Synthesis of 3-Bromo and 3-Methoxy-5-Isoxazolylglycine Derivatives. Hypothetic Precursors of Ibotenic Acid

Dario Chiarino, Mauro Napoletano and Alberto Sala*

Zambon Group Research Laboratories,
Bresso, Milan, Italy

Received February 26, 1988

A simple synthesis of 3-bromo and 3-methoxy analogues of ibotenic acid is reported starting from the corresponding 2-(3-substituted-5-isoxazolyl)-2-oxoacetic acid esters.

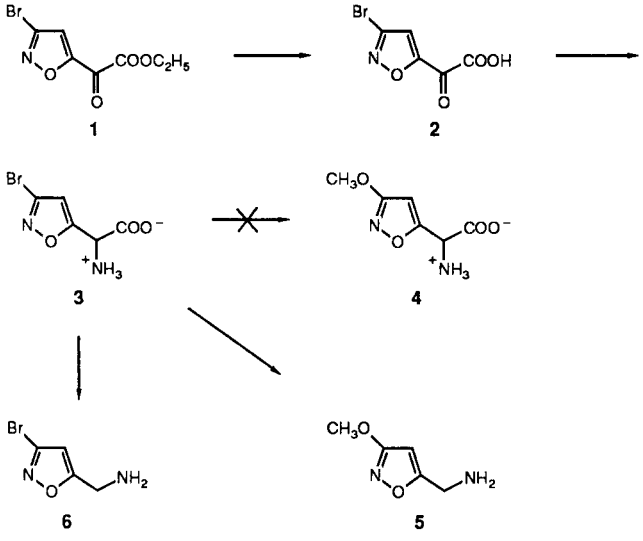
J. Heterocyclic Chem., **25**, 1283 (1988).

During the development of a program devoted to the preparation of 3-bromoisoxazoles [1], we obtained 5-aminomethyl-3-bromoisoxazole **6** which was easily transformed into muscimol **11** [2], a semirigid analogue of γ-aminobutyric acid [3]. Muscimol, 5-aminomethyl-3-isoxazolol, is a centrally active constituent of *Amanita Muscaria* and is formed in the plant material by decarboxylation of the "axon sparing" neurotoxin ibotenic acid **10** [4], which is directly synthetized by the mushroom [5].

The availability of 2-(3-substituted-5-isoxazolyl)-2-oxoacetic acid esters [6] led us to study a possible synthetic approach to the obtainement of ibotenic acid analogues. In this paper we wish to describe the preparation of two possible precursors of ibotenic acid, (*R S*)-α-amino-3-bromoisoxazol-5-ylacetic acid **3** and (*R S*)-α-amino-3-methoxyisoxazol-5-ylacetic acid **4**.

The synthetic route chosen for the preparation of 3-bromoisoxazole derivative **3** is reported in Scheme 1.

Scheme 1

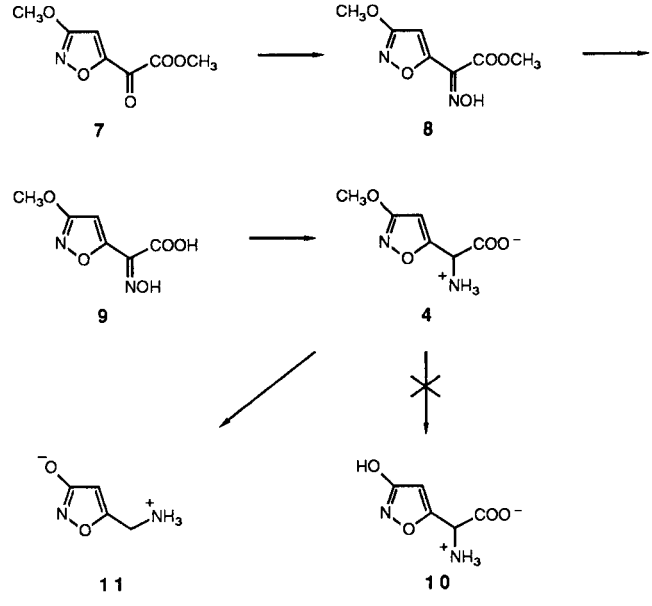


Ethyl 2-(3-bromo-5-isoxazolyl)-2-oxoacetate **1** [6] was hydrolyzed to corresponding acid **2** in 5% hydrochloric acid at 50°. Desired derivative **3** was prepared by reductive amination using concentrated ammonium hydroxide and sodium hyposulfite. Any attempt to obtain 3-methoxyisoxazole compound **4** starting from 3-bromoisoxazole derivative **3** failed. For example when intermediate **3** was refluxed in aqueous methanolic solution of potassium hydroxide, we could only isolate the decarboxylated product, 5-aminomethyl-3-methoxyisoxazole **5** [7], in poor yields.

The stability of (*R S*)-α-amino-3-bromoisoxazol-5-ylacetic acid **3** dissolved in deuterium oxide was studied by ^{1}H-nmr technique. After 24 hours at room temperature we found that aliphatic CH was completely exchanged but compound **3** was practically unmodified. Subsequently we verified that a solid sample, stored at 0-5° for few months, was transformed into decarboxylated derivative, 5-aminomethyl-3-bromoisoxazole **6** [8].

Scheme 2 illustrates the alternative synthetic approach used in order to prepare 3-methoxyisoxazole derivative **4**.

Scheme 2

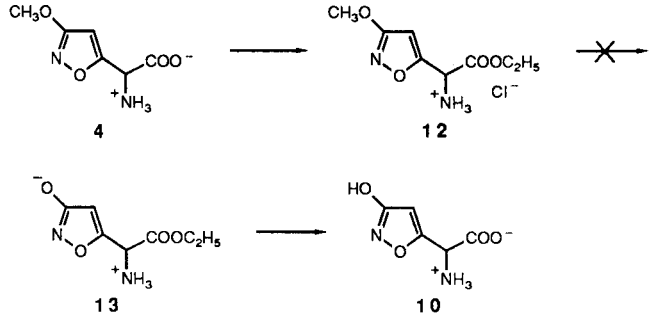


Methyl 2-(3-methoxy-5-isoxazolyl)-2-oxoacetate **7** [6] was treated with hydroxylamine hydrochloride and sodium acetate in refluxing aqueous methanol to give corresponding oxime **8** which was hydrolized in aqueous methanolic solution sodium hydroxide at 50°. Desired (*R S*)-α-amino-3-methoxyisoxazol-5-ylacetic acid **4** was prepared by reduction of intermediate **9** with aluminum amalgam at room temperature.

Compound **4** was first studied from the point of view of its stability. The ^{1}H-nmr spectrum in dimethyl sulfoxide-d_6 showed that derivative **4** was completely unmodified after 2 days at room temperature. A solid sample of (*R S*)-α-amino-3-methoxyisoxazol-5-ylacetic acid **4**, stored at 0-5° for several months, was found to be practically unchanged, confirming that its stability was greater than that observed for 3-bromo analogue **3**.

These data led us to try the demethylation reaction in order to obtain ibotenic acid **10**, but all efforts using known methods [9] were unsuccessful. In particular when 3-methoxyisoxazole derivative **4** was dissolved in a solution of hydrobromic acid in acetic acid (30% by weight) and heated at 120° for a few minutes, we could only isolate muscimol **11** [2] in poor yields. Scheme 3 reports the third alternative route studied to prepare ibotenic acid **10**.

Scheme 3



Compound **4** was transformed into stable ester hydrochloride **12**. The reaction was carried out at room temperature in a solution of hydrochloric acid in ethanol. Derivative **12** was poured into a solution of hydrobromic acid in acetic acid (30% by weight) and heated at 120° for a few minutes. At this time-point tlc study showed only the presence of unreacted starting material. The solution was then heated for several hours until compound **12** completely disappeared, but we could not isolate any interesting derivative.

Briefly we have reported a simple synthesis of two new analogues **3** and **4** of ibotenic acid **10** making feasible the preparation of 3-methoxyisoxazole derivative **4**, unsuccessfully tried by other authors [10].

Although we have not been able to transform these compounds into ibotenic acid **10**, we are convinced of the validity of our synthetic approach. We are now estimating the possibility of changing the protection of the hydroxyl group at 3 position on the isoxazole ring in order to obtain ibotenic acid **10** in mild conditions.

EXPERIMENTAL

Melting points were determined on a Buchi SMP-20 apparatus and are uncorrected. The ^{1}H-nmr spectrum of compound **3** was recorded on a Varian EM-360 L. The ^{1}H-nmr spectra of the other compounds were recorded on a Varian Gemini 200.

2-(3-Bromo-5-isoxazolyl)glyoxylic Acid (**2**).

A mixture of compound **1** (15 g, 0.06 mole) in 5% hydrochloric acid (150 ml) was stirred at 50° for 5 hours. After evaporation of the solvent, the residue was crystallized from dichloroethane to give pure **2** (11.3 g, 86%, mp 120-130°); ^{1}H-nmr (DMSO-d_6): δ (ppm) 7.72 (s, 1H).

Anal. Calcd. for $C_5H_2BrNO_4$: C, 27.30; H, 0.92; N, 6.37. Found: C, 27.42; H, 0.98; N, 6.40.

(*R S*)-α-Amino-3-bromoisoxazol-5-ylacetic Acid (**3**).

Concentrated ammonium hydroxide (10 ml, 0.15 mole) was added at room temperature to a stirred solution of compound **2** (2.2 g, 0.01 mole) in tetrahydrofuran (100 ml), methanol (50 ml) and water (15 ml). After 1 hour sodium hyposulfite (10 g, 0.06 mole) was added portionwise and the mixture was stirred at room temperature for 8 days. After evaporation of the solvents, the residue was dissolved in water and purified by chromatography on the ion-exchange resin Dowex 50 WX4 eluting with 5% ammonium hydroxide. The obtained solution was lyophilized to give pure **3** (0.85 g, 39%, mp 145-146° dec); ^{1}H-nmr (deuterium oxide): δ (ppm) 5.10 (s, 1H), 6.74 (s, 1H).

Anal. Calcd. for $C_5H_5BrN_2O_3$: C, 27.17; H, 2.28; N, 12.67. Found: C, 27.38; H, 2.33; N, 12.50.

Methyl 2-(3-Methoxy-5-isoxazolyl)-2-hydroxyiminoacetate (**8**).

A mixture of compound **7** (37 g, 0.2 mole), hydroxylamine hydrochloride (14.6 g, 0.21 mole) and sodium acetate (17.2 g, 0.21 mole) in methanol (600 ml) and water (600 ml) was refluxed for 1 hour. After evaporation of methanol, the aqueous layer was extracted with ethyl ether which was washed with water, dried and evaporated. The solid residue was crystallized from water to give pure **8** (36.8 g, 92%, mp 130-132°); ^{1}H-nmr (DMSO-d_6): δ (ppm) [11] 3.85 and 3.89 (s, 3H), 3.94 and 3.96 (s, 3H), 6.68 and 6.84 (s, 1H), 13.07 and 13.79 (s, 1H).

Anal. Calcd. for $C_7H_8N_2O_5$: C, 42.00; H, 4.03; N, 14.00. Found: C, 42.04; H, 4.03; N, 14.11.

2-(3-Methoxy-5-isoxazolyl)-2-hydroxyiminoacetic Acid (**9**).

A stirred mixture of compound **8** (35 g, 0.175 mole), sodium hydroxide (17 g, 0.425 mole) in methanol (100 ml) and water (100 ml) was heated at 50° for 1 hour. After evaporation of methanol, the aqueous layer was extracted with ethyl ether, acidified with 37% hydrochloric acid and extracted with ethyl acetate which was washed with water, dried and evaporated. The solid residue was crystallized from water to give pure **9** (31 g, 95%, mp 173-175°); ^{1}H-nmr (DMSO-d_6): δ (ppm) 3.95 (s, 3H), 6.80 (s, 1H), 13.50 (s, 1H), 13.67 (broad, 1H).

Anal. Calcd. for $C_6H_6N_2O_5$: C, 38.72; H, 3.25; N, 15.05. Found: C, 38.31; H, 3.15; N, 15.29.

(*R S*)-α-Amino-3-methoxyisoxazol-5-ylacetic Acid (**4**).

A stirred solution of mercuric chloride (82.1 g, 0.302 mole) in water (1650 ml) was treated with aluminum foil (41.4 g, 1.53 moles). After 1 hour at room temperature, aluminum amalgam was filtered, washed with ethanol and suspended in 50% aqueous methanol (810 ml). The stirred mixture was treated portionwise at room temperature with compound **9** (22 g, 0.118 mole). After stirring overnight, the mixture was filtered and the obtained solution was purified by chromatography on the ion-exchange resin Dowex 50 WX4 eluting with 5% ammonium hydroxide. The resulting solution was lyophilized to give pure **4** (8.4 g, 41%, mp 138-139° dec); ^{1}H-nmr (DMSO-d_6): δ (ppm) 3.89 (s, 3H), 4.46 (s, 1H), 6.17 (s, 1H), 8.00 (broad, 3H).

Anal. Calcd. for $C_6H_8N_2O_4$: C, 41.86; H, 4.68; N, 16.27. Found: C, 41.60; H, 4.19; N, 16.16.

Ethyl (*R S*)-α-Amino-3-methoxyisoxazol-5-ylacetate Hydrochloride (**12**).

A suspension of compound **4** (3.5 g, 0.02 mole) in ethanol (150 ml) saturated with gaseous hydrochloric acid, was stirred overnight at room temperature. The obtained solution was evaporated and the solid residue was crystallized from acetonitrile to give pure **12** (3.7 g, 77%, mp 153-155° dec); ^{1}H-nmr (DMSO-d_6): δ (ppm) 1.22 (t, 3H), 3.94 (s, 3H), 4.28

(q, 2H), 5.72 (s, 1H), 6.56 (s, 1H), 9.37 (broad, 3H).

Anal. Calcd. for $C_8H_{13}ClN_2O_4$: C, 40.60; H, 5.54; N, 11.84. Found: C, 40.50; H, 5.59; N, 11.69.

REFERENCES AND NOTES

[1] D. Chiarino, M. Napoletano and A. Sala, *J. Heterocyclic Chem.*, **24**, 43 (1987).

[2] D. Chiarino, M. Napoletano and A. Sala, *Tetrahedron Letters*, **27**, 3181 (1986).

[3] P. Krogsgaard-Larsen, *J. Med. Chem.*, **24**, 1377 (1981).

[4] R. Schwarcz, A. Foster, E. French, W. Whetsell Jr. and C. Köhler, *Life Sci.*, **35**, 19 (1984).

[5] P. Krogsgaard-Larsen, L. Brehm and K. Schaumburg, *Acta Chem. Scand.*, B, **35**, 311 (1981).

[6] A. Sala, D. Chiarino, M. Napoletano, E. Albini, A. Carenzi and D. Della Bella, *J. Antibiotics*, **40**, 1555 (1987).

[7] A. Gagneux, F. Häfliger, C. Eugster and R. Good, *Tetrahedron Letters*, 2077 (1965).

[8] R. Fusco and S. Rossi, *Rend. Ist. Lomb. Acad. Sci. Let.*, **A94**, 729 (1960); *Chem. Abstr.*, **57**, 16583d (1962).

[9] Selection of demethylation procedures: [a] G. Fleutrill and R. Mirrington, *Tetrahedron Letters*, 1327 (1970); [b] M. Bhatt and S. El-Morey, *Synthesis*, 1048 (1982); [c] D. Landini, F. Montanari and F. Rolla, *Synthesis*, 771 (1978); [d] S. Hanessian and Y. Guindon, *Tetrahedron Letters*, **21**, 2305 (1980).

[10] Y. Kishida, T. Hiraoka, J. Ide, A. Terada and N. Nakamura, *Chem. Pharm. Bull.*, **15**, 1025 (1967).

[11] Compound **8** was isolated as a mixture of *Z*:*E* forms in a ratio of 34:66 respectively.