Synthesis M. Lutz et al. Paper

An Efficient Oxidation of Sulfides to Sulfones with Urea–Hydrogen Peroxide in the Presence of Phthalic Anhydride in Ethyl Acetate

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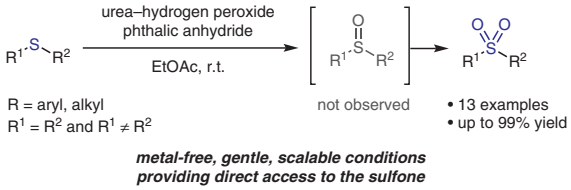

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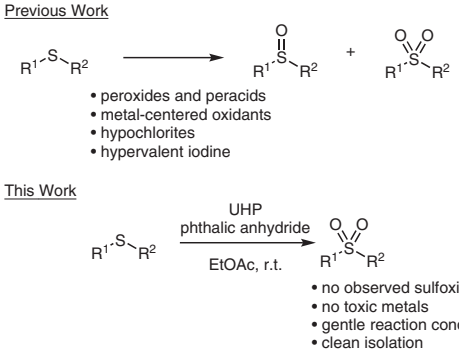
Abstract A metal-free, environmentally benign oxidation of substituted sulfides directly to their corresponding sulfones is described. Using urea-hydrogen peroxide and phthalic anhydride in ethyl acetate clean conversion into the sulfone was achieved without observation of the possible sulfoxide oxidation product.

Key words sulfones, sulfoxides, sulfide oxidation, urea–hydrogen peroxide, UHP, phthalic anhydride

Sulfones are a valuable functional group that confer activity in a variety of industrially relevant categories including pharmaceuticals,[1] agrochemicals,[2] and biologically active natural products.[3] Sulfones also provide useful functional handles for synthetic manipulation.[4]

Selective oxidation of a sulfide to either the sulfoxide or the sulfone is the most common challenge in sulfur chemistry. Currently, sulfide oxidation methods utilize less than desirable oxidizing reagents including heavy metals or strong oxidants, such as hydrogen peroxide, *meta*-chloroperbenzoic acid, potassium permanganate, and sodium (meta)periodate. These reagents generally require long reaction times, high temperatures, or relatively strong basic, acidic, or aqueous conditions (Scheme 1).[5] These harsh conditions are typically not appropriate for the oxidation of sulfides containing sensitive functional groups including highly electron-withdrawing substituents or acid-/base-labile functionalities.[6] Our goal was to design mild conditions with easy to use and readily available materials to access sulfones via sulfide oxidation.

Urea–hydrogen peroxide (UHP) is a safer alternative to hydrogen peroxide that is compatible with a wide variety of gentle and environmentally friendly reaction conditions.[7]



Scheme 1 General conditions for accessing the sulfone from sulfide starting materials

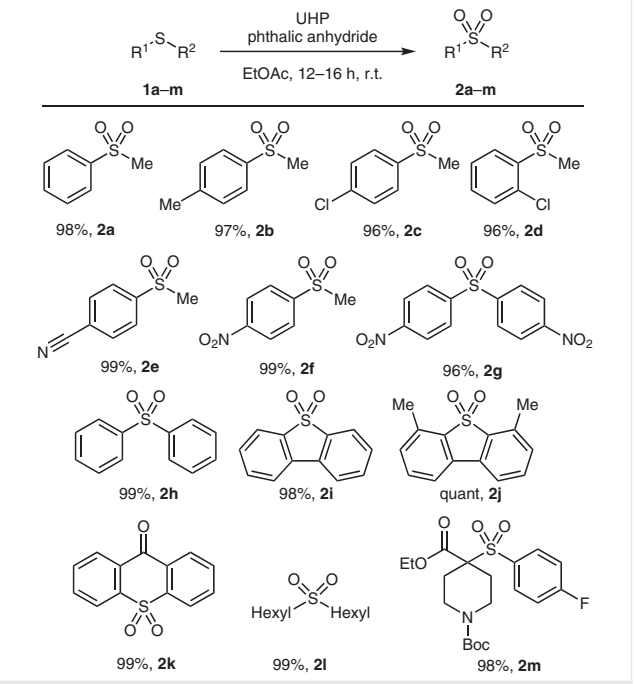
Typical UHP oxidation methods require acetic anhydride[8] or trifluoroacetic anhydride (TFAA);[9] however, these reaction conditions can lead to the formation of diacyl peroxides, which are volatile, highly explosive side products.[8] More recently, transition metal catalysts have been developed for more gentle oxidation conditions;[10] however, these are also unfavorable due to their high cost and potential toxicity. Organocatalysts for UHP oxidation would provide mild conditions for sulfur atom oxidation without the hazards associated with low-boiling acid anhydrides or metal catalysts.

Previously reported sulfide oxidation upon treatment with an excess of up to 5 equivalents of UHP and 2.5 equivalents of phthalic anhydride in either acetonitrile or methanol provided clean conversion into the sulfoxide exclusively, surprisingly without the production of the sulfone.[11] However, when we performed this reaction in ethyl acetate, we found that the sulfoxides were relatively short-lived intermediates, transformed quickly to the sulfone terminal oxidation product, and the reaction required less oxidative re-

agent than previously reported for oxidation in acetonitrile.[12]

Herein we describe sulfide oxidation conditions with UHP and phthalic anhydride that apply to sulfides containing a variety of functional groups, are easy to use on a large scale, and provide high-purity sulfones, in most cases without additional purification.

Both symmetric and asymmetric alkyl, aryl, and heterocyclic sulfides were successfully oxidized to their respective sulfones (Scheme 2). Sulfides containing electron-withdrawing groups, electron-donating groups, acid-sensitive protecting groups, esters and benzylic ketones were well tolerated, providing the respective sulfones in near quantitative yields following either procedure A or procedure B. Procedure A was useful for most crystalline sulfones and enabled isolation of pure products by filtration, eliminating a lengthy extractive workup. Procedure B was followed when the sulfone products were non-crystalline or exhibited relatively high solubility in ethyl acetate.



Scheme 2 Substrate scope for UHP, phthalic anhydride oxidation to the sulfone

In summary, UHP and phthalic anhydride provide clean, organocatalytic oxidation of sulfides directly to the sulfones under conditions that tolerate various substrate functionalities without issue. These conditions scale well, affording high yields and high purity of the sulfone product without the need for column chromatography, thus providing a metal-free, environmentally benign, clean oxidation of sulfides directly to sulfones.

All reagents and solvents used were of commercial grade. Reaction progression was analyzed on an Agilent 1100 HPLC utilizing a Waters Symmetry Shield RP18 column (100Å, 5 µm, 4.6 mm × 250 mm). NMR spectra were acquired on Bruker DPX-400 (400 MHz), spectrometers and are reported relative to deuterated solvent signals ($CDCl_3$ = 7.26 and DMSO-d_6 = 2.50). Data for ^{1}H NMR spectra are reported as follows: chemical shift δ (ppm), multiplicity (standard abbreviations). Mass spectra were recorded on a Waters Acquity I Class UPLC with a Xevo G2-XS QTof utilizing a Waters Acquity UPLC HSS T3 column (100 Å, 1.8 µm, 2.1 mm × 50 mm) or an Agilent series 7890A gas chromatograph with a Agilent series 5975C mass selective detector utilizing an Agilent J & W HP-5 GC column (30 m × 0.32 mm, 0.25 µm, 7 inch cage).

Sulfide Oxidation to the Sulfone; General Procedures

Procedure A: To a solution of sulfide **1** (200 mg, 1–2 mmol, 1 equiv) in EtOAc (5 mL) was added UHP (3 equiv) and phthalic anhydride (3 equiv) and the solution was allowed to stir for 12–16 h at r.t. The reaction slurry was quenched with sat. aq Na_2SO_3 (10 mL) and the crystalline solids were isolated by filtration. The solids were washed with aq 1 N NaOH (2 × 10 mL), H_2O (2 × 15 mL), and EtOAc (5 mL) to provide the desired sulfone, as a spectroscopically pure product.

Procedure B: To a solution of sulfide **1** (200 mg, 1–2 mmol, 1 equiv) in EtOAc (5 mL) was added UHP (3 equiv) and phthalic anhydride (3 equiv) and the solution was allowed to stir for 12–16 h at r.t. The reaction was quenched with sat. aq Na_2SO_3 (10 mL) and then diluted with EtOAc (5 mL). The organics were washed with 1 N aq NaOH (2 × 10 mL), H_2O (10 mL), and brine (10 mL). The organics were dried (Na_2SO_4) and concentrated to give the desired, spectroscopically pure sulfone product.

(Methylsulfonyl)benzene (2a)[13]

Prepared via procedure B to give 248 mg of white crystalline solid (98%); mp 82–84 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.96 (d, *J* = 7.5 Hz, 2 H, ArH), 7.67 (t, *J* = 7.3 Hz, 1 H, ArH), 7.58 (t, *J* = 7.4 Hz, 2 H, ArH), 3.06 (s, 3 H, CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 140.7, 136.2, 133.8, 129.5, 127.4, 125.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_7H_8O_2S$: 157.0318; found: 157.0316.

1-Methyl-4-(methylsulfonyl)benzene (2b)

Prepared via procedure A to give 238 mg of white crystalline solid (97%); mp 87–92 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.83 (d, *J* = 8.3 Hz, 2 H, ArH), 7.37 (d, *J* = 8.0 Hz, 2 H, ArH), 3.04 (s, 3 H, CH_3), 2.45 (s, 3 H, CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 144.8, 137.8, 130.0, 127.5, 44.7, 21.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_8H_{10}O_2S$: 171.0474; found: 171.0464.

1-Chloro-4-(methylsulfonyl)benzene (2c)[14]

Prepared via procedure A to give 230 mg of white crystalline solid (96%); mp 95–103 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.89 (d, *J* = 7.5 Hz, 2 H, ArH), 7.56 (d, *J* = 7.5 Hz, 2 H, ArH), 3.06 (s, 3 H, CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 140.55, 139.1, 129.8, 129.0, 44.6.

GCMS: *m*/*z* calcd for $C_7H_7ClO_2S$: 190.0; found: 190.0.

1-Chloro-2-(methylsulfonyl)benzene (2d)

Prepared via procedure B to give 231 mg of clear oil (96%) that solidified upon standing to give a white solid; mp 86–91 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.16 (dd, *J* = 7.4, 1.5 Hz, 1 H, ArH), 7.58 (dd, *J* = 6.5, 1.6 Hz, 2 H, ArH), 7.48 (dt, *J* = 8.3, 2.2 Hz, 1 H, ArH), 3.28 (s, 3 H, CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 138.1, 134.9, 132.6, 132.0, 130.9, 127.6, 42.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calculated for $C_7H_7ClO_2S$: 190.9928; found: 190.9919.

4-(Methylsulfonyl)benzonitrile (2e)

Prepared via procedure A to give 240 mg of white crystalline solid (99%); mp 143–145 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.09 (d, *J* = 8.6 Hz, 2 H, ArH), 7.90 (d, *J* = 8.6 Hz, 2 H, ArH), 3.11 (s, 3 H, CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 144.6, 133.3, 128.3, 117.7, 117.2, 44.3.

GCMS: *m*/*z* calcd for $C_8H_7NO_2S$: 181.0; found: 181.0.

1-(Methylsulfonyl)-4-nitrobenzene (2f)[14]

Prepared via procedure A to give 236 mg of pale yellow crystalline solid (99%); mp 133–141 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.44 (d, *J* = 7.4 Hz, 2 H, ArH), 8.17 (d, *J* = 7.4 Hz, 2 H, ArH), 3.13 (s, 3 H, CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 151.0, 146.1, 136.2, 129.1, 125.8, 124.8, 44.4.

GCMS: *m*/*z* calcd for $C_7H_7NO_4S$: 201.0; found: 201.0.

4,4′-Sulfonylbis(nitrobenzene) (2g)[15]

Prepared via procedure A to give 214 mg of white solid (96%); mp 256–261 °C.

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 8.44 (t, *J* = 9.0 Hz, 4 H, ArH), 8.32 (t, *J* = 9.0 Hz, 4 H, ArH).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 150.8, 144.8, 129.6, 125.2.

GCMS: *m*/*z* calcd for $C_{12}H_8N_2O_6S$: 308.0; found: 308.0.

Sulfonyldibenzene (2h)[13]

Prepared via procedure A to give 232 mg of white crystalline solid (99%); mp 121–126 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.95 (d, *J* = 6.9 Hz, 4 H, ArH), 7.58–7.48 (m, 6 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 141.7, 133.3, 129.4, 127.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{10}O_2S$: 219.0474; found: 219.0495.

Dibenzo[*b*,*d*]thiophene 5,5-Dioxide (2i)[16]

Prepared via procedure A to give 230 mg of white crystalline solid (98%); mp 234–237 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.82 (d, *J* = 7.7 Hz, 2 H, ArH), 7.79 (d, *J* = 8.0 Hz, 2 H, ArH), 7.63 (t, *J* = 7.5 Hz, 2 H, ArH), 7.52 (t, *J* = 7.5 Hz, 2 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 137.8, 134.0, 131.7, 130.5, 122.2, 121.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_8O_2S$: 217.0318; found: 217.0357.

4,6-Dimethyldibenzo[*b*,*d*]thiophene 5,5-Dioxide (2j)

Prepared via procedure A to give 230 mg of white solid (quant.); mp 278–282 °C.

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.97 (d, *J* = 7.6 Hz, 2 H, ArH), 7.65 (t, *J* = 7.6 Hz, 2 H, ArH), 7.43 (d, *J* = 7.6 Hz, 2 H, ArH), 3.32 (s, 6 H, CH_3), 2.60 (s, 6 H, CH_3).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 134.9, 134.6, 134.2, 132.4, 131.9, 120.0, 16.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{12}NO_2S$: 245.0631; found: 245.0626.

9*H*-Thioxanthen-9-one 10,10-Dioxide (2k)[17]

Prepared via procedure A to give 199 mg of pale yellow crystalline solid (99%); mp 189–191 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.38 (d, *J* = 7.8 Hz, 2 H, ArH), 8.22 (d, *J* = 7.8 Hz, 2 H, ArH), 7.91 (t, *J* = 7.6 Hz, 2 H, ArH), 7.83 (t, *J* = 7.6 Hz, 2 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 178.5, 141.1, 134.8, 133.4, 130.8, 129.3, 123.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_8O_3S$: 245.0267; found: 245.0245.

1-(Hexylsulfonyl)hexane (2l)

Prepared via procedure B to give 230 mg of white solid (99%); mp 73–74 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.94 (t, *J* = 7.8 Hz, 4 H, CH_2), 1.83 (quint, *J* = 7.5 Hz, 4 H, CH_2), 1.44 (m, 4 H, CH_2), 1.32 (m, 8 H, CH_2), 0.90 (m, 6 H, CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 52.8, 31.3, 28.3, 22.4, 22.0, 14.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{26}O_2S$: 235.1726; found: 235.1749.

1-(*tert*-Butyl) 4-Ethyl 4-[(4-Fluorophenyl)sulfonyl]piperidine-1,4-dicarboxylate (2m)[18]

Prepared via procedure A to give 213 mg of white solid (98%); mp 89–97 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.82–7.79 (m, 2 H, ArH), 7.27–7.21 (m, 2 H, ArH), 4.23–4.18 (m, 4 H, CH_2), 2.71–2.47 (m, 2 H, CH_2), 2.32–2.22 (m, 2 H, CH_2), 2.01 (td, *J* = 12.8, 4.8 Hz, 2 H, CH_2), 1.42 (s, 9 H, CH_3), 1.21 (t, *J* = 7.14 Hz, 3 H, CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 167.6, 166.7, 165.1, 154.4, 133.2, 133.1, 131.0, 131.0, 116.3, 116.1, 80.2, 72.5, 62.7, 28.4, 27.7, 14.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{26}FNO_6S$: 438.1357; found: 438.1387.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1609446.

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