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Imide-Catalyzed Oxidation System: Sulfides to Sulfoxides and Sulfones

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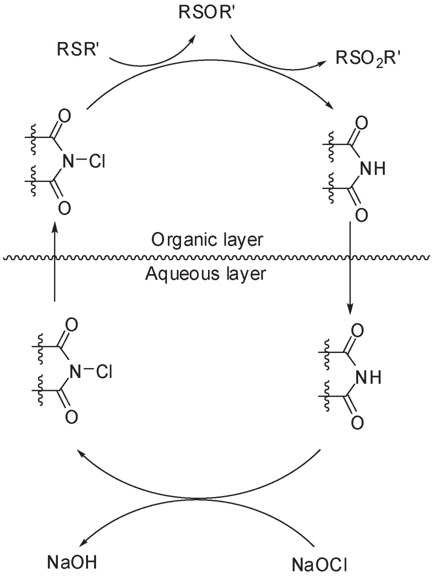
$$R^1SR^2 \xrightarrow[\text{Toluene or DME}]{\text{Imide (cat.), aq.NaOCl}} R^1SOR^2 \quad R^1SO_2R^2$$

A new combination system, the oxidation of sulfides using aqueous NaOCl in the presence of a catalytic amount of imide under two-phase conditions, has been developed. The combination effectively converts various sulfides to the corresponding sulfoxides and sulfones. It was deduced that the imide could react with NaOCl to produce *N*-chloroimide, which would play roles of both the active oxidizing reagent and phase transfer catalyst.

The oxidation of sulfides to sulfoxides and sulfones is one of the most important transformations in organic synthesis, because these functional groups exist in the core structure of many natural, pharmaceutical, and agricultural compounds.[1] Although numerous types of oxidation such as the combinations of metals and co-oxidants,[2] metal oxides,[3] and peroxy-acids[4] have been developed, there are some drawbacks in terms of safety, toxicity, operationality of the reaction, and abolishment of heavy metals from the standpoint of large-scale preparation. Therefore, convenient and environmentally benign methods for the oxidation of sulfides are still required.

SCHEME 1. Imide-Catalyzed NaOCl Oxidation of Sulfide



Aqueous NaOCl as safe and inexpensive reagent is used in the oxidation of sulfide; however, the lower solubility of hypochlorite ions (OCl^-) in organic solvents limits the substrate as a reactant.[5] Although phase transfer catalyst increased the concentration of OCl^- in the organic layer, resulting in the oxidation of sulfide to sulfoxide in two-phase condition, no sulfone was produced under the reported condition.[6] It was also reported that the oxidation

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TABLE 1. Oxidation of Diphenyl Sulfide with NaOCl in the Presence of Additive under Two-Phase Conditions

$$\underset{\mathbf{1}}{\mathrm{PhSPh}} \xrightarrow[\text{Solvent, rt}]{\text{10\% aq. NaOCl (3 equiv), additive (0.1 equiv)}} \underset{\mathbf{2}}{\mathrm{PhSO_2Ph}} + \underset{\mathbf{3}}{\mathrm{PhSOPh}}$$

entry	additive	solvent	time (h)	yield (%)[a] 2	3	1
1	–	toluene	4	1	31	67
2	alliquat 336	toluene	2	13	2	84
3	cyanuric acid	toluene	3	98[b]		
4	succinimide	toluene	2	74	23	< 1
5	succinimide	DME	0.5	95		
6	TCCA	toluene	3	94[b]		
7[c]	cyanuric acid	toluene	4	4	94	
8	acetamide	toluene	4	86	12	
9	$TsNH_2$	toluene	4	5	94	1
10	piperidine	toluene	4		3	96

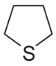
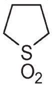
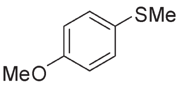
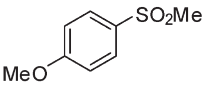
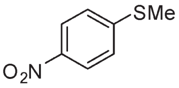
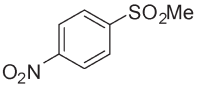
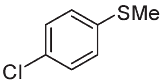
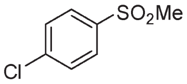
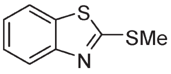
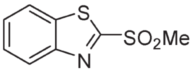
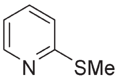
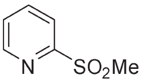
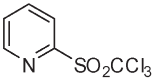
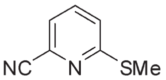
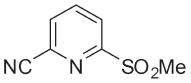
[a]Assay yield by HPLC. [b]Isolated yield. [c]1.2 equiv of NaOCl was used.

of sulfide with aqueous NaOCl in diluted hydrochloric acid or acetic acid produced the corresponding sulfone; however, these reaction conditions involve the risk of chlorine emission.[7] On the other hand, *N*-chloroimides such as *N*-chlorosuccinimide and trichloroisocyanuric acid (TCCA) in the presence of water in an organic solvent widely convert sulfide to sulfoxide or sulfone with the equivalent(s) of resulting imide, which is tedious to remove in workup operation.[8] Meanwhile, imides react with NaOCl (Cl_2 + NaOH) to produce *N*-chloroimide.[9,10] From these reports, we envisioned the new catalytic oxidation system as follows (Scheme 1): (1) NaOCl reacts with the imide in the aqueous layer to produce *N*-chloroimide, which transfers to the organic layer; (2) *N*-chloroimide oxidizes the sulfide with water to yield the oxidative product and regenerate the imide, which moves to the aqueous layer, and this catalytic cycle repeats. Here, we wish to report the novel imide-catalyzed oxidation of sulfide using NaOCl under two-phase conditions.

Diphenyl sulfide **1** as a model compound was used as shown in Table 1, although **1** is generally hard to oxidize.[11] When **1** reacted with 10% aqueous NaOCl (3 equiv) for 4 h at room temperature in toluene as a solvent, **1** was recovered in 67% yield with 1% yield of sulfone **2** and 31% yield of sulfoxide **3** (Table 1, entry 1). The addition of a phase transfer catalyst, methyl tri-*n*-octylammonium chloride (Alliquat 336, 0.1 equiv) according to the literature[6] increased the reaction rate compared with entry 1 to give **2** in 13% yield; however, **1** also remained (entry 2). When the sulfide reacted with NaOCl in the presence of 0.1 equiv of cyanuric acid for 2 h, the oxidation

TABLE 2. Sulfonation of Sulfide with Cyanuric Acid Catalyzed NaOCl Oxidation

$$\text{Sulfide } \mathbf{4} \xrightarrow[\text{Toluene, rt}]{\text{10\% aq. NaOCl (2.3 equiv), cyanuric acid (0.1 equiv)}} \text{Sulfone } \mathbf{5}$$

Entry	Substrate	NaOCl (equiv)	Time (h)	Product	Yield[a] (%)
1	$(n\text{-Bu})_2S$ **4a**	2.3	1	$(n\text{-Bu})_2SO_2$ **5a**	96
2	 **4b**	2.3	1	 **5b**	96
3	PhSBn **4c**	3.0	3	$PhSO_2Bn$ **5c** PhSOBn **6** PhSOCHClPh **7**	13[b] 2[b] 73[b]
4	 **4d**	2.8	2	 **5d**	48
5	PhSMe **4e**	2.3	1	$PhSO_2Me$ **5e**	96
6	 **4f**	2.3	1	 **5f**	96
7	 **4g**	2.3	1	 **5g**	95
8	 **4h**	2.3	1	 **5h**	98
9	 **4i**	3.3	2.5	 **5i**	99
10	 **4j**	2.3	3	 **5j**  **8**	49 11
11	 **4k**	2.3	2	 **5k**	95

[a]Isolated yield. [b]Yield by ^1H NMR.

completed to give **2** in 96% yield, as expected (entry 3). Comparatively, the addition of succinimide as a catalyst for 2 h afforded a mixture of **2** and **3** in 74% and 23% yield, respectively, while the same reaction for 0.5 h in 1,2-dimethoxyethane (DME) converted **1** to **2** in 95% yield (entries 4 and 5). The use of TCCA as an additive provided almost the same result as using cyanuric acid (entry 6). These results show that the active species could be *N*-chloroimide as shown in Scheme 1. These differences from cyanuric acid and succinimide could be explained by the solubility of *N*-chlorosuccinimide and *N*-chlorinated cyanuric acid as the active species in the organic solvents.[12] When 1.2 equiv of NaOCl in the presence of cyanuric acid was used, **3** was selectively obtained in 94% yield (entry 7). The other additives were also examined. Although both acetamide and tosylamide accelerated these oxidation rates, these were slower than that with cyanuric acid (entries 8 and 9). Meanwhile, piperidine inhibited the oxidation to retain most of **1** (entry 10).

Subsequently, the NaOCl oxidation catalyzed by cyanuric acid in toluene was applied to various sulfides **4** to sulfones **5** as shown in Table 2. The oxidation of dialkyl sulfides **4a** and **4b** provided the corresponding sulfones in 96% yield, respectively (entries 1 and 2). Benzyl phenyl sulfide **4c** mainly gave sulfoxide **7** chlorinated at the benzylic position of sulfoxide **6** (entry 3). The reaction of allyl phenyl sulfide **4d** gave **5d** in moderate yield (entry 4). A variety of functional groups were tolerated in methyl phenyl sulfide bearing the ether, nitro, and halogen groups (entries 5−8). Methylsulfanyl benzothiazole **4i** was selectively oxidized at the 2′-position to afford **5i** in almost quantitatively yield (entry 9). Methyl pyridyl sulfide **4j** yielded a mixture of **5j** and trichloromethyl sulfone **8**, while the sulfide containing cyano group on the pyridine ring **4k** selectively afforded **5k** in 95% yield without chlorination on the methyl group (entries 10 and 11). It was supposed that the pummerer rearrangement could be inhibited by the electron-withdrawing effect of the cyano group.

In conclusion, a novel and versatile combination system for the imide-catalyzed NaOCl oxidation of sulfide to sulfone and sulfoxide has been developed. To our knowledge, this is the first reaction with imide as a catalyst. This methodology is applied to various sulfides including other functional groups. The noteworthy feature is that this reaction can be carried out with an inexpensive reagent under safe and environmentally friendly conditions. Moreover, we are free of concern over metal residues in the desired product.

Experimental Section

General Procedure for the Imide-Catalyzed Oxidation of Sulfide: Oxidation of Diphenyl Sulfide 1 (Table 1, Entry 3). To a solution of **1** (10.00 g, 53.69 mmol) and cyanuric acid (0.69 g, 5.37 mmol) in toluene (100 mL) was added 10% (w/w) aqueous NaOCl (119.90 g, 161.07 mmol), and the mixture was stirred for 3 h at ambient temperature. Ethyl acetate (200 mL) and sodium sulfite (6.77 g, 53.69 mmol) were added to the reaction mixture, and the whole mixture was stirred for 0.5 h at ambient temperature. After being separated, the organic layer was washed with aqueous NaOH solution (0.3 M, 100 mL) and concentrated in vacuo. The resulting residue was crystallized in ethanol to afford **2** (11.35 g, 98%). IR (ATR) 427, 559, 583, 681, 688, 698, 725, 759, 999, 1067, 1104, 1152, 1295, 1308, 1317, 1447 cm^{-1}; ^{1}H NMR δ 7.42−7.65 (6H, m), 7.90−7.99 (4H, m); ^{13}C HMR δ 127.7, 129.3, 133.2, 141.7; mp 123.4−124.1 °C. Anal. Calcd for $C_{12}H_{10}O_2S$: C, 66.03; H, 4.62. Found: C, 65.95; H, 4.63.

6-(Methylsulfonyl)pyridine-2-carbonitrile (5k): IR (ATR) 440, 496, 537, 671, 733, 768, 822, 851, 943, 972, 988, 1077, 1114, 1151, 1171, 1221, 1304, 1438, 1551, 1579, 2929, 3015, 3081 cm^{-1}; ^{1}H NMR δ 3.32 (3H, s), 7.92−8.00 (1H, m), 8.14−8.23 (1H, m), 8.27−8.33 (1H, m); ^{13}C HMR δ 39.7, 115.7, 123.8, 131.6, 133.8, 140.0, 159.8; MS (ESI): m/z $[M + H]^+$ 283; mp 119.5−120.5 °C. Anal. Calcd for $C_7H_6N_2O_2S$: C, 46.14; H, 3.32; N, 15.38. Found: C, 46.09; H, 3.25; N, 15.45.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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