The Reaction of 3,5-Dichloro-2,4,6-trimethylbenzonitrile Oxide with Chiral Fluoro-substituted Allyl Sulfoxides

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The title reaction allowed the synthesis, with total regio- and moderate stereo-selectivity, of chiral fluorosubstituted 4,5-dihydroisoxazoles.

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The 1,3-dipolar cycloaddition reactions provide the chemist one of the best tools for the construction of five-membered heterocycles, with in addition the capability of establishing a great number of stereocenters in one synthetic step [1]. Diastereoselective cycloadditions of nitrile oxides and nitrones to carbon-carbon double bonds bearing a stereogenic center in their proximity are a valuable method for the stereocontrolled preparation of chiral 4,5-dihydroisoxazoles or isoxazolidines [2], that can then be transformed into chiral carbon frameworks bearing oxygen and nitrogen functionalities [3].

In the course of our extended program directed toward the development of synthetic strategies for the construction of selectively fluorinated chiral molecules of biological interest [4], we have reported the use of cycloaddition reactions of nitrile oxides and nitrones to fluoro-substituted olefinic dipolarophiles [5]. High facial diastereoselectivity was observed for the cycloadditions onto fluorosubstituted enol ethers bearing a stereogenic arylsulphinyl group in the α-position to the double bond, *i.e.* chiral vinyl sulfoxides [6].

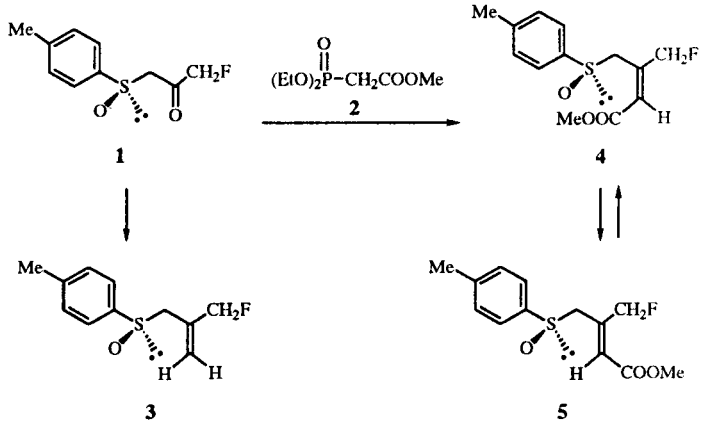
As a continuation of these studies, we report here the cycloaddition of 3,5-dichloro-2,4,6-trimethylbenzonitrile oxide with fluoromethyl substituted alkenes bearing a chiral sulphinyl group in the β-position to the double bond, *i.e.* chiral allyl sulfoxides.

Results and Discussion.

While (R_S)-3-fluoro-2-(*p*-tolylsulfinyl)propene **3** was prepared from (R_S)-3-fluoro-1-(*p*-tolylsulfinyl)propanone **1** by a reported procedure [7], methyl (R_S)-(*Z*)-3-fluoromethyl-4-(*p*-tolylsulfinyl)crotonate **4** was obtained from β-ketosulfoxide **1** by a Wadsworth-Emmons reaction with an equimolar amount of diethyl phosphonoacetate **2** (see Scheme 1).

The reaction was carried out under two phase liquid-solid conditions, both in protic (alcohols) and aprotic (THF) solvents, with different alkaline carbonates as bases; the best reaction conditions proved to be potassium carbonate in methanol, that gave, after 3 days at room temperature, (*Z*)-allyl sulfoxide **4** in 71% total yield as a 87:13 mixture with the (*E*)-form **5**. By flash column chromatography compound **4** could be obtained diastereoisomerically pure in *ca.* 48% yield with respect to the starting reagents. However, it was observed that equilibration occurred from **4** to a *ca.* 87: 13 mixture of **4**:**5** isomers, by prolonged standing in solution, or by heating, both in the presence and in the absence of bases. The stereochemistry of the two isomers was assigned on the basis of nmr nOe difference experiments performed on both of them. In fact, irradiation of 2-H enhanced the signal of the 4-methylene protons in compound **5** (3.5 and 15%), thus establishing their *cis* relationship, but not in compound **4**.

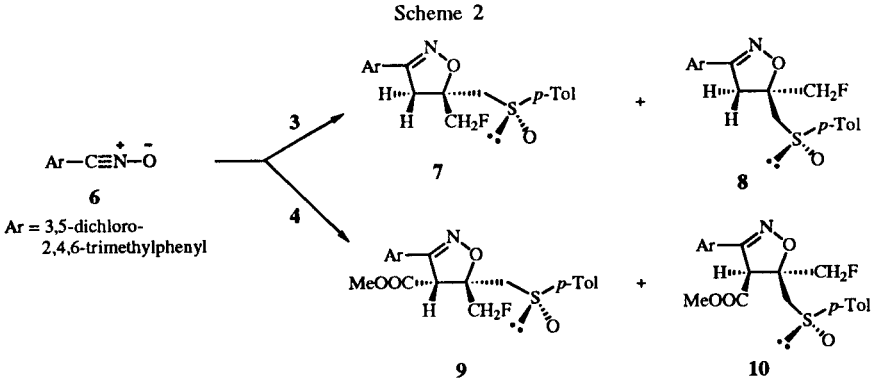
Scheme 1



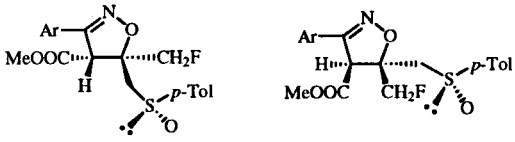
The cycloaddition reactions of the stable nitrile oxide **6** with equimolar amounts of allyl sulfoxides **3** and **4** were run in dioxane at room temperature for 22 days, affording the diastereoisomeric 4,5-dihydroisoxazoles **7**,**8** (81% total yield, 1.4:1 ratio) and **9**,**10** (53% total yield, 2:1 ratio), respectively (see Scheme 2).

In the reaction of **4**, small amounts (14% total yield, 1.3:1 ratio) of the diastereoisomeric cycloadducts **11** and **12** were detected by nmr analysis in the crude reaction mixture: these compounds, in the light of the typical

Scheme 2



stereoconservative mechanism of 1,3-dipolar cycloaddition, are likely to derive from the reaction of nitrile oxide **6** with isomer **5**, that is produced by the equilibration of **4** during the reaction time.



11 **12**

The regiochemistry ofthe cycloadducts relies mainly upon their ^{13}C nmr spectra, where the chemical shifts of C-5 (86-89 ppm), indicative of an ethereal carbon, and of C-4 (58-62 ppm) show their position with respect to the ring oxygen atom. This orientation is in line with literature data on the reactions of nitrile oxides with 1,1-disubstituted or trisubstituted alkenes [8].

The relative stereochemistry at ring carbon atoms in compounds **9** and **10**, as well as in **11** and **12**, follows the stereoconservative mechanism of 1,3-dipolar cycloadditions, and was established through hetero- and homonuclear nOe difference experiments. Specifically, in compounds **9** and **10** irradiation of the fluorine atom enhanced 4-H (6 and 3%), whereas no sizeable nOe (<0.5%) was observed between the corresponding atoms in compounds **11** and **12**, this fact indicating that in the former pair of products the fluoromethyl group and 4-H are disposed on the same face of the isoxazole ring. As expected, in the latter pair of products irradiation of 4-H enhanced the methylene protons of the *cis*-disposed *p*-tolylsulfinyl group (2-13%), while no significant nOe (<0.5%) was observed for the corresponding protons in compounds **9** and **10**.

The absolute sterochemistry of the cycloadducts **7-12** was not determined; the depicted representation of compounds **7,8** is arbitrary, as well as the one for compounds **9-12**: however, the representation of the latter compounds is indicative of the relative configuration at ring carbon atoms.

In conclusion, the described reactions show that chiral allyl sulfoxides have a lower efficiency than vinyl sulfoxides [6] in controlling the diastereoselectivity of 1,3-dipolar cycloadditions with nitrile oxides; however, the facial selectivity is still interesting, leading to the obtainment of chiral, highly functionalised 4,5-dihydroisoxazoles: it should be of interest to extend this study to other classes of 1,3-dipoles, such as nitrile imines or nitrones, in order to prepare other chiral heterocyclic systems.

EXPERIMENTAL

The ^1H, ^{13}C and ^{19}F nmr spectra were taken with a Bruker AC250 or ARX400 spectrometer by using tetramethylsilane or hexafluorobenzene as an internal standard. Mass spectra were measured on a Hitachi Perkin-Elmer RMU-6D apparatus. Compounds **1** and **3** were prepared as described previously [7]. Nitrile oxide **6** was prepared according to literature methods [9].

(R_S)-(*Z*)-3-Fluoromethyl-4-(*p*-tolylsulfinyl)buten-2-oic Acid Methyl Ester (**4**).

To a cooled suspension (0°) of potassium carbonate (9.3 mmoles) in methanol (20 ml) was added slowly the methyl diethylphosphonacetate **2** (9.3 mmoles) was slowly added. After stirring at 0° for 15 minutes, a solution of (R_S)-3-fluoro-1-(*p*-tolylsulfinyl) propan-2-one **1** (9.3 mmoles) in methanol (20 ml) was added. After stirring at room temperature for 3 days, the reaction was quenched with a 5% aqueous solution of citric acid (40 ml), and the aqueous layer was extracted with dichloromethane. After drying over sodium sulfate, the solvent was removed under reduced pressure, and the residue was flash chromatographed on a silica gel column with a *n*-hexane-ethyl acetate mixture as the eluent. The first fractions gave **4** (48%) as an oil; ir: ν CO 1715 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.42 (br s, 3H, CH_3), 3.70 (br s, 3H, OCH_3), 3.76 (br d, 1H, 4- H_a, J = 12.3 Hz), 4.38 (br d, 1H, 4-H_b, J = 12.3 Hz), 4.87 (ddd, 1H, C*H*HF, J = 46.2, 14.9, 2.2 Hz), 5.01 (ddd, 1H, CH*H*F, J = 46.0, 14.9, 2.0 Hz), 6.17 (br s, 1H, 2-H), 7.33 and 7.58 (m, 4H, phenyl protons); ^{19}F nmr (deuteriochloroform): δ -219.0 (br dd, 1F, CH_2F, J = 46.2, 46.0 Hz); $[\alpha]_D^{20}$ (*c* = 1.25, chloroform) +57°; ms: m/z 270 (M^+).

Anal. Calcd. for $C_{13}H_{15}FO_3S$: C, 57.75; H, 5.60. Found: C, 57.52; H, 5.48.

(R_S)-(*E*)-3-Fluoromethyl-4-(*p*-tolylsulfinyl)buten-2-oic Acid Methyl Ester (**5**).

This compound was evidenced in the above described crude reaction mixture, but could not be isolated in the pure state, ^{1}H nmr (deuteriochloroform): δ 2.42 (br s, 3H, CH_3), 3.67 (br dd, 1H, 4-H_a, J = 12.2, 2.8 Hz), 3.70 (s, 3H, OCH_3), 3.78 (br d, 1H, H-4_b, J = 12.2 Hz), 5.24 (ddd, 1H, C*H*HF, J = 48.2, 15.2, 2.2 Hz), 5.47 (ddd, 1H, CH*H*F, J = 48.2, 15.2, 2.2 Hz), 5.82 (br s, 1H, 2-H), 7.33 and 7.50 (m, 4H, phenyl protons); ^{19}F nmr (deuteriochloroform): δ -223.7 (br t, 1F, CH_2F, J = 48.2 Hz).

General Procedure for the Reaction of 3,5-Dichloro-2,4,6-trimethylbenzonitrile Oxide (**6**) with Allyl Sulfoxides **3** or **4**.

To a solution of nitrile oxide **6** (2.5 mmoles) in dioxane (80 ml) was added allyl sulfoxide **3** or **4** (2.5 mmoles), and the mixture was stirred at room temperature for 22 days. After removal of the solvent under reduced pressure, the residue was flash chromatographed on a silica gel column with a *n*-hexane-ethyl acetate mixture as the eluent, to give the 4,5-dihydroisoxazoles **7** (47%) and **8** (34%), or **9** (38%), **10** (15%), **11** (8%) and **12** (6%), respectively.

(5*R*/*S*,R_S)-3-(3,5-Dichloro-2,4,6-trimethylphenyl)-4,5-dihydro-5-fluoromethyl-5-(*p*-tolylsulfinyl)isoxazole (**7**).

This compound was obtained as white powder (diisopropyl ether), mp 196-198°; ^{1}H nmr (deuteriochloroform): δ 2.3-2.6 (br s, 12H, 4 CH_3), 3.16 (dd, 1H, C*H*HS, J = 13.5, 1.7 Hz), 3.23 (dd, 1H, CH*H*S, J = 13.5, 2.1 Hz), 3.24 (br d, 1H, 4-H_a, J = 18.3 Hz), 3.48 (dd, 4-H_b, J = 18.3, 2.5 Hz), 4.82 (dd, 1H, C*H*HF, J = 46.4, 10.3 Hz), 4.96 (dd, 1H, CH*H*F, J = 47.1, 10.3 Hz), 7.36 and 7.57 (m, 4H, phenyl protons); ^{19}F nmr (deuteriochloroform): δ -227.3 (br dd, 1F, CH_2F, J = 47.1, 46.4 Hz); ms: m/z 441 (M^+).

Anal. Calcd. for $C_{21}H_{22}Cl_2FNO_2S$: C, 57.01; H, 5.02; N, 3.17. Found: C, 56.83; H, 5.14; N, 3.02.

(5*S*/*R*, R_S)-3-(3,5-Dichloro-2,4,6-trimethylphenyl)-4,5-dihydro-5-fluoromethyl-5-(*p*-tolylsulfinyl)isoxazole (**8**).

This compound was evidenced in the crude reaction mixture, but could not be isolated in the pure state; ^{1}H nmr (deuteriochloroform): δ 2.3-2.6 (br s, 12 H, 4 CH_3), 3.07 (br d, 1H, C*H*HS, J = 14.0 Hz), 3.20 (br d, 1H, CH*H*S, J = 14.0 Hz), 3.21 (br d, 1H, 4-H_a, J = 18.2 Hz), 4.06 (dd, 1H, 4-H_b, J = 18.2, 2.3 Hz), 4.45 (dd, 1H, C*H*HF, J = 47.1, 9.9 Hz), 4.50 (dd, 1H, CH*H*F, J = 46.7, 9.9 Hz), 7.36 and 7.58 (m, 4H, phenyl protons); ^{19}F nmr (deuteriochloroform): δ -227.7 (br dd, 1F, CH_2F, J = 47.1, 46.7 Hz); ^{13}C nmr (selected signals in the mixture of compounds **7** and **8**, all decoupled, in deuteriochloroform): δ 43.5 and 44.8 (d, C-4, $J_{C,F}$ = 4 and 5.5 Hz, respectively), 62.0 and 62.8 (d, CH_2S, $J_{C,F}$ = 3 and 2 Hz, respectively), 84.1 and 85.3 (d, CH_2F, $J_{C,F}$ = 180.5 and 181.5 Hz, respectively), 84.9 and 85.3 (d, C-5, $J_{C,F}$ = 19.5 Hz for both signals).

(4*R*/*S*,5*R*/*S*,R_S)-3-(3,5-Dichloro-2,4,6-trimethylphenyl)-4,5-dihydro-5-fluoromethyl-4-methoxycarbonyl-5-(*p*-tolylsulfinyl)-isoxazole (**9**).

This compound was obtained as white powder (diisopropyl ether), mp 104-105°; ^{1}H nmr (deuteriochloroform): δ 2.2-2.6 (br s, 12H, 4 CH_3), 3.28 (d, 1H, C*H*HS, J = 13.8 Hz), 3.64 (s, 3H, OCH_3), 3.68 (dd, 1H, CH*H*S, J = 13.8, 4.1 Hz), 4.68 (dd, 1H, C*H*HF, J = 47.5, 10.5 Hz), 4.70 (s, 1H, 4-H), 4.95 (dd, 1H, CH*H*F, J = 46.4, 10.5 Hz), 7.35 and 7.53 (m, 4H, phenyl protons); ^{19}F nmr (deuteriochloroform): δ -227.8 (br dd, 1F, CH_2F, J = 47.5, 46.4 Hz); ^{13}C nmr (selected signals, all decoupled, in deuteriochloroform): δ 53.1 (s, OCH_3), 58.9 (d, C-4, $J_{C,F}$ = 5.5 Hz), 59.7 (d, CH_2S, $J_{C,F}$ = 3.5 Hz), 85.0 (d, CH_2F, $J_{C,F}$ = 181 Hz), 88.3 (d, C-5, $J_{C,F}$ = 17.5 Hz); ms: m/z 499 (M^+).

Anal. Calcd. for $C_{23}H_{24}Cl_2FNO_4S$: C, 55.20; H, 4.84; N, 2.80. Found: C, 55.43; H, 4.71; N, 2.71.

(4*S*/*R*,5*S*/*R*,R_S)-3-(3,5-Dichloro-2,4,6-trimethylphenyl)-4,5-dihydro-5-fluoromethyl-4-methoxycarbonyl-5-(*p*-tolylsulfinyl)-isoxazole (**10**).

This compound was obtained as white powder (diisopropyl ether), mp 82-84°; ^{1}H nmr (deuteriochloroform): δ 2.2-2.6 (br s, 12H, 4 CH_3), 3.22 (dd, 1H, C*H*HS, J = 13.6, 3.0 Hz), 3.53 (dd, 1H, CH*H*S, J = 13.6, 1.4 Hz), 3.56 (s, 3H, OCH_3), 4.61 (s, 1H, 4-H), 4.84 (dd, 1H, C*H*HF, J = 46.2, 10.4 Hz), 5.12 (dd, 1H, CH*H*F, J = 47.6, 10.4 Hz), 7.36 and 7.58 (m, 4H, phenyl protons); ^{19}F nmr (deuteriochloroform): δ -227.1 (br dd, 1F, CH_2F, J = 47.6, 46.2 Hz); ^{13}C nmr (selected signals, all decoupled, in deuteriochloroform): δ 52.9 (s, OCH_3), 58.9 (d, C-4, $J_{C,F}$ = 3.5 Hz), 59.8 (d, CH_2S, $J_{C,F}$ = 5.5 Hz), 83.5 (d, CH_2F, $J_{C,F}$ = 182 Hz), 87.6 (d, C-5, $J_{C,F}$ = 18.5 Hz); ms: m/z 499 (M^+).

Anal. Calcd. for $C_{23}H_{24}Cl_2FNO_4S$: C, 55.20; H, 4.84; N, 2.80. Found: C, 55.08; H, 4.96; N, 2.64.

(4*R*/*S*,5*S*/*R*,R_S)-3-(3,5-Dichloro-2,4,6-trimethylphenyl)-4,5-dihydro-5-fluoromethyl-4-methoxycarbonyl-5-(*p*-tolylsulfinyl)-isoxazole (**11**).

This compound was detected in the crude reaction mixture, but was not isolated in the pure state; ^{1}H nmr (deuteriochloroform): δ 2.2-2.6 (br s, 12H, 4 CH_3), 3.06 (br d, 1H, C*H*HS, J = 14.0 Hz), 3.41 (br d, 1H, CH*H*S, J = 14.0 Hz), 3.60 (s, 3H, OCH_3), 4.60 (dd, 1H, C*H*HF, J = 46.4, 9.8 Hz), 4.63 (dd, 1H, CH*H*F, J = 46.4, 9.8 Hz), 5.81 (s, 1H, 4-H), 7.38 and 7.62 (m, 4H, phenyl protons); ^{19}F nmr (deuteriochloroform): δ -228.0 (br t, 1F, CH_2F, J = 46.4 Hz); ^{13}C nmr (selected signals, all decoupled, in deuteriochloroform): δ 52.7 (s, OCH_3), 59.2 (d, C-4, $J_{C,F}$ = 3 Hz), 59.8 (d, CH_2S, $J_{C,F}$ = 3.5 Hz), 83.6 (d, CH_2F, $J_{C,F}$ = 181 Hz), 86.5 (d, C-5, $J_{C,F}$ = 17.5 Hz).

(4*S*/*R*,5*R*/*S*,R_S)-3-(3,5-Dichloro-2,4,6-trimethylphenyl)-4,5-dihydro-5-fluoromethyl-4-methoxycarbonyl-5-(*p*-tolylsulfinyl)-isoxazole (**12**).

This compound was detected in the crude reaction mixture, but was not isolated in the pure state; ^{1}H nmr (deuteriochloroform): δ 2.2-2.6 (br s, 12H, 4 CH_3), 3.27 (dd, 1H, C*H*HS, J = 13.7, 2.0 Hz), 3.30 (dd, 1H, CH*H*S, J = 13.7, 2.1 Hz), 3.60 (s, 3H, OCH_3), 5.00 (s, 1H, 4-H), 5.11 (dd, 1H, C*H*HF, J = 46.7, 10.5 Hz), 5.13 (dd, 1H, CH*H*F, J = 46.7, 10.5 Hz), 7.37 and 7.57 (m, 4H, phenyl protons); ^{19}F nmr (deuteriochloroform): δ -228.1 (br t, 1F, CH_2F, J = 46.7 Hz); ^{13}C nmr (selected signals, all decoupled, in deuteriochloroform): δ 52.9 (s, OCH_3), 61.1 (d, C-4, $J_{C,F}$ = 3.5 Hz), 62.2 (d, CH_2S, $J_{C,F}$ = 3.5 Hz), 82.5 (d, CH_2F, $J_{C,F}$ = 177.5 Hz), 87.4 (d, C-5, $J_{C,F}$ = 17.5 Hz).

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