Lewis Acid Complexed Heteroatom Carbanions; Synthesis of some α-Pyridyl Alcohols

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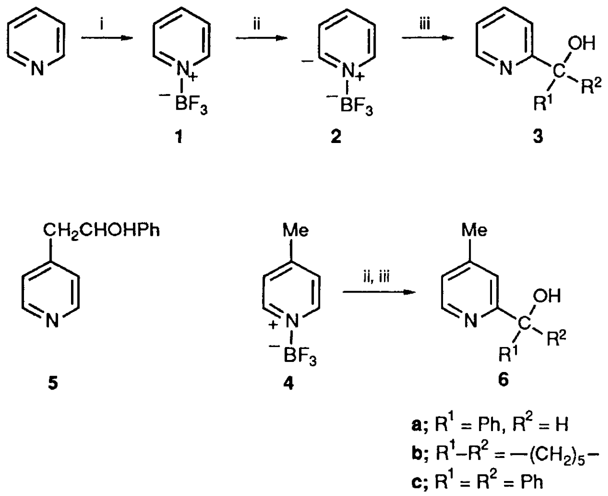
Metallation of BF_3–pyridine complex with lithium tetramethylpiperidide (LTMP) in ether at −78 °C, followed by reaction with carbonyl compounds, affords α-pyridyl alcohols in good yields.

α-Pyridyl alcohols, which are intermediates of some pharmacological interest,[1,2] are often synthesised from halogen derivatives or *N*-oxides of pyridine because direct metallation of this heterocycle is deemed impractical.[3–5] It was, therefore, of interest to see if Lewis acid complexation can be used for this purpose (Scheme 1).[6]

Our attempts to obtain the alcohol **3a** through deprotonation of pyridine with the highly hindered base lithium tetramethylpiperidide (LTMP) furnished only 2,2′-bipyridyl[7] at −78 °C, while no reaction was observed at −120 °C. However, treatment of an ether solution[†] of the BF_3-complex **1** with LTMP at −78 °C, followed by addition of benzaldehyde afforded **3a**[8] in 85% yields.[‡] The alcohol **3b**[9] (87%) was



Scheme 1 *Reagents and conditions*: i, $BF_3\cdot Et_2O$ (1.05 equiv.), 0 °C, 0.25 h, ether; ii, LTMP (1.1 equiv.), −78 °C, 0.25 h, ether; iii, $R^1C(:O)R^2$ (1.1 equiv.), −78 °C, 1 H.

[†] Use of tetrahydrofuran (THF) as solvent gave inferior yields. Also reactions with methyl iodide and benzyl chloride proceeded poorly.

[‡] Yields are for pure materials isolated after chromatography or crystallisation. For all compounds, or their derivatives, m.p.s corresponding to literature values were obtained in addition to spectroscopic characterisation. Selected data for **2b**: picrate m.p. 85–86 °C; H NMR ($CDCl_3$): δ 8.43–8.75 (m, 1H, ArH), 8.05–8.42 (m, 3H, ArH), 4.5–5.0 (br, s, 1H, OH; exchangeable with D_2O) and 1.75 [br s, 10H, $-(CH_2)_5-$]; mass spectrometry: *m*/*z* 177 (M^+).

obtained similarly from cyclohexanone. Under these conditions, reaction of uncomplexed γ-picoline and benzaldehyde led to the side chain alcohol **5**.[10] Again, BF_3 addition had a dramatic effect and from complex **4**, the alcohols **6a**[11] (84%), **6b**[12] (85%) and **6c**[5] (75%) were obtained cleanly. Thus, it is clear that α-lithiation can be promoted even in presence of relatively acidic methyl protons of γ-picoline.

To probe if chiral boron compounds can also be used, reaction between benzaldehyde and a complex of pyridine with diisopinocampheylborane[13] was carried out. Optically inactive alcohol **3a** was obtained, in 45% yield, showing that α-metallation is facilitated but without asymmetric induction in the subsequent step. Chiral Lewis acids with additional metal chelating sites, to provide rigid intermediates,[14] may prove more effective and work along these lines is being pursued.

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References

1 H. Y. Yale in *Pyridine and its Derivatives*, Part 2, ed. E. Klingsberg, Interscience, New York, 1961.

2 N. Spencer, D. Papa, E. Schwenk and M. Sherlock, *J. Am. Chem. Soc.*, 1951, **73**, 3856.

3 For a discussion of the problems encountered in α-metallation of pyridine see: *Comprehensive Heterocyclic Chemistry*, ed. A. R. Katritzky and C. W. Rees, Pergamon Press Ltd., Oxford, 1984, vol. 2; D. Price, B. Iddon and B. J. Wakefield, *Bromine Compounds: Chemistry and Applications*, Elsevier, Amsterdam, 1988. Lithiation is possible in the presence of stabilising substituents on the pyridine nucleus; F. Marsais, G. Le Nard and G. Queguiner, *Synthesis*, 1982, 235. For use of hexafluoroacetone in metallation of pyridines see: S. L. Taylor, D. Y. Lee and J. C. Martin, *J. Org. Chem.*, 1983, **48**, 4157.

4 R. A. Abramovitch and A. R. Vinutha, *J. Chem. Soc. (C)*, 1969, 2104.

5 Emmert reaction or its modified version gives modest yields of α-pyridyl alcohols. C. E. Crawforth and C. A. Russell, *Chem. Commun.*, 1970, 1406.

6 See the preceeding Communication. The intermediate **2** may have some carbene character.

7 This is in conformity with earlier results using lithium diisopropylamide (LDA); A. C. Clarke, S. McNamara and O. Meth-Cohn, *Tetrahedron Lett.*, 1974, **27**, 2373; G. R. Newkome and D. C. Hager, *J. Org. Chem.*, 1982, **47**, 599.

8 A. E. Tschitschibabin, *Berichte*, 1904, **37**, 1370.

9 H. L. Lochte, P. F. Kruse, Jr. and E. N. Wheeler, *J. Am. Chem. Soc.*, 1953, **75**, 4477.

10 V. K. Goel, R. K. Pandey and B. C. Joshi, *J. Ind. Chem. Soc.*, 1977, **LIV**, 538.

11 J. Bosch, R. Grandos, R. Llohera and D. Mauleon, *An. Quim., Ser. C*, 1981, **77**, 166; *Chem. Abstr.*, 1982, **97**, 23599u.

12 R. A. Abramovitch, F. M. Smith, E. E. Knaus and M. Saha, *J. Org. Chem.*, 1972, **37**, 1960.

13 H. C. Brown and N. N. Joshi, *J. Org. Chem.*, 1988, **53**, 4059.

14 K. Rein, M. Goicoechea-Pappas, T. V. Anklekar, G. C. Hart, G. A. Smith and R. E. Gawley, *J. Am. Chem. Soc.*, 1989, **111**, 2211.