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Synthesis of Optically Pure Fluorosubstituted Isoxazolidines by 1,3-Dipolar Cycloaddition of Nitrones to Chiral Methyl Enol Ethers of 3-Fluoro-1-sulphinyl-2-propanones

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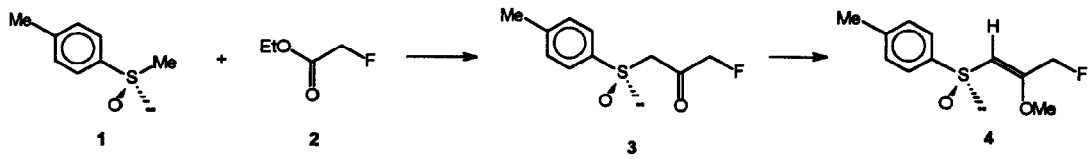
Abstract: Optically pure enol ether **4** undergoes 1,3-dipolar cycloaddition, with *C,N*-diphenylnitrone **5** to give the fluorosubstituted isoxazolidine **6** in a fully regio- and diastereoselective manner. The absolute configuration of **6** has been established by X-ray analysis. When changing the nitrone and/or the fluoro substitution pattern in compounds similar to **4**, the same reactivity is observed.

A large number of heterocyclic compounds bearing fluorine atoms, trifluoromethyl or polyfluoroalkyl groups have been synthesised in the last few years, and are of current interest in both academic and industrial fields. Many of these products have been evaluated as pharmaceuticals or agrochemicals, and some are of interest for their antitumor, antiviral and antifungal activity[1].

In contrast to the well documented synthesis of many classes of achiral fluorinated heterocyclic compounds, the asymmetric synthesis of homochiral selectively fluorinated heterocycles has been explored to a much lesser extent[2]. Among the large variety of strategies available for the synthesis of chiral heterocycles, 1,3-dipolar cycloadditions have a prominent place because of their remarkable regio- and stereochemical control. The key feature of these processes resides in the possibility of transfering the stereochemical information present in the olefin or in the 1,3-dipole to the newly formed stereocenters of the heterocyclic ring[3].

In the context of our continuing interest in developing strategies to homochiral fluoroorganic compounds of biological relevance from fluorinated esters with sulphoxides acting as chiral auxiliaries, we are studying the 1,3-dipolar cycloadditions of nitrones and nitrile oxides to methyl enol ethers of 3-fluorosubstituted-1-sulphinyl-2-propanones such as **4** in order to obtain the corresponding homochiral fluorinated isoxazolidines or 4,5-dihydroisoxazoles, which are central intermediates in strategies to heteroatom substituted carbon chains.

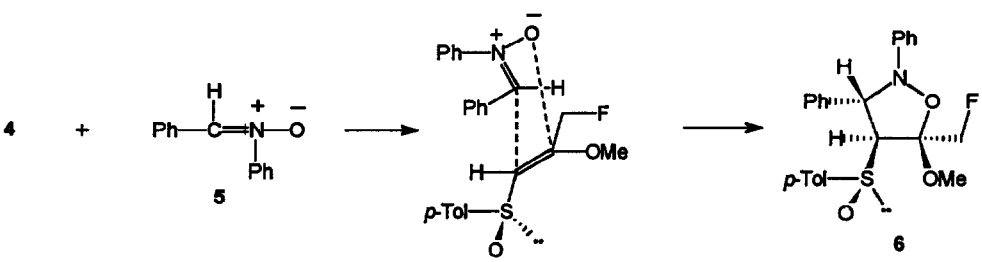
We report here that homochiral fluorosubstituted methyl enol ether **4** exhibits a very high chiral induction in the 1,3-dipolar cycloaddition to typical nitrones[4]. The synthesis of compound **4** is illustrated in Scheme 1.



Scheme 1

β-Ketosulphoxide **3** and polyfluorinated analogues can be synthesised by condensation of the lithium derivative of methyl-*p*-tolylsulphoxide and fluorinated esters such as **2**.[7] By treatment of **3** (or of polyfluorinated analogues) with diazomethane, compounds such as **4** are obtained, always in mixture with the isomeric methylene oxides, in yields ranging from 10 to 40 %, depending on substrate, solvent and reaction conditions used. An alternative synthetic approach involves quenching the corresponding alkali-metal enolate with methylating agents.

A CCl_4 solution of enol ether **4** and an equimolar amount of *C,N*-diphenylnitrone **5** was kept at room temperature when a clean, slow reaction took place[8]. After 10 days the reaction mixture was purified by flash chromatography on silica gel to afford 2,3-diphenyl-5-fluoromethyl-5-methoxy-4-[(4-methylphenyl)sulphinyl] isoxazolidine **6**[9] (>90 % conversion), and unreacted starting materials **4** and **5**. See Scheme 2.



Scheme 2

As shown by ^{1}H-NMR analysis, enol ether **4**[10] has *Z* configuration (N.O.E.s were observed between the vinylic hydrogen and the protons and fluorine atom of the CH_2F group), and the *C,N*-diphenylnitrone at room temperature exibits a stable *E* configuration[11]: therefore, the most probable transition state leading to the cycloadduct **6** appears to have the (*E*)-*exo* arrangement depicted in Scheme 2.

The absolute stereochemistry of isoxazolidine 6 was established by single-crystal X-ray diffraction (Fig. 1).[12]

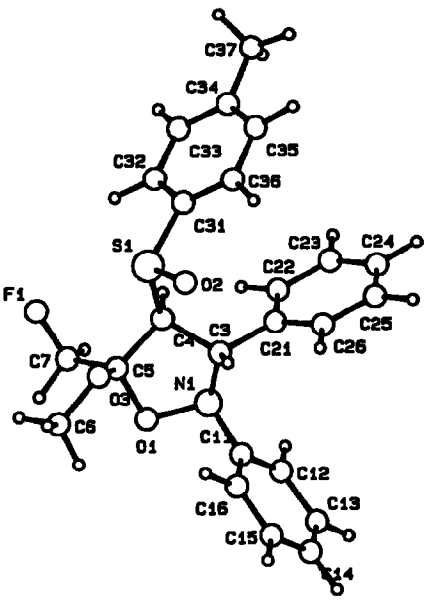


Figure 1

The isoxazolidine ring adopts an envelope conformation[13] with an apex at C(3) displaced by 0.71 Å, on the same side as the S atom, from the least-squares plane through atoms O(1), C(5), C(4) and N(1).

In order to verify the scope and the limits of the reaction, we treated the enol ether 4 also with *N*-methyl-*C*-phenylnitrone and with *N*-benzyl-*C*-ethoxycarbonylnitrone: the corresponding 2- methyl-3- phenyl-5- fluoro methyl-5- methoxy-4- [(4- methylphenyl) sulphinyl]isoxazolidine and 2-benzyl-3-ethoxy carbonyl-5- fluoromethyl-5- methoxy-4- [(4-methylphenyl) sulphinyl]- isoxazolidine were again obtained as a sole product in each case. Moreover, *C,N*-diphenylnitrone 5 reacted with the methyl enol ether of 1-[(4-methylphenyl) sulphinyl]- 3,3,3- trifluoro- 2-propanone and gave the 2,3-diphenyl-4,5-methoxy- [(4-methylphenyl) sulphinyl]- 5-trifluoromethyl-isoxazolidine.

It is interesting to note how methyl enol ethers of fluorinated 1-sulphinyl-2-propanones show the ability to control efficiently the π selectivity of 1,3-dipolar cycloadditions in the same way as some α,β-unsaturated sulphoxides do in [4 + 2] cycloadditions[14].

Further exploration of these reactions and of their applications to asymmetric synthesis of open chain polifunctionalized heterosubstituted compounds, through the removal of the chiral auxiliary and ring opening of the heterocycle, are under way and will be reported in due corse.

References and notes

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4. Although sodium enolates of β-ketosulphoxides **3** react smoothly with nitrile oxides to give 4-[(4-methyl phenyl) sulphinyl]isoxazoles through the corresponding 4,5-dihydro-5-hydroxyisoxazole intermediates[5], they show a marked inertness toward nitrones[6].
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6. Unpublished results.
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8. Heating the reaction mixture at reflux caused a rapid decomposition of the starting materials.
9. ^{1}H-NMR ($CDCl_3$): δ 2.34 (3H, s, CH_3), 3.41 (3H, s, OCH_3), 3.92 (1H, dd, H-4, $J_{(H-4,F)}$ 1.9 , $J_{(H-4,H-3)}$ 6.0 Hz), 4.29 (1H, dd, CHH'F, $J_{(H,H')}$ 10.5, $J_{(H,F)}$ 49.8 Hz), 4.41 (1H, dd, CHH'F, $J_{(H',F)}$ 49.8 Hz), 4.65 (1H, d, H-3), 6.90-7.48 (14H, m, aromatic hydrogens). ^{19}F-NMR ($CDCl_3$): δ -231.3 (t, CH_2F, J (H,F) 49.8 Hz).
10. ^{1}H-NMR ($CDCl_3$): δ 2.40 (3H, s, CH_3), 4.04 (3H, s, OCH_3), 4.62 (1H, dd, CHH'F, $J_{(H,H')}$ 13.5, $J_{(H,F)}$ 46.5 Hz), 4.92 (1H, dd, CHH'F, $J_{(H',F)}$ 46.5 Hz), 5.67 (1H, d, =CH, $J_{(H,F)}$, 1.5 Hz), 7.23-7.60 (4H, m, aromatic hydrogens). ^{19}F-NMR ($CDCl_3$): δ -220.3 (t, CH_2F, $J_{(H,F)}$ 46.5 Hz).
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12. Crystallographic details: $C_{24}H_{24}FNO_3S$, MW=425.52, orthorombic, $P2_12_12_1$, a=13.085 (3), b=29.621 (5), c=5.754 (2) Å, V=2230.2 (9) Å^3, Z=4, d_{calc}=1.267 g cm^{-3}, μ=15.26 cm^{-1}, F(000)=896, Philips PW1100 diffractometer, monochromated Cu-kα radiation, λ=1.5418, 3070 unique reflections measured (±h, +k, +l), 1061 reflections observed [$I \geq 2\sigma(I)$], solved by direct methods, full-matrix least squares refinement, O, S, F, N anisotropic, hydrogen atoms included at calculated position and refined in riding mode, absolute configuration determined at a significance level of over 99% comparing R values at an early stage of refinement; R=0.043, R_w=0.045, max. residual electron density 0.39 e Å^{-3}, positional and thermal parameters available from the Cambridge Crystallographic Data Centre.
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