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A New Straightforward Formation of Aminoisoxazoles from Isocyanides

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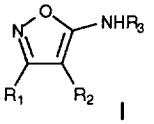
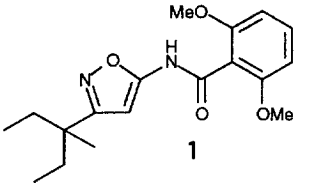
Abstract : The reaction of α-bromoketone oximes with isocyanides and sodium carbonate leads to a new formation of 5-aminoisoxazole derivatives. The reaction probably involves the intermediacy of a nitrosoalkene generated in situ. Good yields are obtained for electron deficient ketone oximes such as ethyl bromopyruvate oxime; the use of a trifluoromethyl substituted oxime gives a high efficient formation of trifluoromethyl isoxazoles. © 1997 Published by Elsevier Science Ltd.

5-aminoisoxazoles **I** and their N-substituted derivatives are interesting heterocyclic compounds with useful biological properties as shown by isoxaben **1**,[1] one of the most used herbicide for winter cereals.



I

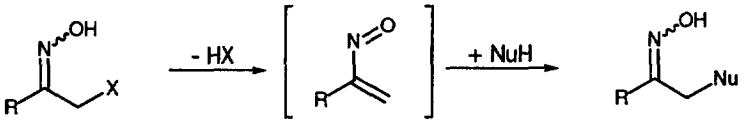


1

Scheme 1

Most 5-aminoisoxazoles derivatives are usually prepared[2] through N-functionalization of a preformed 5-aminoisoxazole. The latter are obtained through addition of hydroxylamine to cyanoacetylenes,[3] propargylcyanides,[4] allenic nitriles[3,5] and β-ketonitriles derivatives;[5,6,7] nitrile N-oxides cycloaddition[8] represent an other possible route as well as reaction of α-chloroketone oximes with sodium cyanide.[9] Yet further functionalization of the amino residue can be impeded by the ambident nucleophilic behaviour of the heterocycle;[10] there is still a need for a convenient preparation of complex N-substituted aminoisoxazoles.

Among the available methods for isoxazole formation, nucleophilic cyanide addition to α-chloroketone oximes deserves particular attention. The mechanism of these additions often relies on a base induced hydrochloric elimination to form a reactive nitrosoalkene rapidly attacked by the nucleophile (scheme 2).

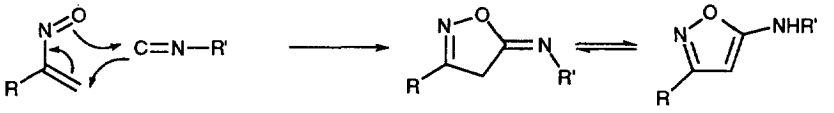


II

Scheme 2

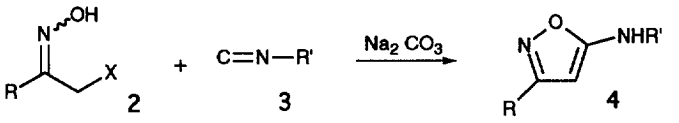
Nitrosoalkene species show interesting chemical behaviour. They are easily generated from α-chloro or bromoketone oximes by weak bases such as triethylamine or sodium carbonate; highly instable, they must be generated and trapped in situ. Apart from nucleophilic displacement of the halogen, nitrosoalkene participate in various [4+2] hetero Diels Alder type reactions with electron rich olefins. [11,12,13]

We believed isocyanides could be involved in a [4+1] cycloaddition reaction with nitrosoalkene (scheme 3). Our assumption was supported by the known nucleophilic behaviour of isocyanides[14] as well as precedents in [4+1] cycloaddition reactions.[15,16,17] If successful, this reaction could give a useful straighforward route to aminoisoxazoles.



Scheme 3

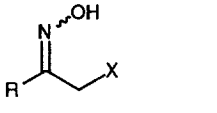
When sodium carbonate was added to a dichloromethane solution of o-tolyl isocyanide **3a** and bromoacetophenone oxime **2a** , and the suspension left under agitation overnight at room temperature, the new isoxazole **4a** was recovered in a modest 40% yield after filtration and purification on a silica gel column. Various isocyanides and oximes have been synthetised and tested in the reaction, the result have been collected in Table 1. They are consistent with known behaviour of nitrosoalkenes with olefines: i) best yields are obtained with electron deficient oximes, ii) a slow generation of the nitroso in the reaction is secured by the choice of an heterogeneous medium (no isoxazole could be recovered from bromoacetophenone oxime using triethylamine as a base), iii) yields are increased by raising the concentration of isocyanide. Best yields are obtained when isocyanides were used as solvent (method B); in this case, isocyanides can be recovered at the end of the reaction either through distillation or column chromatrophy for the less volatile ones. Except for oxime **2c**, the use of equimolar quantities of isocyanide (method C) had to be rejected due to important decrease in yields.



α-halooxime	isocyanide	Products	Yields (Method)
2a	**3a**	**4a**	40% (A) ; 52 % (B)
2a	**3b**	**4b**	63% (B)
2b	**3b**	**4c**	75% (A) ; 78% (B) ; 47% (C)
2b	**3c**	**4d**	39% (A) ; 84% (B)
2b	**3d**	**4e**	51% (A) ; 85% (B)
2b	**3a**	**4f**	61% (A)
2c	**3b**	**4g**	93% (B) ; 86% (C)
2b	**3e**	**4h**	93% (B)
2d	**3b**	none	0% (degradation)

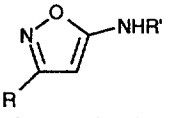
Method A: to a solution of α-haloketone oxime (2 mmol) in dry CH_2Cl_2 (10 ml) is added the isocyanide (8 mmol) and sodium carbonate (850 mg, 8 mmol).
Method B: to a solution of α-haloketone oxime (2 mmol) in the isocyanide (3 ml) is added sodium carbonate (850 mg, 8 mmol).
Method C: to a solution of α-haloketone oxime (2 mmol) in dry CH_2Cl_2 (10 ml) is added the isocyanide (2,2 mmol) and sodium carbonate (850 mg, 8 mmol).

Table 1: formation of isoxazole

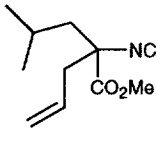


2a R = Ph; X = Br
2b R = CO_2Et; X= Br
2c R =CF_3; X = Br
2d R = Me; X = Cl

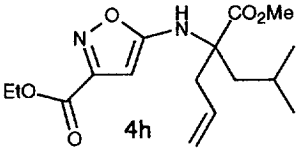
3a R = o-tolyl
3b R = tBu
3c R =CH_2CO_2Et
3d R =$CH_2CH(OEt)_2$



4a R = Ph; R' = o-tolyl
4b R = Ph; R' = tBu
4c R =CO_2Et;R' = tBu
4d R =CO_2Et; R' = CH_2CO_2Et
4e R =CO_2Et; R' = $CH_2CH(OEt)_2$
4f R =CO_2Et; R' = o-tolyl
4g R =CF_3; R' = tBu



3e



Structures for Table 1

In conclusion, we have disclosed an effective formation of aminoisoxazole from isocyanides. Application of this methodology for the synthesis of other heterocyclic compounds is under study in our research group and should be reported soon.

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