Regioselective Synthesis of 3-Hydroxyisoxazoles and 5-Isoxazolones from β-Amino α,β-Unsaturated Esters

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The regioselective synthesis of 3-hydroxyisoxazoles and 5-isoxazolones is accomplished by the reaction of β-amino α,β-unsaturated esters with hydroxylamine hydrochloride in the presence of appropriate bases. The total yield of isoxazole derivatives is sensitively influenced on the β-substituent group of the esters.

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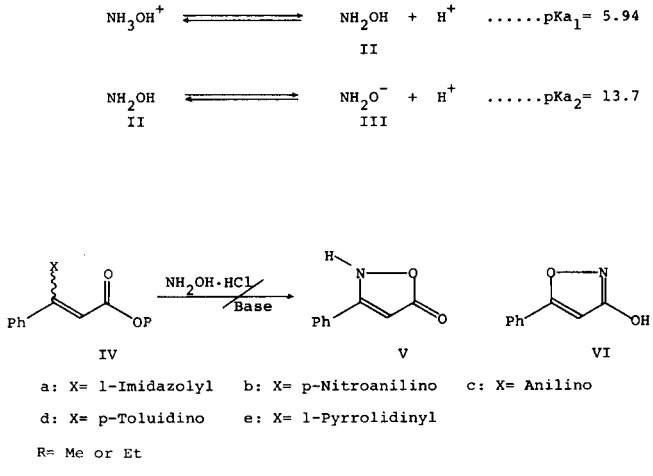
Recently, much attention is being focused upon the biological activities of the hydroxyisoxazoles or its tautomeric isoxazolones, especially 3-hydroxyisoxazoles. 5-Aminomethyl-3-hydroxyisoxazole (muscimol) (1) and [5-(3-hydroxyisoxazolyl)]aminoacetic acid (ibotenic acid) (2) shows potent activity as a soil fungicide and as a neurotransmitter which plays an important role in the human central nervous system. Also 5-methyl-3-hydroxyisoxazole (I) has been widely used as an effective soil fungicide and a germination promotor (3). In spite of such interests, the formations of hydroxyisoxazoles particularly, 3-hydroxyisoxazoles are limited and remain equivocal. Usually, 3-hydroxyisoxazoles are prepared by the reaction of acetylenic (4) or α,β-dihalo esters (5) with hydroxylamine. However, in this preparation, we speculate that the nitrogen atom of the free hydroxylamine II attacks initially on the carbonyl carbon, even if the reaction site of these esters with various nucleophiles seemed to be on the β-carbon.

We reported in the preceeding paper (6) that the hydroxylamine II by the use of triethylamine and into the aminohydroxy anion III by the use of more than 2 molar amounts of sodium methoxide. Also, we report in this communication that the nucleophilic center of III was located on the oxygen atom which was dramatically shifted from that of II. Further, the reaction of β-substituted enones with II or III gave selectively, the isomeric isoxazoles (7). The β-aminoenones were especially well suited for studies of this reaction tendency, because the electronic structure could be made to vary by alterations in β-amino-α,β-unsaturated esters with free hydroxylamine II and aminohydroxy anion III, which were generated from hydroxylamine hydrochloride with triethylamine and more than 2 molar amounts of sodium methoxide, respectively.

β-Aminocinnamic esters (IVa-e) were refluxed with 3 molar amounts of hydroxylamine hydrochloride in methanol for 3 hours in the presence of 9 molar amounts of triethylamine or sodium methoxide. The products were found to be 3-phenyl-5-isoxazolone (V) and 5-phenyl-3-hydroxyisoxazole (VI) by comparison with authentic samples (8,9). The yields of V and VI, which were determined by means of hplc, are summarized in the Table. As a result, VI was predominantly obtained in the reaction with III, while V was the main product in the reaction with II. In addition, the total yields of V and VI were sensitively dependent on the β-substituent group of IV. In the reaction with II, cinnamic esters IV having an electron-donating group such as β-(1-pyrrolidinyl), β-anilino and β-(*p*-toluidino), gave V in high yields. On the other hand, VI was formed rather in high yields in the reaction of III with IV having electron-withdrawing groups such as β-(*p*-nitroanilino) and β-(1-imidazolyl).

For the elucidation of the influence of the β-substituent group on the formation of V and VI, the decrease of IV and the increase of V and VI were followed kinetically by hplc. In the case of II, the decreasing rate of IV, especially IVa and IVb, was found to be slow, and V was formed syn-



Table

The Yields and Product Distributions of V and VI

Substrate	X	Triethylamine Yield (%)	Triethylamine V:VI	Sodium Methoxide Yield (%)	Sodium Methoxide V:VI
IVa	1-Imidazolyl	7	97:3	60	0:100
IVb	*p*-Nitroanilino	14	100:0	42	4:96
IVc	Anilino	80	100:0	18	26:74
IVd	*p*-Toluidino	77	100:0	12	12:88
IVe	1-Pyrrolidinyl	89	100:0	3	100:0

chronously. From the fact that the more electron-withdrawing the β-substituent group was, the slower the rate of nucleophilic attack on β-position of β-aminoenones was (10), the attack of the nitrogen atom of II was suggested to play an important role in the formation of V. On the other hand, IV disappeared spontaneously in the reaction with III, but VI appeared considerably slowly. This fact suggested that the reaction intermediate was formed by the treatment of IV with III, and the formation of VI from this intermediate was the rate determining step. Therefore, the cmr spectrum of the reaction mixture of IVa, hydroxylamine hydrochloride and more than 2 molar amounts of lithium hydride in methanol was measured. When IVa decreased, new singlet signals appeared at δ 98.1 and 161.5 ppm which were assignable to C-5 (sp^3) and C-3 (sp^2), respectively. Further, imidazolyl carbon signals were apparently different from the signals of free imidazole. From these observations, the structure of this intermediate was deduced to be 5-phenyl-5-(1-imidazolyl)-3-isoxazolidinone (VIIa) or its tautomer. After all, in the reaction of II with IV, the nitrogen atom of II attacked selectively on the β-carbon of IV, followed by the elimination of a substituent group. The rate determining step was supposed to be the initial attack of II. On the contrary, the reaction of III with IV was dominated by elimination of the substituent group of VII, which was formed by selective attack of the oxygen atom of III on the β-carbon atom of IV.

At the last, we undertook the preparation of 5-methyl-3-hydroxyisoxazole (I) (9) by the reaction of III with β-(1-imidazolyl)crotonoic ester (VIII), which had a good leaving group on the β-position for accelerating the elimination step. The expected product was obtained in 19% yield.

In conclusion, the regioselective synthesis of 3-hydroxyisoxazoles and 5-isoxazolones, which were of interest for a study of their biological behavior, was accomplished by the reaction of β-amino-α,β-unsaturated esters with hydroxylamine hydrochloride in the presence of appropriate bases.

EXPERIMENTAL

Materials.

Ethyl β-(*p*-nitroanilino)- (IVb), β-anilino- (IVc) (11), β-(*p*-toluidino)-(IVd) (11) and β-(1-pyrrolidinyl)cinnamate (IVe) (12) were prepared from ethyl benzoylacetate and the appropriate amines by the use of a Dean-Stark apparatus. Methyl β-(1-imidazolyl)cinnamate (IVa) and crotonoate (VIII) were prepared from methyl cinnamate and methyl crotonoate respectively, by treatment with imidazole after bromination (13).

Ethyl β-(*p*-Nitroanilino)cinnamate (IVb).

This compound had mp 133.5-134.5°.

Anal. Calcd. for $C_{17}H_{16}N_2O_4$: C, 65.4; H, 5.2; N, 9.0. Found: C, 65.5; H, 5.2; N, 8.9.

Methyl β-(1-imidazolyl)cinnamate (IVa).

This compound had mp 102-103°.

Anal. Calcd. for $C_{13}H_{12}N_2O_2$: C, 68.4; H, 5.3; N, 12.3. Found: C, 68.2; H, 5.3; N, 12.2.

Methyl β-(1-imidazolyl)crotonoate (VIII).

This compound had mp 88-88.5°.

Anal. Calcd. for $C_8H_{10}N_2O_2$: C, 57.8; H, 6.1; N, 16.9. Found: C, 57.9; H, 6.1; N, 16.8.

General Procedure.

A mixture of hydroxylamine hydrochloride (0.6 mmole) and base (1.8 mmoles of triethylamine or sodium methoxide) in methanol (5 ml) was refluxed for 1 hour. Then β-amino-α,β-unsaturated ester (0.2 mmole) was added to the mixture. After refluxing for 3 hours, the reaction mixture was acidified with hydrochloric acid to *p*H 1 and extracted with dichloromethane. The organic extract was dried over anhydrous magnesium sulfate and concentrated. The products were identical with the authentic samples (8,9). The yields of the products were determined by hplc (Jasco Familic-100) using Sil-C_{18}-10 column with sodium acetate-acetic acid (16:1) buffer solution (p*K* 5.9) containing 15% of acetonitrile.

Detection of VIIa.

Methyl β-(1-imidazolyl)cinnamate (IVa, 0.5 mmole) was added to a solution of hydroxylamine hydrochloride (0.9 mmole) and lithium hydride (2.3 mmoles) in methanol (1.5 ml). The mixture was allowed to stand for 1 hour in an nmr tube, and then the intermediate was detected by means of cmr which was measured by JEOL-900 nmr spectrometer; cmr (methanol): δ 98.1 (s), 116.6 (d), 121.7 (d), 127.1 (d), 129.0 (d), 129.3 (d), 130.4 (d), 139.0 (s), 139.7 (d), 161.5 (s).

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