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SELECTIVE SYNTHESIS OF 3,5-DISUBSTITUTED ISOXAZOLES FROM β-SUBSTITUTED ENONES AND HYDROXYLAMINE HYDROCHLORIDE IN THE PRESENCE OF VARIOUS BASES

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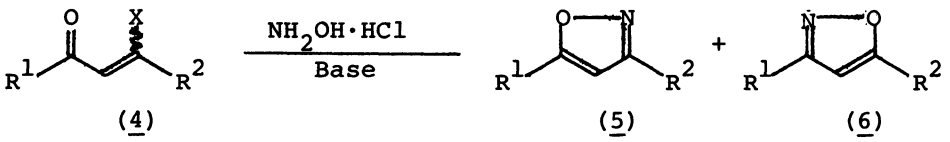
The synthesis of two isomeric isoxazoles could be selectively controlled in the reaction of β-substituted enones with 3 species of hydroxylamine; hydroxyammonium cation (1), free hydroxylamine (2) and aminohydroxy anion (3).

Previously we have shown that 3,5-disubstituted isoxazoles are useful synthones for the preparation of various enones.[1] In these conversions, the substituent groups on isoxazole ring remain as the groups attached on an enone system. Therefore, it is much required to provide the easier preparation of 3,5-disubstituted isoxazoles having the various groups without isomers. Although 3,5-disubstituted isoxazoles are generally prepared from β-substituted enones and β-diketones by the treatment with hydroxylamine as an ambident nucleophile,[2] there have been few selective preparations of 3,5-disubstituted isoxazoles having the various groups.

The preceeding paper[3] communicated that the nucleophilic center of the free hydroxylamine (2) was located on the nitrogen atom, while those of the hydroxyammonium cation (1) and the aminohydroxy anion (3) were located on the oxygen atom. This shift of the nucleophilic center should be applied to prepare 3,5-disubstituted isoxazoles regioselectively by the reaction with β-substituted enones. Therefore, we attempted the reaction of hydroxylamine hydrochloride with β-substituted enones under various conditions.

First of all, 2-(p-methyl)phenoxy-2-hepten-4-one (4a, X=OTol-p) was heated for 8 hr at 150°C with hydroxylamine hydrochloride in the presence of various

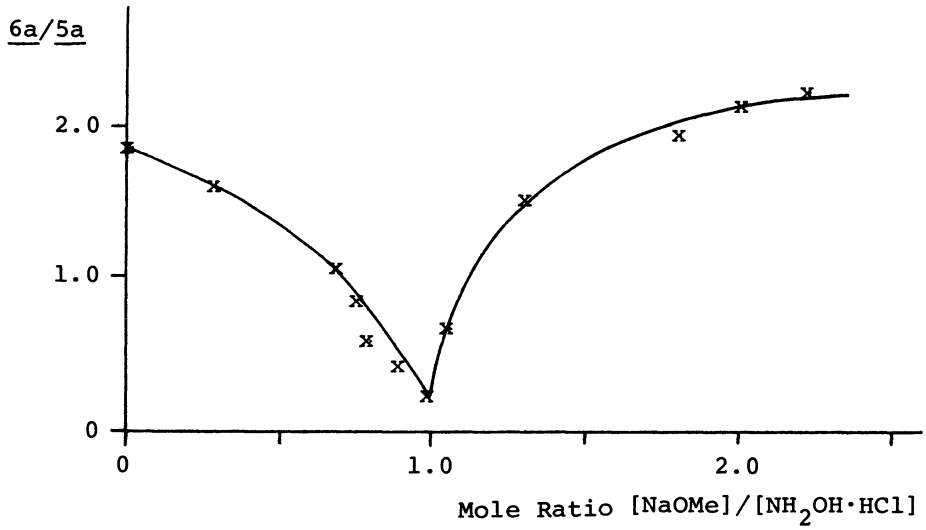
$$NH_3OH^+ \ (1) \rightleftharpoons NH_2OH \ (2) + H^+$$
$$NH_2OH \ (2) \rightleftharpoons NH_2O^- \ (3) + H^+$$



(4) (5) (6)

a: R^1=Pr; R^2=Me, b: R^1=Me; R^2=Pr, c: R^1=Ph; R^2=Me

amounts of sodium methoxide in methanol to give two isomeric isoxazoles, 3-methyl-5-propyl- (5a) and 5-methyl-3-propylisoxazole (6a). The product distribution 6a/5a changed dramatically when it plotted against the amount of sodium methoxide as shown in the Figure. Compound 6a was predominantly yielded in the absence or the presence of more than 2 molar amounts of sodium methoxide. On the contrary, 5a was selectively produced in the presence of an equimolar amount of sodium methoxide. As a result, it was demonstrated that the nucleophiles, 1 or 3, gave selectively one isomeric isoxazole (6a) in the reaction of 4a (X=OTol-p), while 2 gave the alternative isomer (5a). Further, compound 5a was yielded by the reaction of 4a (X=OTol-p) with 2, which was generated from



Figure

Table

The Total Yields and Product Distributions of Isoxazoles in the Reaction of 4 with Hydroxylamine Hydrochloride in the Presence of Various Bases

Substrate			None		K_2CO_3		Et_3N		2NaOMe	
R^1	R^2	X	Yield	5:6	Yield	5:6	Yield	5:6	Yield	5:6
Pr	Me	OTol-p	86%	35:65	77%	74:26	86%	80:20	89%	31:69
Pr	Me	Imida*	98%	14:86	87%	77:23	85%	75:25	92%	14:86
Pr	Me	OMe	78%	69:31	81%	91: 9	95%	94: 6	89%	29:71
Pr	Me	SPh	72%	42:58	70%	74:26	82%	75:25	70%	26:74
Pr	Me	SEt	77%	41:59	78%	90:10	85%	79:21	79%	25:75
Pr	Me	NHPh	81%	94: 6	84%	81:19	83%	85:15	85%	48:52
Pr	Me	NHEt	80%	91: 9	77%	88:12	80%	87:13	89%	74:26
Pr	Me	Pyrro*	84%	90:10	79%	87:13	81%	89:11	61%	90:10
Me	Pr	OTol-p	74%	31:69	87%	49:51	86%	77:23	82%	24:76
Me	Pr	Imida*	50%	20:80	70%	58:42	50%	78:22	98%	7:93
Me	Pr	OMe	80%	33:67	73%	89:11	85%	94: 6	98%	24:76
Me	Pr	SPh	78%	14:86	53%	42:58	——	———	78%	8:92
Me	Pr	SEt	73%	12:88	60%	60:40	——	———	93%	11:89
Me	Pr	NHPh	73%	52:48	64%	72:28	74%	75:25	78%	22:78
Me	Pr	NHEt	61%	87:13	59%	82:18	58%	80:20	41%	79:21
Me	Pr	Pyrro*	84%	90:10	76%	74:26	52%	78:22	52%	78:22
Ph	Me	OTol-p	93%	86:14	69%	89:11	24%	84:16	54%	25:75
Ph	Me	Imida*	55%	52:48	63%	82:18	65%	91: 9	57%	23:77
Ph	Me	OEt	48%	92: 8	83%	99: 1	52%	94: 6	59%	14:86
Ph	Me	SPh	52%	86:14	55%	92: 8	43%	96: 4	41%	21:79
Ph	Me	SEt	61%	98: 2	48%	96: 4	52%	96: 4	22%	22:78
Ph	Me	NHPh	86%	95: 5	92%	90:10	48%	88:12	48%	91: 9
Ph	Me	NHEt	59%	99: 1	79%	93: 7	41%	92: 8	43%	96: 4
Ph	Me	Pyrro*	63%	98: 2	73%	92: 8	58%	97: 3	51%	91: 9

* Imida= 1-Imidazolyl, Pyrro= 1-Pyrrolidinyl.

hydroxylamine hydrochloride by the use of triethylamine or potassium carbonate.

Similarly, β-substituted enones (4) were treated for 8 hr at 150°C with hydroxylamine hydrochloride in the presence of an equimolar amount of triethylamine or potassium carbonate, or 2 molar amounts of sodium methoxide. In the Table, the total yields of resulting isoxazoles and the product distributions are summarized. From the results, the regioselective formation of isoxazoles was accomplished by the reaction of enones having the good leaving group on the β-position. In the case of the treatment with 1 or 3, C-3 carbon of the resulting isoxazole was originated from the carbonyl carbon of enones, and that was from the β-carbon in the case of 2. On the other hand, when β-aminoenones (4, X=NHPh, NHEt, and Pyrrolidinyl) were treated with any species of hydroxylamine, 1, 2 or 3, the C-3 carbon of the resulting isoxazoles was originated from β-carbon of enones.

In conclusion, the general method, in which 3,5-disubstituted isoxazoles were regioselectively prepared from one starting material, was provided on a base of the shift of nucleophilic center of hydroxylamine. The studies concerning the limitations and the mechanism of this reaction are now in progress; the details will be reported in another article.

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