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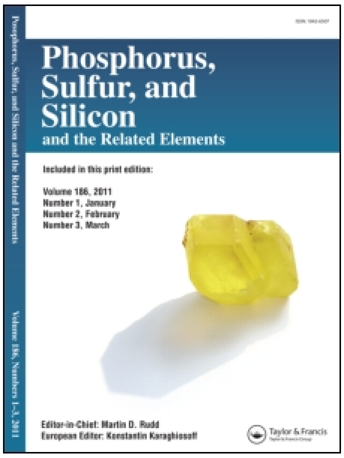

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A Clean, Mild, and Selective Oxidation of Sulfides to Sulfoxides Using NaClO/H_2SO_4 in Aqueous Media

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A Clean, Mild, and Selective Oxidation of Sulfides to Sulfoxides Using $NaClO/H_2SO_4$ in Aqueous Media

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A range of sulfides can be selectively oxidized to the corresponding sulfoxides in good yields using $NaClO/H_2SO_4$ in both water and 50:50 water:EtOH as solvent. Two new compounds are reported that show a diastereoselective oxidation in 2-phenylthioalcohols with possible neighboring hydroxyl group participation with a logic proposed mechanism.

Keywords Green chemistry; oxidation; sodium hypochlorite; sulfide; sulfoxide

INTRODUCTION

The oxidation of sulfides is the major method for the synthesis of sulfoxides, which are versatile intermediates in organic synthesis and are usable for C–C bond formation,[1] functional group transformations,[2] and are useful for the preparation of biologically and medically important compounds.[3] Sulfoxides could easily be converted to carboxylic acid derivatives by Pummerer rearrangement.[4]

Although many reagents are available for the oxidation of sulfides to sulfoxides,[5] catalytic processes with environmentally benign oxidants have become increasingly important. Recently, hydrogen peroxide has been a very attractive "green oxidant," offering such advantages as it is inexpensive, environmentally benign, and readily available, and produces only water as a byproduct.[6] But a frequent drawback of these convenient methods is often the use of chlorohydrocarbon solvents or anhydrous H_2O_2 in ethanol,[7] and the over-oxidation to sulfones as side products.

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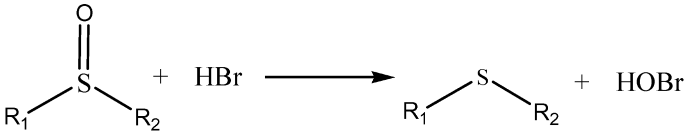
It is further known that the hypochlorous acid oxidation of certain sulfides leads to corresponding sulfoxides,[8] most probably via the corresponding chlorosulfonium ion as demonstrated by Johnson and McCants[9] in the oxidation of thianes with *tert*-butyl hypochlorite. These types of oxidations are very pH- and solvent-dependent.

RESULTS AND DISCUSSION

In this article, we wish to report an efficient protocol in which NaClO in acid sulfuric media has been used as the oxidizing agent in water and a mixture of H_2O:EtOH (50:50) for the chemoselective oxidation of sulfides to their sulfoxides in high chemical yield and short reaction times.

The oxidation of sulfides in water or water/EtOH is desirable, since using water and EtOH instead of an organic solvent has become more important due to environmental consideration in recent years. It is very important to note that the nature and amount of added sulfuric acid is very important. While hydrochloric acid initiated the oxidation, the concentration of the desired sulfoxides reached a maximum and then began decreasing drastically as monitored by TLC. This is most probably due to a reaction analogous to the known reductive effect of hydrogen bromide on sulfoxides, which takes place under the present conditions[10] (Scheme 1).

In a typical general experimental procedure, a solution of sulfide (1 mmol) and 1 mmol NaClO in a 50:50 mixture of H_2O:EtOH in sulfuric acid media was stirred for a period of time, and this resulted in the formation of the corresponding sulfoxides without any over-oxidation and with good to excellent yields. In the case of water as solvent, vigorous stirring is necessary because the reaction takes place in the surface of suspension or emulsion sulfide in water. To study the scope of this procedure, a series of various substituted sulfides including alkyl aryl sulfides and dialkyl sulfides was reacted according to optimized reaction conditions. The results are summarized in Table I.



SCHEME 1 Reduction of sulfoxides by hydrobromic acid.

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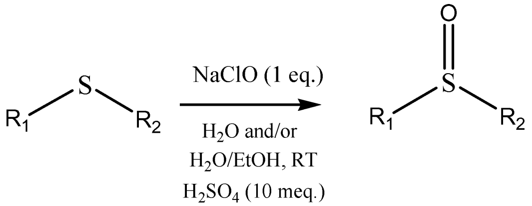
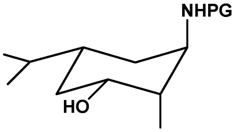
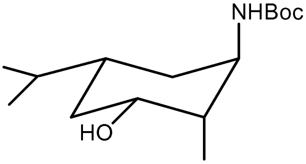
TABLE I Oxidation Sulfides to Sulfoxides by NaClO in Water and a 50:50 Mixture of H_2O/Ethanol



Entry	R_1	R_2	Time (min)	Yield (%)[a] In water	Yield(%)[a] In 50:50 Water/EtOH
1	Ph	Me	45	62	75
2	Ph	Et	35	70	84
3	Ph	Ph	50	75	93
4	Ph	Bn	60	78	95
5	Et	Et	50	70	85
6	Et	Me	55	60	72
7	n-Pr	n-Pr	60	65	78
8	Ph		30	73	82
9[b]	Ph		90	70	85[c]
10[b]	Ph		90	72	85[c]

[a] Isolated yield.

[b] The starting material was prepared according to ref. no.[14].

[c] Only one diastereoisomer was observed.

The process is devoid of sulfone formation, a byproduct common to most other peroxide-based oxidations. These oxidations exhibited striking solvent effects. We found that reaction rates were very slow in chloroform and dichloromethane, but increased dramatically in the H_2O/EtOH mixture. Furthermore the nature and the amount of acid are very important.

The most stable conformations of protected 2-phenylthio-3-aminocyclohexanols (Table I, entries 9 and 10), using AM1 calculation, are shown in Figure 1. Based on these results and on the literature,[11–13]

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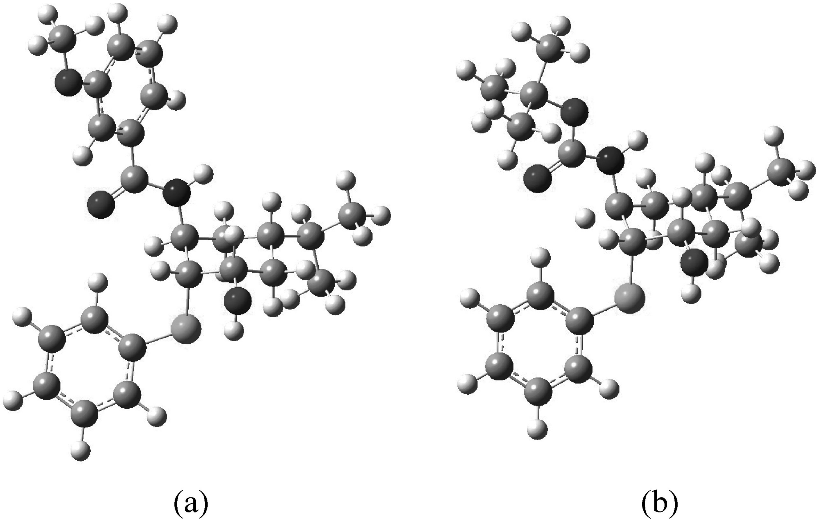

(a) (b)

FIGURE 1 The most stable calculated conformations of (a) N-(3-hydroxy-5-isopropyl-2-(phenylthio)cyclohexyl)-3-methoxybenzamide and (b) tert-butyl 3-hydroxy-5-isopropyl-2-(phenylthio)cyclohexylcarbamate.

a neighboring hydroxyl group effect could be considered. We have proposed a mechanism, shown in Scheme 2.

In conclusion, the results reported in this article clearly indicate that by using 1 mol of NaClO, it is possible to obtain a mild and chemoselective synthesis of sulfoxides from both aromatic and aliphatic sulfides. The procedure is run in a safe solvent. Furthermore, appropriate reaction times are needed to obtain a high yield of sulfoxides. Last, this oxidation shows a big hydroxyl neighboring group participation and finally a logic mechanism are proposed.

EXPERIMENTAL

The IR spectra were taken on a Perkin-Elmer, model 783 spectrophotometer. The NMR spectra have been recorded by a Bruker AMX-300 (300 MHz) spectrometer. The chemical shifts are expressed in parts per million (ppm), and tetramethylsilane (TMS) was used as internal reference. The mass spectra (MS) were taken by an AEI MS-902 model.

General Procedure for the Synthesis of Sulfoxides

A solution of sulfide (1 mmol) and diluted NaClO (1 mmol, 1.25 mL) (5.84% w/v) in a mixture of H_2O/EtOH (50:50) (10 mL) and H_2SO_4 (10

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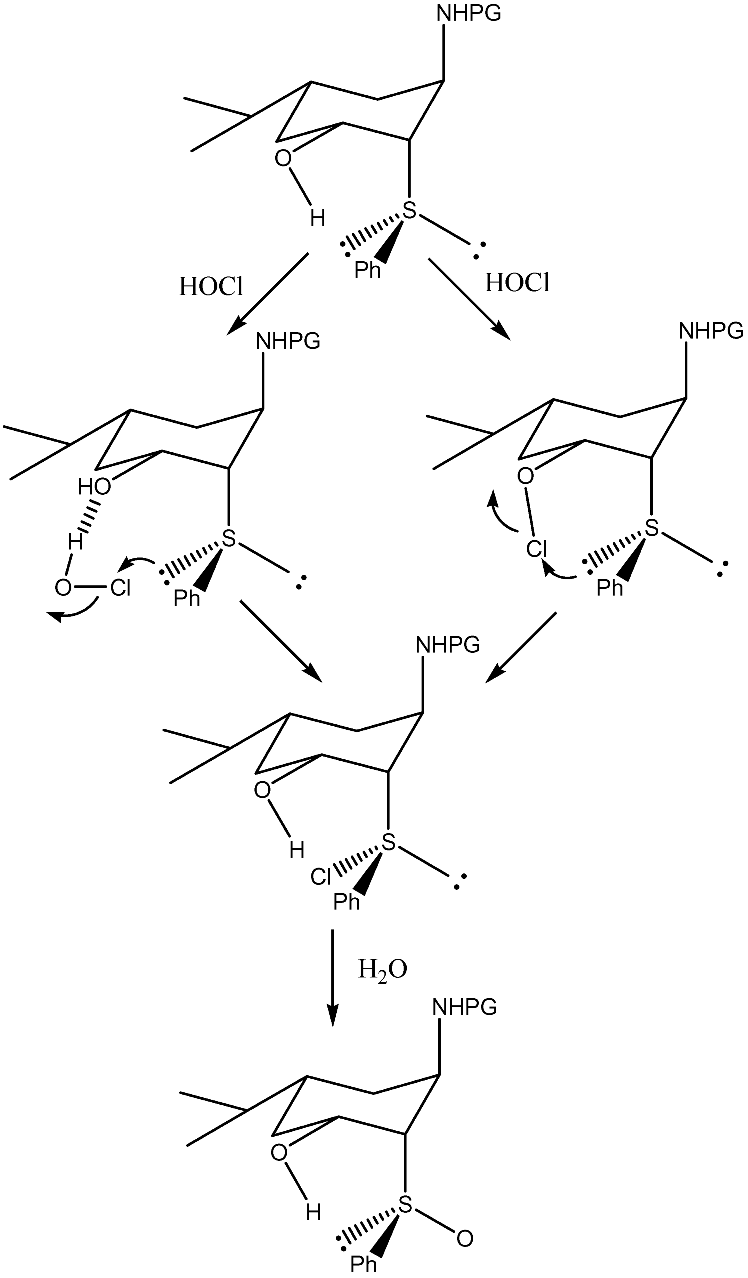

SCHEME 2 Proposed mechanism for stereoselective oxidation of protected 2-phenylthio-3-aminocyyclohexanol (Table I, entries 9 and 10).

meq.) was stirred vigorously for appropriate time (30–90 min) (TLC follow-up). The organic products were extracted by diethyl ether (4 × 5 mL). The ether layer was washed by 2 mL of water and dried over $MgSO_4$. The organic solvent was removed under vacuum. The residue was purified by recrystallization in an appropriate solvent. The sulfoxide from entry 9 was separated and purified by flash chromatography as oily product.

Known compounds were identified by IR and ^1H NMR spectral data.

N-(3-Hydroxy-5-isopropyl-2-(phenylsulfinyl)cyclohexyl)-3-methoxybenzamide

^1H NMR (300 MHz, $CDCl_3$): δ 7.70 (m, 2H), 7.20 (m, 6H), 7.00 (m, 1 H), 6.10 (d, J = 12 Hz, 1H), 4.65 (m, 1H), 4.20 (m, 1H), 4.00 (m, 1H), 3.80 (s, OCH_3), 2.50 (broad, 1H), 1.90 (m, 2H), 1.60 (m, 2H), 1.30 (m, 2H), and 1.00 (dd, J = 17, 6 Hz, $2CH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.9 159.8, 135.9, 135.2, 131.0, 130.2, 129.2, 126.8, 118.5, 117.7, 112.4 67.6 66.2, 56.6, 51.5, 37.9, 34.5, 32.1, 28.3, 19.9, 19.3. IR (NaCl): v max/cm^{-1} 3460, 2970, 2895, 1700, 1590, 1525, 1490, 1445, 1345, 1295, 1245, 1140, 1090, 1055, 910, 745, 695. *m/z* = 416 (MH+), Calculated: 416.18956, Obtained: 416.18954.

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tert-Butyl 3-hydroxy-5-isopropyl-2-(phenylsulfinyl) cyclohexylcarbamate

^1H NMR (300 MHz, $CDCl_3$): δ 7.75 (dd, J = 15 and 7 Hz, 2H), 7.50 (m, 3H), 4.60 (s, broad, 1H), 4.20 (m, 2H), 3.20 (s, broad, 1 H), 1.90 (d, J = 13 Hz, 1H), 1.70 (m, 2H), 1.50 (m, 3H), 1.35 (s, 9H), and 0.90 (d, J = 9 Hz, $2CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.0, 135.6, 132.0, 130.0, 129.1, 79.0, 67.1, 64.0, 52.0, 34.6, 32.1, 28.5, 28.3, 19.8, and 19.4. IR (NaCl): v max/cm^{-1} 3500, 3000, 2870, 1690, 1580, 1480, 1450, 1435,1360, 1285, 1250, 1160, 1105, 1085, 1055, 920, 770, 680. *m/z* = 382 (MH+), Calculated: 382.20521, Obtained: 382.20518.

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