Highly selective 30% hydrogen peroxide oxidation of sulfides to sulfoxides using micromixing

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The highly selective oxidation of sulfides to sulfoxides using 30% hydrogen peroxide has been achieved under catalyst-free conditions using a T-shaped micromixer.

Sulfoxide compounds are important synthetic intermediates,[1] and a wide range of methods for the selective oxidation of sulfides to sulfoxides have been developed for this transformation.[2] For example, aqueous hydrogen peroxide,[3] peracetic acid,[4] *m*CPBA,[5] sodium metaperiodate,[6] nitrogen tetraoxide,[7] and halogens[8] and their derivatives[8] have all been used as oxidants. Among them, aqueous 30% hydrogen peroxide is a particularly attractive oxidant because it is cheap, environmentally benign, easy to handle, safely stored and produces only water as a by-product.[3h] However, aqueous hydrogen peroxide by itself requires a long reaction time to oxidize sulfides to sulfoxides.[3c] Therefore, many transition metal (Ti,[3d] Mo,[3e] Fe,[3f] V,[3g] W,[3h] Re,[3i] Cu[3j] and Au[3k]) compounds have been used as catalysts with aqueous hydrogen peroxide. Although these reactions efficiently provide the desired sulfoxides, their over-oxidation to the corresponding sulfones is a common problem. The conditions of the reaction, which include temperature, reaction time, and the relative amounts of oxidant and catalyst, have to be controlled to prevent over-oxidation from occurring.

Recently, organic reactions using microreactors (miniaturized chemical reactors) have been proved to present several advantages in organic synthesis.[9] The short molecular diffusion distance, as a result of the very narrow channel width, allows for rapid mixing of the reagents. Highly efficient heat transfer allows rapid heating and cooling, and makes it easy to control the temperature of a reaction mixture. The reaction system can be scaled up readily by using a number of microreactors in parallel. The actual reactor (reaction volume) is very small, and thus reactions can be conducted more safely when explosive compounds are being used. When organic and aqueous phases are introduced through two inlets of a microreactor, a large specific interfacial area can be obtained without any stirring. By utilizing the large specific interfacial area provided by organic and aqueous phases, it is expected that efficient phase transfer occurs. Based on this idea, Yoshida and co-workers recently developed a highly selective Friedel–Crafts monoalkylation reaction using a microreactor.[9a] Reactions in the microreactor proceeded with a short reaction time
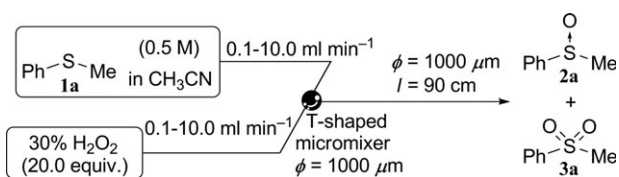
and selectively afforded monoalkylated products in high yields. On the other hand, reactions in a batch reactor provided 1 : 1 mixtures of the monoalkylated and dialkylated products in moderate yields. Efficient 1 : 1 mixing using the micro-scale mixer enabled them to selectively form monoalkylated products. We envisioned that oxidation of sulfides with hydrogen peroxide using a microreactor would facilitate selective formation of the corresponding sulfoxides.

We first chose thioanisol (**1a**) as a model sulfide and undertook the reaction with 30% hydrogen peroxide in a T-shaped micromixer ($\phi = 1000$ μm).[10] The experimental system for this reaction is shown in Fig. 1. A solution of **1a** in CH_3CN (0.5 M) was injected into the T-shaped micromixer using a syringe pump (syringe A).[11] At the same time, a solution of 30% hydrogen peroxide was also injected into the micromixer by another syringe pump (syringe B).[11] The flow rates of syringe A and syringe B were identical. The reaction mixture was then allowed to flow through a stainless steel reactor tube ($\phi = 1000$ μm, $l = 0.9$ m).[12]

The results of the reaction of **1a** (2.0 mmol) with hydrogen peroxide (40 mmol) are shown in Table 1. The mean residence time in the microreactor was determined by the total reactor volume and the flow rate of the reaction mixture. We also examined the reaction of **1a** (2.0 mmol) with hydrogen peroxide (40 mmol) in CH_3CN (4 ml) using a conventional batch reactor (a 50 ml round-bottomed flask) (Table 1).

The desired sulfoxide, **2a**, was obtained in 97% yield after using the microreactor for 212 or 2.12 s at 25 °C (Table 1, runs 3 and 4). The undesirable, over-oxidised sulfone product, **3a**, was not detected at all in either case. However, sulfone **3a** was obtained in 9% yield at 50 °C (Table 1, run 5). On the other hand, using the batch reactor, a long reaction time was required to complete the reaction of **1a** with 30% hydrogen peroxide in acetonitrile, and **2a** was obtained in a relatively low yield together with undesirable sulfone **3a** (Table 1, runs 1 and 2). These results mean that effective agitation is very important in this reaction.

We then examined the oxidation of **1a** for 2.12 s with several equiv. of 30% hydrogen peroxide using the microreactor. The profile of this oxidation is shown in Fig. 2. The reaction with 5.0 equiv. of 30% hydrogen peroxide provided **2a** in low yield,

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Fig. 1 Schematic diagram of the microreactor system for the 30% hydrogen peroxide oxidation of **1a** to sulfoxide **2a**.

Table 1 Oxidation of **1a** with 30% hydrogen peroxide using micro-reactor and batch systems[a]

Run	Method	Time[b]	Temp./°C	Isolated yield (%)		
				1a	**2a**	**3a**
1	Batch (0 rpm)	24 h	25	Trace	75	9
2	Batch (1200 rpm)	3.0 h	25	0	82	15
3	Microreactor[c]	212 s	25	0	97	0
4	Microreactor[d]	2.12 s	25	0	97	0
5	Microreactor[d]	2.12 s	50	0	89	9

[a] The reaction was started by introducing a CH$_3$CN solution of **1a** (0.5 M, 2.0 mmol) to 30% hydrogen peroxide (40.0 mmol). [b] Residence time. [c] Reaction mix solution **1a** (flow rate 0.1 ml min^{-1}) and 30% hydrogen peroxide (flow rate 0.1 ml min^{-1}) in the microreactor. [d] Reaction mix solution **1a** (flow rate 10.0 ml min^{-1}) and 30% hydrogen peroxide (flow rate 10.0 ml min^{-1}) in the microreactor.

Fig. 2 The profile for the reaction of **1a** (2.0 mmol) with 30% hydrogen peroxide (5.0 equiv. to 40.0 equiv.) in the microreactor for 2.12 s.

and 78% of the starting material was recovered. In contrast, the oxidation with 40.0 equiv. of 30% hydrogen peroxide afforded **2a** in 72% yield, accompanied by over-oxidised sulfone **3a**. The optimal condition to prepare **2a** was the reaction with 20.0 equiv. of 30% hydrogen peroxide.

Next, we investigated the reaction of **1a** with 20.0 equiv. of 30% hydrogen peroxide in several solvents using both the microreactor and the batch reactor (Table 2). When EtOAc or MeOH was employed as the solvent, sulfone **3a** was obtained as a by-product (Table 2, runs 2 and 3). Decent yields of sulfoxide **2a** were obtained with other solvents, such as THF and toluene (Table 2, runs 4 and 5). Oxidation in CH$_3$CN using the microreactor afforded the best result (Table 2, run 1). The desired sulfoxide, **2a**, was obtained in 97% yield in the shorter reaction time of 2.12 s.

Finally, several kinds of sulfides, **1**, in CH$_3$CN were treated with 30% hydrogen peroxide using both the microreactor and the batch reactor (Table 3). The yields of the corresponding sulfoxides, **2**, were higher in all cases for the microreactor when compared with the batch reactor. A series of aryl-alkyl and dialkyl sulfides were effectively oxidized to their corresponding sulfoxides, **2**, in most cases (Table 3, runs 1 and 3–7). However, sterically-bulky sulfides **1h** and **1i** were, to some

extent, over-oxidized to sulfones **3h** and **3i** (Table 3, runs 8 and 9). The reaction of diphenyl sulfide (**1b**), which is generally very hard to oxidize, provided diphenyl sulfoxide (**2b**) in relatively good yield using the microreactor (Table 3, run 2). In this case, 12% of unreacted **1b** was recovered. It is notable that the alkene functionality of **1c** was not oxidized at all to the corresponding epoxide (Table 3, run 3). The diastereotopic sulfur atom on sulfide **1e** was transformed into the corresponding sulfoxide **2e** with a *syn* : *anti* ratio of 25 : 75 (Table 3, run 5). A similar stereoselectivity was observed when using the batch reactor.

In conclusion, we have revealed that the oxidation of sulfides **1** to sulfoxides **2** with 30% hydrogen peroxide in a microreactor is more effective than when undertaken in a round-bottomed flask with vigorous stirring at room temperature. Rapid mixing using the micromixer enabled us to oxidize sulfides in a shorter reaction time, and regulation of the relative amount of hydrogen peroxide to the sulfides by using syringe pumps prevented over-oxidation. This method gave the desired sulfoxides **2** in high yields, while producing only non-toxic water as a by-product.

Batch reaction; general procedure. To a solution of **1** (2.0 mmol) in CH$_3$CN (4.0 ml) in a round-bottomed flask was added 30% hydrogen peroxide (40 mmol, 4.0 ml) at room temperature. The reaction was monitored by TLC. After **1** had disappeared, on the basis of TLC results, the reaction mixture

Table 2 Oxidation of **1a** with 30% hydrogen peroxide using the microreactor and batch systems in several different solvents[a]

Run	Solvent	Time/s	Isolated yield (%, microreactor)			Time/h	Isolated yield (%, batch reactor)		
			1a	**2a**	**3a**		**1a**	**2a**	**3a**
1	CH$_3$CN	2.12	0	97	0	3	0	82	15
2	EtOAc	2.12	0	90	8	3	0	94	6
3	MeOH	2.12	0	89	10	3	0	80	16
4	THF	2.12	0	93	0	3	0	92	0
5	Toluene	2.12	0	87	0	24	12	62	7

[a] The reaction was started by introducing a CH$_3$CN solution of **1a** (0.5 M, 2.0 mmol) to 30% hydrogen peroxide (40.0 mmol).

Table 3 Oxidation of sulfides **1a–i** to sulfoxides **2a–i** with 30% hydrogen peroxide using the microreactor and batch systems[a]

Run	Substrate	Product	By-product	Time/s	Isolated yield (%, microreactor)			Time/h	Isolated yield (%, batch reactor)		
					1	2	3		1	2	3
1	Ph–S–Me **1a**	**2a**	**3a**	2.12	0	97	0	3	0	82	15
2	Ph–S–Ph **1b**	**2b**	**3b**	2.12	12	87	0	100	0	66	16
3	Ph–S– **1c**	**2c**	**3c**	2.12	0	97	0	2	0	58	20
4[b]	Ph–S–Ph **1d**	**2d**	**3d**	2.12	0	93	0	6	0	92	0
5	Ph–S–Ph Me **1e**	**2e**	**3e**	2.12	0	97 (syn : anti = 25 : 75)[c]	0	24	0	82 (syn : anti = 24 : 76)[c]	5
6	Me–S–Ph **1f**	**2f**	**3f**	2.12	0	90	0	1	0	78	20
7	n-Bu–S–n-Bu **1g**	**2g**	**3g**	2.12	0	100	0	3	0	86	10
8	i-Pr–S–i-Pr **1h**	**2h**	**3h**	2.12	0	82	9	2	0	69	22
9	t-Bu–S–t-Bu **1i**	**2i**	**3i**	2.12	0	66	26	1	0	64	27

[a] The reaction was started by introducing a CH$_3$CN solution of **1** (0.5 M, 2.0 mmol) to 30% hydrogen peroxide (40.0 mmol). [b] The temperature of this reaction was 45 °C. [c] The diastereomeric ratio was determined by ^{1}H NMR analysis.

was quenched with saturated aqueous Na$_2$S$_2$O$_3$ at 0 °C. The mixture was extracted with EtOAc, and the extract washed with brine, dried over Na$_2$SO$_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel using *n*-hexane/ethyl acetate as the eluent.

Microreactor reaction; general procedure. A solution of **1** (2.0 mmol) in CH$_3$CN (4.0 ml) was injected by syringe pump into a T-shaped micromixer at a flow rate of 10.0 ml min^{-1} for 24 s. At the same time, a solution of 30% hydrogen peroxide (40 mmol, 4.0 ml) in a syringe was also injected into the micromixer by another syringe pump at a flow rate of 10.0 ml min^{-1} for 24 s at room temperature. The reaction mixture was then allowed to flow at room temperature for an additional 2.12 s though a stainless steel reactor tube (ϕ = 1000 µm, l = 0.9 m). The reaction mixture was quenched with a saturated aqueous Na$_2$S$_2$O$_3$ solution at 0 °C. The mixture was extracted with EtOAc, washed with brine, dried over Na$_2$SO$_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel using *n*-hexane/ethyl acetate as the eluent.

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10. A GL Sciences SL (SWAGELOK)-type fitting union tee (SUS-316), cat. no. 3006-43310 (http://www.glsciences.com/) was used. The reactor was made of stainless steel and the inner diameter was 1000 µm.
11. A GL Sciences pre-cleaned 316 stainless steel tubing (bright annealed), cat. no. 3004-28081 (http://www.glsciences.com/), was used. The channel diameter was 1000 µm.
12. A Harvard syringe pump, model 11E Econoflo, cat. no. 70-2205 (http://www.harvardapparatus.com/), was used.