Functionalization of Pyridine *via* Direct Metallation

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The isolation of mixtures of 2-, 3-, and 4-deuteriopyridine, 2-, 3-, and 4-trimethylsilylpyridine, or 2-, 3-, and 4-methylthiopyridine indicates successful metallation of pyridine with a 1 : 1 mixture of BuLi–Bu^tOK in tetrahydrofuran–hexane at −100 °C.

Whereas for most heterocyclic compounds α-metallated derivatives have been obtained by direct metallation with strongly basic organometallic reagents, all efforts to metallate pyridine have so far failed.[1] Very strong bases such as butyl- and phenyl-lithium preferentially add to the azomethine double bond.[2] Interaction between pyridine and lithium di-isopropylamide (LDA) in diethyl ether–hexamethylphosphoric triamide (HMPT) was reported[3] to give mainly α,α′-bipyridyl; 2-lithiopyridine was assumed to be an intermediate species. Very recently Epsztajn *et al.*[4] showed that pyridine derivatives with an activating carboxamide substituent are metallated in up to 25% yield with one equivalent of LDA. LDA and pyridine itself give a much lower equilibrium concentration of lithiopyridine. The direct metallation of pyridine derivatives possessing an activating substituent has been the subject of continuous interest.[5—10]

We report herein the successful, complete metallation of pyridine. Addition at −105 °C of pyridine to a 50% excess of the 1 : 1 complex of butyl-lithium and potassium butoxide[11] in hexane–tetrahydrofuran (THF) (1 : 2, v/v) followed after 90 min by quenching with deuteriomethanol (3 mol. equiv.), dimethyl disulphide (20% excess), or trimethylchlorosilane (20% excess) gave mixtures of 2-, 3-, and 4-deuteriopyridine, 2-, 3-, and 4-methylthiopyridine, or 2-, 3-, and 4-trimethylsilylpyridine, respectively in yields of 90—94%. The isolation of these products was carried out by extracting the reaction mixtures with dilute hydrochloric acid and subsequently liberating the pyridines by addition of potassium hydroxide.

The ratio of the 2-, 3-, and 4-deuteriated pyridines was approximately 6 : 1 : 3 as determined by ^{1}H n.m.r. spectroscopy which agreed with the ratio of the products obtained.†

These data unambiguously prove that metallation of pyridine had taken place and suggest a kinetic acidity ratio for the protons (2 + 6) : (3 + 5) : 4 of 6 : 1 : 6. This is quite different from the ratios derived by Zoltewicz *et al.*[12] from the methoxide-catalysed deuteriation of pyridine in MeOD [(2 + 6) : (3 + 5) : 4 = 1 : 9.3 : 12] and the NH_2^--catalysed replacement of D in [$^2H_5$]pyridine in liquid NH_3 (1 : 72 : 240). Repulsion between the free electron pair on N and the negative charge on the 2- and 6-positions was invoked to explain the decreased acidity of the 2- and 6-protons. Our deprotonation conditions, involving the use of an extremely strong base in a mildly polar solvent system may, however, give rise to ratios which are completely different from those in thermodynamically controlled conditions.‡

Reaction of quinoline or isoquinoline with BuLi–Bu^{t}OK resulted in addition of the organometallic reagent to the hetero-ring. With equimolar quantities of Bu^{t}OK and LDA in THF–hexane with HMPT as co-solvent, the extent of metallation was small as shown by the formation of only a *ca.* 5% yield of deuteriated heterocycle on quenching with D_2O (the position of the introduced D was not determined). Successive treatment of quinoline or isoquinoline with LDA–Bu^{t}OK in THF-hexane at −60 °C and then dimethyl disulphide surprisingly afforded 3-methylthioquinoline and 4-methylthioisoquinoline, respectively, in *ca.* 60% yields (*cf.* ref. 4 where the reaction of pyridine carboxamides with LDA and derivatization with MeOD and $PhCONMe_2$ is described). Reaction of the solutions of the partially metallated quinoline or isoquinoline with Me_3SiCl or alkyl halides led to the formation of intractable material, from which the expected derivatives were absent.

Received, 22nd September 1983; Com. 1253

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† The ratio was the same when the interval between metallation and functionalization was shortened to 10 min. The only difference with longer intervals was that the yields of the deuteriated derivatives were only *ca.* 50%; incomplete deuteriation {50% [$^2H_1$]pyridine, and 50% non-deuteriated pyridine} indicates that the deprotonation at −100 °C was not instantaneous.

‡ *Added in proof:* Treatment of pyridine with BuLi–Bu^{t}OK in diethyl ether affords mainly (≥85%) 2-potassiopyridine, while in a more polar medium (THF, HMPT as cosolvent) *ca.* 90% (rel.) of 4-potassiopyridine is formed.

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