

Direct Side Chain Amination of Picoline 1-Oxides: A New Rearrangement

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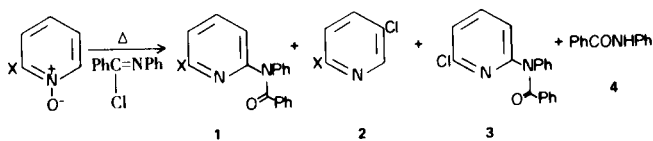
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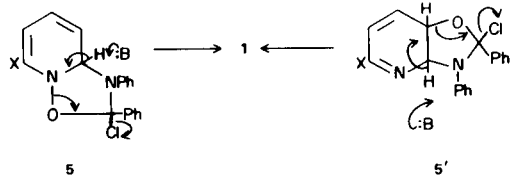
Sir:

The acylation (1) of heteroaromatic *N*-oxides with imidoyl chlorides leads to the introduction of the acylamino group in the α -position in moderate to good yields; 3-chloropyridines and benzanilide are also often formed in substantial quantities. We now report that the addition of external base has a marked effect on the yields of these products and, in the case of 2-picoline, changes the course of the reaction and leads to a new rearrangement.

The influence of the nature of the base and its concentration is summarized in the Table. As the proton basicity of the base and/or its concentration is increased the yield of acylation product (1) increases, those of 3-chloropyridine (2), benzanilide (4) and 6-chloro-2-*N*-benzoylanilinopyridine (3) (2) generally decrease.



These results can be rationalized if it is assumed that the added base abstracts the 2-proton, possibly from the 1,2- (5) or 2,3-dihydro-intermediate (5') (3), leading to aromatization rather than byproduct formation. This improvement in yields clearly enhances the value of the direct acylation reaction.



When 2-picoline 1-oxide was treated with *N*-phenylbenzimidoyl chloride in the absence of base the expected 2-*N*-benzoylanilino-6-methylpyridine (1; X = Me) (54.2%) was obtained, together with 2-chloromethylpyridine (18.2%) (6) (1c) and 4 (46.4%). As base was added, however, the yield of 1 (X = Me) dropped, eventually to zero with 1 equivalent of DBU, as did the amount of 6 [4 (27%)]. A new product was formed, however, which proved to be *N*-benzoylanilinomethylpyridine (7; R = H)

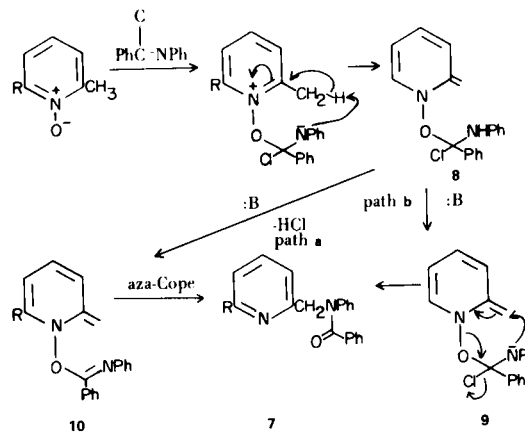
Table I

Effect of Added Base on the Yields in the Acylation of Pyridine 1-Oxides with *N*-Phenylbenzimidoyl Chloride (a)

Subst. X in pyridine 1-oxide	Added base	1	2	3	4
H (b)	-	48.8	18.2	-	32.6
H (c)	Et ₃ N (1 equiv.)	42.6	0	0	51.9
H (c)	Et ₃ N (2 equiv.)	60.4	0	0	39.1
H (b)	DBU (1)	98.3	0	0	-
Cl (d)	-	59.0	-	-	40.2
Cl	Et ₃ N (1 equiv.)	93.4	-	-	1.6
CN	-	51.0	-	3.0	49.8
CN	Et ₃ N (1 equiv.)	87.0	-	1.1	11.9
CN	DBU (1 equiv.)	91.0	-	0	7.0
Br (b)	-	49.0	-	27.0	20.5
Br (b)	Et ₃ N (1 equiv.)	76.0	-	19.0	2.1
Ph (c)	-	16.1	17.9	-	79.3
Ph (c)	Et ₃ N (2 equiv.)	66.1	0.6	-	29.1
Ph (c)	DBU (1 equiv.)	86.8	0	-	10.8

(a) The reactions were carried out with a 2:1 molar ratio of *N*-oxide to imidoyl chloride in dichloromethane at 80° for 24 hours. (b) Analyzed by glc as 2-anilinopyridine after hydrolytic work up. (c) Analyzed by glc without hydrolytic work up. (d) All new products were completely characterized.

(60%) m.p. 81-83°. 2,6-Lutidine 1-oxide and *N*-phenylbenzimidoyl chloride in the presence of DBU gave 7 (R = Me) (36%), m.p. 107-108°, in contrast to the reaction in the absence of DBU which gives mainly the



1,5-sigmatropic rearrangement product (1c). At least two possible routes can be envisaged leading to **7**. In the absence of base intermediate **8** gives 2-chloromethylpyridines (1c). With base, either **9** can be formed which then undergoes an intramolecular addition-elimination to give **7** (path **b**), or hydrogen chloride can be lost (path **a**) to give **10** which then undergoes an aza-Cope rearrangement, for which there is a precedent (4). Other, non-concerted, radical- or ion-pair processes are also conceivable. This reaction provides a convenient synthesis of aminomethylpyridine derivatives, the scope of which is being explored.

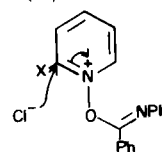
Acknowledgement.

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(2) This results from the nucleophilic displacement of the α -cyano- and α -bromo- group by chloride ion in the reaction of 2-cyano- and 2-bromopyridine 1-oxide with *N*-phenylbenzimidoyl chloride, probably as in (A).



(A)

(3) R. A. Abramovitch and I. Shinkai, unpublished results (1975).

(4) R. E. Ireland and A. K. Willard, *J. Org. Chem.*, **39**, 421 (1974). Although the known aza-Cope rearrangement requires heating at 190° 1,5-dienes conjugated with other π systems rearrange at lower temperatures (5).

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