Selective Formylation of 2-Aminopyridines

By PAUL G. GASSMAN*† and CHIN TEH HUANG
(*Department of Chemistry, The Ohio State University, Columbus, Ohio* 43210)

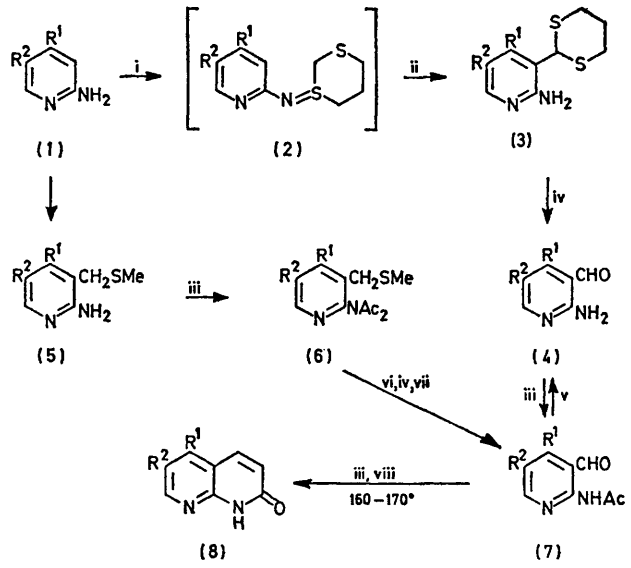
Summary The specific *ortho*-formylation of 2-aminopyridines has been accomplished *via* the rearrangement of azasulphonium salts derived from 2-aminopyridines and dithian, and through the effective oxidation of 2-amino-3-methylthiomethylpyridines.

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)

† *Correspondence to:* Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455.

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·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·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·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.

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[1] P. G. Gassman and C. T. Huang, *J. Amer. Chem. Soc.*, 1973, **95**, 4453.
[2] E. Vedejs and P. L. Fuchs, *J. Org. Chem.*, 1971, **36**, 366.
[3] A. Albert and F. Reich, *J. Chem. Soc.*, 1960, 1372.
[4] T. G. Majewicz and P. Caluwe, *J. Org. Chem.*, 1974, **39**, 720.
[5] P. G. Gassman and H. R. Drewes, *J. Amer. Chem. Soc.*, 1974, **96**, 3002.