Solvent-free Fluorination of Partially-chlorinated Heterocyclics: Synthesis of 2,6-Difluoropyridine from 2,6-Dichloropyridine

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Previous studies on the solvent-free fluorination of partially-chlorinated heterocyclics such as 2-chloropyridine, 2,3,4,6- and 2,3,5,6-tetrachloropyridine, and 2,4,6-trichloropyrimidine with alkali metal fluorides or bifluorides revealed an inconsistent product pattern: degradation, partial or complete halogen exchange could occur. The present study concerned application of the solvent-free halogen exchange technique (potassium fluoride) to 2,6-dichloropyridine (I). The latter, as well as its fluorination products, exhibited good stability at 400° to provide an 80% yield of 2,6-difluoropyridine (III). Moderation of fluorination conditions also permitted isolation of the precursor, 2-chloro-6-fluoropyridine (II), a new compound. The above solvent-free process to III is superior to the previously-reported halogen-exchange route in dimethyl sulfone solvent on the basis of yield, reaction time and number of processing steps.

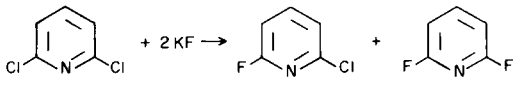
The solvent-free halogen exchange technique with anhydrous potassium fluoride at elevated temperatures with perchlorinated heterocyclic substrates such as cyanuric chloride (1), pentachloropyridine (2,3), tetrachloropyrimidine (4), tetrachloropyridazine (5), tetrachloropyrazine (4b), heptachloroquinoline (6) and heptachloroisoquinoline (6) is a convenient one-step route to the corresponding perfluorinated heterocyclic.

In contrast, solvent-free fluorination of partially-halogenated heterocyclics (devoid of exocyclic activating groups, *e.g.*, nitro) does not follow a consistent pattern: partial or complete halogen exchange, as well as degradation, can occur. Thus, treatment of 2,3,4,6- and 2,3,5,6-tetrachloropyridine with potassium fluoride at 400° resulted in partial fluorination (primarily in the 2,6-position) to give 3-chloro-2,4,6-trifluoropyridine (34% yield) and 3,5-dichloro-2,6-difluoropyridine (63% yield), respectively (2). Attempts to effect complete halogen exchange by use of higher temperatures (420°) resulted in decomposition. This instability was attributed by Chambers, *et al.*, to the presence of hydrogen in the molecule (2).

Decomposition also resulted when 2-chloropyridine was subjected to solvent-free fluorination with potassium fluoride under milder conditions (315°) (7). However, employment of potassium bifluoride effected facile transformation to 2-fluoropyridine in 74% yield.

Treatment of another partially-halogenated heterocyclic, 2,4,6-trichloropyrimidine, with potassium fluoride at 310° resulted in complete halogen exchange to give a 72% yield of 2,4,6-trifluoropyrimidine (8).

The present investigation involved extension of the solvent-free fluorination technique (potassium fluoride) to another partially-chlorinated substrate, 2,6-dichloropyridine (I). The latter, as well as its fluorination products, exhibited good stability during a reaction period of 16 hours at 400° to give an 80% yield of 2,6-difluoropyridine (III) and < 1% yield of its precursor, 2-chloro-6-fluoropyridine (II). The yield of II could be increased (38%) by moderation of fluorination conditions (6 hours, 340°).



I II III

The factors which may have contributed to the degradation encountered during the solvent-free fluorination (potassium fluoride) of 2-chloropyridine (7) did not play a dominant role in the corresponding reaction with I.

The above solvent-free halogen exchange route to III represents an improvement over earlier procedures. The first published synthesis of III involved a multi-step process based on methyl 6-fluoropicolinate as starting material (9,10). The subsequent discovery of a one-step route (11, 12) involving the conversion of I to III by use of the potassium fluoride exchange technique in a polar

solvent (dimethylsulfone) simplified the initial 2,6-difluoropyridine process. However, the polar solvent route proceeds sluggishly (200°/100 hours), requires additional product isolation steps (steam distillation, ether extraction) and gives lower yields of III (52%) as compared with the solvent-free process.

EXPERIMENTAL

1. Analytical

The following VPC conditions were employed: F and M Chromatograph, Model 300: 2 meter, 1/4 in. aluminum; 15% Se 30 on Chromosorb W. (80-100 mesh); column temp., 100-150°; rate, 6.4°/minute; helium flow, 7.2 sec./10 ml., injection port temperature, 243°; block temperature, 255°. The following retention times were noted: 2,6-difluoropyridine, 1.3 cm.; 2-chloro-6-fluoropyridine, 3.0 cm.; and 2,6-dichloropyridine, 6.0 cm.

Infrared spectra were obtained by use of a Perkin-Elmer Model 137 spectrophotometer.

2. Fluorination of 2,6-Dichloropyridine.

A 300 ml. monel rocking microautoclave containing 2,6-dichloropyridine (0.392 mole; 56.8 g.; Olin Mathieson; 98% assay (VPC)) and potassium fluoride (2.0 moles; 116.2 g. Baker and Adamson, dried at 100°/0.5 mm. for 18 hours) was purged with nitrogen and the contents heated at 400° (300 p.s.i.g.) for 16 hours. The organic products were transferred under vacuum (4 mm) into a receiver cooled at -78° to give 36.2 g. of a colorless liquid ($n_D^{25.5}$ 1.4361), which consisted (VPC) of: 2,6-difluoropyridine (0.318 mole; 79.5% uncorrected yield); 2-chloro-6-fluoropyridine (0.002 mole); and, 2,6-dichloropyridine (0.001 mole). Distillation provided a center fraction, b.p. 125.0-125.5°, $n_D^{26.5}$ 1.4342 (reported for III: b.p. 124.5°; n_D^{25} 1.4349 (9, 10)). The product had the characteristic infrared spectral bands of (III) (13). Mass spectral analysis showed a molecular weight ion peak at m/e 115. Analysis of the inorganic salt cake revealed the presence of 0.727 g. -atom of chloride ion, which corresponded to 92.8% conversion of I.

A mixture of 2,6-dichloropyridine (0.49 mole, 71.0 g.) and potassium fluoride (2.0 moles; 116.2 g.) was heated at 340° for 6 hours. The organic products were transferred under vacuum (4 mm.) to give 48.0 g. of liquid. VPC revealed: 2,6-difluoropyridine (0.183 mole; 37.3% yield) and 2-chloro-6-fluoropyridine (0.185 mole; 37.8% yield). Distillation provided 2,6-difluoropyridine, b.p. 125°, and 2-chloro-6-fluoropyridine, b.p. 81-82°/51 mm.; m.p. 24-25°.

Anal. Calcd. for C_5H_3ClFN: Cl, 27.0. Found: Cl, 26.9.

Mass spectral analysis showed a molecular weight ion peak at m/e 131. The inorganic salt residue contained 0.652 g. -atom chloride ion. The infrared spectrum of II showed absorptions (μ) at: 3.22 (w) 6.30(vs): 6.35(vs); 6.50(w); 6.90(sh); 7.00(vs); 7.12(sh); 7.90(s); 8.60(s); 8.80(w); 9.36(w); 10.10(m); 11.06(s); 11.25(sh); 12.60(s), 13.89(w); and, 14.62(m).

REFERENCES

(1) British Patent, 873,251 (July 19, 1961).

(2a) R. D. Chambers, J. Hutchinson and W. K. R. Musgrave, *Proc. Chem. Soc.*, 83, (1964); (b) *J. Chem. Soc.*, 3573 (1964).

(3a) R. E. Banks, R. N. Haszeldine, J. V. Latham and I. M. Young, *Chem. Ind.* (London), 835 (1964); (b) *J. Chem. Soc.*, 594 (1965).

(4a) Belgian Patent, 660,907 (Sept. 10, 1965). *Chem. Abstr.*, 64, 3568 (1966); (b) R. D. Chambers, J. A. H. MacBride and W. K. R. Musgrave, *Chem. Ind.* (Longon), 1721 (1966); (c) R. E. Banks, D. S. Field and R. N. Haszeldine, *J. Chem. Soc.* (C), 1822 (1967).

(5) R. D. Chambers, J. A. H. MacBride and W. K. R. Musgrave, *Chem. Ind.* (London), 904 (1966).

(6) R. D. Chambers, M. Hole, B. Iddon, W. K. R. Musgrave and R. A. Storey, *J. Chem. Soc.* (C), 2328 (1966).

(7) M. M. Boudakian, *J. Heterocyclic Chem.*, 4, 381 (1967).

(8) M. M. Boudakian, E. H. Kober and E. R. Shipkowski, U. S. Patent, 3,280,124 (Oct. 18, 1966). This reaction has also been effected at 260-310° (48-71% yield) in the presence of antimony trioxide catalyst; B. A. Ivin, V. P. Slesarev and E. G. Sochilin, *J. Gen. Chem.* (U.S.S.R.), 34, 4120 (1964). *Chem. Abstr.*, 62, 9127 (1965). (See also ref. 4c.).

(9) G. C. Finger and L. D. Starr, *Nature*, 595 (1961).

(10) G. C. Finger, L. D. Starr, A. Roe and W. J. Link, *J. Org. Chem.* 27, 3965 (1962).

(11) J. Hamer, W. J. Link, A. Jurevich and T. L. Vigo, *Rec. Trav. Chim.*, 81, 1058 (1962).

(12) G. C. Finger, L. D. Starr, D. R. Dickerson, H. S. Gutowsky and J. Hamer, *J. Org. Chem.*, 28, 1666 (1963).

(13) R. T. Bailey and D. Steele, *Spectrochim. Acta*, 23A, 2997 (1967).

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