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BASE CATALYZED REARRANGEMENT OF 5-CYANOMETHYL-2-ISOXAZOLINES; NOVEL PATHWAY FOR THE FORMATION OF 2-AMINOPYRIDINE N-OXIDES

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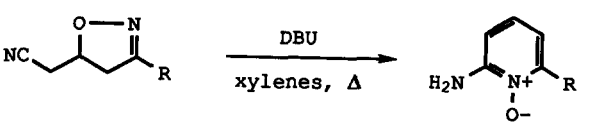
SUMMARY: 2-Aminopyridine N-oxides are readily prepared by the base catalyzed rearrangement of 5-cyanomethyl-2-isoxazolines.

2-Isoxazolines are readily available compounds which have proven to be synthetically useful intermediates due to their ability to undergo reductive ring opening[1] as well as oxidation to isoxazoles.[2] Upon treatment with base, however, 2-isoxazolines fail to react predictably but instead may undergo fragmentation,[3] ring opening,[4] and/or rearrangement.[5] Here we report a novel base catalyzed transformation of 3-substituted-5-cyanomethyl-2-isoxazolines to 2-aminopyridine N-oxides.

5-Cyanomethyl-2-isoxazolines 1 are readily accessible in high yield via a 1,3-dipolar cycloaddition reaction of nitrile oxides with allylcyanides.[6] On treatment with catalytic amounts of base, such as 1,5-diazabicyclo(5.4.0)undec-5-ene (DBU) in boiling xylenes, 1 reacts to form 6-substituted-2-aminopyridine N-oxides 2, which in some cases can be isolated from the cold reaction mixture as a white precipitate (2c, 2e).

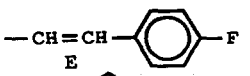
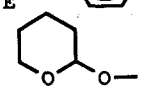


1 2

The reaction proceeds smoothly when R is alkyl, alkenyl, or phenyl and high yields of the corresponding 2-aminopyridine N-oxide are obtained.

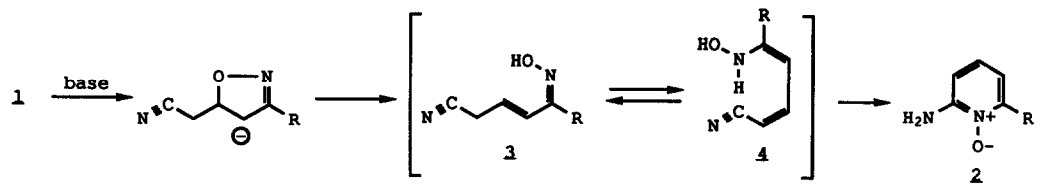
However, when R contains a carbonyl moiety present at the 3-position (Entry 2g), complete decomposition of 1 takes place.

Yields from the Base Catalyzed Reaction of 5-Cyanomethyl-2-isoxazoline 1[a,b] to 2

Entry	R	Reaction Conditions	Reaction Time (h)	Yield[c] %	mp (°C)
2a	Me	DBU, xylenes	16	58	153-154
2b	Et	DBN, o-xylene	18	79	122-123
2c	Ph	DBU, xylenes	48	90	236
2d	-CH=CH-Ph (E)	DBU, xylenes	48	96	154-155
2e		NaOMe,[d] MeOH	36	82	159-160
2f		DBU, xylenes	24	75	123-124
2g	-COPh	DBU, xylenes	16	dec.	

[a] The reactions were typically carried out in refluxing solvent using 10 mmol of 1 and 0.2 equivalents of base.
[b] All reported pyridine N-oxides displayed spectral characteristics (IR, MS, ^{1}H-NMR) which were consistent with their assigned structure. Satisfactory analysis for all new compounds.
[c] Yields shown do not represent optimized values.
[d] 1.1 equivalent of NaOMe was used.

We postulate that the transformation 1 to 2 is initiated by an intramolecular elimination reaction[7] (Scheme 1). It should proceed through the reactive Z-vinyl-ene-hydroxylamine 4, which cyclizes spontaneously to give the final product 2. More than likely the E-isomer, if present, can isomerize to the Z-form 4 under the given reaction conditions. The assumption of 4 as the reactive intermediate is in agreement with results by Gewald[8] who synthesized 2-amino pyridine N-oxides by reacting α-ylidene malonitrile with various nitrile oxides. In no case, however, were we able to isolate any putative open chain intermediates such as 4 or the α,β-enoxime 3.[7]



The structure 2 was established by ^{1}H-NMR, mass spectrum analysis and reduction with zinc (example 2a) in acetic acid[9] to give the substituted pyridine which was identical to an authentic sample.[10]

This rearrangement of 5-cyanomethyl-2-isoxazolines opens a novel entry to 6-substituted-2-amino pyridines and their N-oxides.

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