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PRELIMINARY NOTE

Replacement of α-Chlorine in N-Heteroaromatics by the $(CF_3)_2NO$ Group using Mercurials derived from Bistrifluoromethyl Nitroxide: Synthesis of 2-(Bistrifluoromethylamino-oxy)-pyridine, -pyrimidine and -pyrazine

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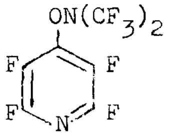
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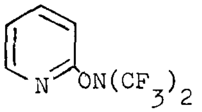
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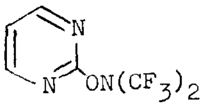
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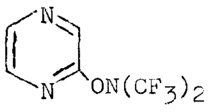
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4-(Bistrifluoromethylamino-oxy)tetrafluoropyridine (1), the sole azine bearing the $(CF_3)_2NO$ group as a nuclear substituent reported hitherto [1], can be prepared by treating pentafluoropyridine with the salt $(CF_3)_2NO^-Na^+$ [2]; even under forcing conditions, however, this reagent fails to convert 2-chloro- or 2-bromo-pyridine into 2-(bistrifluoromethylamino-oxy)pyridine (2) [3]. Studies on methods for introduction of the bistrifluoromethylamino-oxy function into bioactive N-heterocycles have now revealed that smooth $(CF_3)_2NO$-for-Cl exchange in 2-chloropyridine can be accomplished by heating (50 °C) this substrate with a mixture of mercury(I) and mercury(II) bistrifluoromethylnitroxide of approximate composition $[(CF_3)_2NO]_{1.3}Hg$ (4) [4]. Furthermore, this 'mixed' mercurial also converts 2-chloro-pyrimidine and -pyrazine into the corresponding (bistrifluoromethylamino-oxy)diazines 3 and 4, the simplest members of their class to be synthesised to-date [8]. This approach to the introduction of a $(CF_3)_2NO$ group alpha to nitrogen in an azine or diazine was conceived following studies on reactions between imidoyl halides and mercury(II) bistrifluoromethylnitroxide [9-11], particularly the sequence $Me_3CN{=}CCl_2$ + $[(CF_3)_2NO]_2Hg$ (5) $\longrightarrow$ $Me_3CN{=}CClON(CF_3)_2$ $\longrightarrow$ (with 5) $Me_3CN{=}C[ON(CF_3)_2]_2$ [10].

In a typical experiment, a mixture of 2-chloropyrimidine (0.84 g, 7.3 mmole), mercury bistrifluoromethylnitroxide {from 2.04 g (10.2 mmole) of Hg and 2.25 g (13.4 mmole) of $(CF_3)_2NO$. [4]} and 1,1,2-trichlorotrifluoroethane (5 g; inert solvent) was heated at 50 °C for 3 days under anaerobic conditions in a Pyrex ampoule (50 cm^3). The product was filtered to remove a yellowish solid, which was washed with a fresh portion of solvent (20 cm^3); distillation of the combined liquid fractions yielded 2-(bistrifluoromethylamino-oxy)pyrimidine (3) (1.18 g, 4.78 mmole, 65%), b.p. 158 °C at 753 mmHg. Similarly, 2-chloropyridine and 2-chloropyrazine were converted into 2-(bistrifluoromethylamino-oxy)pyridine [2; 39% yield after separation from unchanged $2\text{-}ClC_5H_4N$ by preparative g.l.c. (2 m TXP, 100 °C); b.p. 122 °C] and 2-(bistrifluoromethylamino-oxy)pyrazine [4; 22% yield after g.l.c. (2 m APL, 100 °C); b.p. 107 °C] on a 7 mmole scale. Products were identified by elemental analysis and spectroscopic methods [i.r., n.m.r. (^1H and ^{19}F), and mass]. Yields were not optimised, and treatment of 2-chloropyrimidine with a reagent of composition $[(CF_3)_2NO]_{1.98}Hg$, i.e. virtually mercury(II) bistrifluoromethylnitroxide, did not improve the yield of 3 [12].

In the absence of detailed mechanistic information, currently being sought, we conjecture that the conversions outlined above proceed via an addition-elimination process involving regiospecific addition of an $Hg{-}ON(CF_3)_2$ moiety across an N=CCl linkage. Lack of an exchange reaction between 3-chloropyridine and $[(CF_3)_2NO]_{1.5}Hg$ supports this idea; note that in the non-aromatic field, $[(CF_3)_2NO]_2Hg$ has been shown to combine with perfluoro-2-azapropene to yield the novel mercurial $[(CF_3)_2NOCF_2N(CF_3)]_2Hg$, which decomposes when heated to give, inter alia, the product of $(CF_3)_2NO$-for-imidoyl F exchange $CF_3N{=}CFON(CF_3)_2$ [9].

1 Several azines containing a bistrifluoromethylamino-oxy group as a side-chain component are known, <u>e.g</u>., $4\text{-}(CF_3)_2NOCH_2.C_5F_4N$ {from $4\text{-}CH_3.C_5F_4N$ + $(CF_3)_2NO\bullet$ [R.E. Banks, R.N. Haszeldine and G. Shaw, unpublished results (see G. Shaw, Ph.D. Thesis, University of Manchester, 1968)]} , $3\text{-}(CF_3)_2NOCH_2.C_5H_4N$ {from $3\text{-}CH_3.C_5H_4N$ + $(CF_3)_2NO\bullet$ [R.E. Banks, R.N. Haszeldine and R.A. Hughes, unpublished results]}, and $2\text{-}(CF_3)_2NOC(O).C_5H_4N$ {from $2\text{-}HOCH_2.C_5H_4N$ or $2\text{-}HC(O).C_5H_4N$ + $(CF_3)_2NO\bullet$ [R.E. Banks, R.N. Haszeldine, R.A. Hughes, C.M. Irvin, and A.E. Tipping, unpublished results (see C.M. Irvin, Ph.D. Thesis, University of Manchester, 1980)]}.

2 R.E. Banks, R.N. Haszeldine and D.L. Hyde, Chem. Comm., (1967) 413.

3 R.E. Banks, R.N. Haszeldine, R.A. Hughes, C.M. Irvin and A.E. Tipping, unpublished results.

4 Prepared by shaking mercury with a two-molar equivalent of bistrifluoromethyl nitroxide at 20 °C for 2 h, followed by removal of the unreacted radical (<u>in vacuo</u>) from the reaction vessel (Pyrex ampoule) after it had been kept in the dark at room temperature for 12 h; the chlorinated substrate under investigation and the solvent were then distilled into the ampoule using vacuum transference procedures; the ampoule was fitted with a PTFE needle valve (4 mm Rotaflo) to facilitate the manipulations required. Details of the preparation of mercurials of composition $[(CF_3)_2NO]_2Hg$ [5] and $(CF_3)_2NOHg$ [6] can be found in the literature; production of the mercury(II) derivative requires the use of at least a threefold excess of bistrifluoromethyl nitroxide [7] and preferably [5] a 10:1 $(CF_3)_2NO\bullet$: Hg stoicheiometry — a costly business. Note that an upper temperature limit of <u>ca</u>. 50 °C must be imposed on reactions involving these mercurials to restrict their dissociation, which occurs cleanly and efficiently in the range 65 — 85 °C [5,6] and provides the basis for a method of purification of bistrifluoromethyl nitroxide [6].

5 H.J. Emeléus, J.M. Shreeve and P.M. Spaziante, J. Chem. Soc. (A), (1969) 431.

6 R.R. Reinhard and W.D. Blackley, U.S.P. 3,644,449/1972.

7 A.R. Bailey, R.E. Banks and D.R. Choudhury, unpublished observations.

8 Two (bistrifluoromethylamino-oxy)diazines of the fluorocarbon class have been synthesised previously, *viz.* 4-(bistrifluoromethylamino-oxy)-2,5,6-trifluoropyrimidine [from tetrafluoropyrimidine + $(CF_3)_2NOH$-CsF] and 2-(bistrifluoromethylamino-oxy)-4,6-difluoro-5-(trifluoromethyl)-pyrimidine [from trifluoro-5-(trifluoromethyl)pyrimidine + $(CF_3)_2NOH$-CsF] (R.E. Banks, J.M. Birchall, R.N. Haszeldine and S.C. Hillyard, unpublished results). In the hydrocarbon field previous work was restricted to the synthesis of barbituric acid derivatives, using bistrifluoromethyl nitroxide as the bistrifluoromethylamino-oxylating agent {*e.g.* 5-phenylbarbituric acid + $2(CF_3)_2NO\bullet \longrightarrow$ 5-(bistrifluoromethylamino-oxy)-5-phenylbarbituric acid; 5-benzylidenebarbituric acid + $2(CF_3)_2NO\bullet \longrightarrow$ 5-(bistrifluoromethylamino-oxy)-5-[(α-bistrifluoromethylamino-oxy)benzyl]barbituric acid} (R.E. Banks, J.M. Birchall, R.N. Haszeldine and W.J. Nicholson, unpublished results).

9 R.E. Banks, D.R. Choudhury, R.N. Haszeldine and C. Oppenheim, J. Organometal. Chem., **43** (1972) C20.

10 R.E. Banks, R.N. Haszeldine and C.W. Stephens, Tetrahedron Letters, (1972) 3699.

11 R.E. Banks and C. Oppenheim, J. Fluorine Chem., **12** (1978) 27.

12 We are indebted to Allan R. Bailey for carrying out this experiment.