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A TWO-STEP SYNTHESIS OF 5-AMINOISOXAZOLES FROM OLEFINS

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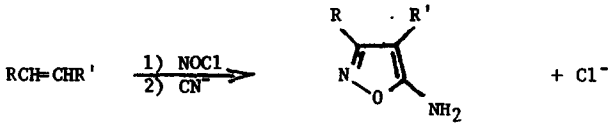
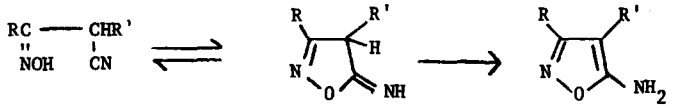
Synthetic approaches to 5-aminoisoxazoles have involved, for the most part, reactions of hydroxylamine with either beta-substituted nitriles (2) or amidines (3) or with cyanoacetylenes (4). We wish to report a facile, high yield pathway to 3,4-disubstituted-5-aminoisoxazoles (I) comprising two synthetic steps from olefins. The method involves treatment of olefin-nitrosyl chloride adducts with inorganic cyanide in acetonitrile to give I directly.



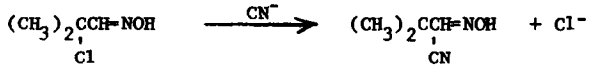
I

The formation of 5-aminoisoxazoles in this manner likely involves the intermediacy of an alpha-cyanooxime (II). Such a compound is geometrically well-positioned to undergo cyclization to the heterocyclic intermediate III, which can in turn tautomerize to give the aromatic isoxazole system.



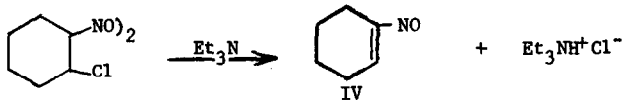
II III I

An obvious condition of such an isomerization is the presence of a hydrogen on the carbon atom initially bearing the nitrile group. Thus, the product from reaction of nitrosyl chloride with isobutylene, 2-chloro-2-methylpropionaldoxime simply yields 2-cyano-2-methylpropionaldoxime (5) on treatment with sodium cyanide in dimethyl sulfoxide or acetonitrile.

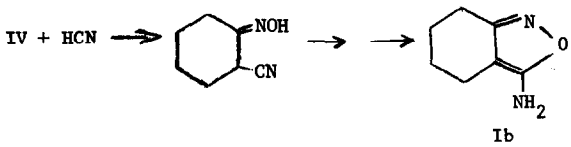


It is desirable to use the nitrosochloride dimers rather than the corresponding chloroximes to prepare 5-aminoisoxazoles, since mixtures of products containing unsaturated material are obtained on reaction of 1,2-chloroximes with cyanide ion. Thus terminal olefins, which form nitrosyl chloride adducts that undergo facile isomerization to alpha-chloraldoximes are not readily converted to 5-aminoisoxazoles.

The nitrosyl chloride adducts obtained from either cis- or trans-2-butene are converted in yields exceeding 80% to 3,4-dimethyl-5-aminoisoxazole (Ia, $R=R'=CH_3$) (6) by the action of excess dry potassium or sodium cyanide in acetonitrile at ambient temperature for three days. Only 25% yields of Ia are obtained when starting with the corresponding oxime, 3-chlorobutan-2-one oxime. A high yield of 3,4-cyclohexeno-5-aminoisoxazole (Ib, $R,R'=-(CH_2)_4-$) (7) is obtained on treatment of dimeric 1-nitroso-2-chlorocyclohexane with inorganic cyanide in refluxing acetonitrile. The reaction is catalyzed by triethylamine; however, when excess triethylamine is employed, dehydrochlorination and isomerization to 2-cyclohexenone oxime occurs. The catalytic effect of tertiary amines may well be associated with dehydrochlorination of the nitrosochloride dimer to 1-nitrosocyclohexene (IV). The latter can add hydrogen cyanide to give the cyanooxime which rearranges further to product. Similar mechanisms involving the intermediacy of nitrosoolefins have been advanced to explain the reaction of olefin-NOCl adducts with primary and secondary amines (8).



$$CN^- + Et_3NH^+Cl^- \rightleftharpoons HCN + Et_3N + Cl^-$$



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7. White needles from hot water, mp 116-118°. Nmr ($CDCl_3$): broad singlet δ4.60 (2H), multiplet δ2.55 (2H), multiplet δ2.25 (2H), multiplet 1.70 (4H). Anal: Calc'd for $C_7H_{10}N_2$: C, 60.85; H, 7.30; N, 20.28. Found: C, 61.20; H, 7.42; N, 19.88%.

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