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Synthesis and reactivity of a stable crystalline diastereomerically pure trifluoromethanesulfinic acid derivative: (*S*)-(−)-1-trifluoromethylsulfinyl-(*R*)-4-phenyloxazolidin-2-one

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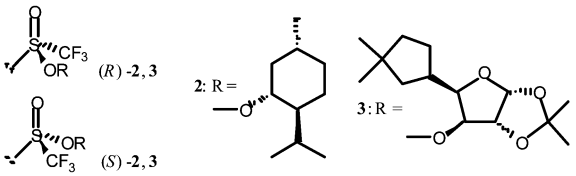
Efficient synthesis of the title compound, the first diastereomerically pure trifluoromethanesulfinic acid derivative (8), has been achieved by direct trifluoromethanesulfinylation of the lithiated (4*R*)-(−)-4-phenyloxazolidin-2-one; in contrast to the reaction between $CF_3S(O)Cl$ and (1*R*,2*S*,5*R*)-(−)-menthol which occurs with low stereoselectivity (< 10% de), 8 affords the O-menthyl trifluoromethanesulfinate derivative in > 98% de.

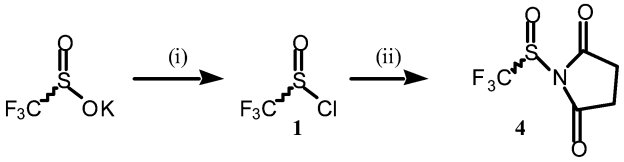
Because of the high lipophilicity and electron-withdrawing ability of the $CF_3S(O)$ functional group, trifluoromethanesulfinic acid derivatives are of great interest for the pharmaceutical and agrochemical industries.[1] Interestingly, although the corresponding alkane and arene derivatives [R–S(O)X, R = Alk, Ar; X = Alk_2N or AlkO] belong to the oldest group of chiral organosulfur compounds prepared as enantiopure species,[2] and despite their long recognized importance as intermediates in many synthetic strategies,[3] the synthesis of optically active trifluoromethanesulfinic acid derivatives has never been reported.

Current methods for the synthesis of trifluoromethanesulfinic acid derivatives include nucleophilic trifluoromethylation of sulfinyl chlorides *via* CF_3SiMe_3/F^- [4] and the reaction of nucleophilic HY-substrates with CF_3SCl, followed by the difficult selective mono-oxidation of the resulting CF_3SY species.[5] The direct introduction of a $CF_3S(O)$ group into organic molecules is a less popular strategy, probably because trifluoromethanesulfinyl halides $CF_3S(O)F$ and $CF_3S(O)Cl$ are highly toxic, volatile and poorly stable.[6] Recently some attention has been devoted to the preparation of elaborate new trifluoromethanesulfinylation reagents. However, due to the strong acid media necessary for the generation of the $CF_3S(O)^+$ cation,[7] the scope of these new approaches has again been limited to racemic compounds.

The condensation of an optically active secondary alcohol with an alkane- or arene-sulfinyl chloride in the presence of a base is a general method for the asymmetric synthesis of sulfinate esters.[2,8] However, we found that the degree of asymmetric induction in the reaction of $CF_3S(O)Cl$ **1** with chiral alcohols was quite low. For example, the condensation of **1** with (1*R*,2*S*,5*R*)-(−)-menthol in the presence of triethylamine (toluene, −78 °C) afforded a 55 : 45 ratio of (S_s/R_s)-diastereomeric menthyl sulfinates **2**,† whereas with diacetone-D-glucose (pyridine, thf, −78 °C) the corresponding DAG-sulfinates **3** were obtained with only a 16% de (Scheme 1). For comparison, under similar conditions, reactions with $CH_3S(O)Cl$ afforded the DAG-(R_s)-sulfinate having a diastereomeric purity as high as 93%.[9]



Scheme 1

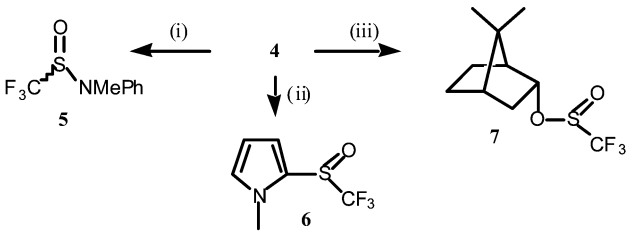


Scheme 2 *Reagents and conditions*: (i) $SOCl_2$ (1 eq.), 1,2,4-trichlorobenzene, 20 °C, 3 h; (ii) *N*-silver succinimide (1 eq.), toluene, 20 °C, 14 h.

Close scrutiny of the literature reveals that among diverse types of sulfinic acid derivatives, *N*-(alkane- and arene-sulfinyl) imides are readily available and can be used as sulfinylation agents.[10] Treatment of **1**, generated *in situ* from readily available $CF_3S(O)OK$ and $SOCl_2$, with the silver salt of succinimide afforded **4** as a stable white crystalline solid (no appreciable decomposition upon storage at rt for over one month) in 72% yield (Scheme 2).

As expected, **4** reacts with a variety of proton-donor N–H, O–H and C–H functionalities to give the corresponding products resulting from nucleophilic displacement (Scheme 3). For example, *N*-methylaniline is sufficiently nucleophilic to generate the corresponding sulfinamide **5**. With *N*-methylpyrrole a mixture of 2- and 3-trifluoromethylsulfinyl derivatives was obtained in an 87 : 13 ratio, from which the major isomer **6** was isolated in 67% yield by flash chromatography. The trifluoromethanesulfinylation of (1*S*)-*endo*-(−)-borneol required 6 h at 60 °C, but is complete within 2 h at rt in the presence of one equivalent of triethylamine. Derivative **7** was isolated in 92% yield, however with a very low diastereoselectivity (< 10% de). This is in contrast to the effective production of diastereomerically pure menthyl benzenesulfinate obtained from *N*-(benzenesulfinyl)phthalimide and (1*R*,2*S*,5*R*)-(−)-menthol.[11] Thus, being useful as an easily handled reagent for electrophilic trifluoromethylsulfinylation, compound **4** presents limited interest for the chiral version of nucleophilic displacement reactions.

In search for a more efficient stereocontrolling trifluoromethanesulfinylation agent, our investigations were extended to Evans'-type chiral auxiliaries.[12,13] $CF_3S(O)Cl$ cleanly reacted with optically active lithiated oxazolidin-2-ones; the diastereoisomeric excesses were evaluated by ^{19}F NMR spectroscopy. Poor selectivities were obtained with (*S*)-



Scheme 3 *Reagents and conditions*: (i) Me_2NH (1.1 eq.), toluene, 20 °C, 3 h; (ii) *N*-methylpyrrole (1 eq.), chlorobenzene, 70 °C, 5 h; (iii) (1*S*)-*endo*-(−)-borneol (1 eq.), Et_3N (1 eq.), touene, 20 °C, 2 h.

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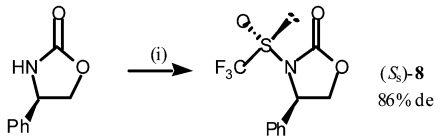


Scheme 4 *Reagents and conditions*: (i) CF_3SOCl (1.1 eq.), thf, −78 °C, 6 h.

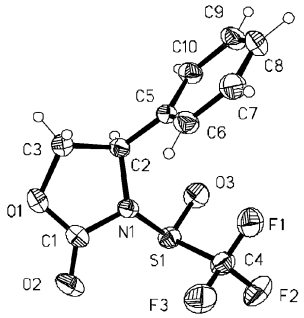
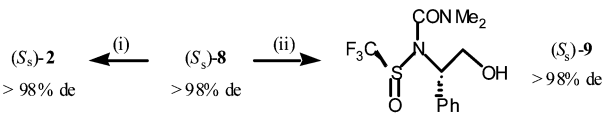


Fig. 1 Molecular structure of (S_s)-**8**.

(−)-4-benzyloxazolidin-2-one (58 : 42), (4*R*,5*S*)-(+)-4-methyl-5-phenyloxazolidin-2-one (65 : 35), and (*S*)-(−)-4-isopropyloxazolidin-2-one (61 : 39). However, with (*R*)-(−)-4-phenyloxazolidin-2-one not only an 86% de was obtained, but the major diastereomer turned out to be crystalline (Scheme 4). A single recrystallization from a toluene–pentane mixture (3 : 1) was sufficient to isolate the desired trifluoromethanesulfinic acid derivative **8** (75% yield) with a diastereomeric purity greater than 98%.‡ The (S_s) configuration at the sulfur atom has been determined by a single crystal X-ray diffraction study (Fig. 1).§

The synthesis of diastereomerically pure sulfinylimide (S_s)-**8** provides a basis for its use in asymmetric reactions (Scheme 5). Derivative (S_s)-**8** acts as a trifluoromethylsulfinylation agent. For example, with (1*R*,2*S*,5*R*)-(−)-menthol, at 20 °C in ether in the presence of triethylamine, the menthyl sulfinate (S_s)-**2** was isolated in 43% yield with a diastereoselectivity higher than 98%. On the other hand, (S_s)-**8** can undergo a ring-opening reaction. For example, it was successfully converted by treatment with dimethylamine into the corresponding 2-aminoalcohol **9** (>98% de). The absolute configuration of the products **2** and **9** was tentatively assigned on the basis of NMR data.[9] The retention of configuration at the sulfur centre has been observed previously in the reaction of chiral *N*,*N*-diisopropyl *p*-toluenesulfinamide with some alcohols catalyzed by acids.[14]



Scheme 5 *Reagents and conditions*: (i) (1*R*,2*S*,5*R*)-(−)-menthol (3 eq.), Et_3N (1 eq.), ether, 20 °C, 24 h; (ii) Me_2NH (neat), −10 °C, 1 h.

Further work is currently in progress to define the scope of applications of diastereomerically pure *N*-trifluoromethanesulfinimides.

Notes and references

† Selected NMR [$CDCl_3$, ppm (*J*/Hz)] data: [(S_s)-**2**]: ^{19}F (ref. $CFCl_3$): −81.32, ^{13}C: 15.70, 20.75, 21.95, 23.37, 25.58, 31.94, 33.82, 42.29, 47.99, 84.60, 122.82 (q, J_{CF} = 334.1). [(R_s)-**2**]: ^{19}F: −80.71, ^{13}C: 15.51, 20.82, 21.92, 23.18, 25.43, 32.05, 33.82, 48.18, 85.47, 122.88 (q, J_{CF} = 335.4). [(S_s)-**3**]: ^{19}F: −81.08, ^{1}H: 1.33, 1.35, 1.43, 1.51 (4s, 12H, $OCMe_2O$), 3.94–4.25 (m, 4H, H-4, H-5, H-6), 4.61 (d, 1H, *J* = 3.6, H-2), 4.94 (d, 1H, *J* = 2.7, H-3), 5.96 (d, 1H, *J* = 3.6, H-1), ^{13}C: 24.84, 26.15, 26.61, 26.75, 67.44, 72.08, 80.51, 83.36, 83.98, 105.30, 109.73, 112.78, 122.85 (q, J_{CF} = 336.8). [(R_s)-**3**]: ^{19}F: −80.07, 1H: 1.32, 1.34, 1.42, 1.51 (4s, 12H, $OCMe_2O$), 3.90–4.20 (m, 4H, H-4, H-5, H-6), 4.70–4.76 (m, H-2, H-3), 5.96 (d, 1H, *J* = 3.6, H-1), ^{13}C: 24.81, 26.15, 26.61, 26.75, 67.65, 71.83, 80.65, 83.61, 83.78, 105.39, 109.82, 112.78, 122.65 (q, J_{CF} = 335.4). **4**: ^{19}F: −69.20, ^{13}C: 28.8, 124.3 (q, J_{CF} = 340), 172.4. **5**: ^{19}F: −77.0. **6**: ^{19}F: −79.43. **7**: ^{19}F: −80.75 and −81.40; [(S_s)-**8**]: ^{19}F: −73.65, ^{1}H: 4.48 (dd, 1H, *J* = 9.3, 4.5, H-5), 4.86 (t, 1H, *J* = 9.3, H-4), 5.39 (dd, 1H, *J* = 9.3, 4.5, H-5), 7.27–7.48 (m, 5H, H_{arom}); ^{13}C (C_6D_6): 53.0, 72.6, 123.3 (q, J_{CF} = 337.5), 126.9, 128.8, 128.9, 136.9, 155.2. [(R_s)-**8**]: ^{19}F: −72.70; [(S_s)-**9**]: −78.21, ^{13}C: 35.84, 36.53, 56.31, 68.14, 123.68 (q, J_{CF} = 335.4), 126.98, 128.36, 128.81, 137.52, 156.47.

‡ *Synthesis* of (S_s)-**8**: To a solution of the (*R*)-(−)-4-phenyloxazolidin-2-one (6 mmol) in thf (30 ml) under argon at −78 °C was added dropwise 4.4 ml of n-butyllithium (1.6 M in hexane, 7.0 mmol) over a 10 min period. The solution was stirred at −78 °C for 30 min and then a solution of $CF_3S(O)Cl$ (7.0 mmol) in toluene (10 ml) was added over a 30 min period. After being stirred for 6 h at −78 °C, the solvent and volatile compounds were removed. After extraction with toluene, a 93 : 7 mixture of (S_s)- and (R_s)-diastereomers was obtained. Recrystallization from toluene–pentane (3 : 1) afforded pure (S_s)-**8** in 75% yield. Mp 132–134 °C, $[\alpha]_D$ = −197 (*c* = 2, $CHCl_3$).

§ *Crystal data* for [(S_s)-**8**]: $C_{10}H_8F_3NO_3S$, *M* = 279.23, monoclinic, *a* = 7.905(2), *b* = 8.231(2), *c* = 8.659(3) Å, *β* = 98.557(6)°, *V* = 557.1(3) Å^3, *T* = 223(2) K, space group *P*2(1), *Z* = 2, Mo-radiation, *λ* = 0.71073 Å, 4183 reflections measured, 2409 [*R*(int) = 0.0180] independent reflections, Flack parameter = 0.07(6), final *R* indices [$I > 2\sigma(I)$]: *R*1 = 0.0284, *wR*2 = 0.0742, *R* indices (all data): *R*1 = 0.0294, *wR*2 = 0.0757. CCDC reference number 207699. See http://www.rsc.org/suppdata/cc/b3/b303574c/ for crystallographic data in CIF or other electronic format.

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