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Xiaojing Ye, Hongliang Fu, Jiahao Ma & Weihui Zhong

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# Efficient and mild Swern oxidation using a new sulfoxide and *bis*(trichloromethyl)carbonate

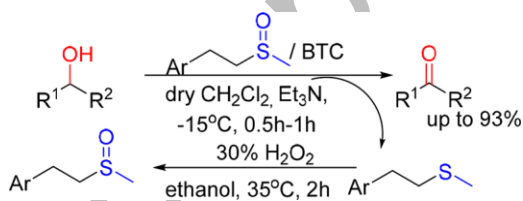
Xiaojing Ye<sup>1</sup>, Hongliang Fu<sup>1</sup>, Jiahao Ma<sup>1</sup>, Weihui Zhong<sup>1</sup>

<sup>1</sup>Collaborative Innovation Center of Green Pharmaceutical Engineering, College of Pharmaceutical Sciences, Zhejiang University of Technology, Hangzhou, P.R. China

Corresponding author: Weihui Zhong, Collaborative Innovation Center for Green Pharmaceutical Engineering, College of Pharmaceutical Sciences, Zhejiang University of Technology, Hangzhou 310014, P. R. China. E-mail: weihuizhong@zjut.edu.cn.

## Abstract

A new type of sulfoxide, 4-(2-(2-(methylsulfinyl) ethyl)-4-nitrophenyl)- morpholine (**I**) was designed and prepared in good yield. **Upon the combination of I and *bis*(trichloromethyl)carbonate**, the Swern oxidation of primary and secondary alcohols was significantly promoted under mild condition which afford the corresponding aldehydes or ketones in good yields. It's noteworthy that the re-oxidation of the isolated byproduct sulfide **V** could be further recycled in Swern oxidation.



**KEYWORDS:** Swern oxidation, Alcohols, Sulfoxide, *Bis*(trichloromethyl)carbonate, Sulfide

## INTRODUCTION

The oxidation of alcohols to the corresponding aldehydes or ketones is one of the most fundamental and important reactions widely used in the laboratories for manufacturing and productivity.<sup>[1]</sup> **The method by applying activated DMSO in the oxidation of various alcohols to produce carbonyls has been successfully developed by Swern *et al* since 1976,<sup>[2]</sup> in particular oxalyl chloride is recognized as the most powerful “activator”<sup>[3]</sup> and applied in the preparation of medicinal intermediate.**<sup>[4a-4e]</sup>

Unfortunately, the condition of Swern reaction is **relatively harsh which usually requires the reaction to be performed under lower temperature** and the byproduct dimethyl sulfide is the highly volatile compound with foul smell. Lots of efforts have been contributed to **develop** modified reagents to overcome these drawbacks. **Several research groups endeavored to develop the odorless Swern oxidation system by using a modified sulfoxide to replace DMSO**, although the low reaction temperature was still required.<sup>[5a-5e]</sup> **Upon switching the activated reagents from oxalyl chloride to other reagents** such as 2,4,6-trichloro-1,3,5-triazine,<sup>[6]</sup> dichlorotriphenylphosphorane,<sup>[7]</sup> trichloro(methyl)-silane,<sup>[8]</sup> 1,1-dichlorocycloheptatriene,<sup>[9]</sup> and 4-methylbenzene-1-sulfonyl chloride,<sup>[10]</sup> **the reaction temperature could be slightly raised to -30 °C but the generation of dimethyl sulfide was still observed.** In 2008, an on-line reactor was designed **to enable** a high-temperature semi-continuous process possible.<sup>[11]</sup>

In this article, we wish to report a new oxidation system which contained **a new type** of sulfoxide, 4-(2-(2-(methylsulfinyl)ethyl)-4-nitrophenyl)morpholine **I** (Scheme 1) and *bis*(trichloromethyl)carbonate (BTC) as the activator. The reaction temperature could be **increased at -15 °C** for the oxidation of primary aromatic alcohols, **as well as -10 °C** for the oxidation of secondary aromatic alcohols. To our delight, the byproduct 4-(2-(2-(methylthio)ethyl)-4-nitrophenyl)morpholine **V generated** in our system is **odorless** which could be **easily** recovered and **recycled**.

## RESULTS AND DISCUSSION

Initially, (2-(methylsulfinyl)ethyl)benzene was designed and prepared for the **oxidation of benzyl alcohols at -15 °C** (Figure 1), in which the byproduct methyl(phenethyl)sulfane was still stinking. **In order to reduce and eventually eliminate** the reaction odor, the basic group such as morpholine on aromatic cycle **was further introduced** which **might benefit** the isolation of our product and the recovery of the byproduct.

**A new type** of sulfoxide, 4-(2-(2-(methylsulfinyl)ethyl)-4-nitrophenyl)morpholine **I** was designed and prepared from 2-(2-chloro-5-nitrophenyl)ethanol **II** by several steps (Scheme 1). The starting material **II** is a dye intermediate of hair which has been prepared in our previous project. **After the substitution from morpholine to generate III, the intermediate IV was then achieved through the subsequent** chloration using

BTC. Treatment of **IV** with 20% sodium methyl mercaptide aqueous solution, **followed by** 30% hydrogen peroxide, gave the target sulfoxide **I** in 76% yield.

**The sulfoxide I was combined with** BTC to afford a **novel** Swern oxidation system, which was tested in the oxidation of benzyl alcohol as a model substrate to screen **the optimized condition towards** the loading of **I** and BTC **at various temperatures**. (Table 1)

In entry 1, not only benzaldehyde (**a**) could be formed but the byproduct benzyl chloride (**b**) was also detected **due to the excess amount of** BTC was **applied. Moreover , the excess** BTC was used at higher temperature (entries 5, 6), **resulting in the formation of** more byproduct benzyl chloride. **Furthermore** the reaction temperature was increased to 0 °C, **only trace amount of product a and byproduct b** were detected due to the **fast** decomposition of **the generated sulfonium salt** and sulfoxide **I** was almost recovered (entry 7). So we choose -15 °C as the optimum reaction temperature and **the ratio of alcohol, sulfoxide I and BTC was recognized as 1 : 1.8 : 0.6 or 1 : 1.5 : 0.5 (entries 8-9).**

**It's worth pointing out** that simple ice salt bath could be used to control the reaction temperature (about -15 °C), which **is thought to be a big advantage compared** to the original Swern oxidation system (**usually around -60 °C**) or other alternative methods

(**lower than -30 °C**).<sup>[7-10]</sup> Another **improvement** of our method is that the byproduct sulfide **V** derived from sulfoxide **I** has no stink odor and **it turns out to be less volatile**.

It's worth mentioning that the sulfide **V** could be recovered by adjusting pH with the recovery of 90% and re-oxidized with 30% H<sub>2</sub>O<sub>2</sub> aqueous solution to **produce** sulfoxide **I** with **excellent** yield (94%), **which could be reused for the oxidation of substrates in the next round**.

The scope of this new oxidation method was studied under the optimum condition (Table 2). The oxidations of the primary aromatic alcohols were carried out at -15 °C to give aromatic aldehydes with good yields (entries 1-8), while the oxidations of secondary aromatic alcohols were carried out at a slightly higher temperature (**-10 °C or -5 °C, entries 9-16**) to give aromatic ketones. No obvious electronic effect was observed (entries 2-6 or entry 10, entries 12-14). The oxidations of secondary aliphatic alcohols could be carried out **under -15 °C to afford the desired products** (entries 19-20) with good yields. **Unfortunately**, the oxidations of primary aliphatic alcohols were still **required to be performed** at -30 °C and gave the corresponding aldehyde in moderate yields (entry 18). **As for long alkyl chain** alcohol (entry 17), it was difficult to isolate a pure product due to the formation of byproduct at -30 °C. **In general**, our method is more efficient for the oxidations of secondary aromatic alcohols above -15°C, which could be used **for** the selective oxidation of alcohols.

**The selective oxidation of alcohols was observed** when we treated 1-phenylethanol and benzyl alcohol with the sulfoxide **I** and BTC. 1-Phenylethanol was transformed into acetophenone while more than 95% benzyl alcohol was recovered (Scheme 2). Under the similar condition, benzyl alcohol was selectively transformed into benzaldehyde in the presence of 4-phenylbutan-1-ol (Scheme 2).

According to the mechanism of the original Swern oxidation, the alkoxyulfonium salt **A** was the key intermediate and formed as a precursor of the carbonyl compound once alcohol was added (Figure 2). We **suspected** the key intermediate **C** in our method might be more stable than **A** **therefore the high reaction temperature could be tolerated.**

**The proposed mechanism was outlined in** Scheme 3. Treatment of sulfoxide **I** with BTC gave an intermediate **B**, which was then reacted with alcohols to form the key intermediate **C**, with the emission of carbon dioxide and hydrogen chloride. However, the gas emission was not obvious before the base was added **under lower temperature. A plausible equilibrium between B and C was proposed** in which **B is sufficiently stable to be further converted from intermediate C. The increase of** the reaction temperature (0 °C, Table 1, entry 7, or higher) **resulted that none of the desired product** was detected, **possibly** due to the decomposition of intermediate **B** to recover the sulfoxide **I**. On the other hand, once triethylamine was added at lower temperature, the equilibrium

**status** between **B** and **C** was broken and the intermediate **D** could be formed, which was **then** transformed into the carbonyl compounds and the sulfide **V**.

## CONCLUSION

A **novel** Swern oxidation system, derived from the new type of sulfoxide 4-(2-(2-(methylsulfinyl)ethyl)-4-nitrophenyl)morpholine (**I**) with *bis*(trichloromethyl) carbonate, **displays** good reactivity **towards** the oxidation of aromatic alcohols to **achieve** the corresponding carbonyl compounds in good yields **under mild condition**. Moreover, the inodorous byproduct 4-(2-(2-(methylthio)ethyl)nitrophenyl)morpholine (**V**) could be easily isolated, re-oxidized and reused in Swern oxidation.

## EXPERIMENTAL

All starting materials were commercially available except **II** and were used without further purification. Melting points were determined on a Büchi B-540 capillary melting point apparatus and uncorrected. Optical rotations were determined by using an AUTOPOL V Polarimeter.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were recorded on a Varian-400 MHz spectrometer at 400 and 100 MHz for solution in  $\text{CDCl}_3$  with tetramethylsilane (TMS,  $\delta$  0) as an internal standard. The chemical shifts ( $\delta$ ) were reported in ppm and coupling constants  $J$  were expressed in Hertz. Less solution mass spectra were obtained with a Trace DSQ mass spectrometer in ESI mode. High resolution mass spectra were acquired with an Agilent 6210 TOF mass spectrometer.



### Typical Procedure For The Preparation Of I:

A solution of **IV** (5.0 g, 18.5 mmol) in EtOH (10 mL) was stirred, and a **20% aqueous solution** of  $\text{CH}_3\text{SNa}$  (9.07 g, 25.9 mmol) was added dropwise over 0.5 h at rt. The flask was heated to  $60^\circ\text{C}$  and the reaction was monitored by TLC until completed. A **30% aqueous solution** of  $\text{H}_2\text{O}_2$  (3.15 g, 27.8 mmol) was added dropwise over 0.5 h at rt. and then the reaction mixture was heated to  $30^\circ\text{C}$  in an  $\text{O}_2$  atmosphere. After stirred for 1h, the reaction was completed. EtOH was recovered by vacuum distillation, the mixture was extracted with EtOAc (15 mL x 2), decanted, and washed with brine. After drying over  $\text{Na}_2\text{SO}_4$  and concentration, the crude was purified by flash chromatography ( $\text{SiO}_2$ ;  $\text{CH}_2\text{Cl}_2$ ). 4-(2-(2-(methylsulfinyl)ethyl)-4-nitrophenyl)morpholine **I** was acquired, an orange red liquid (4.20 g, 76%).

**I**:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.99 (dd,  $J_1$  8.8 Hz,  $J_2$  2.4 Hz, 1H), 7.84 (m, 1H), 6.27 (d,  $J$  8.8 Hz, 1H), 3.94 – 3.84 (m, 2H), 3.79 – 3.66 (m, 4H), 3.51 – 3.38 (m, 2H), 3.07 (t,  $J$  8.4 Hz, 2H), 2.97 – 2.80 (m, 2H), 2.58 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  156.8, 137.7, 129.5, 126.3, 120.5, 103.3, 68.8, 63.6, 54.8, 53.0, 46.9, 39.3, 27.2. LRMS ( $\text{ESI}^+$ ):  $m/z$  = 299.3  $[\text{M}+\text{H}]^+$ , 321.3  $[\text{M}+\text{Na}]^+$ . HRMS ( $\text{ESI}$ ): calcd. for  $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}_4\text{S}$   $[\text{M}+\text{Na}]^+$  321.0893; found 321.0879.

### Typical Procedure For The Oxidation Of Alcohols

A solution of BTC (0.41 g, 1.39 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (5 mL) was cooled in ice salt bath under an atmosphere of  $\text{N}_2$ . A solution of **I** (1.24 g, 4.17 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (5 mL) was added dropwise for 0.5 h, at  $-15^\circ\text{C}$ . Stirring was continued for 0.5 h, a solution of benzyl alcohol (0.3 g, 2.78 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (5 mL) was added dropwise for 0.5 h, at  $-15^\circ\text{C}$ . After stirred for 0.5 h,  $\text{Et}_3\text{N}$  (0.84 g, 8.34 mmol) was added slowly while the temperature should be controlled below  $-15^\circ\text{C}$ . When the reaction was completed, 10% HCl solution in water was added dropwise until the pH of the reaction solution reached 2 under ice bath. The mixture was extracted with n-hexane or petroleum ether (10 mL x 2), decanted. The product was acquired after organic layer was concentrate and purified by flash chromatography ( $\text{SiO}_2$ ; n-hexane). (0.27 g, 92%) The water layer was used for the recovery of **V** and the excess **I**.

### Typical Procedure For The Recovery And Re-Oxidized Of Co-Product

#### 4-(2-(2-(Methylthio)Ethyl)-4-Nitrophenyl)Morpholine **V**

An aqueous solution of 25% NaOH was added dropwise in the water layer from the oxidation procedure until the pH reached 12. The mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (15 mL x 2), decanted, and washed with brine. The byproduct 4-(2-(2-(methylthio)-ethyl)-4-nitrophenyl)-morpholine **V** was recovered after concentration (90%). Treated **V** with **30% aqueous solution of  $\text{H}_2\text{O}_2$**  at r.t. and then the reaction mixture was heated to  $30^\circ\text{C}$  in an  $\text{O}_2$  atmosphere. After stirred for 1h, the reaction was completed. EtOH was recovered by vacuum distillation, the mixture was

extracted with EtOAc (15 mL x 2), decanted, and washed with brine. After drying over Na<sub>2</sub>SO<sub>4</sub> and concentration, the crude was purified by flash chromatography (SiO<sub>2</sub>; CH<sub>2</sub>Cl<sub>2</sub>), (94%).

**V:** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.98 (dd, *J*<sub>1</sub> 8.8 Hz, *J*<sub>2</sub> 2.4 Hz, 1H), 7.82 (d, *J* 2.4 Hz, 1H), 6.26 (d, *J* 8.8 Hz, 1H), 3.76 (t, *J* 8.4 Hz, 2H), 3.69 – 3.60 (m, 4H), 3.43 (t, *J* 5.2 Hz, 2H), 3.06 (t, *J* 8.4 Hz, 2H), 2.65 (t, *J* 6.4 Hz, 2H), 2.11 (s, 3H). LRMS (ESI<sup>+</sup>): *m/z* = 283.0 [M+H]<sup>+</sup>.

#### Typical Procedure For The Reuse Of I

The procedure was the same as the typical procedure for the oxidation of alcohols. The yield of benzaldehyde was 90%.

#### ACKNOWLEDGEMENTS

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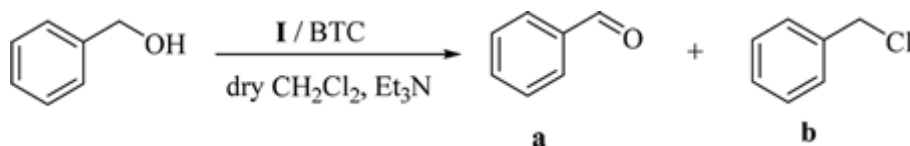
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**Table 1** Optimization of conditions for the oxidation of benzyl alcohol with **I** in the presence of bis(trichloromethyl)carbonate

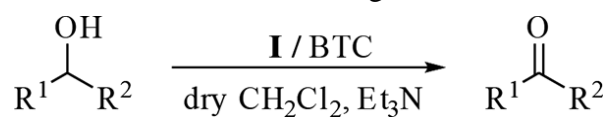


Entry	Temp (°C)	The mole ratio of Alcohol : <b>I</b> : BTC	Yield (%) <sup>[a]</sup>	
			<b>a</b>	<b>b</b>
1	-30	1 : 2.1 : 1.1	65	35
2	-30	1 : 2.1 : 0.7	93	trace
3	-15	1 : 2.1 : 0.7	91	trace
4 <sup>[b]</sup>	-15	1 : 2.1 : 0.4	73	trace
5	-10	1 : 2.1 : 0.7	84	15
6	-5	1 : 2.1 : 0.7	36	63
7 <sup>[c]</sup>	0	1 : 2.1 : 0.7	trace	trace
8	-15	1 : 1.8 : 0.6	94	trace
9	-15	1 : 1.5 : 0.5	90	trace
10 <sup>[b]</sup>	-15	1 : 1.2 : 0.4	74	trace

<sup>[a]</sup>. Yield determined after purification by flash chromatography (SiO<sub>2</sub>; n-hexane).

<sup>[b]</sup>. The conversion was less than 80%.

<sup>[c]</sup>. The sulfoxide **I** was recovered.

**Table 2.** Swern oxidation of various alcohols using **I** / BTC <sup>[a]</sup>

Entry	R <sup>1</sup>	R <sup>2</sup>	Temp(°C)	Products	Yield (%) <sup>[b]</sup>
1	Ph	H	-15	PhCHO	91(90) <sup>[c]</sup>
2	4-MeC <sub>6</sub> H <sub>4</sub>	H	-15	4-MeC <sub>6</sub> H <sub>4</sub> CHO	81
3	4-MeOC <sub>6</sub> H <sub>4</sub>	H	-15	4-MeOC <sub>6</sub> H <sub>4</sub> CHO	80
4	2-ClC <sub>6</sub> H <sub>4</sub>	H	-15	2-ClC <sub>6</sub> H <sub>4</sub> CHO	93
5	2-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	H	-15	2-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CHO	77
6			-15		76
7			-15		70
8			-15		68
9	C <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	-10	PhCOCH <sub>3</sub>	92(89) <sup>[d]</sup>
10	4-MeC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	-5	4-MeC <sub>6</sub> H <sub>4</sub> COCH <sub>3</sub>	80
11	Ph	Ph	-5	PhCOPh	80
12	4-FC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	-10	4-FC <sub>6</sub> H <sub>4</sub> COCH <sub>3</sub>	83
13	3,5-(CF <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	CH <sub>3</sub>	-10	3,5-(CF <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> COCH <sub>3</sub>	81
14	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	-10	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> COCH <sub>3</sub>	83
15			-10		89
16			-10		86
17	Ph(CH <sub>2</sub> ) <sub>3</sub>	H	-15	Ph(CH <sub>2</sub> ) <sub>3</sub> CHO	trace(30) <sup>[e]</sup>
18			-15		25(71) <sup>[e]</sup>
19			-15		70
20			-15		78

<sup>[a]</sup>. Reaction conditions: substrates (2.5 mmol), **I** (3.75 mmol), BTC (1.25 mmol), Et<sub>3</sub>N (7.5 mmol), dry CH<sub>2</sub>Cl<sub>2</sub> as solvent (15 mL).

<sup>[b]</sup>. Yield determined after purification by flash chromatography (SiO<sub>2</sub>; n-hexane).

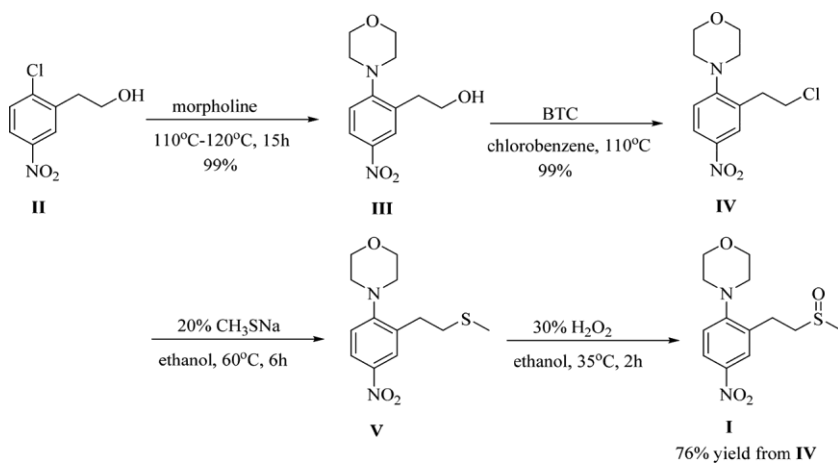
<sup>[c]</sup>. The sulfoxide **I** recovered from co-product **V** was employed.

<sup>[d]</sup>. at -5°C.

<sup>[e]</sup>. at -30°C.

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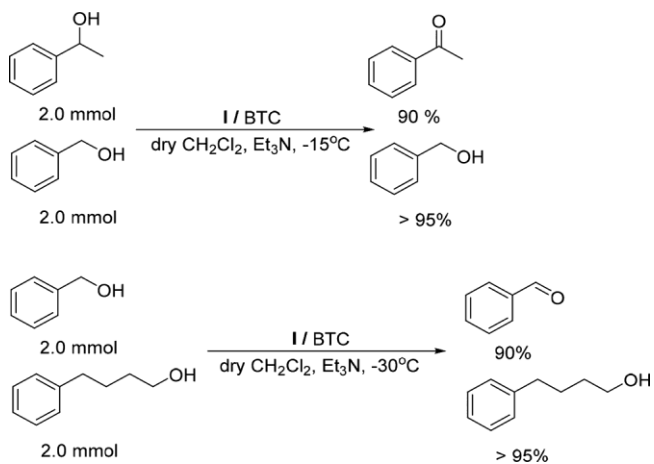
**Scheme 1.** Preparation of 4-(2-(2-(methylsulfinyl)ethyl)-4-nitrophenyl)morpholine **I**



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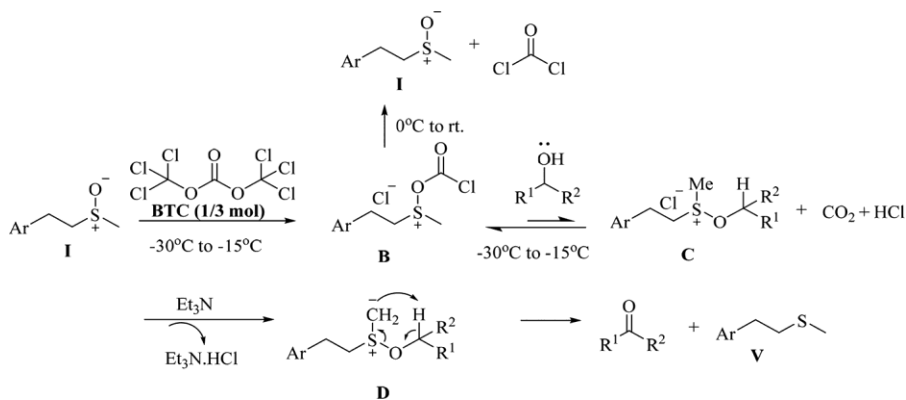


**Scheme 2.** Selective oxidation of alcohols with **I** / BTC



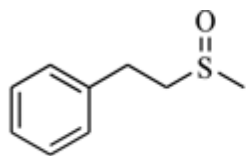
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**Scheme 3.** A plausible reaction mechanism

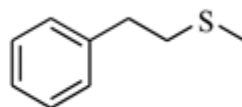


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**Figure 1** The sulfoxide we firstly designed and prepared



**(2-(methylsulfinyl)ethyl)benzene**



**methyl(phenethyl)sulfane**

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**Figure 2** The key intermediates **A** and **C** in Swern oxidation

