Preparation of Isopropyl- and t-Butyl-pyridines from Methylpyridines by Phase-transfer Catalysed Alkylation

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Summary Methyl groups in the 2,4, and 6 positions of pyridine rings have been converted into isopropyl (2 and 6 positions) and t-butyl (4 position) groups by alkylation of the *N*-methylpyridinium iodides with methyl iodide, using a phase-transfer catalyst; attempts to prepare 2,6-diethylpyridine, or to alkylate 3-methylpyridine, by this technique were unsuccessful.

WE required several 2,6-dialkylpyridines in connection with the investigation of a reaction mechanism, and whilst 2,6-dimethyl- and 2,6-di-t-butylpyridine were commercially available, 2,6-diethyl- and 2,6-di-isopropyl-pyridine were not. These latter compounds (and the di-t-butylpyridine) may be prepared by alkylation of pyridine with the appropriate alkyl-lithium,[1] but this process generally,[2] and certainly in our experience, gave complex mixtures which we were unable to separate economically. The alkyllithium compounds also require careful handling. A synthesis of the alkylpyridines which gives in each case a single product with the alkyl substituents correctly oriented, and that also involves simpler practical procedures, has obvious advantages.

The alkylation of carbanions in the presence of phase-transfer catalysts has been studied by many different groups.[3] The title compounds have been synthesised by using this technique to generate a carbanion from the appropriate quaternised pyridine as starting material, and then alkylating the carbanion with iodomethane.

2,6-Dimethylpyridine was quaternised with iodomethane,[4] the salt recrystallised from ethanol, and then alkylated in the presence of a large excess of iodomethane in a two-phase system consisting of aqueous NaOH and CH_2Cl_2. The catalyst was tetra-n-butylammonium hydroxide (the commercially available 40% aqueous solution). The progress of the reaction was monitored by g.l.c., the quaternary salts undergoing dequaternisation in the heated injection port of the gas chromatograph.

The reaction product was dequaternised using refluxing aqueous sodium 4-methylbenzenethiolate.[5]† (Triphenylphosphine in dimethylformamide could also be used,[6] but the work-up procedure was simpler when the thiolate was used. Thiosulphate anion[7] as a dequaternising agent proved unsuccessful. Use of slightly less than the theoretical amount of thiolate led to preferential dequaternisation of the *N*-methyl-2,6-di-isopropylpyridinium iodide, leaving two other trace products, shown in the chromatogram of the reaction mixture, unaffected.)

2-Methyl- and 2,6-dimethyl-pyridine gave only the corresponding 2-isopropyl- and 2,6-di-isopropyl-pyridine. 4-Methylpyridine gave 4-t-butylpyridine more slowly. G.l.c. analysis of the reaction mixture at intervals showed that the alkylation proceeded stepwise *via* two intermediates, presumably 4-ethyl- and 4-isopropyl-pyridine. No attempt was made to isolate these intermediate products. 2,4,6-Trimethylpyridine underwent a fairly rapid reaction to give two major products in comparable amounts, as indicated by g.l.c., but prolonged alkylation converted the one of lower retention time into the one of higher retention time,

TABLE. Products of phase-transfer catalysed alkylation of (quaternised) methylpyridines.

Pyridine	Product[a]	Yield (%)[b]
2-Methylpyridine	2-Isopropylpyridine	36
4-Methylpyridine	4-t-Butylpyridine	37
2,6-Dimethylpyridine	2,6-Di-isopropylpyridine	40
2,4,6-Trimethylpyridine	4-t-Butyl-2,6-di-isopropylpyridine	20

[a] Satisfactory n.m.r. and mass spectral data were obtained for all products [b] No attempt has been made to optimise reaction conditions. The yields quoted refer to isolated samples of at least 99% purity. (The alkylpyridines are difficult to distil because of frothing). Yields of the quaternised alkylated compounds are high (80—90% of crystalline material), the main losses occurring in the dequaternisation step.

† *Caution:* Contact with a CH_2Cl_2 solution of the products of the dequaternisation may lead to an allergic reaction resulting in extreme sensitivity to contact with the thiol.

which proved to be 4-t-butyl-2,6-di-isopropyl-pyridine. The compound of lower retention time is believed to be 2,4,6-tri-isopropyl-pyridine. The results are summarised in the Table.‡

2,6-Di-t-butylpyridine could not be prepared by this method, nor was 3-methylpyridine alkylated by this technique. (See, however, ref. 8). Attempts to attach a group having a larger steric requirement (*e.g.*, diphenylmethyl or 2,4,6-trimethylbenzyl) to the nitrogen atom of 2,6-dimethylpyridine ('steric blocking') so that the alkylation would stop (because of steric hindrance) at *N*-alkyl-2,6-diethylpyridinium iodide, were unsuccessful. ^{1}H N.m.r. spectra of mixtures of 2,6-dimethylpyridine and the intended blocking group showed that no quaternisation had occurred.

Control experiments involving alkylation of the various methylsubstituted pyridinium iodides in aqueous NaOH, using iodomethane in the absence of CH_2Cl_2 and without a phase-transfer catalyst, led to slower reactions and more complex mixtures of products, as indicated by g.l.c.

Added in proof: If the quaternised alkylated compounds are heated with anhydrous $MeCO_2Na$[9] or KNCS, dequaternisation occurs rapidly to give the alkylated pyridines in much higher yields.

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‡ In all the above reactions, the prior quaternisation of the pyridine to be alkylated could be omitted, the excess of iodomethane partly being used to effect this step in the reaction mixture. However, this procedure led to slower reactions in some cases.

[1] See, *e.g.* H. C. Brown and B. Kanner, *J. Amer. Chem. Soc.*, 1966, **88**, 986; R. F. Francis, J. T. Wisener, and J. M. Paul, *Chem. Comm.*, 1971, 1420.
[2] F. V. Scalzi and N. F. Golob, *J. Org. Chem.*, 1971, **36**, 2541.
[3] For reviews, see: J. Dockx, *Synthesis*, 1973, 441; E. V. Dehmlow, *Angew. Chem. Internat. Edn.*, 1974, **13**, 170; 1977, **16**, 493; M. Makosza, *Pure. Appl. Chem.*, 1975, **43**, 439; *Russ. Chem. Rev.*, 1977, **46**, 1151; R. A. Jones, *Aldrichimica Acta*, 1976, **9**(3), 35; see also W. P. Weber and G. W. Gokel, 'Phase Transfer Catalysis in Organic Synthesis,' Springer-Verlag, Berlin, 1977.
[4] Iodomethane is toxic, see the warning in *Org. Synth.*, 1977, **56**, 127.
[5] T. Kametani, K. Kigasawa, M. Hiiragi, N. Wagatsuma, K. Wakisaka, and O. Kusama, *J. Medicin Chem.*, 1969, **12**, 694.
[6] V. Berg, R. Gallo, and J. Metzger, *J. Org. Chem.*, 1976, **41**, 2621.
[7] M. C. Whiting, personal communication.
[8] H. C. Brown and W. A. Murphey, *J. Amer. Chem. Soc.*, 1951, **73**, 3308. The alkylation of 3-methylpyridine using $NaNH_2$ and MeCl is described.
[9] U. Gruntz, A. R. Katritzky, D. H. Kenny, M. C. Rezende, and H. Sheikh, *J.C.S. Chem. Comm.*, 1977, 701.