

## **LIST OF PUBLICATION:**

1. **Umesh V Chaudhari and Pradeep T Deota** “Selective Oxidation of Sulfides to Sulfoxides With Cetyltrimethylammonium Periodate”. *Organic Preparations and Procedures International* **2012**, *44*, 381–386.
2. **Umesh V. Chaudhari, Deepak Singh, Pradeep T. Deota and Ashutosh V. Bedekar** “Steric considerations on improving diastereomeric ratio of (+)- and (-)-neomenthyl phenyl sulfoxides using bulky-headed oxidant hexadecyltrimethylammonium periodate and assignment of their configuration” *Chirality* **2015**, *27(6)*, 370-374.
3. **Umesh V. Chaudhari, Pradeep T. Deota, Ashish M. Kanhed , Mange Ram Yadav, Daniel Afosah, Umesh R. Desai** “Synthesis and biological evaluation of novel neutral 2-substituted benzamidobenzene derivatives as human factor Xa inhibitors” *Medicinal Chemistry Research* (communicated)

## OPPI BRIEFS

# Selective Oxidation of Sulfides to Sulfoxides with Cetyltrimethylammonium Periodate

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The selective oxidation of sulfides to sulfoxides is an important transformation,<sup>1</sup> since sulfoxides are useful building blocks especially as chiral auxiliaries.<sup>2,3</sup> Furthermore sulfoxides also play an important role for the acquisition of many biologically and chemically important compounds.<sup>4–6</sup> A number of oxidizing agents such as hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>),<sup>1</sup> sodium periodate (NaIO<sub>4</sub>),<sup>7,8</sup> *m*-CPBA,<sup>9</sup> ozone,<sup>10</sup> oxygen and *t*-BuOOH<sup>11</sup> have been employed. Although, H<sub>2</sub>O<sub>2</sub> is environmentally benign and NaIO<sub>4</sub> may be stored and used safely, they oxidize sulfides slowly; for example, NaIO<sub>4</sub> requires 12 hours or more,<sup>7,8</sup> while H<sub>2</sub>O<sub>2</sub> in the absence of catalyst requires 18 hours or more.<sup>12</sup> Moreover H<sub>2</sub>O<sub>2</sub> should be used in a controlled manner to avoid over-oxidation. Therefore most of the oxidizing agents are either hazardous peroxy acids or involve toxic heavy metals or rare oxidants that are difficult to prepare thus detracting their practical application in many cases. Hydrogen peroxide in the presence of complexes or salts of metals such as vanadium, molybdenum, tungsten as catalysts selectively furnishes sulfoxides.<sup>1,13</sup> A variety of oxidants in combination with metal Schiff base complexes as catalysts have also been used for this purpose;<sup>14,15</sup> however, this method has low operational stability due to facile oxidative degradation of porphyrin rings, phthalocyanines and salens.<sup>16</sup> Thus, many of the reagents and catalysts used suffer from drawbacks such as over-oxidation, long reaction times, low selectivity and low yields. Oxidizing agents based on quaternary ammonium salts have been exploited in many organic reactions<sup>17–21</sup> due to their solubility in several solvents which provide advantages in terms of mildness, operational simplicity, selectivity, high reaction rates, low reaction temperatures and absence of side-reactions. However, some of them require catalysts for activation. For example, tetrabutylammonium periodate (TBAPI) alone is not able to convert sulfides to sulfoxides. In the presence of a Lewis acid (AlCl<sub>3</sub> or BF<sub>3</sub>·Et<sub>2</sub>O) as catalyst and at reflux temperature, TBAPI oxidizes sulfides to sulfoxides in CH<sub>3</sub>CN.<sup>22</sup> Cetyltrimethylammonium

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## Short Communication

# Steric Considerations on Improving the Diastereomeric Ratio of (+)- and (–)-Neomenthyl Phenyl Sulfoxides Using Bulky-Headed Oxidant Hexadecyltrimethylammonium Periodate and Assignment of Their Configuration

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**ABSTRACT** The bulky-headed oxidant hexadecyltrimethylammonium periodate affords the diastereomeric pairs, (Ss)-(+)/(Rs)-(+) and (Ss)-(-)/(Rs)-(-)-neomenthyl phenyl sulfoxides in stereochemically pure states with improved diastereomeric excess (48% diastereomeric excess [de]) as compared to its nonbulky counterpart, sodium metaperiodate (28% de) from respective (+)/(-)-neomenthyl phenyl sulfides. Steric effects involving the head group volume of hexadecyltrimethylammonium periodate is found to play a role in improving the diastereomeric ratio of the products. The two diastereomers can be readily separated by column chromatography. Absolute configuration at the sulfur center in (+)-neomenthyl phenyl sulfoxide was determined by single-crystal X-ray crystallography and found to be Ss. Relative configurations of other sulfoxides were assigned based on the configuration of (+)-neomenthyl phenyl sulfoxide. *Chirality* 27:370–374, 2015. © 2015 Wiley Periodicals, Inc.

**KEY WORDS:** diastereoselective; hexadecyltrimethylammonium periodate; steric hindrance; neomenthyl phenyl sulfoxides

Optically active sulfoxides are often used as chiral auxiliaries and ligands for numerous asymmetric transformations.<sup>1,2</sup> The past two decades have seen an extensive use of chiral sulfoxides in asymmetric synthesis, establishing their role as one of the most efficient and versatile chiral controllers.<sup>3,4</sup> Various methods have been developed to carry out asymmetric oxidation of sulfides to optically pure sulfoxides in either diastereoselective or enantioselective mode.<sup>1–4</sup> The diastereoselectivity achieved has been generally accounted for by invoking either steric or neighboring group participation.<sup>5</sup>

Menthol and its derivatives are among those that have found application as chiral auxiliaries for the preparation of optically active sulfoxides.<sup>6</sup> Chiral (+)-methyl neomenthyl sulfoxides (**2a** and **2b**) are often intermediates in the synthesis of chiral oxiranes via corresponding sulfoximines in asymmetric methylene transfer reactions. Oxidation of (*1S,2S,5R*)-(+)-methyl neomenthyl sulfide (**1**) using hydrogen peroxide furnished the epimeric sulfoxides (**2a** and **2b**) (Scheme 1) in a ratio of 35:65, with the major isomer (**2b**) having sulfoxide oxygen oriented away from the C-2 isopropyl group.<sup>7,8</sup>

Similar observations are reported in the literature for the oxidation of different neomenthyl sulfides. Recently, Demakova et al. reported the oxidation of (*1S,2S,5R*)-(+)-hetaryl neomenthyl sulfides using various reagents to yield two diastereomeric hetaryl neomenthyl sulfoxides in different ratios.<sup>9</sup>

In the above examples, the skeleton of the neomenthyl group behaves as a chiral auxiliary, with the equatorial isopropyl appendage exerting steric hindrance to the oxidant. However, the diastereoselectivity for this sulfoxidation is moderate using achiral oxidants.

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It was envisaged that a better diastereomeric excess of neomenthyl sulfoxides could be achieved using bulkier oxidants, which would have limited access to the sulfur center from the more hindered side having isopropyl group. Consequently, the oxidation would result via the approach of the oxidant from a less hindered side, giving better stereodifferentiation.

## EXPERIMENTAL

### General Methods

(–)-Menthol (enantiomeric excess [ee]: 99%) and (+)-menthol (ee: 99%) were purchased from Sigma Aldrich (St. Louis, MO). All solvents were distilled prior to use and stored on oven-dried molecular sieves (4Å). Thin-layer chromatography (TLC) analyses were done on glass plates using silica gel G containing 13% calcium sulfate as binder. The spots were visualized in iodine vapor. Column chromatography was performed using Acme's silica gel (60–120 mesh size) and elution was done using light petroleum (60–80) and ethyl acetate mixtures. Melting points were recorded in open capillary tubes and are uncorrected. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded on a Bruker (Billerica, MA) (400/500) FTNMR spectrometer (<sup>1</sup>H NMR 400/500 MHz and <sup>13</sup>C NMR at 100 MHz) using CDCl<sub>3</sub> as solvent. The chemical shifts, in parts per million (ppm), are either relative to tetramethylsilane (TMS) as an internal standard or the residual peak of the solvent. Multiplicities of signals are denoted as doublet (d), doublet of quartet (dq), and multiplet (m). Mass spectra were recorded on a Thermo-Fisher (Waltham, MA) DSQ II

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