Synthesis and Enantioselective Fluorodehydroxylation Reactions of (*S*)-2-(Methoxymethyl)pyrrolidin-1-ylsulphur Trifluoride, the First Homochiral Aminofluorosulphurane†

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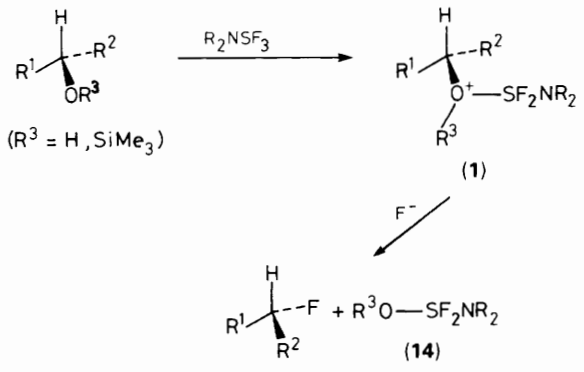
(*S*)-2-(Methoxymethyl)pyrrolidin-1-ylsulphur trifluoride (**7**), the first homochiral aminofluorosulphurane and one of the most stable aminofluorosulphuranes yet reported, has been prepared, and has been shown to be an effective enantioselective fluorodehydroxylating agent.

Homochiral organofluorine compounds bearing fluorine at a stereogenic centre are important in a number of areas.[1—3] However, almost all the methods that are available for the enantioselective synthesis of such compounds from prochiral or chiral racemic non-fluorinated precursors require fluorination and enantioselection to be achieved in two distinct steps.[4] A strategy that combines fluorination and enantioselection into a single step would constitute a significant advance over these methods. The only reported approach of this type to date used homochiral *N*-fluorosultams as sources of electrophilic fluorine to produce α-fluorocarbonyl compounds, albeit with only low to moderate enantioselectivities and in variable yields.[5] We have undertaken a program aimed at the development of homochiral aminofluorosulphuranes as potential enantioselective nucleophilic fluorinating agents.

Diethylaminosulphur trifluoride (DAST)[6] achieves the fluorodehydroxylation‡ of homochiral alcohols[7] and silyl ethers[8] with overall inversion of configuration. In moderate polarity solvents, the reaction proceeds *via* an intermediate aminodifluorosulphanyloxonium ion (**1**).[9] S_N2 Attack by fluoride ion then affords the fluorinated product (**2**) (Scheme 1). If 0.5 equivalents of a homochiral analogue of DAST were employed in such a reaction, we considered that it might be possible to achieve enantioselective fluorodehydroxylation *via* kinetic resolution in the step leading to (**1**). A cyclic homochiral aminofluorosulphurane of general structure (**3**) might be expected to achieve fluorodehydroxylation with maximum enantioselectivity, since the stereogenic centre is held rigidly and is proximate to the electrophilic sulphur.

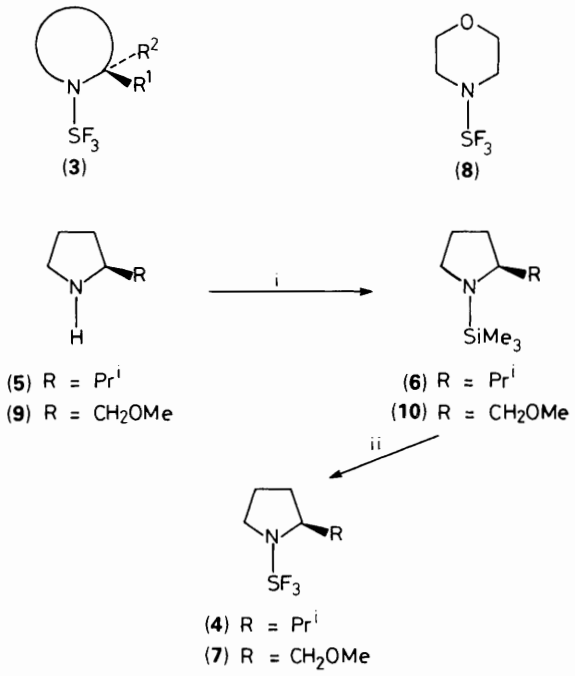


Scheme 1

Several achiral cyclic DAST analogues have been synthesised,[6] and have been shown to be useful agents for the fluorodehydroxylation of alcohols with inversion of configuration.

Initial attempts were made to prepare (*S*)-2-isopropylpyrrolidin-1-ylsulphur trifluoride (**4**) from (*S*)-2-isopropylpyrrolidine (**5**),[10—12] proceeding *via* the *N*-silylamine (**6**),[13] as outlined in Scheme 2. However, these studies were thwarted by the rapid and exothermic decomposition of the presumed aminofluorosulphurane product on warming to room temperature.

Since aminofluorosulphuranes containing a simple secondary alkyl group at nitrogen appeared to be thermally unstable,§ attention was turned to the preparation of (*S*)-2-(methoxymethyl)pyrrolidin-1-ylsulphur trifluoride (**7**). The known high thermal stability of *N*-morpholinosulphur trifluoride (**8**)[14] suggested that the side-chain oxygen might help to stabilise (**7**). Further stabilisation might be expected from co-ordination of the side-chain oxygen to the electron-deficient sulphur. Such interactions might also be expected to afford a more conformationally rigid reagent, presumably enhancing the prospects for high enantioselectivity during its



Scheme 2. *Reagents*: i, Bu^{n}Li, Me_3SiCl; ii, SF_4.

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‡ For convenience, the term 'fluorodehydroxylation' has been used to refer to the conversion of either alcohols or silyl ethers to alkyl fluorides.

§ Di-isopropylaminosulphur trifluoride, the only previously reported aminofluorosulphurane to contain a secondary alkyl group at nitrogen, decomposed on attempted distillation (see ref. 6b).

application as a fluorodehydroxylating agent. (*S*)-2-(Methoxymethyl)pyrrolidine (**9**) was prepared from (*S*)-proline according to a known literature procedure.[15] *N*-Silylation gave compound (**10**), and subsequent treatment with SF_4 in $CFCl_3$ at −78 °C afforded a product which did not decompose on warming to room temperature. Purification by distillation afforded the target aminofluorosulphurane (**7**) in multigram quantities as a clear colourless liquid, b.p. 44—48 °C (0.27 mmHg), $[\alpha]_D^{24}$ −56.2° (*c* 50.8, CH_2Cl_2) [76% yield from (**9**)].¶ Since no racemisation is possible during its preparation from the homochiral amine (**9**), essentially homochiral (**7**) should be produced. This material appeared thermally stable below 80 °C and did not decompose violently even when a small sample was heated to 180 °C.[14] It was distilled *in vacuo* at temperatures as high at 67 °C without incident. Variable temperature n.m.r. studies in [$^2H_8$]dioxane showed very little decomposition at temperatures as high as 95 °C. This thermal stability augers well for the application of reagents of this type as enantioselective fluorodehydroxylating agents.

Only a broad and featureless ^{19}F n.m.r. spectrum for compound (**7**) was observed in $CDCl_3$ solution.[16] However, on addition of a fluoride ion scavenger,[16b] considerably sharpened signals due to two diastereotopic axial fluorines and one equatorial fluorine were clearly observed.¶ To our knowledge this is the first reported example of a compound that bears two diastereotopic fluorines attached to sulphur.

Fluorination of racemic 2-(trimethylsiloxy)octane (**11**) using 1.1 equivalents of (**7**) in CH_2Cl_2 for 5 h at −78 °C cleanly afforded a 74/26 mixture of 2-fluoro-octane and octenes, as indicated by g.l.c. analysis. This compares closely to the reaction of (**11**) with DAST under identical conditions, where a 71/29 ratio of these products was obtained. Therefore, it appears that the increased thermal stability of (**7**) over DAST is not achieved at the expense of a reduced fluorinating ability.

Preliminary studies aimed at evaluating the potential of (**7**) as an *enantioselective* fluorodehydroxylating agent have begun. Compound (**11**) was treated with 0.5 equivalents of (**7**) under the conditions employed above. Examination of the unchanged alcohol derived from (**11**) by ^{19}F n.m.r. analysis of its MPTA [methoxy(trifluoromethyl)phenylacetatel] esters indicated that only 8% kinetic resolution had been achieved during the first step of the fluorodehydroxylation, with a slight preference for the reaction of (*S*)-(**11**). Fluorination of racemic ethyl 2-(trimethylsiloxy)propanoate (**12**) with 0.5 equivalents of (**7**) at 0 °C for 4 h cleanly afforded ethyl 2-fluoropropanoate (**13**), with no evidence of elimination products. A 50% enantiomeric excess (e.e.) for the unchanged alcohol derived from (**12**) was determined by ^{19}F n.m.r. analysis of its MTPA esters. A 16% e.e. for the fluorinated product (**3**) was established by $LiAlH_4$ reduction to 2-fluoropropan-1-ol, followed by ^{19}F n.m.r. analysis of its MTPA esters.[17] These results indicate that moderate kinetic resolution was achieved during the formation of the aminodifluorosulphanyloxonium ion intermediate. The discrepancy in e.e. between (**13**) and the alcohol derived from residual (**12**) may be due to over-fluorination by the presumed siloxyaminosulphur difluoride by-product (**14**) [R^3 = $SiMe_3$, NR_2 = 2-(methoxymethyl)pyrrolidinyl] derived from (**7**). Alternatively, partial racemisation during the reaction of the aminodifluorosulphanyloxonium ion intermediate with fluoride ion could account for this result. Studies designed to provide additional insight into these results, and examine further the utility of (**7**) and related compounds as enantioselective fluorodehydroxylating agents are in progress, and will be reported in due course.

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¶ (**7**), ^1H n.m.r. (300 MHz, $CDCl_3$) δ 3.51 [ABX, H^A, -C*H*(H)O-], 3.46 [H^B, -CH(*H*)O-], 4.44 (m, H^X, -NC*H*CH_2-) (J_{AB} 9.65, J_{BX} 7.87, J_{AX} 5.25 Hz), 3.72 (m, 2H, -CH_2N-), 3.37 (s, 3H, OMe), 2.01 (m, 4H, -CH_2CH_2-); ^{13}C n.m.r. (75 MHz, $CDCl_3$) δ 74.49 (C-6), 61.35 (C-2), 59.09 (C-8), 50.41 (C-5), 28.10 (C-3), 23.09 (C-4); ^{19}F n.m.r. in the presence of F^- scavenger (282 MHz, $CDCl_3$, ref. $CFCl_3$) δ 61.42 (dd, 1F, *J* 277.9, 49.2 Hz), 57.30 (dd, 1F, *J* 277.9, 59.9 Hz), 32.70 (pseudo-dd, 1F).

References

1 'Biomedicinal Aspects of Fluorine Chemistry,' eds. R. Filler and Y. Kobayashi, Elsevier, Amsterdam, 1982; 'Biochemistry Involving Carbon-Fluorine Bonds,' ed. R. Filler, ACS Symposium Series No. 28, Washington DC, 1976; 'Preparation, Properties and Industrial Applications of Organofluorine Compounds,' ed. R. E. Banks, Ellis Horwood, Chichester, 1982; 'Organofluorine Chemicals and Their Industrial Applications,' ed. R. E. Banks, Ellis Horwood, Chichester, 1979; 'Carbon-Fluorine Compounds—Chemistry, Biochemistry and Biological Activities,' Ciba Foundation Symposium, Elsevier, Amsterdam, 1972.

2 J. T. Welch, *Tetrahedron*, 1987, **43**, 3123.

3 K. Yoshino, M. Ozaki, H. Taniguchi, M. Ito, K. Satoh, N. Yamasaki, and T. Kitazume, *Jpn. J. Appl. Phys.*, 1987, **26**, L22; D. M. Walba, H. A. Razavi, N. A. Clark, and D. S. Parmar, *J. Am. Chem. Soc.*, 1988, **110**, 8686.

4 See, for example, T. Kitazume and T. Yamamoto, *J. Fluorine Chem.*, 1987, **35**, 467; T. Kitazume, K. Murata, and T. Ikeya, *ibid.*, 1986, **32**, 233; U. Groth and U. Schollkopf, *Synthesis*, 1983, 673; J. T. Welch and K. W. Seper, *J. Org. Chem.*, 1988, **53**, 2991, and references cited therein.

5 E. Differding and R. W. Lang, *Tetrahedron Lett.*, 1988, **29**, 6087.

6 (a) M. Hudlicky, *Org. React.*, 1988, **35**, 513; (b) W. J. Middleton, *J. Org. Chem.*, 1975, **40**, 574.

7 J. Leroy, E. Hebert, and C. Wakselman, *J. Org. Chem.*, 1979, **44**, 3406.

8 T. Asai, A. Yasuda, Y. Matsumura, M. Kato, and K. Uchida, *Asahi Garasu Kenkyu Hokoku*, 1986, **36**, 49; Asahi Glass Co., Ltd., Jpn. Pat., 85 32,718, 1985 (*Chem. Abstr.* 1985: **103**; 87488 g); T. Asai, A. Yasuda, M. Kato, K. Uchida, and M. Yamabe, presented at International Congress of Pacific Basin Societies, December 1984, Honolulu (abstr. no. 10F03).

9 K. C. Mange and W. J. Middleton, *J. Fluorine Chem.*, 1989, **43**, 405.

10 T. Sone, K. Hiroi, and S. Yamada, *Chem. Pharm. Bull.*, 1973, **21**, 2331.

11 M. Asami, H. Ohno, S. Kobayashi, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, 1978, **51**, 1869.

12 A. Hassner and V. Alexanian, *Tetrahedron Lett.*, 1978, 4475.

13 J. R. Pratt, W. D. Massey, F. H. Pinkerton, and S. F. Thames, *J. Org. Chem.*, 1975, **40**, 1090.

14 For studies concerning the thermal stability of aminofluorosulphuranes, see: P. A. Messina, K. C. Mange, and W. J. Middleton, *J. Fluorine Chem.*, 1989, **42**, 137; W. J. Middleton, *Chem. Eng. News*, May 21, 1979, p. 43; J. Cochran, *Chem. Eng. News*, March 19, 1979, p. 4.

15 (*S*)-2-(Methoxymethyl)pyrrolidine is commercially available from Aldrich Chemical Co. For preparative details, see: D. Enders and H. Eichenauer, *Chem. Ber.*, 1979, **112**, 2933; D. Seebach, H. O. Kalinowski, B. Bastani, G. Crass, H. Daum, H. Dorr, N. P. DuPreez, V. Ehrig, W. Langer, C. Nussler, H. A. Oei, and M. Schmidt, *Helv. Chim. Acta*, 1977, **60**, 301.

16 (a) J. A. Gibson, D. G. Ibbott, and A. F. Janzen, *Can. J. Chem.*, 1973, **51**, 3203; (b) A. F. Janzen, J. A. Gibson, and D. G. Ibbott, *Inorg. Chem.*, 1972, **11**, 2853; (c) D. J. Ibbott and A. F. Janzen, *Can. J. Chem.*, 1972, **50**, 2428.

17 S. Watanabe, T. Fujita, Y. Usui, and T. Kitazume, *J. Fluorine Chem.*, 1986, **31**, 247.