Selective oxidation of sulfides to sulfoxides with cyanuric chloride and urea–hydrogen peroxide adduct

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ABSTRACT

Although a number of methods have been developed for the selective oxidation of sulfides to sulfoxides, the need remains for alternative efficient, reliable strategies that can be generally applied to various sulfides and that use readily available reagents under mild reaction conditions. Herein, we report the use of urea–hydrogen peroxide adduct (UHP) and cyanuric chloride in CH_3CN at room temperature to convert sulfides to sulfoxides in excellent yields. In particular, this protocol produced sulfoxides with aromatic rings bearing electron-withdrawing groups in excellent yields.

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The selective oxidation of sulfides to sulfoxides is a fundamental and important functional group transformation in organic synthesis because organic sulfoxides are useful synthetic intermediates for the construction of various chemically and biologically significant molecules[1] and sulfoxide reactions are significant in medicinal chemistry and drug metabolism.[2] The increasing interest in and applications of sulfoxides have prompted investigations on novel methodologies for the preparation of these compounds.

During the last few decades, numerous strategies have been developed to selectively oxidize sulfides to sulfoxides because sulfide oxidation is considered the most direct and facile approach for preparing sulfoxides. Among these strategies, the use of hydrogen peroxide (H_2O_2) is one of the most popular methods.[3] However, an activator is essential for the success of this reaction because H_2O_2 alone oxidizes sulfides rather slowly. Therefore, a variety of transition metal complexes that include titanium (Ti),[4] molybdenum (Mo),[5] iron (Fe),[6] vanadium (V),[7] tungsten (W),[8] rhenium (Re),[9] scandium (Sc),[10] zirconium (Zr),[11] manganese (Mn),[12] copper (Cu),[13] and cerium (Ce)[14] have been widely employed as activators with H_2O_2 for the oxidation of sulfides. Other reagents such as cyanuric chloride,[15] 1,3,5-triazo-2,4,6-triphosphorine-2,2,4,4,6,6-tetrachloride,[16] phosphorus oxychloride,[17] organic acids,[18] and boric acid[19] have also been utilized as activators. Recently, we became interested in the oxidation and reduction of organosulfur compounds. In our previous endeavors, sulfoxides were readily reduced to sulfides with thionyl chloride and triphenylphosphine.[20] However, the selective oxidation of sulfides to sulfoxides in good yield proved difficult due to the low reactivity of diaryl sulfides with aromatic rings bearing electron-withdrawing groups or because of overoxidation to sulfones (e.g., with other aryl and alkyl sulfides). Particularly, the oxidation of diaryl sulfides with aromatic rings bearing electron-withdrawing groups to sulfoxides has only been reported in a few papers and uses inconvenient reagents, toxic and odorous reagents, or harsh reaction conditions.[9a,16,21] For these reasons, a need remains for alternative efficient and reliable methods that utilize readily available reagents under mild reaction conditions for the selective, general oxidation of various sulfides to sulfoxides. Thus, we considered the use of urea–hydrogen peroxide adduct (UHP) as an oxidant in the presence of cyanuric chloride. Both reagents are inexpensive, commercially available, easy to handle, and stable during long-term storage. Although UHP alone could not oxidize sulfides at room temperature, sulfide oxidation can occur at high temperatures[22] and in the presence of catalysts such as Ti-beta zeolite,[23] metalloporphyrin,[24] and molybdatophosphoric acid.[25] In our effort to discover a novel, efficient, and reliable oxidation method using an easily available activator with UHP under mild reaction conditions, we report herein that cyanuric chloride is an excellent activator for the selective oxidation of different sulfides to sulfoxides.

Initial selective oxidation experiments of a diaryl sulfide with aromatic rings bearing electron-withdrawing groups to obtain the corresponding sulfoxide were performed and optimized using

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bis(4-nitrophenyl) sulfide to determine suitable reaction conditions (i.e., oxidant, additive, and solvent) (Table 1). No reaction occurred when 30% hydrogen peroxide (H_2O_2) was used in the absence of an additive and in the presence of 0.1 equiv of cyanuric chloride (CC) (entries 1 and 2). The use of 1.5 equiv of cyanuric chloride as an additive with 30% H_2O_2 afforded the desired sulfoxide in 5% yield (entry 3). Activation with cyanuric chloride may have been less effective because of interference by H_2O in 30% H_2O_2. Accordingly, we determined to change the oxidant to UHP from 30% H_2O_2 to perform the reaction in organic solvents. When 1.5 equiv of UHP was employed as the oxidant in the presence of 1.5 equiv of cyanuric chloride in THF, sulfoxide was obtained in 38% yield (entry 4). After obtaining this promising result, we performed the reactions in different solvents, including CH_3CN (entry 5), THF/CH_3CN (entry 6), CH_2Cl_2 (entry 7), $CHCl_3$ (entry 8), EtOAc (entry 9), acetone (entry 10), and DMF (entry 11). Surprisingly, using CH_3CN as the solvent increased the yield of the desired product to 80% (entry 5). When we used 2 and 2.5 equiv of UHP with 2 and 2.5 equiv of cyanuric chloride in CH_3CN to obtain better yields, the desired sulfoxides were produced in 88% yield (entries 12 and 13). When the amount of cyanuric chloride was reduced to 1 equiv, the yield of the desired product decreased to 80% (entry 14). As expected, the reaction did not occur in the presence of UHP without cyanuric chloride (entry 15). These results indicate that UHP and cyanuric chloride can be employed as an oxidant and activator, respectively, in the selective oxidation of diaryl sulfides with aromatic rings bearing electron-withdrawing groups to afford the corresponding sulfoxides, providing a new efficient oxidation method using mild reaction conditions. In addition, when the reaction of UHP and cyanuric chloride with thianthrene 5-oxide was performed to examine the high selectivity for sulfoxide as a predominant product, Xso value was 0.03.[26] This value means that UHP/ cyanuric chloride system is a powerful selective oxidation method to sulfoxide working as electrophilic oxidant.

Next, the generality of this UHP/cyanuric chloride combination as reagents for the selective oxidation of sulfides into sulfoxides was investigated, as shown in Table 2.[27] First, a variety of diaryl sulfides with aromatic rings bearing electron-withdrawing groups were treated with UHP (2 equiv) and

cyanuric chloride (2 equiv) in CH_3CN at room temperature. All diaryl sulfides with aromatic rings bearing electron-withdrawing groups, including acetyl- (entry 2), cyano- (entry 3), trifluoro-methyl- (entry 4), fluoro- (entry 5), and methoxycarbonyl-groups (entry 6), were converted to their corresponding sulfoxides in excellent yields. With methyl 4-acetylphenyl sulfide (entry 7) and methyl 4-nitrophenyl sulfide (entry 8), which have an aromatic ring bearing an electron-withdrawing group, the selective oxidation reactions produced the corresponding sulfoxides in yields of 92% and 88%, respectively, under the same reaction conditions as those used for bis(4-nitrophenyl) sulfide (entry 1). When methyl phenyl sulfide, which does not possess an electron-withdrawing group, was oxidized under the same reaction conditions, the desired sulfoxide was obtained in only 57% yield and the rapid generation of an undesired sulfone was observed (entry 9). To reduce sulfone formation (i.e., overoxidation), we varied the amounts of UHP and cyanuric chloride. As a result, the reaction of methyl phenyl sulfide with 1 equiv of UHP and 1 equiv of cyanuric chloride produced the desired sulfoxide in 96% yield. Other aryl methyl sulfides with aromatic rings bearing methyl- (entry 10), methoxy- (entry 11), and chloro-groups (entry 12) were converted to their corresponding sulfoxides in excellent yields under the same reaction conditions. When diphenyl sulfide (entry 16) and dialkyl sulfides, such as dioctyl sulfide (entry 13), dibenzyl sulfide (entry 14), and difurfuryl sulfide (entry 15), were treated with UHP (1 equiv) and cyanuric chloride (1 equiv), the desired sulfoxides were obtained in excellent yields. Clearly, the use of UHP and cyanuric chloride produced the desired sulfoxides from all types of sulfides with excellent yields. Our results prove that cyanuric chloride is a good activator and that UHP is a more reactive oxidant than aqueous H_2O_2 when utilized with cyanuric chloride.

In conclusion, we obtained the desired sulfoxides in excellent yield when aliphatic and aromatic sulfides were treated with UHP and cyanuric chloride in CH_3CN at room temperature and we found that UHP is more powerful oxidizing agent than aqueous H_2O_2 when they are employed with cyanuric chloride as an activator. Notably, diaryl sulfides with aromatic rings bearing electron-withdrawing groups were also converted to their

Table 1
Oxidation of bis(4-nitrophenyl)sulfide to bis(4-nitrophenyl)sulfoxide using various reaction conditions[a]
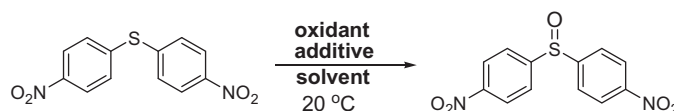
Entry	Oxidant (equiv)	Additive (equiv)	Solvent	Time[b] (h)	Yield[c] (%)
1	H_2O_2 (5)			12	NR
2	H_2O_2 (2)	CC (0.1)	CH_3CN	12	NR
3	H_2O_2 (2)	CC (1.5)	CH_3CN	12	5
4	UHP (1.5)	CC (1.5)	THF	12	38
5	UHP (1.5)	CC (1.5)	CH_3CN	3.5	80
6	UHP (1.5)	CC (1.5)	THF/CH_3CN	5	80
7	UHP (1.5)	CC (1.5)	CH_2Cl_2	12	5
8	UHP (1.5)	CC (1.5)	$CHCl_3$	12	12
9	UHP (1.5)	CC (1.5)	EtOAc	12	8
10	UHP (1.5)	CC (1.5)	Acetone	4.5	57
11	UHP (1.5)	CC (1.5)	DMF	4	37
12	UHP (2)	CC (2)	CH_3CN	3	88
13	UHP (2.5)	CC (2.5)	CH_3CN	2.5	88
14	UHP (2)	CC (1)	CH_3CN	3.5	80
15	UHP (2)		CH_3CN	12	NR
16	Oxone (1)		H_2O	12	10

[a] UHP means urea–hydrogen peroxide adduct and CC means cyanuric chloride.
[b] 12 h means slow reaction without generation of sulfone and other reaction times mean the reaction was stopped when sulfone was observed on TLC.
[c] Isolated yields and NR means no reaction.