THE RING CLEAVAGE OF 3,5-DISUBSTITUTED ISOXAZOLIUM SALTS WITH ALKOXIDES

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This paper communicates the reaction of 3,5-disubstituted N-alkylisoxazolium salts with alkali alkoxide in alcohol to give the β-aminoenones. Also, this reaction was applied to the synthesis of curcumin.

We have investigated that the 3,5-dimethylisoxazole reacts with some electrophiles regioselectively on C-5 methyl group.[1] We have also investigated the hydrogenolysis of resulting 5-substituted 3-methylisoxazoles to obtained β-aminoenones. These β-aminoenones are very useful intermediate for the synthesis of enones, β-diketones, and some heterocycles.[2]

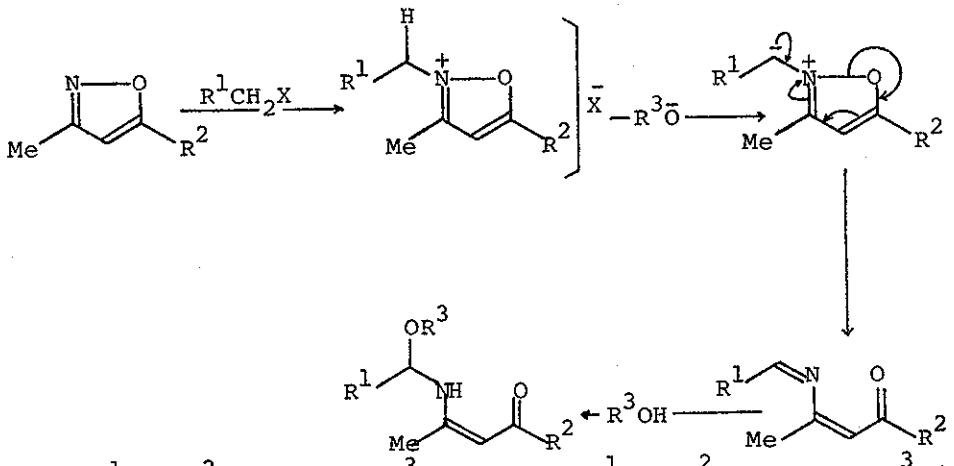
It is well known that the isoxazolium salts are easily prepared from the corresponding isoxazoles.[3] The reactions of 3-substituted isoxazolium salts have extensively been investigated by Woodward et al. as the "Reagent K" for the

peptide synthesis.[4] But there are a few papers in which 3,5-disubstituted isoxazolium salts show very different and complicated behaviors against the bases. The reaction of isoxazolium salts with soft bases such as butyllithium and sodium borohydride gave the corresponding 4-isoxazolines.[5] On the other hand, N-methylisoxazolium salts were attacked by hard bases at methyl group on nitrogen. The reaction of 2,3-dimethyl-5-phenylisoxazolium perchlorate with methyl Grignard reagent gave 2,3,3-trimethyl-5-phenyl-4-isoxazoline and 3-ethylamino-1-phenyl-2-buten-1-one.[6] By the treatment of aqueous sodium hydroxide, 3,4,5-triphenyl-2-methylisoxazolium chloroferrate gave 4,5,6-triphenyl-2H-1,3-oxazine.[7] In Stork's annelation reaction,[8] isoxazolium salts are cleaved by aqueous sodium hydroxide followed by the spontanious cyclization to phenols and anilines. In the every reactions with hard bases, the ring of isoxazolium salts are cleaved to β-aminoenones.

Therefore, we investigated the reactions of 3,5-disubstituted 2-methylisoxazolium salts with alkoxides, which are the typical hard bases. 2,3-Dimethyl-5-phenethylisoxazolium iodide (1) was treated with potassium t-butoxide in t-butanol at room temperature. After 28 hr, the reaction mixture was poured into water and extracted with dichloromethane. From the organic extract, the liquid product was shown only one tlc spot, which was colored by ferric chloride solution. The nmr spectrum of the product shows methyl singlet at δ 2.10,

t-butyl singlet at 1.32, two methylene signals at 2.5-3.1, phenyl signal at 7.30, olefinic proton at 5.12 and methylene proton doublet at 4.74 ppm, which is proved to be CH_2-NH by the deuterium exchange. From these data and the elemental analysis, the structure was confirmed to be 5-(t-butoxymethylamino)-1-phenyl-4-hexen-3-one (8). Similarly, 1 was treated with potassium methoxide to give 5-methoxymethylamino-1-phenyl-4-hexen-3-one (9). Also 2-ethyl-3-methyl-5-phenethylisoxazolium iodide (2), 2,3,5-trimethylisoxazolium iodide (3), 2,3-dimethyl-5-phenylisoxazolium iodide (4), and 2,3-dimethyl-5-phenylisoxazolium perchlorate (5) were treated with alkoxides to give a corresponding β-aminoenones listed in Table. In the case of isoxazole having the olefinic substituent, hydrogenolysis of isoxazole ring competes with the reduction of olefin and occurs the complex reaction. Thus, the ring cleavage of 3-methyl-5-(3-butenyl)isoxazole was tried by the quaternarization with methyl iodide and then treatment with potassium methoxide. The reaction product was found to be 7-methoxymethylamino-1,6-octadien-5-one (13).

From these results, the N-alkylisoxazolium salts were cleaved to β-alkoxyalkylaminoenones in high yield by the treatment with alkali alkoxides. The reaction mechanism was speculated as shown in Fig. 1. This new ring cleavage will be very useful for the synthesis of the natural compounds and the other complex molecules, starting from the simple β-diketones of isoxazoles.



8 R^1=H, R^2=CH_2CH_2Ph, R^3=t-Bu 9 R^1=H, R^2=CH_2CH_2Ph, R^3=Me

10 R^1=Me, R^2=CH_2CH_2Ph, R^3=Me 11 R^1=H, R^2=Me, R^3=Me

12 R^1=H, R^2=Ph, R^3=Me 13 R^1=H, R^2=$CH_2CH_2CH{=}CH_2$, R^3=Me

14 R^1=H, R^2=t-Bu, R^3=Me

Fig. 1

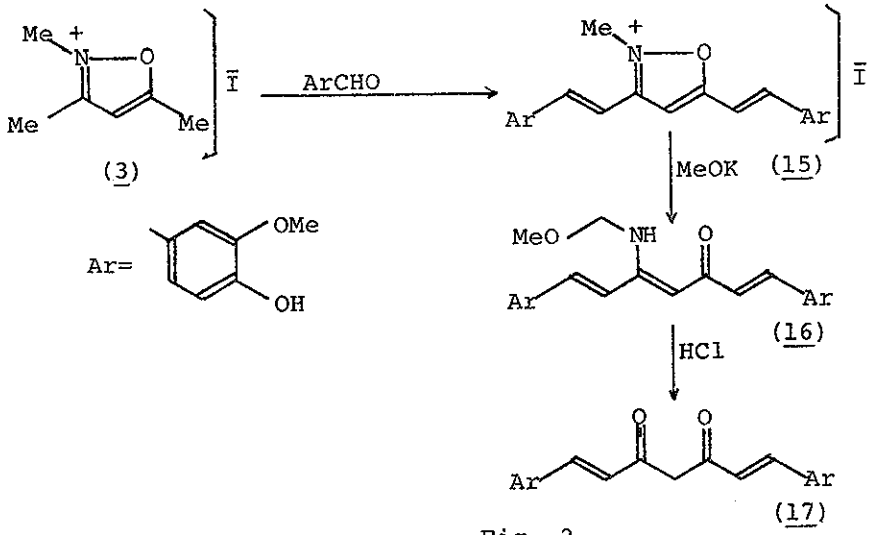


Fig. 2

Finally, the naturally occuring β-diketone, curcumin, was synthesized by this new ring opening reaction. 3,5-Bis-(4-hydroxy-3-methoxystyryl)-2-methylisoxazolium iodide (15) was prepared from vaniline and 3 by the method of Lampe.[9] Compound 15 was treated with sodium methoxide to give the corresponding β-aminoenone (16), which was hydrolyzed by dilute hydrochloric acid in methanol. The product (17) was identified with authentic curcumin by tlc, ir and mixed melting.

Table

	Isoxazolium Salt R^1	R^2	X	Alkoxide	Product	Yield (%)
1	H	CH_2CH_2Ph	I	t-BuOK	8	44
1	H	CH_2CH_2Ph	I	MeOK	9	72
2	Me	CH_2CH_2Ph	I	MeOK	10	78
3	H	Me	I	MeOK	11	48
3	H	Me	I	MeONa	11	67
4	H	Ph	I	MeOK	12	79
5	H	Ph	ClO_4	MeOK	12	46
5	H	Ph	ClO_4	MeONa	12	91
6	H	$CH_2CH_2CH=CH_2$	I	MeOK	13	49
7	H	t-Bu	I	MeOK	14	75

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