Regiospecific Synthesis of Isoxazoles by the Reaction of α-Bromoenones with Hydroxylamine

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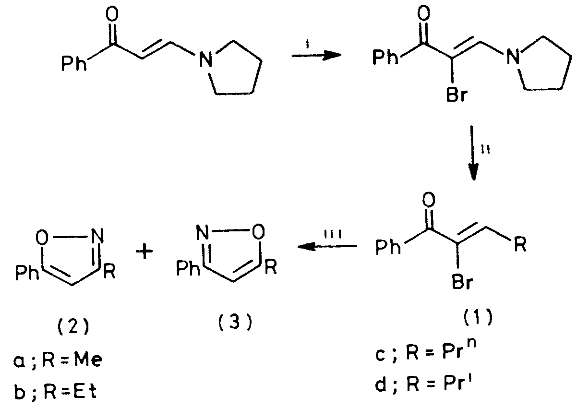
Summary In the reaction of α-bromoenones with hydroxylamine, the synthesis of isomeric isoxazoles could be controlled regiospecifically by changing the base

PREVIOUSLY we have shown that 3,5-disubstituted isoxazoles are useful synthons for the preparation of various enones[1] Although the preparations of isoxazoles have been studied extensively, the regiospecific synthesis of either isomer of unsymmetrical 3,5-disubstituted isoxazoles, particularly starting from one compound, has not been reported We have now investigated the regiospecific synthesis of isoxazoles from α-bromoenones and hydroxylamine hydrochloride

The α-bromoenones (**1**) were prepared by α-bromination of *NN*-disubstituted β-aminoenones[2], followed by reaction with Grignard reagents (Scheme)[3]



SCHEME. Reagents: i, Br_2 then Et_3N; ii, RMgI; iii, $NH_2OH.HCl$, base.

When a mixture of the bromobutenone (**1a**), hydroxylamine hydrochloride, and potassium carbonate in 95% ethanol was heated for 7 h, a mixture of 3-methyl-5-phenylisoxazole (**2a**) and 5-methyl-3-phenylisoxazole (**3a**) was obtained. The structure of (**2a**) was confirmed by its n.m.r. signals at δ 2·34 (s, 3H), and 6·35 (s, 1H), while that of (**3a**) was confirmed by its signal at δ 2·45 (d, J 1 Hz, 3H), together with that at δ 6·30 (q, J 1 Hz, 1H). Increasing the amount of potassium carbonate caused a decrease in the isomer ratio (**2a**) : (**3a**) (Table 1). A change in the base from potassium carbonate to potassium hydrogen carbonate also caused a change in the isomer ratio.

In a further study, a mixture of 1 mol equiv. of hydroxylamine hydrochloride and 1·5 mol equiv. of potassium carbonate was stirred for 1 h, and then 1 mol equiv. of (**1a**) was added; the isoxazole (**2a**) was obtained regiospecifically. However, when 2 mol. equiv. of sodium ethoxide was used as the base under similar conditions, the isomeric isoxazole (**3a**) was obtained regiospecifically. Similarly, 3-ethyl- (**2b**), 3-propyl- (**2c**), and 3-isopropyl-5-phenylisoxazoles (**2d**) and their isomers (**3b**), (**3c**), and (**3d**) could be synthesized regiospecifically (Table 2).

TABLE 1

Mole ratio			Product ratio	
(**1a**)	: $NH_2OH{\cdot}HCl$	: K_2CO_3	(**2a**)	: (**3a**)
1	: 2	: 1·5	4	: 1
1	: 2	: 2	2·5	: 1
1	: 2	: 3	2	: 1
1	: 2	: 6	1·8	: 1

TABLE 2

	Base	
	K_2CO_3 in 95% EtOH % Yield of (**2**)[a]	NaOEt in abs. EtOH % Yield of (**3**)[b]
a	49	33
b	33	30
c	33	25
d	30	25

[a] (**3**) was not formed. [b] (**2**) was not formed.

Thus, the regiospecific synthesis of isoxazole isomers from one starting substance could be accomplished by using α-bromoenones and hydroxylamine in the presence of potassium carbonate or sodium ethoxide.

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