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Synthesis of Highly Reactive Organosulfur Compounds

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ABSTRACT: *Application of novel bowl-type and dendrimer-type steric protection groups to the first synthesis of stable aromatic S-nitrosothiols is described. These compounds showed remarkable thermal stability whereas they easily reacted with appropriate reagents. X-ray crystallographic analysis established their structures, where the C—S—N—O linkage adopts only the syn conformation. Synthesis of a stable sulfenic acid by taking advantage of the bowl-type substituent is also delineated.* © 2002 Wiley Periodicals, Inc. Heteroatom Chem 13:414–418, 2002; Published online in Wiley Interscience (www.interscience.wiley.com). DOI 10.1002/hc.10068

INTRODUCTION

In 1983 Oae et al. wrote a review on *S*-nitrosothiols (RSNO) and *S*-nitrothiols ($RSNO_2$), which are the sulfur analogs of nitrites and nitrates, and summarized their pioneering work on these sulfur compounds [1]. Some stable *S*-nitrosothiols were already known at that time, but much more attention has been focused on *S*-nitrosothiols, since they have been revealed to be an excellent precursor of nitric oxide (NO) [2], which has been of current interest because of its key roles in a wide range of human physiological processes. As for aliphatic *S*-nitrosothiols, there have been several compounds isolated and structurally characterized so far [3–6]. By contrast, aromatic *S*-nitrosothiols are much less stable than aliphatic derivatives and there has been no example of the isolation of an aromatic *S*-nitrosothiol. Usually, such compounds accumulate only transiently and rapidly decompose to the corresponding disulfides and NO [7,8]. We have been investigating the synthesis of highly reactive species by taking advantage of kinetic stabilization afforded by bowl-type substituents [9]. In this paper, we describe the synthesis, structure, and reactivities of the first stable aromatic *S*-nitrosothiols bearing bowl-type and newly designed dendrimer-type substituents. The stabilization of some related highly reactive organosulfur compounds is also delineated.

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RESULTS AND DISCUSSION

Concept and Molecular Design

For kinetic stabilization of reactive species, various types of steric protection groups have been developed so far. Among sulfur-containing reactive species, there are many compounds to which only one substituent can be introduced. Steric protection of such species is a hard task, especially when an aromatic substituent is employed; in comparison with an aliphatic substituent extending toward three directions, it is rather difficult to protect a reactive functionality from all sides by an aromatic

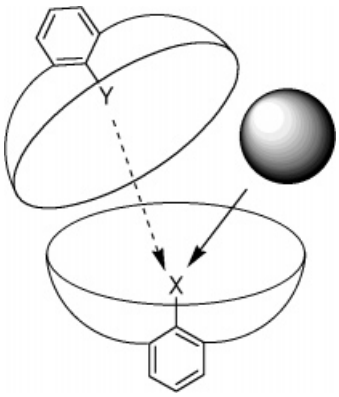
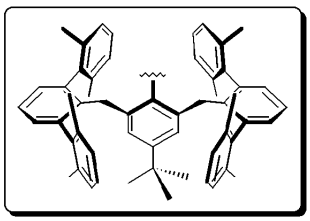


FIGURE 1 Concept of bowl-type molecules.

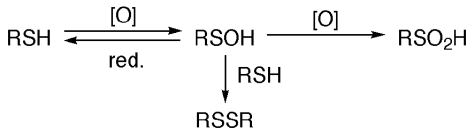
substituent. *S*-Nitrosothiols are typical examples as described above and so are sulfenic acids (RSOH). While several alkanesulfenic acids have been isolated by kinetic stabilization [10], no stable arenesulfenic acid has been obtained, even with bulky substituents such as a 2,4,6-triisopropylphenyl or a 2,4,6-tri-*tert*-butylphenyl (denoted as Mes*) group [11]. For stabilization of such species, we designed bowl-shaped molecules that are schematically depicted in Fig. 1. In these molecules, the functional groups X and Y cannot approach each other because of the steric repulsion of the brims of the bowls, whereas they can react with other reagents because there is relatively large space around them. The functionalities X and Y can be either of the same kind or of different kinds. We have designed several kinds of molecular bowls such as bimacrocyclic cyclophanes [9a,e] and bridged calix[6]arenes [9b,d,e], and recently we have developed a novel substituent **1** (denoted as Bmt hereafter) [9c,e–g] where two rigid *m*-terphenyl groups form the brim of the bowl. The inert, all-carbon framework of the Bmt group is considered to be favorable for the investigation of the intrinsic reactivities of the chemical species.



1 ≡ Bmt

Stabilization of a Sulfenic Acid by a Bowl-Type Substituent

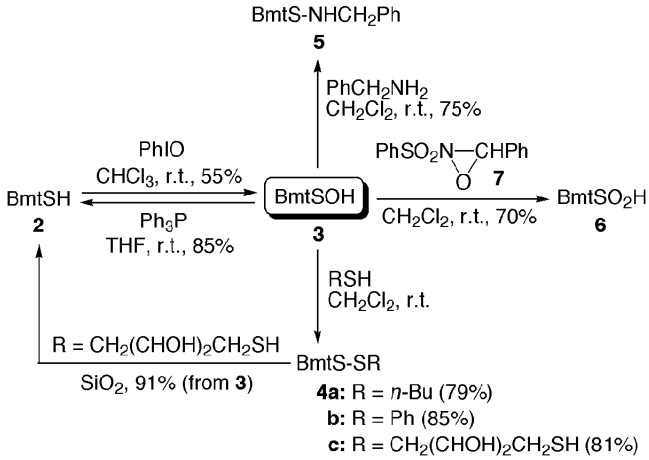
Sulfenic acids are generally assumed to be transient intermediates in the oxidation of thiols both



SCHEME 1 Redox reactions of a sulfenic acid.

to disulfides and to sulfinic acids (Scheme 1) [12]. However, the evidence for these processes is entirely circumstantial due to the instability of sulfenic acids; they usually undergo very easy self-condensation to the corresponding thiosulfinates. The reaction of thiol **2** bearing a Bmt group with iodosobenzene, a mild oxidant which usually converts thiols to disulfides, afforded sulfenic acid **3**, which was isolated by silica gel chromatography as stable crystals (Scheme 2) [9c]. X-ray crystallographic analysis has established the structure of **3**, where two rigid *m*-terphenyl units surround the SOH group like a brim of a bowl (Fig. 2). This represents the first example of direct oxidation of a thiol to a stable sulfenic acid.

The reactions of sulfenic acid **3** with 1-butanethiol and thiophenol afforded the corresponding unsymmetrical disulfides **4a** and **4b**, respectively (Scheme 2). Dithiothreitol reduced **3** to thiol **2** via the intermediary disulfide **4c**. Treatment of **3** with benzylamine afforded sulfenamide **5**. These reactions of **3** with nucleophiles demonstrate that a sulfenic acid exhibits electrophilic reactivity even under basic conditions. Sulfenic acids can be regarded as sulfur analogs of hydroperoxides and trivalent phosphorus reagents have been suggested to reduce a transient sulfenic acid. The reduction of **3** with triphenylphosphine gave thiol **2** in a good yield. Sulfenic acid **3** was oxidized to sulfinic acid **6** by oxaziridine **7**. By



SCHEME 2 Synthesis and reactions of BmtSOH (**3**).

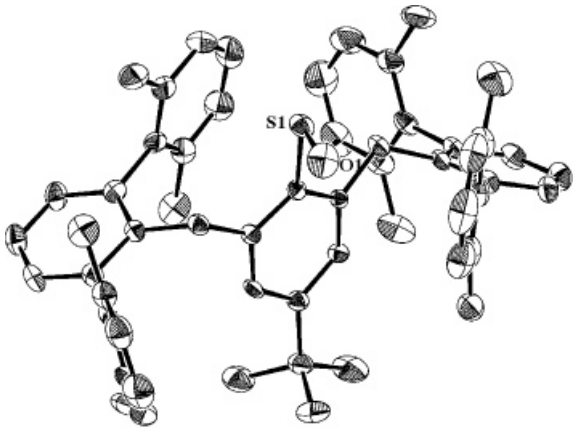


FIGURE 2 Crystal structure of BmtSOH (**3**).

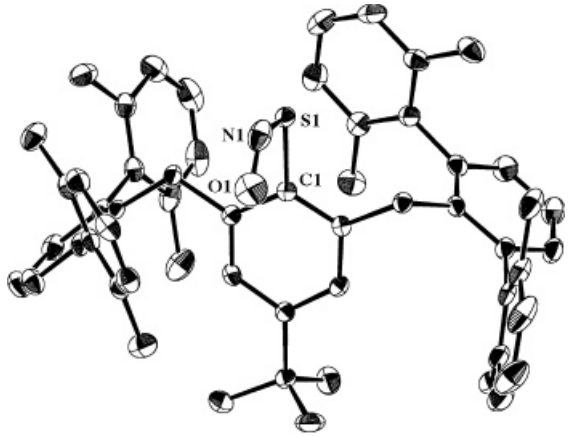


FIGURE 3 Crystal structure of BmtSNO (**8**).

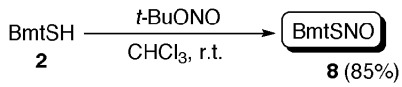
taking advantage of a Bmt group, all the processes in Scheme 1 have been demonstrated conclusively.

Stabilization of an Aromatic S-Nitrosothiol by a Bowl-Type Substituent

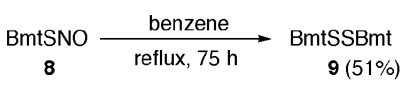
Okazaki has recently applied the Bmt group to the stabilization of an aromatic *S*-nitrosothiol [13]. Reaction of thiol **2** with *tert*-butyl nitrite (1.2 equiv) in chloroform at room temperature gave the corresponding *S*-nitrosothiol **8** as deep green crystals (Scheme 3). The structure of **8** was definitively established by X-ray crystallography (Fig. 3). The SNO group is almost perpendicular to the benzene ring attached to it and adopts the syn conformation with regards to the S—N bond. The conformation of the S—N=O group of *S*-nitrosothiols is one of the current topics, and several theoretical and experimental studies on this subject have recently been reported. While *S*-nitrosoacetyl-D,L-penicillamine (SNAP) [3] and Ph_3CSNO [4] adopt anti conformation with regard to the S—N bond, TrmSNO (Trm: tris(2,2″,6,6″-tetramethyl-*m*-terphenyl-5′-yl)methyl) [6] exists as a mixture of the anti and syn isomers. The bond lengths of N—O, S—N, and C—S in the C—S—N=O group of **8** are 1.208, 1.806, and 1.796 Å, respectively. It should be noted that the C—S bond length is considerably shorter than those reported for SNAP (1.842 Å), Ph_3CSNO (1.867 Å), and TrmSNO (1.841 Å) although the N—O and S—N bond lengths are similar to those of the aliphatic analogs.

S-Nitrosothiol **8** showed high thermal stability. No reaction took place in benzene-d_6 at 50°C for 12 h, but the decomposition was completed in refluxing benzene for 75 h to give the corresponding disulfide **9** (Scheme 4). Considering the reported fact that the half-life times of ArSNO (Ar = phenyl, *p*-methoxyphenyl, *p*-nitrophenyl, 3,5-di-*tert*-butyl-4-hydroxyphenyl) are 7–14 min in dichloromethane at room temperature [8], the stability of **8** is remarkable. In order to know the efficiency of the Bmt group, Mes*SNO was synthesized. The reaction of Mes*SH with *tert*-butyl nitrite in the presence of excess trifluoroacetic acid gave Mes*SNO as reddish-brown crystals. Mes*SNO was found to be much less stable than **8** and completely decomposed after 48 h at room temperature in chloroform, indicating that the stabilization by the Bmt group is much more effective than that by Mes*.

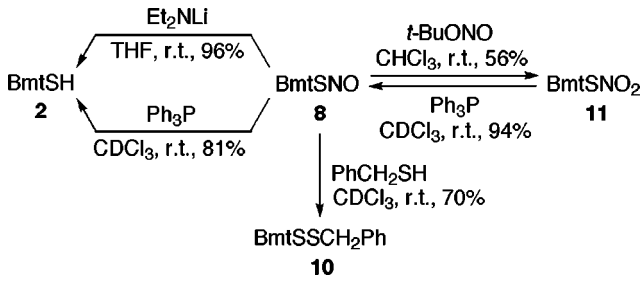
In spite of high thermal stability, *S*-nitrosothiol **8** undergoes some reactions as shown in Scheme 5. The reaction with α-toluenethiol gave unsymmetrical disulfide **10**, while the reaction of triphenylphosphine and lithium diethylamide afforded thiol **2**. Less reactive nitrogen nucleophiles such as *N*-methylaniline and diethylamine did not react with **8**. Oxidation of **8** with *tert*-butyl nitrite gave *S*-nitrothiol **11**. *S*-Nitrothiol **11** is quite stable in contrast to the reported instability of simple aromatic nitrothiols such as *p*-$XC_6H_4SNO_2$ (X = Cl, Br, CH_3),



SCHEME 3 Synthesis of BmtSNO (**8**).



SCHEME 4 Thermal reaction of BmtSNO (**8**).

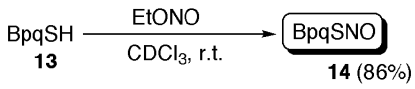


SCHEME 5 Reactions of BmtSNO (**8**)

which decompose rapidly at room temperature [14]. The reaction of **11** with triphenylphosphine gave *S*-nitrosothiol **8**, providing an alternative synthetic approach to **8**.

Stabilization of an Aromatic S-Nitrosothiol by a Dendrimer-Type Substituent

Although the efficiency of the Bmt group was found to be remarkable, the prolonged heating of *S*-nitrosothiol **8** afforded the corresponding disulfide **9**. Recently, Goto designed a novel *m*-terphenyl based dendrimer-type substituent **12** (denoted as Bpq hereafter) as a more effective steric protection group and synthesized a stable *S*-nitrosothiol bearing this substituent [15]. Treatment of thiol **13** with an equimolar amount of ethyl nitrite afforded *S*-nitrosothiol **14**, which was isolated as brownish-green crystals (Scheme 6). X-ray crystallographic analysis established the structure of **14** (Fig. 4). In the crystalline state, there was a rotational disorder of the N—O moiety around the C—S bond in the ratio of 0.55:0.45. In both fragments, the C—S—N—O linkage adopts only the syn conformation, which is similar to the case of BmtSNO (**8**). BpqSNO (**14**) showed a much higher thermal stability than hitherto known for *S*-nitrosothiols, even in comparison with BmtSNO (**8**). It was found that, even after heating in C_6D_6 at 80°C for 60 h, 38% of **14** remained unchanged. The rest of **14** was converted to the dibenzothiophene derivative **15** (46%) and thiol **13** (15%), which are considered to be formed via thiyl radical **16** (Scheme 7). In this reaction, the formation of the symmetrical disulfide **17** was not detected. The mechanism of thermolysis of *S*-nitrosothiols



SCHEME 6 Synthesis of BpqSNO (**14**).

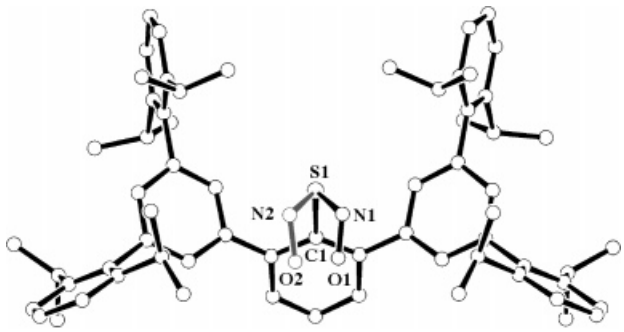
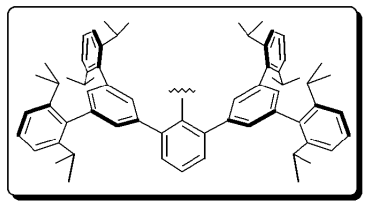


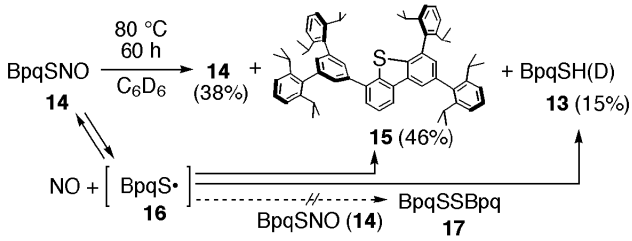
FIGURE 4 Crystal structure of BpqSNO (**14**). The disorder ratio of N(1)—O(1) to N(2)—O(2) is 0.55:0.45.

in hydrocarbon solvents is usually considered to involve the bimolecular reaction of an initially formed thiyl radical with the second molecule of *S*-nitrosothiol [2d]. The present results suggest that the Bpq group effectively suppressed the reaction of thiyl radical **16** with the second molecule of *S*-nitrosothiol **14**, which enabled the very slow conversion to **15** and **13** to take place.

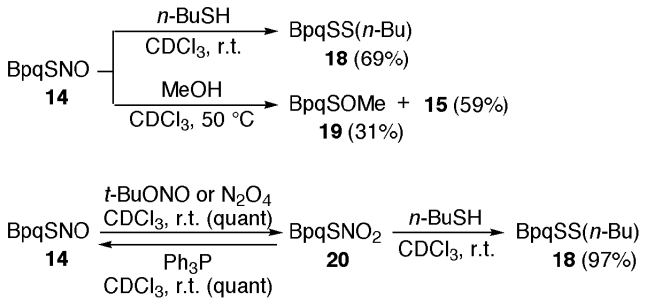


12 ≡ **Bpq**

S-Nitrosothiol **14** also reacted with several reagents (Scheme 8). The reaction of **14** with 1-butanethiol or methanol afforded the unsymmetrical disulfide **18** or methyl sulfenate **19**, respectively. Oxidation of **14** with an excess amount of *tert*-butyl nitrite or N_2O_4 afforded the corresponding *S*-nitrothiol **20** quantitatively, which was isolated as stable crystals. *S*-Nitrothiol **20** reacted with 1-butanethiol to give the unsymmetrical disulfide **18** which was similar to *S*-nitrosothiol **14**. Reduction of **14** with triphenylphosphine afforded **14** quantitatively. These



SCHEME 7 Thermal reaction of BpqSNO (**14**).



SCHEME 8 Reactions of BpqSNO (**14**).

results indicate that the Bpq group effectively stabilizes the *S*-nitrosothiol and *S*-nitrothiol without diminution of their intrinsic reactivities towards appropriate molecules.

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