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SYNTHESIS OF STERICALLY HINDERED 4-DIALKYLAMINO PYRIDINES

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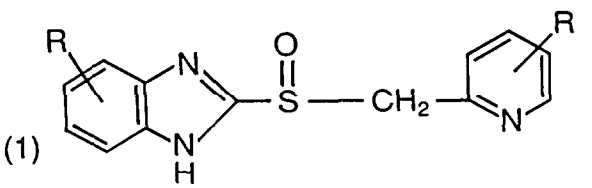
Summary: The synthesis of sterically hindered 4-dialkylamino pyridines from a 2,3,5-trisubstituted 4-nitropyridine-N-oxide was found to proceed via a different reaction sequence under acidic and basic conditions.

The 2-(2-pyridylmethylsulphinyl)benzimidazoles (1) undergo an acid-catalysed rearrangement which is necessary for the (H^+ + K^+)-ATPase enzyme inhibitory activity of these compounds[1,2]. The initial step in this rearrangment is thought to be a nucleophilic attack by the pyridyl nitrogen at the 2-position of the benzimidazole ring.



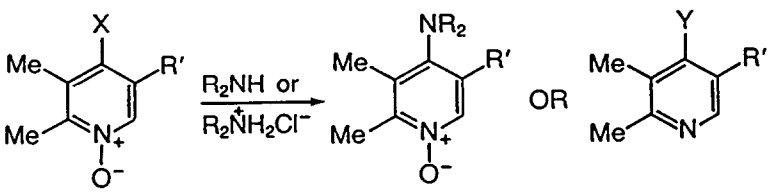
(1)

In order to investigate the effects of substituents in the pyridine ring on the rate and ease of this rearrangement we required a selection of sterically hindered 4-dialkylamino pyridines. Although nucleophilic displacement of a 4-halo group is a well known method for the synthesis of 4-substituted pyridines[3], there has only been one report on the displacement of sterically hindered 4-chloropyridine-N-oxides by amines and this method failed for the more hindered pyridines[4]. We repeated this synthesis with 4-chloro-2,3-dimethylpyridine-N-oxide (2) using both dimethylamine and morpholine and obtained good yields of the expected pyridine-N-oxides (5) and (6). Using the less nucleophilic N-methyl-aniline, however, the reaction failed (see Table, entry a). Under more

vigorous conditions a low yield of (7) was obtained which proved to be the free pyridine (entry b). Similarly, reaction of morpholine with 4-chloro-2,3,5-trimethylpyridine-N-oxide (3) required more forcing conditions and a good yield of (8) was obtained, which again proved to be the free pyridine (entry c). These deoxygenations were unexpected in that we were unaware of amines being used to reduce pyridine-N-oxides[3] and although in one instance amine displacement had been reported to give the pyridine, this was only after distillation with no indication as to when the deoxygenation had occurred[4].

Further investigation of the synthesis of (8) showed that after 2h little of the product had been formed, yet no (3) remained. Work-up provided the chloropyridine (13) in 80% yield and further heating of (13) with morpholine (18h, 190°, NMP) gave (8) as before. Thus it would appear that under basic conditions, N-deoxygenation occurs first followed by nucleophilic displacement on the less activated pyridine.

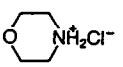
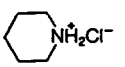
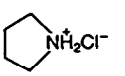
For the more volatile amines it was desirable to develop a method which did not involve using a sealed tube. The use of morpholine hydrochloride with (3) was therefore investigated and it was found that not only did this effect the displacement, but also that the reaction was significantly quicker. Again the free pyridine (8) was isolated but in this case none of the intermediate (13) was detected (entry d).



(2) X=Cl, R′=H
(3) X=Cl, R′=Me
(4) X=NO_2, R′=Me
(5) R′=H; R_2N=Me_2N-
(6) R′=H; R_2N=  N-
(7) R′=H; Y=Ph(Me)N-
(8-11) R′=Me; Y=R_2N-
(12) R′=Me; Y=Ph(H)N-
(13) R′=Me; Y=Cl

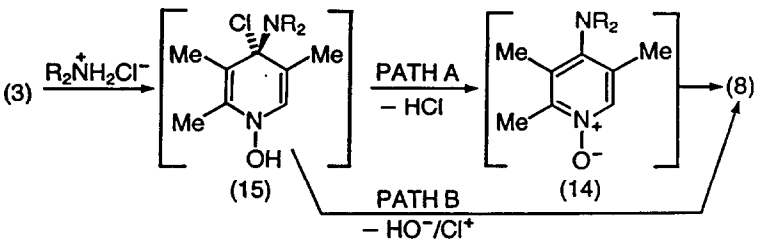
As (3) was prepared from the 4-nitropyridine-N-oxide (4), the direct reaction between morpholine hydrochloride and (4) was investigated. Under mild conditions (DMF, 150°, 2h) (4) was cleanly converted to (3) whereas under the more forcing conditions (entry e), (8) was isolated in 60% yield. Reaction of (3) with other amine hydrochlorides gave the 4-aminopyridines (9-12) in moderate yields (not optimised). With aniline hydrochloride (entry i) a longer reaction time was required and, surprisingly, the same product (12) was obtained with N-methylaniline hydrochloride (entry j). Presumably an N-demethylation had occurred either in the transition state or product to relieve steric strain.

Table: Synthesis of 4-aminopyridines (7-12)

Entry	Pyridine N-oxide	Amine	Conditions	Product[5]	Yield %
a	2	PhNHMe	A	-	-
b	2	PhNHMe	B	7	25
c	3		B	8	70
d	3		C	8	80
e	4		C	8	60
f	4	$Me_2NH_2^+Cl^-$	C	9	40
g	4		C	10	35
h	4		C	11	45
i	4	$PhNH_3^+Cl^-$	B	12	45
j	4	$Ph(Me)NH_2^+Cl^-$	B	12	50

A) 6 molar equivalents amine, methoxyethanol, 140°
B) NMP 190°, N_2, 20h; C) NMP 190°, N_2, 4h

As no (13) or (14) were detected under the acid conditions, it was considered that a different mechanism from the addition/elimination, Path A, may be involved, for example Path B where the pyridine could be obtained by a direct elimination of Cl^+/OH^- from the intermediate Meisenheimer complex (15).



An attempt to trap Cl^+ by electrophilic substitution of added 1,3-dimethoxybenzene failed and only O-demethylation to 3-methoxyphenol was observed. In a parallel experiment (14) was rapidly converted to (8) (<2h) under the displacement conditions so that (14) could be a transient intermediate.

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5. All new compounds were characterised by ^1H-nmr, i.r., high resolution m.s. and their structure confirmed by further chemical modification.

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