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Selective oxidation of sulfides to sulfoxides and sulfones using hydrogen peroxide (H_2O_2) in the presence of zirconium tetrachloride

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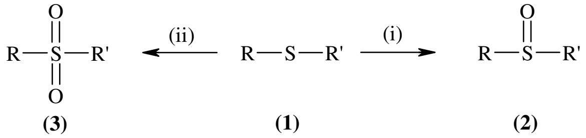
Abstract—Hydrogen peroxide (H_2O_2) in the presence of zirconium tetrachloride is a very efficient reagent for the oxidation of sulfides to sulfoxides and sulfones in methanol at room temperature. It is noteworthy that under such conditions, the sulfide function is highly reactive, and various other functional groups such as alkenes and a ketone are tolerated.

1. Introduction

Oxidation of sulfides is the most straightforward method for the synthesis of sulfoxides and sulfones,[1] some examples of which are important as commodity chemicals and, in some cases, as pharmaceuticals.[2] This transformation has been accomplished in a variety of ways.[3–15] However, the reported methods rarely offer the ideal combination of simplicity of method, rapid and selective reactions, and high yields of products and often suffer from a lack of generality and economic applicability. On the other hand, selective oxidation of sulfides to sulfoxides and sulfides to sulfones with the same reagent system under adjusted reaction conditions is an important process in synthetic organic chemistry and only a few reports are available in the literature for this purpose.[16] As a consequence, the introduction of new methods and/or further work on technical improvements to overcome the limitations is still an important experimental challenge. The chemoselective oxidation of sulfides is also another point of interest. During recent years, very useful procedures involving aqueous hydrogen peroxide (H_2O_2) as the terminal oxidant, due to the effective oxygen content, low cost, safety in storage and operation and environmentally friendly character of H_2O_2 and a Lewis acid as an activator have been developed to promote this transformation,[17] The activator is essential for the success of the reaction because H_2O_2 oxidizes sulfides rather slowly. A novel method for activating hydrogen peroxide using titanium(III) chloride, was described by Shigerue and co-workers.[18] Herein, we describe the successful use of the $H_2O_2/ZrCl_4$ system as a method to oxidize sulfides efficiently to either sulfoxides or sulfones and selectively oxidize sulfides containing other easily oxidized groups. The route for the synthesis of sulfoxides and sulfones is shown in Scheme 1.

The applicability of the $H_2O_2/ZrCl_4$ system was then examined for the sulfoxidation of diaryl, dibenzyl, aryl benzyl, dialkyl and cyclic sulfides in methanol at room temperature. A ratio of 2:14:4 sulfide/H_2O_2/$ZrCl_4$ was found to be optimum for complete conversion of sulfides to sulfoxides and the results are presented in Table 1. As shown, all the reactions were complete within a very short time and the sulfoxides were obtained in almost quantitative yields as the sole oxidation products.



Scheme 1. Reagents and conditions: (i) H_2O_2 (14 equiv), $ZrCl_4$ (4 equiv), CH_3OH, rt; (ii) H_2O_2 (20 equiv), $ZrCl_4$ (5 equiv), CH_3OH, rt.

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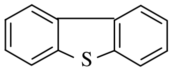
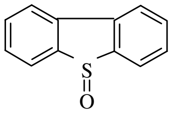
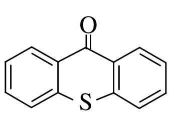
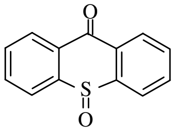
Table 1. Oxidation of sulfides to sulfoxides using the H_2O_2 (14 equiv)/$ZrCl_4$ (4 equiv) system

Sulfide **1**	Sulfoxide **2**[a]	Time (min)	Yield[b] (%)
$(C_6H_5)_2S$ **1a**	$(C_6H_5)_2SO$ **2a**	1	96
$C_6H_5CH_2SC_6H_5$ **1b**	$C_6H_5CH_2SOC_6H_5$ **2b**	2	96
$(C_6H_5CH_2)_2S$ **1c**	$(C_6H_5CH_2)_2SO$ **2c**	2	97
4-$O_2NC_6H_4CH_2SC_6H_5$ **1d**	4-$O_2NC_6H_4CH_2SOC_6H_5$ **2d**	3	95
4-$MeC_6H_4SCH_2C_6H_5$ **1e**	4-$MeC_6H_4SOCH_2C_6H_5$ **2e**	2	94
4-$ClC_6H_4SCH_2C_6H_5$ **1f**	4-$ClC_6H_4SOCH_2C_6H_5$ **2f**	3	94
4-$BrC_6H_4CH_2SCH_2C_6H_5$ **1g**	4-$BrC_6H_4CH_2SOCH_2C_6H_5$ **2g**	3	96
4-$BrC_6H_4CH_2SC_6H_4$4-Me **1h**	4-$BrC_6H_4CH_2SOC_6H_4$4-Me **2h**	2	95
4-$BrC_6H_4CH_2SC_6H_4$4-Cl **1i**	4-$BrC_6H_4CH_2SOC_6H_4$4-Cl **2i**	3	97
4-$O_2NC_6H_4CH_2SC_6H_4$4-Cl **1j**	4-$O_2NC_6H_4CH_2SOC_6H_4$4-Cl **2j**	3	93
 **1k**	 **2k**	3	99
 **1l**	 **2l**	3	99
C_6H_5SMe **1m**	C_6H_5SOMe **2m**	1	97
4-MeC_6H_4SMe **1n**	4-MeC_6H_4SOMe **2n**	1	95
4-ClC_6H_4SMe **1o**	4-ClC_6H_4SOMe **2o**	1.5	94
$C_6H_5SCH_2CH{=}CH_2$ **1p**	$C_6H_5SOCH_2CH{=}CH_2$ **2p**	1	95
$(CH_2{=}CHCH_2)_2S$ **1q**	$(CH_2{=}CHCH_2)_2SO$ **2q**	1	96
(n-$C_4H_9)_2S$ **1r**	(n-$C_4H_9)_2SO$ **2r**	1	94

[a] All products were identified by comparison of their physical and spectral data with those of authentic samples.

[b] Isolated yields.

The chemoselectivity is noteworthy. Under such conditions, the sulfide function was highly reactive, and various other functional groups such as alkenes and a ketone (Table 1, entries **1p**, **1q** and **1l**), were tolerated.

In order to demonstrate the efficiency and applicability of the $H_2O_2/ZrCl_4$ system further, the chemoselective oxidation of sulfides to sulfones was also investigated. The reaction conditions specified in Table 2 were optimized for carrying out the reaction in methanol at room temperature (sulfide/H_2O_2/$ZrCl_4$ ratio = 2:20:5). In practice, using a lower amount of oxidant produced a mixture of sulfoxide and sulfone. It was found that a wide variety of diaryl, dialkyl, dibenzyl, aryl benzyl, alkyl aryl and cyclic sulfides were oxidized to their corresponding sulfones in excellent yields in methanol at room temperature. The results are summarized in Table 2.

In conclusion, $ZrCl_4$ is an excellent Lewis acid for promoting the highly chemoselective and rapid oxidation of functionalized sulfides with 30% H_2O_2 under very mild conditions. It is noteworthy that the reaction tolerates oxidatively sensitive functional groups and that the sulfur atom is selectively oxidized.

2. General procedure for the oxidation of sulfides

In a round-bottomed flask (50 mL) equipped with a magnetic stirrer, a solution of sulfide (2 mmol) in CH_3OH (15 mL) was prepared. H_2O_2 (30%, 14 mmol, 1.4 mL) and $ZrCl_4$ (4 mmol, 0.93 g) were added and the mixture was stirred at room temperature for the time indicated in Table 1. The progress of the reaction was monitored by TLC (eluent: n-hexane/ethyl acetate: 7/3). When the starting sulfide had completely disappeared, the reaction mixture was quenched by adding water (15 mL), extracted with chloroform (4 × 10 mL) and the extract dried with anhydrous $MgSO_4$. The filtrate was evaporated and the corresponding sulfoxide was obtained as the only product (Table 1). An identical procedure was employed using 30% H_2O_2 (20 mmol, 2 mL) and $ZrCl_4$ (5 mmol, 1.16 g) for the oxidation of sulfides to sulfones (Table 2).

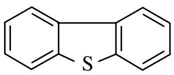
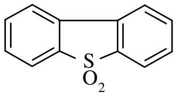
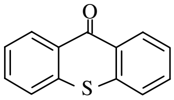
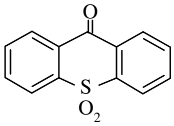
2.1. 4-Nitrobenzyl phenyl sulfoxide 2d

Mp 161–163 °C; IR (KBr, cm^{-1}) 1026, 1345, 1515; ^1H NMR (200 MHz, $CDCl_3$): δ 4.04 (d, 1H, $J = 12.0$ Hz), 4.24 (d, 1H, $J = 12.0$ Hz), 7.13 (d, 2H, $J = 6.5$ Hz), 7.40–7.51 (m, 5H), 8.12 (d, 2H, $J = 6.5$ Hz). Anal. Calcd for $C_{13}H_{11}NSO_3$: C, 59.76; H, 4.24; N, 5.36; S, 12.27. Found: C, 59.65; H, 4.32; N, 5.25; S, 12.40.

2.2. Benzyl 4-bromobenzyl sulfoxide 2g

Mp 139–140 °C; IR (KBr, cm^{-1}) 1028; ^1H NMR (500 MHz, $CDCl_3$): δ 3.78 (d, 1H, $J = 13.1$ Hz), 3.89 (d, 1H, $J = 13.09$ Hz), 3.95 (s, 2H), 7.2 (d, 2H, $J = 8.3$ Hz), 7.32–7.33 (m, 2H), 7.40–7.44 (m, 3H), 7.54 (d, 2H, $J = 8.3$ Hz). Anal. Calcd for $C_{14}H_{13}SOBr$: C, 54.38; H, 4.24; S, 10.37. Found: C, 54.30; H, 4.20; S, 10.47.

Table 2. Oxidation of sulfides to sulfones using the H_2O_2 (20 equiv)/$ZrCl_4$ (5 equiv) system

Sulfide **1**	Sulfone **3**[a]	Time (min)	Yield[b] (%)
$(C_6H_5)_2S$ **1a**	$(C_6H_5)_2SO_2$ **3a**	1.5	99
$C_6H_5CH_2SC_6H_5$ **1b**	$C_6H_5CH_2SO_2C_6H_5$ **3b**	2	98
$(C_6H_5CH_2)_2S$ **1c**	$(C_6H_5CH_2)_2SO_2$ **3c**	2	97
4-$O_2NC_6H_4CH_2SC_6H_5$ **1d**	4-$O_2NC_6H_4CH_2SO_2C_6H_5$ **3d**	3.5	99
4-$MeC_6H_4SCH_2C_6H_5$ **1e**	4-$MeC_6H_4SO_2CH_2C_6H_5$ **3e**	2	96
4-$ClC_6H_4SCH_2C_6H_5$ **1f**	4-$ClC_6H_4SO_2CH_2C_6H_5$ **3f**	3.5	95
4-$BrC_6H_4CH_2SCH_2C_6H_5$ **1g**	4-$BrC_6H_4CH_2SO_2CH_2C_6H_5$ **3g**	3	96
4-$BrC_6H_4CH_2SC_6H_4$4-Me **1h**	4-$BrC_6H_4CH_2SO_2C_6H_4$4-Me **3h**	2	95
4-$BrC_6H_4CH_2SC_6H_4$4-Cl **1i**	4-$BrC_6H_4CH_2SO_2C_6H_4$4-Cl **3i**	3	97
4-$O_2NC_6H_4CH_2SC_6H_4$4-Cl **1j**	4-$O_2NC_6H_4CH_2SO_2C_6H_4$4-Cl **3j**	4	99
 **1k**	 **3k**	2	99
 **1l**	 **3l**	2	99
C_6H_5SMe **1m**	$C_6H_5SO_2Me$ **3m**	1	97
4-MeC_6H_4SMe **1n**	4-$MeC_6H_4SO_2Me$ **3n**	1	98
4-ClC_6H_4SMe **1o**	4-$ClC_6H_4SO_2Me$ **3o**	2	95
$C_6H_5SCH_2CH{=}CH_2$ **1p**	$C_6H_5SO_2CH_2CH{=}CH_2$ **3p**	1	95
$(CH_2{=}CHCH_2)_2S$ **1q**	$(CH_2{=}CHCH_2)_2SO_2$ **3q**	1	98
$(n\text{-}C_4H_9)_2S$ **1r**	$(n\text{-}C_4H_9)_2SO_2$ **3r**	2	97

[a] All products were identified by comparison of their physical and spectral data with those of authentic samples.

[b] Isolated yields.

2.3. 4-Nitrobenzyl phenyl sulfone 3d

Mp 204–205 °C; IR (KBr, cm^{-1}) 1142, 1300, 1345, 1515; ^1H NMR (200 MHz, $CDCl_3$): δ 4.44 (s, 2H), 7.10 (d, 2H, $J = 6.5$ Hz), 7.40–7.70 (m, 5H), 8.18 (d, 2H, $J = 6.5$ Hz). Anal. Calcd for $C_{13}H_{11}NSO_4$: C, 56.31; H, 3.99; N, 5.05; S, 11.56. Found: C, 56.17; H, 4.10; N, 4.97; S, 11.70.

2.4. Benzyl 4-bromobenzyl sulfone 3g

Mp 176–178 °C; IR (KBr, cm^{-1}) 1116, 1299; ^1H NMR (80 MHz, $CDCl_3$): δ 4.02 (s, 2H), 4.14 (s, 2H), 7.17–7.60 (m, 9H). Anal. Calcd for $C_{14}H_{13}BrSO_2$: C, 51.70; H, 4.03; S, 9.86. Found: C, 51.60; H, 4.15; S, 9.90.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.01.051.

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