual arrangement of substituents in the cyclopropane analogs of aspartic acid was revealed by ^1H NMR spectroscopy (Table 1). The ^1H NMR spectra of cyclopropanes characteristically display upfield ring proton signals. The 2-COOH substituent in the ring affects the chemical shifts of the H^A and H^B ring protons in different isomers. In the *Z* isomer it shifts downfield the H^A signal and in the *E* isomer, the H^B signal. In the three-spin *ABX* system of ring protons, the geminal J_{AB} constant has the lowest value, which is characteristic of three-membered rings [13, 14]. The



greater of the two vicinal constants relates to *cis* orientation of the protons (J_{AB} in the *Z* isomer and J_{BX} in the *E* isomer).

Experimental evidence for the stereochemical assessment of the molecules is provided by the fact that anhydrides are formed exclusively from the *E* isomers. The spectral characteristics of ring protons of anhydrides **IX** and **XIV** are fully consistent with the fixed *E* configuration of the molecule.

Salt **XVII** and hydrochloride **XIX** presumably have *E* arrangement of substituents with respect to the ring plane. However, a more exact configurational assessment could not be performed because of the overlap of signals of vicinal ring protons and the methylene group of the substituent (Table 2).

Thus, we showed that hydrolysis of amino acids of the cyclopropane series under mild conditions with consecutive elimination of the *C*- and *N*-protective

Table 1. Yields, ^{1}H NMR spectra, and elemental analyses of compounds **VIII–XV**

Comp. no.	Yield, %	^{1}H NMR spectrum (D_2O), δ, ppm; *J*, Hz								Found, %			Formula	Calculated, %		
		H^A	H^B	H^X	NH	NHAc	J_{AB}	J_{AX}	J_{BX}	C	H	N		C	H	N
Z-**VIII**	15	2.00 m (1H)	2.06 m (1H)	3.09 m (1H)	8.00 s (2H)		4.5	9.5	8.0	33.05 33.06	4.41 4.50	7.60 7.69	$C_5H_8ClNO_4$	33.06	4.41	7.71
IX	60	2.01 m (1H)	1.83 m (1H)	2.98 m (1H)	7.50 s (2H)		4.5	7.5	9.5	36.90 36.95	3.69 3.72	8.36 8.42	$C_5H_6ClNO_3$	36.70	3.67	8.56
X	6	2.18 m (1H)	2.00 m (1H)	2.32 m (1H)	8.20 s (2H)		4.5	7.5	9.5	33.05 33.08	4.45 4.50	7.63 7.70	$C_5H_8ClNO_4$	33.06	4.41	7.71
Z-XI	70	1.85 m (1H)	1.96 m (1H)	2.66 m (1H)	8.00 s (1H)	2.00 s (3H)	4.5	9.5	7.0	36.50 36.52	2.85 2.95	5.89 5.99	$C_7H_7NNa_2O_5$	36.36	3.03	6.06
E-**XII**	70	2.17 m (1H)	1.86 m (1H)	2.45 m (1H)	8.10 s (1H)	1.99 s (3H)	5.0	7.5	10.0	36.42 36.52	2.90 3.00	5.90 6.04	$C_7H_7NNa_2O_5$	36.36	3.03	6.06
Z-**XIII**[a]	60	1.38 m (1H)	1.46 m (1H)	2.43 m (1H)	8.80 s (1H)	2.00 s (3H)	4.5	8.5	7.0	44.90 44.92	4.81 4.82	7.50 7.51	$C_7H_9NO_5$	44.92	4.81	7.49
XIV[a]	60	1.99 m (1H)	1.87 m (1H)	2.96 m (1H)	7.90 s (1H)	2.00 s (3H)	4.5	7.0	8.0	50.00 50.11	4.15 4.20	7.99 8.00	$C_7H_7NO_4$	49.70	4.14	8.28
Z-**XV**[b]	90	2.00 m (1H)	2.32 m (1H)	2.61 m (1H)	7.36 s (2H)	3.63 s (6H)[c]	4.5	9.5	7.5	39.90 40.00	5.75 5.80	6.58 6.68	$C_7H_{12}ClNO_4$	40.10	5.73	6.68

[a] The ^{1}H NMR spectrum was measured in DMSO. [b] The ^{1}H NMR spectrum was measured in $CDCl_3$. [c] $2CO_2Me$.

Table 2. Yields, melting points, ^{1}H NMR spectra, and elemental analyses of compounds **XVII–XIX**

Comp. no.	Yield, %	mp, °C	^{1}H NMR spectrum (D_2O), δ, ppm			Found, %			Formula	Calculated, %		
			CH_2 (ring)	CH (ring)	substituent	C	H	N		C	H	N
XVII	90	Oil	1.46 m, 1.97 m (2H)	2.13 m, 3.05 m (1H)	1.71 s (3H, NHAc), 3.35 m (2H, CH_2)	36.80 36.90	3.00 3.1	4.08 4.10	$C_{10}H_{10}NNa_3O_7$	36.92	3.00	4.31
XVIII	90	128–130	1.44 m, 1.63 m (2H)	2.10 m, 2.55 m (1H)	2.35 s (3H, NHAc), 3.09 m (2H, CH_2)	45.99 46.10	5.01 5.02	5.39 5.40	$C_{10}H_{13}NO_7$	46.33	5.02	5.41
XIX	90	83–85	1.20 m, 1.44 m (2H)	2.00 m, 2.55 m (1H)	3.09 m (CH_2CH)	40.11 40.16	5.79 5.80	6.71 6.72	$C_7H_{12}ClNO_4$	40.10	5.73	6.68

groups allows preparation in high yields of hydrochlorides **III** and **IV** (containing one COOH group) and acid **XIX**, where one of the COOH groups and the three membered ring are intervened by a methylene unit.

A possible reason for the low yields with esters **V** and **VI** is that the two deprotected COOH groups attached directly to the ring increase strain in the system. As a result, with *Z*-**V**, the three-membered ring is cleaved, while with *E*-**VI**, a more stable anhydride **IX** is formed.

EXPERIMENTAL

The ^{1}H NMR spectra were measured on a Tesla VS-470 instrument (working frequency 80 MHz) in D_2O, DMSO, and $CDCl_3$; internal reference HMDS.

Column chromatography was performed on Silica gel L 100/250 (Chemapol); the R_f values were determined on Silufol-254 plates, eluent hexane–acetone, 3:2.

Cyclopropane amino acid derivatives **I, II, V, VI**, and **XVI** were prepared by the procedured described in [8, 9, 15–17].

1-Aminocyclopropanecarboxylic acid hydrochloride (III) and 1-amino-2-phenylcyclopropanecarboxylic acid hydrochloride (IV) were prepared by a modified procedure [8, 9, 18]. A solution of ester **I** or **II** in 30 ml of 3 N hydrochloric acid was heated under reflux for 15–20 min, after which the water was removed by distillation, and the crystals that precipitated were washed with diethyl ether. The ether extracts were evaporated. Compound **III**: yield 1.58 g (90%), mp 223–225°C (from water) (mp 229–230°C [9]). ^{1}H NMR spectrum (D_2O), δ, ppm: 1.80 m, 1.91 m (ring protons). Compound **IV**: yield 1.28 g (70%), mp 217–219°C (from water) (mp 219–220°C [9, 18]). ^{1}H NMR spectrum (D_2O), δ, ppm: 1.48 m and 1.80 m (2H, ring CH_2), 1.34 m (1H, CH), 7.76 m (5H, Ph).

Hydrochlorides VIII–X. A solution of 2 g of compound **V** or **VI** in 30 ml of 3 N hydrochloric acid was heated under reflux for 10–20 min. The reaction mixture was allowed to stand for 6 h and then neutralized with 3 N aqueous sodium hydroxide to pH 8–9. The solvent was removed by distillation, and the dry residue was washed with acetone (3 × 50 ml). The extracts were evaporated, and the oily residue was subjected to chromatography. Hydrochloride *Z*-**VIII**: yield 0.14 g (8%), eluent acetone. Compound **X**: yield 0.1 g, mp 187–190°S. Compound **IX**: yield 0.91 g, mp 160–163°C, eluent methanol.

The residue after washing with acetone was recrystallized from water to obtain 1.01 g of oxoglutaric acid **VII**.

Sodium 1-(acetylamino)cyclopropane-1,2-dicarboxylates (***Z*-XI and *E*-XII) and sodium 2-(acetylamino)-2-carboxy-3-(2-carboxycyclopropyl)propanoate (XVII).** A solution of 2 g of compound **V**, **VI**, or **XVI** in 30 ml of 1 N aqueous sodium hydroxide was allowed to stand at 22°C for 10 h. The reaction mixture was evaporated to dryness, the crystalline residue was washed witrh diethyl ether (3 × 50 ml), the ether extracts were combined, evaporated, and recrystallized from water to isolate salts *Z*-**XI**, *E*-**XII**, and **XVII**. Compound *Z*-**XI**: yield 1.5 g, mp 228–230°C (decomp.). Compound *E*-**XII**: yield 1.49 g, mp 210–212°C (decomp.). Compound **XVII**: yield 1.96 g.

1-(Acetylamino)cyclopropane-1,2-dicarboxylic

acid (*Z*-XIII) and 1-(acetylamino)cyclopropane-1,2-dicarboxylic anhydride (XIV), and 2-(acetylamino)-2-carboxy-3-(2-carboxycyclopropyl)propanoic acid (XVIII). A solution of 1.5 g of salt **XI**, **XII**, and **XVII** in 30 ml of water was acidified with 2 N hydrochloric acid to pH 5–6 and then evaporated to dryness. The residue was recrystallized. Isomer *Z*-**VIII**: yield 0.7 g, mp 113–115°C (from aqueous acetone). Anhydride **XIV**: yield 0.63 g, mp 118–120°C (from water). Compound **XVIII**: yield 1.05 g.

1-Aminocyclopropane-1,2-dicarboxylic acid hydrochloride (*Z*-VIII), 1-aminocyclopropane-1,2-dicarboxylic anhydride hydrochloride (IX), 2-amino-3-(2-carboxycyclopropyl)propanoic acid hydrochloride (XIX), and 2-oxoglutaric acid (VII). A solution of 1.29 g of compound **XIII**, **XIV**, or **XVIII** in 20 ml of 2.5 N hydrochloric acid was heated under reflux for 10–15 min (with **XVIII**, 30 min) and then neutralized with 3 N aqueous sodium hydroxide to pH 9–10. The solvent was removed, the residue was washed with acetone (5×50 ml), and the extract was evaporated. Compound **VIII**: yield 0.19 g, mp 208–210°C (from water).

The residue after washing with acetone was recrystallized from water to obtain 1.2 g (60%) of oxoglutaric acid **VII**, mp 95–97°C (mixed sample with commercial sample shows no melting point depression). Compound **IX**: yield 0.75 g, mp 161–163°C (from water). Compound **XIX**: yield 0.91 g, oil, R_f 0.65.

Dimethyl 1-aminocyclopropane-1,2-dicarboxylate hydrochloride (XV). Ethereal diazomethane, 10 ml, was added dropwise to a stirred solution of 0.5 g of hydrochloride **VIII** in 10 ml of acetone. The reaction mixture was allowed to stand for 24 h at 22°C. The solvent was removed by distillation, and the oily residue was subjected to column chromatography (eluent chloroform) to obtain 0.52 g of hydrochloride **XV** as a yellow oil, R_f 0.70, n_D^{20} 1.4650.

REFERENCES

1. Wagner, I. and Musso, H., *Angew. Chem.*, 1983, vol. 95, no. 11, p. 827.
2. Anisimova, N.A., Deiko, L.I., and Mandel'shtam, T.V., in *Sovremennye problemy organicheskoi khimii* (Modern Problems of Organic Chemistry), St. Petersburg: Sankt-Peterb. Gos. Univ., 1996, no. 13, p. 136.
3. Dambinova, S.A., *Neirony glutamata* (Neurons of Glutamate), Leningrad: Nauka, 1989.
4. Mandel'shtam, Yu.E., *Neiron i myshtsa nasekomogo* (Neuron and Insect Muscle), Leningrad: Nauka, 1983.
5. Hansen, J.J. and Krossgaard-Larsen, P., *J. Chem. Soc., Perkin Trans. 1*, 1980, no. 8, p. 1826.
6. Shimamoto, K. and Ohfune, Y., *Tetrahedron Lett.*, 1989, vol. 30, no. 29, p. 3803.
7. Stammer, C.H., *Tetrahedron*, 1990, vol. 46, no. 7, p. 2231.
8. Bregowec, J. and Jakovcic, T., *Monatsh. Chem.*, 1972, vol. 103, no. 1, p. 288.
9. Cativiela, C., Diaz De Willegas, M., and Melendez, E., *Tetrahedron*, 1986, vol. 42, no. 2, p. 583.
10. Wakamija, T., Oda, Y., Fugita, H., and Scibo, T., *Tetrahedron Lett.*, 1886, vol. 27, no. 19, p. 2143.
11. Pellicciari, R., Natalini, B., and Marinozzi, M., *Tetrahedron Lett.*, 1990, vol. 31, no. 1, p. 139.
12. Lindberg, P., Bergman, R., and Wickberg, B., *Chem. Commun.*, 1975, no. 22, p. 946.
13. Nagai, W. and Hirata, Y., *J. Org. Chem.*, 1978, vol. 43, no. 4, p. 626.
14. Kimpe, N., Sulmon, P., Brunet, P., and Lambei, F., *Tetrahedron Lett.*, 1989, vol. 30, no. 14, p. 1863.
15. Anisimova, N.A., Deiko, L.I., and Berkova, G.A., *Zh. Org. Khim.*, 1992, vol. 28, no. 1, p. 205.
16. Anisimova, N.A., Deiko, L.I., and Berkova, G.A., *Zh. Obshch. Khim.*, 1998, vol. 68, no. 7, p. 1165.
17. Anisimova, N.A., Deiko, L.I., and Berkova, G.A., *Zh. Org. Khim.*, 1998, vol. 34, no. 8, p. 1263.
18. Suzuki, M., Goach, E.E., and Stammer, C.C., *Tetrahedron Lett.*, 1983, vol. 24, no. 36, p. 3839.