Metal-free oxidative coupling of alkyl chlorides with thiols: an efficient access to sulfoxides

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Metal-free oxidative coupling of alkyl chlorides with thiols: an efficient access to sulfoxides

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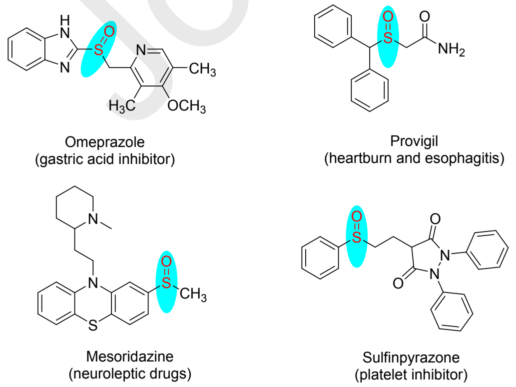
ABSTRACT

An efficient and step-economical access to sulfoxides from thiols and alkyl halides in the presence of I_2O_5 and DBU via direct oxidative couplings is described here. It is the first case that combined Williamson sulfide synthesis and subsequent sulfide oxidation into one step manipulation for sulfoxides preparation. This protocol features wide substrate scope, mild and metal-free conditons, the use of naturally abundant starting materials and avoidance of over-oxidation.

Introduction

Sulfoxides are the most privileged scaffolds in natural products,[1] medicinal chemistry,[2] and functionalized materials.[3] Their derivatives were generally employed as important intermediates in the preparation of biologically active molecules, especially marketed pharmaceuticals such as Omeprazole,[4a] Provigil,[4b] Mesoridazine,[4c] and Sulfinpyrazone (Figure 1).[4d] Furthermore, they have been extensively applied to reactions of carbon-carbon bond formation, molecular rearrangements, and chemical transformations.[5] In recent years, sulfoxides have also been utilized to serve as chiral ligands in enantioselective catalysis[6] or as tunable directing groups in metal-catalyzed C-H bond functionalization reactions.[7]


Omeprazole
(gastric acid inhibitor)

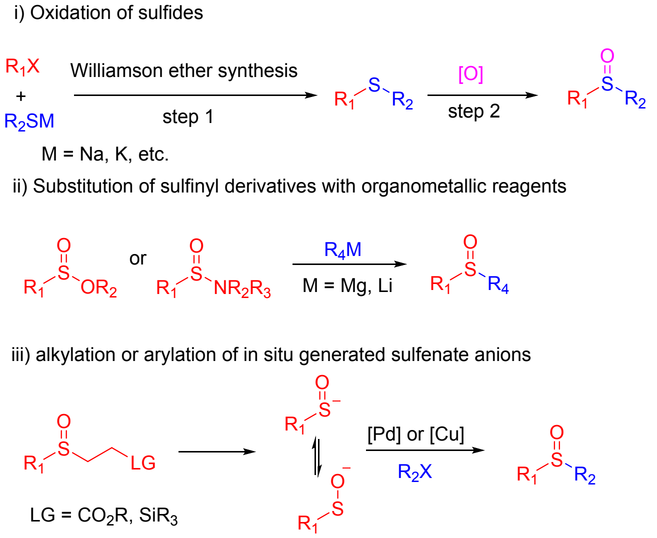
Provigil
(heartburn and esophagitis)

Mesoridazine
(neuroleptic drugs)

Sulfinpyrazone
(platelet inhibitor)

Figure 1. Sulfoxides in marketed pharmaceuticals

Because of this, a number of reagents and protocols have been established to produce sulfoxide analogues,[8] mainly including i) oxidation of sulfides;[8a,9] ii) nucleophilic substitution of sulfinyl derivatives with organometallic reagents;[10] and iii) recently developed trapping of in situ generated sulfenate anions with electrophiles;[11] Among them, the selective oxidation of thioethers is undoubtly the most straightforward and widely applied strategy for the synthesis of corresponding sulfoxides. Although a wide range of oxidizing systems have been well established and shown excellent performance in sulfoxidation, there are still various limitations such as the utilization of expensive or heavy metal

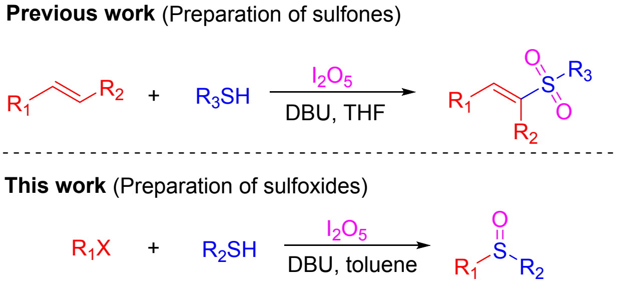


Scheme 1. Representative strategies for the synthesis of sulfoxides

ca

wastes, over-oxidation to sulfones and so on. Hence, the development of metal-free, mild, efficient and highly selective methods to prepare sulfoxides is still highly desirable.

Recently, iodine pentoxide (I_2O_5) as a cheap, green, and reliable inorganic oxidant has received increasingly attention and been successfully applied for metal-free oxidative couplings of alkenes with thiols to obtain sulfones (Scheme 2).[12] On the other hand, the thiols are generally employed as starting materials to prepare sulfides by Williamson's method, which could be easily further oxidized to sulfoxides. Nevertheless, so far, the direct synthesis of sulfoxides from thiols and halides via a direct oxidative coupling process has remained unreported. Herein, we wish to report a novel, efficient and step-economical access to sulfoxides from thiols and alkyl halides via direct oxidative couplings (Scheme 2).

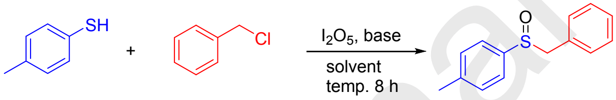


- Step-economical synthesis
- Metal-free conditions
- Without super acid or base
- Simple and widely available starting materials
- Avoidance of over-oxidation

Scheme 2. Preparation of sulfones and sulfoxides via oxidative couplings with I_2O_5

Results and discussion

Table 1. Optimization of the reaction conditions[a]



1a **2a** **3aa**

Entry	Base	Solvent	Temp./°C	Yield[b]/%
1	KOH	CH_3CN	90	60
2	K_2CO_3	CH_3CN	90	10
3	KOtBu	CH_3CN	90	trace
4	NEt_3	CH_3CN	90	nd
5	DBU	CH_3CN	90	84
6	DMAP	CH_3CN	90	45
7[c]	DBU	CH_3CN	90	78
8[d]	DBU	CH_3CN	90	82
9	DBU	1,4-dioxane	90	60
10	DBU	ethyl acetate	reflux	84
11	DBU	THF	reflux	89
12	DBU	H_2O	90	nd
13	DBU	MeOH	reflux	87
14	DBU	EtOH	reflux	89
15	DBU	toluene	90	95
16[e]	DBU	toluene	90	90
17[f]	DBU	toluene	90	85
18	DBU	toluene	80	78
19	DBU	toluene	100	87

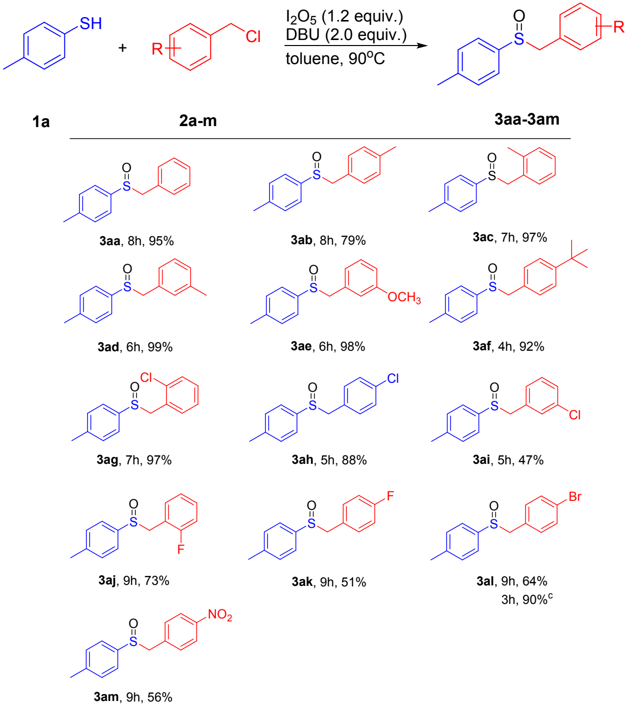
[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), I_2O_5 (1.2 equiv.), base (2 equiv.), solvent (2 mL). [b] Isolated yields. [c] DBU (1.5 equiv.). [d] DBU (2.5 equiv.). [e] I_2O_5 (1.5 equiv.). [f] I_2O_5 (1 equiv.).

Initially, 4-methylbenzenethiol (**1a**) and benzyl chloride (**2a**) were selected as the model substrates to determine the optimized reaction conditions for sulfoxide synthesis in the presence of

d in 60% yield when potassium hydroxide was used as a base in acetonitrile at 90 °C (Table 1, entry 1). We next investigated the effects of other bases, including K_2CO_3, KO^tBu, Et_3N, DBU and DMAP. It can be found that KO^tBu and K_2CO_3 both led to sharply decreased yields and DBU proved to be the most effective to enhance the yield into 84% (Table 1, entry 5). Attempt to increase and reduce the amounts of DBU both failed to improve the reaction performance (Table 1, entries 7 and 8). Further screening of the solvents suggested that toluene was the best reaction medium, affording the desired sulfoxide **3aa** in 95% yield (Table 1, entry 15). The reaction was ineffective in water. Nevertheless, it is important to emphasize that alcohols can also serve as suitable mediums, albiet with a slightly dropped yield without consuming any oxidant. Further increase of the loading of I_2O_5 failed to improve the reaction performance (Table 1, entry 16). In contrast, decreased yield was found when the loading of the oxidant was reduced to 1 equivalent (Table 1, entry 17). The reaction temperature was next examined. When the reaction was performed at 80°C, only 78% yield of sulfoxide **3aa** was isolated. When the reaction was carried out at 100°C, the sulfoxide **3aa** was delivered in 87% yield. Thus, the optimal conditions were determined as I_2O_5 (1.2 equiv.) and DBU (2.0 equiv.) in toluene at 90°C.

With the optimal reaction conditions in hand, we next investigated the scope and generality of this transformation using various benzyl halides and 4-methylbenzenethiol. In general, benzyl chlorides bearing either electron-withdrawing or electron-donating groups on the phenyl rings were suitable for this transformation, affording the desired sulfoxides in moderate to excellent yields. It should be noted that electron-rich benzyl chlorides are more reactive than electron-poor ones, generating the corresponding sulfoxides in much higher yields (up to 99%

Table 2. Results for oxidative coupling between 4-methylbenzenethiol and various alkyl halides[a,b]



1a **2a-m** **3aa-3am**

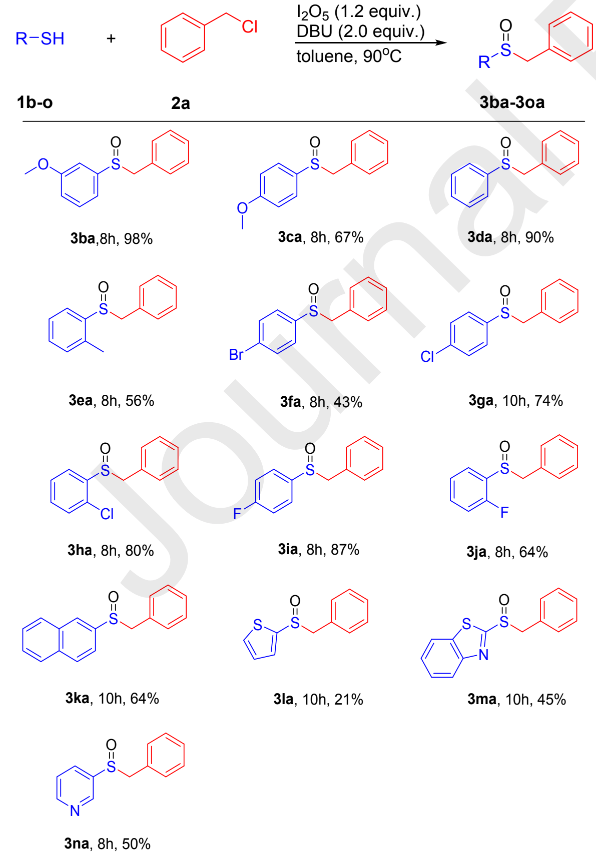
3aa, 8h, 95%
3ab, 8h, 79%
3ac, 7h, 97%
3ad, 6h, 99%
3ae, 6h, 98%
3af, 4h, 92%
3ag, 7h, 97%
3ah, 5h, 88%
3ai, 5h, 47%
3aj, 9h, 73%
3ak, 9h, 51%
3al, 9h, 64%
3h, 90%[c]
3am, 9h, 56%

[a] Reaction conditions: **1a** (0.5 mmol), **2a-m** (0.5 mmol), I_2O_5 (1.2 equiv.), DBU (2 equiv.), toluene (2 mL), 90 °C. [b] Isolated yields. [c] 4-bromobenzyl bromide was used.

yiel and bromo on the benzene ring were well tolerated in this oxidative coupling process. The sulfoxides with halo substituents are very useful for they can be easily further derivatized by means of simple coupling strategies and the likes. It can be found that these transformations were seriously affected by the steric effect. Especially, steric-demanding *ortho*-substituted benzyl chlorides showed exceptionally high reactivity than *para*-substituted ones in those transformations (Table 2, products **3ac**, **3ag** and **3aj**). When 4-bromobenzyl chloride was replaced by 4-bromobenzyl bromide to perform the transformation, the yield of product **3al** was greatly enhanced from 64% to 90% within 3 hours.

Inspired by the success of the benzyl chlorides, we next explored the generality of a variety of thiols. The representative results were summarized in Table 3. All the examined aromatic and heteroaromatic thiols reacted well and provided the corresponding benzyl sulfoxides in yields ranging from 21% to 98% (Table 3). A majority of aryl thiols with electron-donating groups or electron-withdrawing groups exhibited excellent reactivities, affording the expected sulfoxides in good to excellent yields. Notably, halogens were also tolerable, which benefits further functionalization. When heteroaromatic thiols such as 2-thiophenthiol, 2-benzothiazolethiol and 3-pyridinethiol were investigated, the corresponding sulfoxides still smoothly formed, albeit with decreased yields (Table 3, products **3la**, **3ma** and **3na**). Besides these aryl thiols, several typical alkyl thiols such as cyclohexanethiol, 1-butanethiol and α-toluenethiol were also selected to perform the transformations under standard conditions. Unfortunately, no desired product was observed for these thiols even if stronger base such as KOH was utilized.

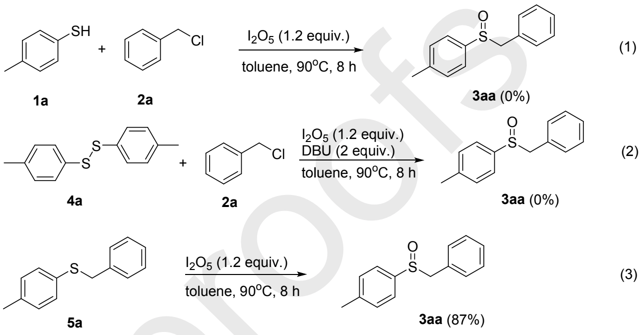
Table 3. **Results for oxidative coupling between benzyl chloride with various thiols**[a,b]



3ba,8h, 98%
3ca, 8h, 67%
3da, 8h, 90%
3ea, 8h, 56%
3fa, 8h, 43%
3ga, 10h, 74%
3ha, 8h, 80%
3ia, 8h, 87%
3ja, 8h, 64%
3ka, 10h, 64%
3la, 10h, 21%
3ma, 10h, 45%
3na, 8h, 50%

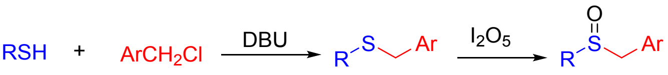
[a] Reaction conditions: **1b-o** (0.5 mmol), **2a** (0.5 mmol), I_2O_5 (1.2 equiv.), DBU (2 equiv.), toluene (2 mL), 90 °C. [b] Isolated yields.

to understand the reaction mechanism as shown in eqs1-3 in Scheme 3. When the template reaction was carried out in the absence of DBU as a base, sulfoxide **3aa** was completely not detected in the reaction system. Furthermore, when disulfide was employed to replace thiol to reacted with benzyl chloride under standard reaction conditions, it still failed to give any desired sulfoxide **3aa**. This result indicated that disulfide, which was easily formed by the dimerization of thiyl radical,[12] was not a reaction intermediate. Nevertheless, benzyl tolyl sulfide did successfully afforded the desired sulfoxide **3aa** in 87% yield in the presence of I_2O_5. The above results indicated that benzyl tolyl sulfide might be a key intermediate in current reaction system.



Scheme 3. Control experiments

On the basis of the above results, a tentative reaction pathway was proposed in Scheme 4. Initially, the thiols reacted with benzyl chlorides in the presence of DBU as a base, producing the corresponding sulfides. Then the generated sulfides were oxidized to sulfoxides. This suggested pathway was in accordance with our preliminary thoughts.



Scheme 4. Tentative reaction pathway

Conclusions

In conclusion, a novel and convenient method has been successfully developed for the preparation of sulfoxides through direct oxidative couplings between thiols and alkyl chlorides in the presence of I_2O_5 and DBU. This is the first case that combined Williamson sulfide synthesis and subsequent sulfide oxidation into one step manipulation for sulfoxides preparation. A wide range of functionalized benzyl sulfoxides were generated in good to excellent yields. The salient features of this protocol including metal-free conditions, without super acid or base, avoidance of over-oxidation to sulfones, well functional group tolerance, and readily available starting materials make this transformation extremely attractive.

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Supplementary Material

Graphical Abstract

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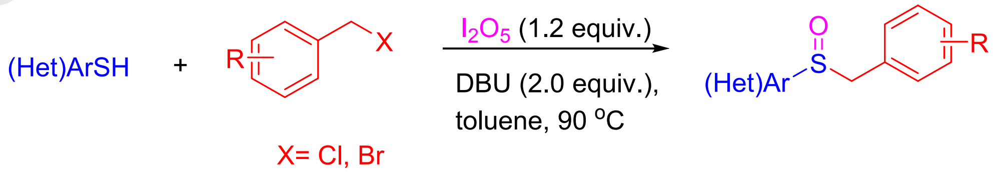

Highlights

- Step-economical synthesis
- Metal-free conditions
- Without super acid or base
- Simple and widely available starting materials
- Avoidance of over-oxidation

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: