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Stereodivergent synthesis of sulfoxide-containing oxazolidinone antibiotics

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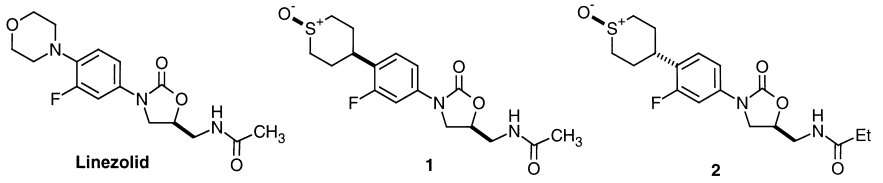
Abstract

Carbamate **5** was prepared under mild conditions via a novel metal–halogen exchange procedure without competing benzyne formation. Selection of an appropriate oxidation/reduction sequence afforded access to either the *cis*- or *trans*-1-oxo-4-aryltetrahydrothiopyran system, important intermediates in the synthesis of a new class of oxazolidinone antibiotics.

Oxazolidinones are a new class of synthetic antibacterial agents having activity against important human pathogens including *S. aureus*, *S. pneumoniae*, *E. faecalis*, and *H. influenzae*.[1] Significantly, these new agents show activity against multiple-drug resistant strains of the Gram-positive organisms. A New Drug Application has been filed with the US FDA for linezolid, the lead development compound, for treatment of respiratory tract, skin, and soft tissue infections.

Recently, we had occasion to prepare some 1-oxo-4-aryltetrahydrothiopyran-substituted oxazolidinones represented by structures **1** and **2** (Scheme 1). The major synthetic challenges involved in approaching these compounds were efficient construction of the carbon–carbon bond linking the fluorinated aromatic ring to the sulfur heterocycle and control of the stereochemistry at sulfur to obtain either the *cis* or *trans* sulfoxide relative to the aromatic linker. Solutions to both problems are described below.



Scheme 1.

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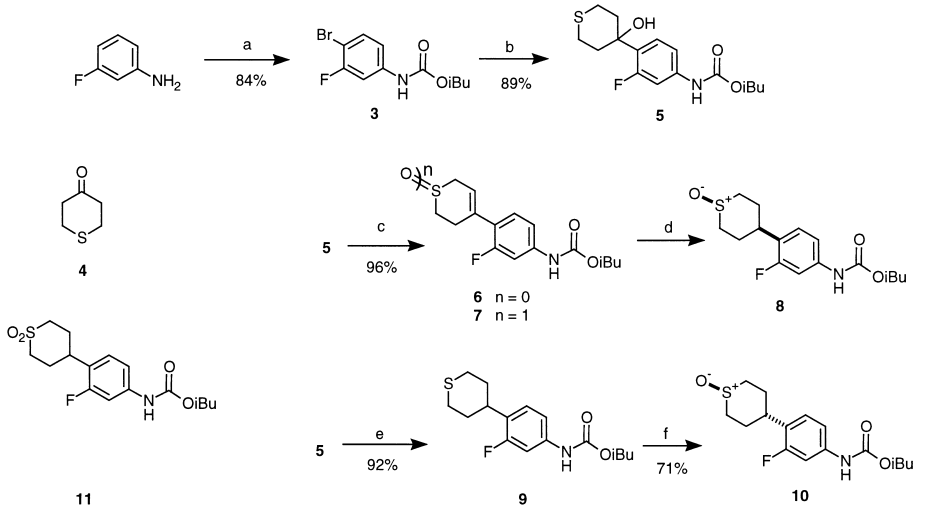
3-Fluoroaniline was chosen as the starting material (Scheme 2). Acylation with isobutylchloroformate under Schotten–Baumann conditions proceeded smoothly. The carbamate solution was reacted without purification with 1,3-dibromo-5,5-dimethylhydantoin to give an 87:13 mixture of carbamate **3** and a regioisomer derived from bromination *para* to the fluorine.[2] Pure **3** was obtained following crystallization from heptane. Because lithium/halogen exchange reactions are often times fast enough to suffer reprotonation by unreacted acidic functional groups,[3] **3** was normally treated with a base to deprotonate the carbamate moiety before addition of butyllithium. In the course of reaction optimization, it was found that the *o*-fluoroarylmetal intermediate was stable to relatively high temperatures when magnesium was chosen as the counterion to the base. The stability toward decomposition via a benzyne pathway presumably stemmed from transmetallation of the initially formed aryllithium with the magnesium carbamate. In the optimized procedure, a solution of **3** in THF at –20°C was treated first with EtMgBr and then *n*BuLi. The resulting solution was treated with a slurry of MgBrCl (conveniently prepared from EtMgBr and TMSCl)[4] before reacting with ketone **4** to obtain the tertiary alcohol **5** in high yield.[5] The added magnesium salt helped to suppress undesired enolization of ketone **4**.



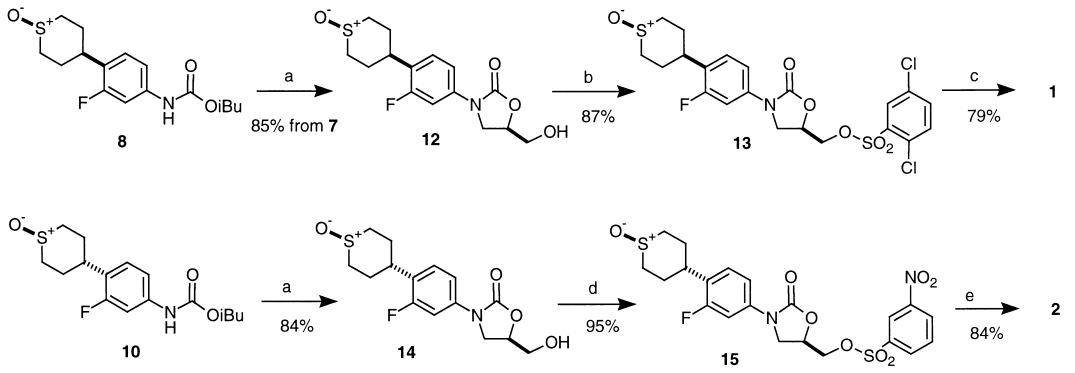
Scheme 2. *Reagents and conditions*: (a) isobutylchloroformate, K_2CO_3, CH_2Cl_2/water, 1,3-dibromo-5,5-dimethylhydantoin; (b) EtMgBr, *n*-BuLi, MgBrCl, THF, then **4**; (c) TFA, CH_2Cl_2, $NaIO_4$, MeOH/water; (d) 5% Pt/C, H_2, DMF; (e) $(Me_3Si)_2O$, PMHS, *p*TSA, toluene; (f) $Ti(OiPr)_4$, D-diisopropyl tartrate, *t*BuOOH, CH_2Cl_2

With the key bond in hand, attention was turned next to elaborating the tetrahydrothiopyran. Alcohol **5** was readily dehydrated by treatment with trifluoroacetic acid. Oxidation with $NaIO_4$ afforded sulfoxide **7**. Remarkably, Pt/C-catalyzed hydrogenation gave exclusively the *cis*-sulfoxide **8** in which hydrogen had been added to the face opposite the oxygen atom. Palladium catalysts reacted with the same stereoselectivity but with unsatisfactory chemoselectivity; deoxygenation of the sulfoxide competed with saturation of the alkene, thereby amplifying a catalyst deactivation problem as well.[6] No conditions were found for the reduction of **7** to the *trans*-sulfoxide **10**.

In order to obtain access to compounds in the *trans* series, recourse was made to selective oxidation of the saturated tetrahydrothiopyran, an avenue pioneered by Johnson in 1965.[7] Tertiary alcohol **5** was subjected to a silane reduction using poly(methylhydrosiloxane) (PMHS) as the hydride donor to afford **9**, the oxidation substrate. Under these conditions, a very fast elimination to the

alkene **6** is followed by a slower reduction step. Of the various oxidants surveyed in the Johnson paper, the highest selectivity for trans-1-oxo-4-aryltetrahydrothiopyrans was obtained using ozone. Unfortunately, in our hands the yield of the desired sulfoxide was unacceptably low due to competing overoxidation to the sulfone **11**. Better, more reproducible results were obtained by the application of Kagan's conditions for asymmetric oxidation of sulfides.[8] Thus, reaction with *t*-butylhydroperoxide, $Ti(OiPr)_4$, and diisopropyl D-tartrate in CH_2Cl_2 at –20°C afforded **8**, **10**, and **11** in yields (HPLC) of 17.9, 77.5, and 1.3%, respectively. *Trans*-sulfoxide **10** was still the major product at 71.5% without the chiral tartrate ligand.[9] It was isolated in sufficient purity for use in the subsequent chemistry by a single crystallization from methanol. Although about 6% of the *cis* diastereomer **8** was present at this stage as an impurity, the level could be reduced if desired to less than 1% by one or more high-yielding recrystallizations from ethyl acetate.

Both **8** and **10** were converted to their respective end targets by the application of chemistry developed for the synthesis of linezolid (Scheme 3).[10] Thus, carbamate lithiation and reaction with glycidol generated in situ from (*S*)-3-chloro-1,2-propanediol afforded the oxazolidinone alcohols **12** and **14**. Sulfonylation proceeded smoothly in both series. Because the *m*-nitobenzene sulfonate in the *cis* series was an oil, the crystalline 2,5-dichlorobenzene sulfonate was prepared instead as a suitably activated substrate for the next reaction. Ammonolysis followed by acylation of the intermediate amines gave **1** and **2**.[11] It is important to note that no equilibration of sulfoxide diastereomers or other unwanted sulfoxide chemistry occurred during this sequence.



Scheme 3. *Reagents and conditions*: (a) lithium *t*-amylate, (*S*)-3-chloro-1,2-propanediol, DMF; (b) 2,5-dichlorobenzenesulfonyl chloride, Et_3N, CH_2Cl_2; (c) NH_4OH, MeOH, CH_3CN, Ac_2O; (d) 3-nitrobenzenesulfonyl chloride, Et_3N, CH_2Cl_2; (e) NH_4OH, MeOH, CH_3CN, propionic anhydride

In conclusion, a versatile synthesis of 1-oxo-4-aryltetrahydrothiopyran-substituted oxazolidinones has been developed. Key features are a robust method to form the carbon–carbon bond between rings via a Mg/Li dianion and the ability to access the diastereomeric sulfoxides by choosing an appropriate oxidation/reduction sequence.

References

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2. Gray, G. W.; Hird, M.; Toyne, K. J. *Mol. Cryst. Liq. Cryst.* **1991**, *204*, 43–64.
3. Beak, P.; Musick, T. J.; Chen, C. W. *J. Am. Chem. Soc.* **1988**, *110*, 3538–3542.

4. Sommer, L. H.; Kerr, G. T.; Whitmore, F. C. *J. Am. Chem. Soc.* **1948**, *70*, 434–435.
5. To EtMgBr (348.13 mmol, 1.18 equiv. in THF (530 ml) was added chlorotrimethylsilane (35.4 g, 325.85 mmol, 1.11 equiv.) with an exotherm from 22 to 43°C. The resultant MgBrCl solution was then cooled to give a slurry at –30°C. To a solution of **3** (85.00 g, 292.97 mmol) and 1,10-phenanthroline monohydrate (0.580 g, 2.93 mmol, 0.010 equiv.) in TMEDA (103.76 g, 892.9 mmol, 3.05 equiv.) and THF (1.15 l) was added EtMgBr in THF (243.2 g at 1.36 mol; 332 mmol; 1.13 equiv.) to the colorless to pink endpoint. The resultant solution was cooled to –26°C and butyllithium in hexane (163 g at 23.8 wt%, 590 mmol, 2.01 equiv.) was added over 1.5 h while maintaining –26 to –23°C. The MgBrCl slurry was added to the resultant dianion slurry while maintaining –25 to –19°C. A solution of tetrahydrothiopyran-4-one (44.39 g, 382 mmol, 1.30 equiv.) in THF (252 ml) was then added while maintaining –26 to –23°C. The reaction solution was then added to a solution of acetic acid (115 g, 1.92 mol, 6.54 equiv.) in water (570 ml) while maintaining 0 to 10°C. The phases were separated and the lower aqueous phase was back extracted with a mixture of MTBE (568 ml) and branched octanes (220 ml). The organics were washed with a mixture composed of aqueous ammonia (29.3 wt%, 43 g), ammonium chloride (43 g), and water (570 ml) and then washed with water (570 ml). The organics were combined and concentrated in vacuo to 1500 ml. A constant volume vacuum distillation was then performed while maintaining 1500 ml and adding branched octanes (3000 ml). Branched octanes (400 ml) were added and the slurry cooled to 3°C. The product was collected by vacuum filtration, washed with 3°C branched octanes (570 ml) and dried in a nitrogen stream to afford a white solid, **5** (86.20 g, 89.9%).
6. Other heterogeneous catalyst systems based on ruthenium, cobalt, or nickel all failed to react with the desired chemoselectivity if at all. No reaction was observed with diimide, and deoxygenation predominated with silanes.
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8. Zhao, S. H.; Samuel, O.; Kagan, H. B. *Tetrahedron* **1987**, *43*, 5135–5144.
9. A trend toward equatorial attack (leading to the *trans* product) and decreasing reaction rate was observed with increasing steric demand of the oxidant. In practice, the conditions reported here afforded the most acceptable trade-off between the two.
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11. Compound **3**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 (2H, J=8.4), 6.96 (1H, J=2.0, 8.4), 6.87 (1H), 3.96 (2H, J=6.4), 1.97 (1H, J=13.5), 0.96 (6H, J=6.6); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.2 (J_{C-F}=245.5), 153.4, 139.0 (J_{C-F}=10.1), 133.3, 115.1, 107.1 (J_{C-F}=28.2), 102.0 (J_{C-F}=21.1), 71.8, 27.9, 19.0; anal calcd for $C_{11}H_{13}BrFNO_2$: C, 45.54; H, 4.52; N, 4.83; found: C, 45.40; H, 4.54; N, 4.86. Compound **5**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38 (1H, J=8.8), 7.32 (1H, J=14.4), 7.00 (1H, J=1.6, 8.4), 6.74 (1H), 3.96 (2H, J=6.4), 3.23 (2H, J=12.8), 2.44 (2H, J=14.0), 2.37 (2H, J=3.6, 13.6), 2.05 (2H, J=14.4), 1.96 (1H, J=6.8), 0.96 (6H, J=6.8); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.3 (J_{C-F}=243.0), 153.5, 138.7 (J_{C-F} =12.0), 129.9 (J_{C-F}=44), 126.7 (J_{C-F}=6), 113.8, 107.0 (J_{C-F}=29.4), 71.6, 71.2 (J_{C-F}=4.0), 37.7, 37.6, 27.9, 23.9, 19.0; anal calcd for $C_{16}H_{22}FNO_3S$: C, 58.69; H, 6.77; N, 4.28; found: C, 58.39; H, 6.68; N, 4.27. Compound **8**: ^{1}H NMR (DMSO-d_6, 500 MHz) δ 9.76 (1H), 7.35 (1H, J=13), 7.26–7.20 (2H), 3.88 (2H, J=6.6), 3.31 (1H), 3.02–2.89 (3H), 2.81 (2H, J=14), 2.51 (1H), 2.33 (2H, J=13), 1.92 (1H, J=6.7), 1.66 (2H, J=12), 0.93 (2H, J=6.7); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 159.5 (J_{C-F}=241), 153.5, 139.0 (J_{C-F}=11) 127.7 (J_{C-F}=6.3), 125.8 (J_{C-F}=15), 114.1, 105.0 (J_{C-F}=29), 70.1, 44.9, 34.2, 27.5, 21.3, 18.8; anal calcd for $C_{16}H_{22}FNO_3S$: C, 58.69; H, 6.77; N, 4.28; found: C, 58.56; H, 6.59; N, 4.19. Compound **10**: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.88 (1H), 7.44 (1H, J=12.8), 7.38–7.27 (2H), 3.98 (2H, J=6.6), 3.49–3.41 (2H), 3.14–3.08 (1H), 2.90 (1H, J=11.0), 2.62 (2H), 2.10–1.91 (5H), 1.04 (6H, J=6.7); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 160.0 (J_{C-F}=241.1), 153.9, 143.5, 128.4 (J_{C-F}=6.0), 124.8 (J_{C-F}=15.1), 114.4, 105.4 (J_{C-F}=27.2), 70.6, 51.5, 34.6, 29.1, 27.9, 19.2; anal calcd for $C_{16}H_{22}FNO_3S$: C, 58.69; H, 6.77; N, 4.28; found: C, 58.46; H, 6.83; N, 4.23. Compound **12**: ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.51 (1H, J=2.0, 13.2), 7.36 (1H, J=8.5), 7.30 (1H, J=2.1, 8.6), 5.21 (1H, J=5.6), 4.71 (1H, J=3.5, 9.3), 4.08 (1H, J=9.0), 3.83 (1H, J=6.2, 8.8), 3.69–3.66 (1H), 3.59–3.56 (1H), 3.05 (1H, J=12.5), 2.95 (2H, J=12.4), 2.82 (2H, J=13.4), 2.51 (1H), 2.35 (2H, J=12.9), 1.68 (2H, J=12.0); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 159.5 (J_{C-F}=241), 154.3, 138.2 (J_{C-F}=11.3), 127.9 (J_{C-F}=6.3), 126.9 (J=15.1), 113.6, 104.9 (J=28), 73.2, 61.6, 45.9, 44.8, 34.2, 21.3, 21.3; anal calcd for $C_{15}H_{18}FNO_4S$: C, 55.03; H, 5.54; N, 4.28; found: C, 55.01; H, 5.57; N, 4.36. Compound **13**: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.03 (1H, J=2.4), 7.88 (1H, J=2.4, 8.4), 7.79 (1H, J=8.4), 7.44 (1H, J=1.2, 13.2), 7.37 (1H, J=8.4), 7.23 (1H, J=2.4, 8.8), 4.99–4.96 (1H), 4.56–4.49 (2H), 4.16 (1H, J=9.6), 3.77 (1H, J=6.0, 9.2), 3.06 (1H, J=12.0), 2.96 (2H, J=12.8), 2.83 (2H, J=2.8, 13.6), 2.51 (1H, J=1.6), 2.36 (2H, J=12.0), 1.69 (2H, J=12.0); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 159.5 (J_{C-F}=242.5), 153.3, 137.7 (J_{C-F}=12.1), 135.6, 134.1 (J_{C-F}=17), 134.0,

132.5, 130.8, 130.3, 128.0 ($J_{C-F}=7.0$), 127.3 ($J_{C-F}=15.1$), 113.8, 105.1 ($J_{C-F}=29.2$), 71.6, 69.7, 45.6, 44.8, 34.2, 21.3; anal calcd for $C_{21}H_{20}Cl_2FNO_6S_2$: C, 47.02; H, 3.76; N, 2.61; found: C, 46.90; H, 3.55; N, 2.77. Compound **14**: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.69 (1H, $J=2.2$, 13.3), 7.54 (1H, $J=8.6$), 7.47 (1H, $J=2.2$, 8.6), 5.40 (1H, $J=5.5$), 4.26 (1H, $J=9.0$), 4.01 (1H, $J=6.2$, 8.9), 3.89–3.85 (1H), 3.78–3.74 (1H), 3.59–3.56 (2H), 3.54 (1H), 3.25–3.22 (1H), 3.01 (2H, $J=10.8$), 2.71 (1H, $J=1.7$), 2.20 (2H, $J=12.8$), 2.08 (2H, $J=13.0$); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 160.1 ($J_{C-F}=242.5$), 154.7, 138.7 ($J_{C-F}=12.1$), 128.6 ($J_{C-F}=6.0$), 125.9 ($J_{C-F}=14.1$), 113.9 ($J_{C-F}=2.0$), 105.3 ($J_{C-F}=28.2$), 73.6, 62.0, 51.4, 46.3, 34.6, 29.0; anal calcd for $C_{15}H_{18}FNO_4S$: C, 55.03; H, 5.54; N, 4.28; found: C, 54.95; H, 5.56; N, 4.32. Compound **15**: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.82 (1H, $J=8.2$), 8.75 (1H), 8.57 (1H, $J=7.9$), 8.19 (1H, $J=8.1$), 7.61 (1H, $J=10.5$), 7.53 (1H, $J=8.6$), 7.38–7.32 (1H), 4.76–4.68 (2H), 4.31 (1H, $J=9.4$), 3.91 (1H, $J=5.9$, 9.2), 3.58 (2H, $J=11.6$), 3.55 (1H), 3.25 (1H, $J=11.9$), 3.01 (2H, $J=12.2$), 2.71 (1H), 2.21 (2H, $J=13.2$), 2.08 (2H, $J=13.0$); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 160.0 ($J_{C-F}=242.5$), 153.7, 148.4, 138.1 ($J_{C-F}=11.1$), 136.6, 133.9, 132.3, 129.4, 126.3 ($J_{C-F}=15.1$), 1223.0, 114.0, 105.5 ($J_{C-F}=29.2$), 71.7, 70.1, 51.4, 46.0, 34.6, 29.0; anal calcd for $C_{21}H_{21}FN_2O_8S_2$: C, 49.21; H, 4.13; N, 5.47; found: C, 48.98; H, 4.05; N, 5.44. Compound **1**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.45 (1H, $J=2.0$, 12.4), 7.29 (1H, $J=8.4$), 7.15–7.11 (2H), 4.83–4.78 (1H), 4.06 (1H, $J=8.8$), 3.82 (1H, $J=6.8$, 9.2), 3.66 (2H, $J=4.8$), 3.14 (2H, $J=12.8$), 3.04 (1H, $J=12.0$), 2.62 (2H, $J=12.8$), 2.55 (1H, $J=4.4$, 13.2), 2.03 (3H), 1.83–1.80 (2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.5, 160.1 ($J_{C-F}=244.5$), 154.4, 137.8 ($J_{C-F}=11.1$), 127.8 ($J_{C-F}=6.0$), 127.6 ($J_{C-F}=15.1$), 113.7 ($J_{C-F}=3.0$), 106.0 ($J_{C-F}=28.2$), 72.1, 47.5, 46.0, 41.8, 34.8, 23.0, 21.5, 21.5; anal calcd for $C_{17}H_{21}FN_2O_4S$: C, 55.42; H, 5.75; N, 7.60; found: C, 55.40; H, 5.71; N, 7.55. Compound **2**: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.15 (1H, $J=6.0$), 7.45 (1H, $J=2.4$, 13.2), 7.35 (1H, $J=8.8$), 7.24 (1H, $J=2.0$, 8.4), 4.10 (1H, $J=9.2$), 3.74 (1H, $J=6.0$, 9.2), 3.43–3.34 (3H), 3.32 (1H), 3.08–3.02 (1H), 2.81 (2H, $J=10.8$), 2.51 (1H), 2.10 (2H, $J=7.6$), 2.00 (2H, $J=12.8$), 1.88 (2H, $J=13.2$), 0.96 (3H, $J=7.6$); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 173.7, 159.6 ($J_{C-F}=242.5$), 153.9, 138.2 ($J_{C-F}=11.1$), 128.2 ($J_{C-F}=7.0$), 125.7 ($J_{C-F}=15.1$), 113.7 ($J_{C-F}=3.0$), 105.1 ($J_{C-F}=28.2$), 71.6, 51.0, 47.1, 41.3, 34.2, 28.6, 28.3, 9.8; anal calcd for $C_{18}H_{23}FN_2O_4S\cdot H_2O$: C, 53.99; H, 6.29; N, 6.99; S, 8.01; found: C, 53.85; H, 6.24; N, 6.90; S, 7.91.