Selective Formylation of 2-Aminopyridines

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Summary The specific *ortho*-formylation of 2-aminopyridines has been accomplished *via* the rearrangement of azasulphonium salts derived from 2-aminopyridines and dithian, and through the effective oxidation of 2-amino-3-methylthiomethylpyridines.

RECENTLY, we reported a method for the *ortho*-alkylation of aromatic heterocyclic amines.[1] We now report two processes for the selective *ortho*-formylation of 2-aminopyridine, one of which is based on an adaptation of our *ortho*-alkylation procedure, while the other involves oxidation of an intermediate from our previously described[1] alkylation process.

Treatment of the 2-aminopyridine with Bu^tOCl, 1,3-dithian, and NaOMe as in the Scheme gave the crude sulphilimines (**2**). A solution of the crude sulphilimines in Bu^tOH containing $KOBu^t$ (1 equiv.) was refluxed for 2—3 h to yield the dithioacetals (**3**). When the starting material was 2-aminopyridine (**1a**) the overall yield of (**3a**) was 19% (37% based on unrecovered 2-aminopyridine)

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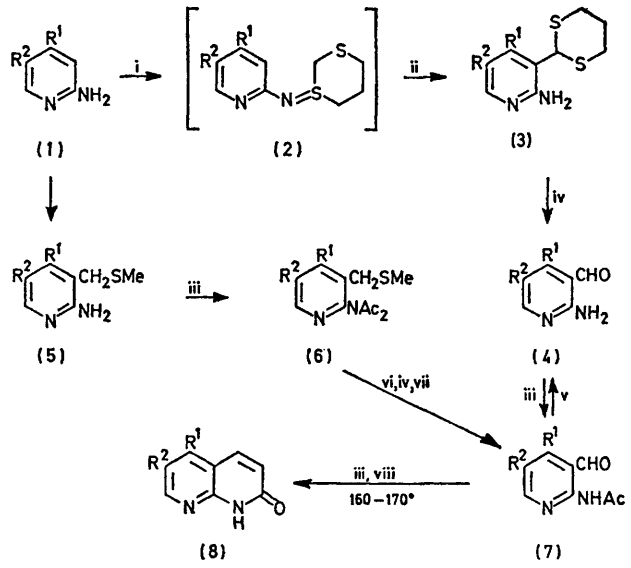
while 2-amino-4-methylpyridine (**1b**) gave 26% of (**3b**) (49% based on unrecovered 2-amino-4-methylpyridine). The recovery of (**1**) in these reactions was the result of the formal hydrolysis of (**2**) since the crude sulphilimines were shown to contain only traces of (**1**) whereas (**3**) was contaminated with large amounts of (**1**) following the base treatment. Using a modification of the Vedejs–Fuchs procedure for the hydrolysis of thioacetals,[2] (**3**) was treated with HgO–$BF_3{\cdot}Et_2O$ (2:3) in 15% aqueous tetrahydrofuran. Under these conditions (**3a**) gave a 68% yield of (**4a**), m.p. 96—98°[3,4] and (**3b**) gave 70% of (**4b**), m.p. 158—159°.



a; $R^1 = R^2 = H$; **b**; $R^1 = Me$, $R^2 = H$; **c**; $R^1 = H$, $R^2 = Cl$.

SCHEME. Reagents: i, a, Bu^tOCl (1 equiv.); b, dithian (1 equiv.); c, NaOMe (1·5 equiv.); ii, $KOBu^t$ (1 equiv.); iii, Ac_2O; iv, HgO–$BF_3{\cdot}Et_2O$; v, HCl; vi, *N*-chlorosuccinimide; vii, 10% aq. Na_2CO_3; viii, K_2CO_3.

Compound (**1**) was converted into (**5**) according to the published procedure.[1] Stirring of a solution of (**5**) in Ac_2O at 110—115° for 3 days gave the bisacetylated product (**6**). In order to convert the methylene group of (**6**) into a more highly oxidized methine group, (**6**) was treated with *N*-chlorosuccinimide (1·1 equiv.) in CCl_4 for 5 h at room temperature, which resulted in monochlorination of (**6**).[5] Hydrolysis of this chlorinated intermediate with HgO–$BF_3{\cdot}Et_2O$ (1:2), followed by treatment with aqueous Na_2CO_3 gave (**7**); yields: (**7a**), 42%; (**7b**), 66%; (**7c**), 65%. Compounds (**7**) were hydrolysed to (**4**) by refluxing in 2N-HCl for 1 h; yields: (**4a**), 74%; (**4b**), 93%; (**4c**), 98%. Compound (**4**) could be converted into (**7**) in near-quantitative yield through stirring with Ac_2O.

Compounds (**7**) were converted into the 1,8-naphthyridine derivatives (**8**) on heating with Ac_2O (3 equiv.) containing anhydrous K_2CO_3 (0·8 equiv.) at 160—170° for 2—3 h; yields: (**8a**), 70%; (**8b**), 64%.

The ease with which these procedures can be applied to aminopyridines suggests that the processes should also be useful in the selective formylation of other heterocyclic amines.

We thank the National Institute of General Medical Science for partial support of this study and the Phillips Petroleum Corp. for a fellowship (C.T.H.).

(*Received*, 23*rd May* 1974; *Com.* 602.)

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