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Tetrahedron Letters 46 (2005) 4205–4208

Tetrahedron Letters

Activation of superoxide by boron trifluoride: chemoselective and efficient oxidation of sulfides to sulfoxides via tetrafluorodiboronperoxide

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Received 23 February 2005; revised 11 April 2005; accepted 13 April 2005
Available online 29 April 2005

Abstract—Activation of superoxide with boron trifluoride in dry acetonitrile can facilitate highly chemoselective and efficient oxidation of sulfides to corresponding sulfoxides at ice-water bath in excellent yields without any interference in the presence of ketone, olefin, ether, and hydroxyl functionalities. This new method also offers further advantages of a short reaction time, no overoxidation to sulfones, and none of complex catalysts and toxic metallic compounds used. A tetrafluorodiboronperoxide intermediate formed in situ from this new process is proposed.

Sulfoxides have been well known to act as useful synthetic intermediates for the construction of various chemically and biologically significant molecules,[1] especially for the synthesis of drugs and natural products.[2] The direct oxidation of sulfide is one of the most important and widely studied reactions for the preparation of sulfoxide. Although a great number of methods are available for the conversion of sulfides to corresponding sulfoxides,[3] different kinds of disadvantages for those methods include: (i) using toxic metallic compounds, complex catalysts, or sophisticated reagents; (ii) the formation of sulfones as side products from the overoxidation of sulfides and the undesired reaction occurring from other functional groups; and (iii) a longer reaction time commonly required. Therefore, there still is a need for the development of new, efficient, highly selective and widely applicable methods for this transformation, as well as concerning about all the above important protocols under the mild reaction condition.

Superoxide anion radical ($O_2^{-\bullet}$), easily formed in the body, has been known as a toxic species to cause a serious damage to living organisms.[4] Recently, much effort has been made not only on its biological toxicity but also on its application in organic synthesis.[5] In general, superoxide acts as a moderate reducing agent but a very weak oxidizing agent.[6] However, several studies have been reported that the activation of superoxide by reacting with various organic substrates can form a new peroxy intermediate to act as a stronger oxidizing agent.[7] For example, some sulfinyl, sulfonyl, sulfonimidoyl, and phosphorous peroxy intermediates generated from the reaction of superoxide with each of the corresponding chlorides have been testified for their oxidizing abilities toward various organic substrates.[7] According to our previous study,[8] the result indicates that trimethylsilylperoxy radical, formed from the reaction of superoxide with trimethylsilyl chloride, also performs as a strong-oxidizing agent toward organic sulfides, but the longer reaction time ($\geqslant 2$ h) usually required is one of the drawbacks. However, it is still of great interest to explore more new methods for the generation of stronger oxidizing agents, activated from superoxide, to use in organic synthesis. In this report, we wish to present a new method for the activation of superoxide with boron trifluoride, which can facilitate highly chemoselective and efficient oxidation of sulfides to corresponding sulfoxides at ice-water bath in excellent yields without any interference in the presence of ketone, olefin, ether, and hydroxyl functionalities.

The results for the oxidation of methyl phenyl sulfide mediated with superoxide and boron trifluoride, as a

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Keywords: Superoxide; Activation; Tetrafluorodiboronperoxide; Boron trifluoride; Oxidation; Sulfide; Sulfoxide.

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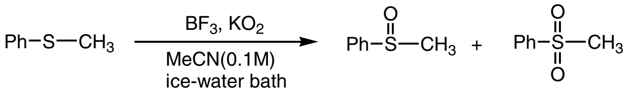
doi:10.1016/j.tetlet.2005.04.058

Table 1. Oxidation of methyl phenyl sulfide mediated by KO_2 and BF_3 in MeCN at ice-water bath



Entry	KO_2 (equiv)	BF_3 (equiv)	Reaction time	Sulfoxide yield (%)[a]	Sulfone yield (%)[a]
1	1.2	1.2	5 h	6	Trace[b]
2	1.2	2.5	5 h	50	—
3	2.5	1.2	5 h	3	Trace[b]
4	2.5	2.5	5 h	31	Trace[b]
5	2.5	5.0	5 h	97	—
6	2.5	5.0	5 min	98	—
7	2.5	5.0	40 h	95	Trace[b]
8	2.5	—	24 h	—	—

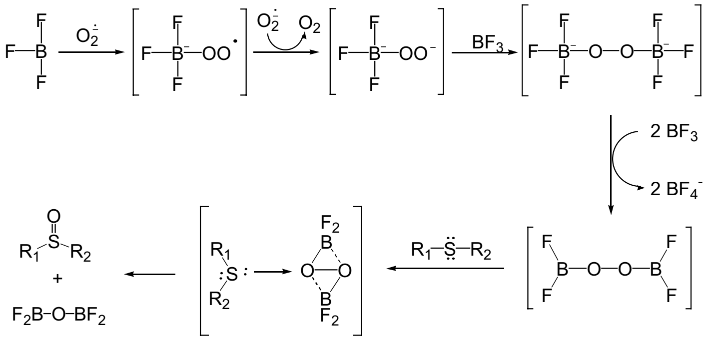
[a] Isolated yields. All compounds were characterized by IR, LRMS, and ^1H NMR spectroscopy.

[b] Determined by ^1H NMR spectroscopy.

model study, were summarized in Table 1. In a general procedure (entry 6), BF_3 diethyl etherate (0.54 mL, 4.26 mmol) was added slowly within 2 min to a heterogeneous solution of KO_2 (0.1514 g, 2.13 mmol)[9] in dry acetonitrile (8.5 mL) at ice water bath with vigorous stirring under nitrogen. After stirring for 2 min, methyl phenyl sulfide (0.10 mL, 0.85 mmol) was added in one portion. The reaction mixture was reacted for further 5 min and then quenched by addition of water (5 mL) and saturated $NaCl_{(aq)}$ (10 mL), and followed by extraction with dichloromethane (3 × 20 mL) at room temperature. The combined organic portions were dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by preparative TLC or column chromatography using ethyl acetate/hexane (1:1) as eluent to give methyl phenyl sulfoxide (0.1175 g, 98%).

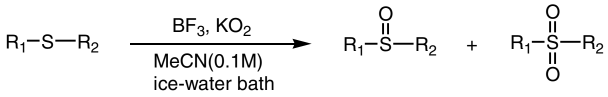
Based on the results obtained from the stoichiometry study (entries 1–5), the best molar ratio of sulfide, KO_2, and BF_3OEt_2 was found to be 1.0:2.5:5.0, respectively. Hence, it is plausible to propose that this new reaction pathway for the oxidation of sulfide to sulfoxide might undergo through a tetrafluorodiboronperoxide[10] intermediate formed in situ from this new process, as shown in Scheme 1. Although the reaction of KO_2 with BF_3 has been reported by Sauka et al.,[11] to the best of our knowledge, tetrafluorodiboronperoxide only has been mentioned once before in Holliday's report.[12] It was proposed to be formed from the reaction of B_2F_4 and O_2, but no structural confirmation and further applications in organic synthesis were reported in their studies.[12] Although it is also unsuccessful for isolation and identification of tetrafluorodiboronperoxide in this study, the result from ^{19}F NMR study of isolated colorless solid residue indicates that KBF_4 (δ −152.54 ppm in CD_3OD) seems to be formed as a side product of the reaction.[10] For the optimized condition, it is surprising to find that the oxidation of methyl phenyl sulfide underwent highly efficiently and selectively to afford 98% yield of the corresponding sulfoxide within 5 min at a lower temperature (entry 6). Interestingly, only traceable amount of the corresponding sulfone, an overoxidation product, was isolated with almost no interference in 95% yield of the sulfoxide obtained even though the reaction time was prolonged to 40 h (entry 7). For a blank test (entry 8), the oxidation of methyl phenyl sulfide to the corresponding sulfoxide underwent extremely slowly (no detectable amount of sulfoxide found even for 24 h), while the reaction was only treated with KO_2 without BF_3 under the same reaction condition described above.

To testify tetrafluorodiboronperoxide formed in situ from KO_2 and BF_3 in the compatibility of functional group of the reaction, various sulfides bearing several different kinds of functional groups were studied and the results were collected in Table 2. In all cases, only



Scheme 1. The reaction pathway proposed for oxidation of sulfides mediated by KO_2 and BF_3 in MeCN at ice-water bath.

Table 2. Oxidation of sulfides to the corresponding sulfoxides[a]



Entry	R_1	R_2	Reaction time (min)	Sulfoxide yield (%)[b]	Sulfone yield (%)
1	C_6H_5–	–CH_3	5	98	—
2	4-$CH_3OC_6H_4$–	–CH_3	5	96	1
3	4-$CH_3C(O)C_6H_4$–	–CH_3	5	94	2
4	C_6H_5–	–CH_2Ph	5	96	—
5	C_6H_5–	–CH_2CH_2OH	5	93	—
6	–$H_2CH_2CH_2CH_2$–		5	95	—
7	Ph–	–$CH_2CH{=}CH_2$	5	91	—

[a] Molar ratio = sulfide:KO_2:BF_3 = 1:2.5:5.0.

[b] Isolated yields. All compounds were characterized by IR, LRMS, and ^{1}H NMR spectroscopy.

traceable amounts of the sulfones were isolated or detected by ^{1}H NMR spectroscopy, which shows the same result observed as in the case of the model study. Based on the results we obtained, it should be noted that tetrafluorodiboronperoxide, rapidly generated in situ from KO_2 and BF_3, performs as a very strong-oxidizing agent to allow the highly selective and efficient oxidation of sulfides to sulfoxides at a lower temperature in 5 min without any interference in the presence of ketone, olefin, ether, and hydroxyl functionalities and with no further oxidation to sulfones. It has been known that oxidants commonly used for these reactions, such as *m*-chloroperoxybenzoic acid, hydrogen peroxide, iodosyl benzene, sodium periodate, oxone, peroxymonosulfate, *o*-iodoxybenzoic acid, sodium bromate, etc.,[13] require higher reaction temperatures than that needed by tetrafluorodiboronperoxide. Especially, this new method provides the following advantages: (i) a very short reaction time and under the very mild reaction; (ii) no overoxidation of sulfides to sulfones; (iii) no undesired side reactions of other functional groups; and (iv) all reagents used are commercially available without using complex catalysts and toxic metallic compounds. It must be mentioned that all of them are important protocols for the direct oxidation of sulfides to sulfoxides in organic synthetic studies.

It has also been rationalized that the oxidation of sulfides to sulfoxides is found to be electrophilic in contrast to the nucleophilic oxidation of sulfoxides to sulfones.[14] Besides the selective oxidation of sulfides to sulfoxides without further oxidation to sulfones, a competition oxidation of methyl 4-acetyl-, 4-methoxy-, and nonsubstituted-phenyl sulfides was carried out under the same reaction condition described above for 5 min to give 15%, 49%, and 30% yields of the corresponding sulfoxides, respectively. The results indicate that the sulfur atom of these sulfides bearing an electron-donating group of 4-methoxy is oxidized more rapidly than that bearing an electron-withdrawing group of 4-acetyl due to its more nucleophilic character. Based on the results mentioned above, tetrafluorodiboronperoxide generated in situ from KO_2 and BF_3 performs more likely to be electrophilic. However, more studies for the detail of this reaction mechanism are still needed.

In conclusion, we have demonstrated that tetrafluorodiboronperoxide, rapidly generated in situ from KO_2 and BF_3, performs a strongly electrophilic oxidizing ability to undergo the highly chemoselective and efficient oxidation of sulfides to corresponding sulfoxides in excellent yields without any interference in the presence of ketone, olefin, ether, and hydroxyl functionalities under mild conditions. Besides, this new method also offers further advantages of a short reaction time, no overoxidation to sulfones, and none of the complex catalysts and toxic metallic compounds used. The confirmation of tetrafluorodiboronperoxide formed from this new process and its applications used more widely in organic synthesis have been under investigation.

Acknowledgment

We gratefully acknowledge generous support from the National Science Council of the Republic of China.

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9. Potassium superoxide is a commercially available inorganic salt. It, generally acted as an oxidizer, is corrosive and moisture sensitive. Manipulation of this salt must be very careful without contacting with skin directly. Although potassium superoxide is generally insoluble in aprotic organic solvents, it is slightly soluble in those of higher polar aprotic solvents such as DMSO and acetonitrile.
10. Tetrafluorodiboronperoxide can be formed from the reaction of potassium superoxide with boron trifluoride in acetonitrile at ice-water bath. After evaporated under reduced pressure, the reaction solution afforded a mixture of viscous solid, which was unsuccessful to be purified, but could be studied by NMR method directly. ^{19}F NMR (400 MHz, CD_3OD) spectrum of this mixture shows two peaks appeared at δ −152.48 and −152.54 ppm. Among them, one appeared at δ −152.54 ppm is assigned to be as the signal of KBF_4 compared with that for an authentic sample (−152.56 ppm), while the other one appeared at δ −152.48 ppm is still remained unclear. On the other hand, ^{11}B NMR (400 MHz, CD_3CN) spectrum of the above viscous mixture appears only one new peak at δ −0.376 ppm, which might be appropriate to be assigned as the signal of tetrafluorodiboronperoxide, while the signal of $BF_3 \cdot OEt$ appears at δ −0.613 ppm. It should be noted that the signal of KBF_4 was not observed probably due to its low solubility in acetonitrile. According to our results from this study, a low concentration of tetrafluorodiboronperoxide solution in acetonitrile (~0.12 M) formed in situ could be handled with safety and perform the reasonable stability and reactivity for use in the course of reaction studied under nitrogen at 0–4 °C. However, much more works for the identification of tetrafluorodiboronperoxide existing in the course of reaction are still needed.
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