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A Mild, Inexpensive and Practical Oxidation of Sulfides

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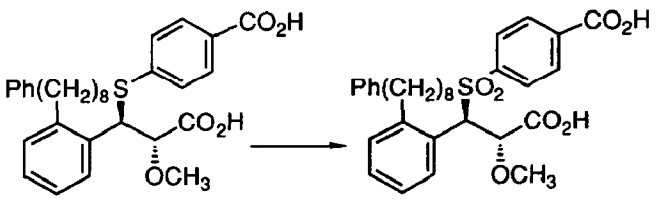
Abstract: Several sulfides have been converted to sulfoxides or sulfones in modest to excellent yields. The oxidant was oxone® and the reactions were performed in 12.5% aqueous acetone and buffered to pH 7.5 - 8.0 with sodium bicarbonate.

The peptidic leukotrienes LTC_4, LTD_4 and LTE_4 which comprise a special class of arachidonic acid metabolities have been shown to play important roles in cell and tissue biology. In particular, these leukotrienes (C_4, D_4 and E_4) are now believed to be directly involved in a variety of immediate hypersensitivity diseases, among these allergic asthma.[1] A new peptidoleukotriene receptor antagonist, (R*,S*) - β-[(4-carboxyphenyl)sulfonyl)-α-methoxy-2-(8-phenyloctyl)benzene propanoic acid (**1**), has been discovered and subsequently chosen as a candidate for the treatment of bronchial asthma.

As part of this ongoing leukotriene antagonist program, we became interested in the selective oxidation of a sulfide (SK&F 105633) to a sulfone (SK&F 107310, **1**) (Scheme I). Although a plethora of chemical reagents is known in the literature for this oxidation, each appeared unacceptable for the synthesis of kilogram quantities. In particular, we required an oxidation which was amenable to scale-up, operationally simple to perform, and environmentally sound.

Scheme I



SK&F 105633 SK&F 107310
1

Several oxidation procedures were investigated to try to find the optimal conditions for this class of compounds. For instance, the use of sodium tungstate dihydrate in the presence of 30% hydrogen peroxide[2] gave a mixture of sulfoxide and sulfone (3:1) and prolonged heating (60 °C) produced a major undesired impurity as evidenced by HPLC [25%(PAR)]. Alternatively, the use of ammonium molybdate(VI) tetrahydrate and 30% hydrogen peroxide[3] resulted in a rather sluggish reaction. After 96 hours at ambient temperature, the reaction was incomplete with 16% of the intermediate sulfoxide remaining. This same reaction at elevated temperatures was unsuccessful; the desired product was found to be unstable to the reaction conditions.

Sodium perborate in glacial acetic acid[4] proved to be an effective and useful procedure for synthesizing small quantities of SK&F 107310. However, the physical properties of the drug substance prepared in this manner, rendered the use of sodium perborate in glacial acetic acid unacceptable for kilogram conversions. Differential Scanning Calorimetry (DSC) and microscopy on the sulfonyl diacid isolated from the above reactions support a non-crystalline amorphous structure and independent studies illustrate the compound's ability to occlude organic solvents. The sulfonyl diacid has been isolated free of glacial acetic acid when heated (60 °C) under vacuum (0.5 torr) for extended periods of time (24 to 48 hours). Several permutations of the reaction conditions were investigated in hopes of obtaining a workable and reliable procedure, but the replacement of acetic acid by formic acid (88% or 96%) or by 50% aqueous methanol (with acid catalysis) were ineffective in producing a clean conversion of sulfide to sulfone.

Oxone® in 50% aqueous methanol[5] has been used for sulfide oxidations, but this was not a useful procedure for the oxidation of SK&F 105633. Thus, a phase transfer catalyst, gentle heating (55 °C) and excess oxidant were required to produce SK&F 107310 in only 65 to 70% isolated yields of inconsistent purity. The use of tetra-n-butylammonium oxone[6] was deemed impractical due to the large amounts of tetra-n-butylammonium bisulfate (5 eq.) needed to produce a salt which contained 37.5% by weight of tetra-n-butylammonium hydrogen persulfate.

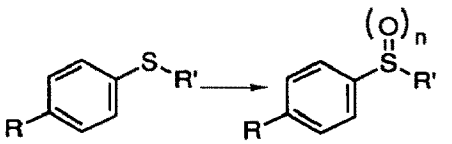
The physical nature of SK&F 107310 forced us to investigate alternative FDA approved salt forms[7] in hopes of finding a solid dosage form for the drug substance. During these studies it was found that the disodium salt of SK&F 107310 was highly soluble in water. This observation, coupled with our marginal success with the oxone® oxidation, led us to question the possibility of performing this sulfide oxidation in water, but in order to accomplish this task a buffer was required. Sodium bicarbonate was investigated and found to be an ideal buffer, which easily neutralized the excess acid generated from the degradation of oxone® thereby allowing the substrate to remain ionized as the disodium salt. Initial results were encouraging, but incomplete oxidation was always observed as evidenced by HPLC (after 72 hours at 55 °C 2.6% of the undesired sulfoxide was detected).

We hoped to find a catalyst to accelerate the reaction rate at ambient temperature and the use of a co-solvent was appealing. The overwhelming synthetic interest in dimethyldioxirane[8] suggested the evaluation of acetone as the first candidate. Indeed, satisfactory results were obtained when the oxone® oxidations were performed in 12.5% aqueous acetone and buffered to pH 7.5 - 8.0 with sodium bicarbonate. Under these optimal conditions, the oxidation was complete within 30 minutes at ambient temperature, and the desired drug substance (SK&F 107310) was isolated in 96% yield with only trace amounts of the intermediate sulfoxide (< 0.1%) detected by HPLC. Particularly noteworthy was the fact that no epimerization was

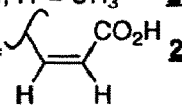
observed under the reaction conditions, and also no elimination of the sulfonyl acid moiety occured, which would have led to cinnamic acid derivatives.

Table 1 illustrates the usefulness of this oxidation procedure. When the reaction was performed at 0 °C to 2 °C, with 0.65 equivalents of oxone®, and quenched after 5 minutes with sodium bisulfite, the intermediate sulfoxides were isolated.[9a] Conversely, the use of 1.35 equivalents of oxone® at ambient temperature for 1 to 2 hours produced the desired sulfones.[9b] Also noteworthy is that this oxidation has been carried out in the presence of primary, secondary[10], and benzylic alcohols and conjugated double bonds. The low yield observed in the oxidation of 3-(phenylthio)acrylic acid (**3e**) was attributed to competing epoxide formation.[11] The low yield observed in the oxidation of 4-(methylthio)benzyl alcohol (**2d**) was due to partial solubility of the starting material giving rise to a heterogeneous reaction medium.

Table 1



1 **2** n = 1, **3** n = 2

Entry		Yield (%)[a] Sulfoxide	Sulfone
1a	R = H, R' = CH_2CO_2H	**2a** 98.6	**3a** 96.7
1b	R = CO_2H, R' = CH_3	**2b** 76.8	**3b** 92.6
1c	R = H, R' = CH_2CH_2OH	**2c** 81.5	**3c** 92.8
1d	R = CH_2OH, R' = CH_3	**2d** 46.6	**3d** 83.4
1e	R = H, R' = 	**2e** 95.0	**3e** 35.0

a) All compounds were characterized by ^{1}H NMR and FTIR. The reported yields are representative for material which gave satisfactory elemental anlaysis.

In conclusion, this mild and inexpensive oxidation procedure has enabled kilogram quantities of SK&F 107310 to be produced and should be widely accepted as a safe, useful, and environmentally sound replacement of the more common oxidation procedures described in the literature.

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9a. A vigorously stirred solution of sodium hydroxide (0.6173 g) and deionized water (30 mL) was treated with thiophenoxyacetic acid (2.03 g). The resulting suspension was stirred at ambient temperature for 10 minutes. To this was added sodium bicarbonate (8.00 g) and acetone (10 mL) and cooled to 1 °C. The oxone® solution (4.85 g in 20 mL of 4 x 10^{-4} M EDTA) was added over 10 minutes keeping the reaction below 5 °C. The suspension was stirred for 5 minutes and immediately quenched at 2 °C with sodium bisulfite (3 g in 6 mL of deionized water). Ethyl acetate (75 mL) was added and the solution was acidified with 6N (aq) HCl (18 mL). The aqueous phase was isolated, treated with NaCl (15 g), and re-extracted with ethyl acetate (75 mL). The organic layers were combined and washed with deionized water (15 mL), washed with brine (15 mL), dried over anhydrous $MgSO_4$, filtered and concentrated via rotary evaporation. The crystals were placed on the vacuum pump (2.0 torr) for 16 hours to afford 2.20 g (98.6%) of pure phenylsulfinyl acetic acid: mp 107-108°C; ^{1}H NMR ($CDCl_3$) δ: 3.82 (s, 2H), 7.56 - 7.60 (m, 3H), 7.69 - 7.72 (m, 2H). FT-IR(KBr, cm^{-1}) 3000, 2583, 1733, 1582, 1478, 1445, 1244, 1013, 994. Anal Calcd. for $C_8H_8O_3S$: C, 52.16; H, 4.38; S, 17.41. Found: C, 51.91; H, 4.41; S, 17.21.

9b. A vigorously stirred solution of sodium hydroxide (0.5771 g) and deionized water (30 mL) was treated with thiophenoxyacetic acid (2.01 g). The resulting suspension was vigorously stirred at ambient temperature for 20 minutes. To this was added sodium bicarbonate (8.00 g) and acetone (10 mL). The oxone® solution (9.70 g in 36 mL of 4 x 10^{-4} M EDTA) was added over 5 minutes. The suspension was vigorously stirred for 1 hour at ambient temperature. The reaction was quenched with sodium bisulfite (6 g in 12 mL of deionized water) and stirred for 15 minutes. Ethyl acetate (75 mL) was added and the solution was acidified with 6N (aq) HCl (18 mL). The aqueous phase was isolated, treated with NaCl (15 g), and re-extracted with ethyl acetate (50 mL). The organic layers were combined and washed with deionized water (15 mL), washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated via rotary evaporation. The crystals were placed on the vacuum pump (0.5 torr) for 4 hours to afford 2.31 g (96.7%) of pure phenylsulfonyl acetic acid: mp 110.5-111.5°C; ^{1}H NMR ($CDCl_3$) δ: 4.15 (s, 2H), 7.60 (t, J = 7.5, 2H), 7.71 (t, J =7 .4, 1H), 7.97 (d, J = 7.5, 2H). FT-IR(KBr, cm^{-1}) 3000, 1730, 1667, 1582, 1453, 1328, 1241, 1152, 768, 739, 689, 673. Anal Calcd. for $C_8H_8O_4S$: C, 47.99; H, 4.03; S, 16.02. Found: C, 47.85; H, 4.07; S, 16.10.

10. The chemical structure of this leukotriene antagonist can not be disclosed.

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