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SYNTHESES OF BIOLOGICALLY RELEVANT REACTIVE SULFUR SPECIES BY UTILIZING A PRIMARY ALKYL STERIC PROTECTION GROUP

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Abstract *A novel primary alkyl steric protection group (BpqCH$_2$ group) bearing a cavity-shaped framework was designed and successfully applied to the stabilization of a sulfenyl iodide. The sulfenyl iodide showed remarkable stability, demonstrating that the BpqCH$_2$ group is very effective for kinetic stabilization of primary-alkyl-substituted reactive species.*

Keywords Cysteine models; reactive sulfur species; steric protection; sulfenyl iodides

INTRODUCTION

While there are a variety of biologically important chemical species derived from cysteine thiols, some of them are notoriously unstable because of facile bimolecular decomposition, such as dimerization, self-condensation, and disproportionation reactions.[1] As chemical models for the reactive species derived from a –CH$_2$SH side chain of cysteine residues, compounds bearing a primary alkyl substituent are considered to be the most appropriate. However, it is a common idea that the synthesis of primary-alkyl derivatives of such reactive species is difficult because the steric demands of primary alkyl groups are too small to prevent the bimolecular decomposition of reactive species. A new molecular design for steric protection with a primary alkyl group is required for modeling the cysteine-derived reactive species. We have recently developed an aromatic steric protection group, a Bpq group, with a nanosized cavity-shaped framework and applied it to the stabilization of various highly reactive species.[2] It is expected that a large cavity of the Bpq group could include the $-$CH$_2$X (X = reactive functionality) moiety in its inside and confer sufficient kinetic stability upon the reactive species (Figure 1). In this article, we report the development of an effective primary alkyl steric protection group, a BpqCH$_2$ group, and its

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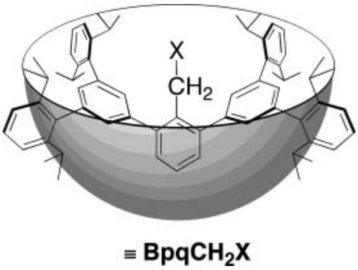
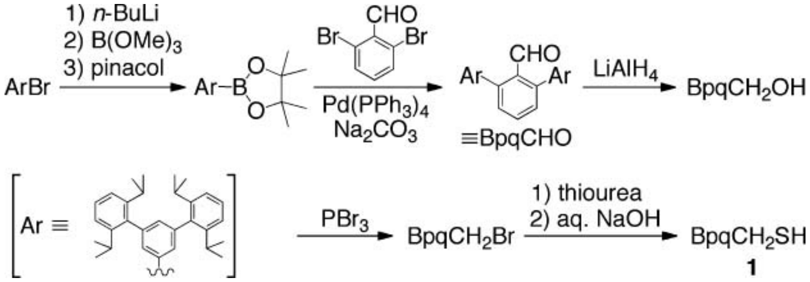


Figure 1 Schematic representation of a cavity-shaped molecule with a primary alkyl group.

application to the synthesis of a stable sulfenyl iodide (R-SI), a sulfur-containing reactive species of biological importance.[3]

RESULTS AND DISCUSSION

Thiol **1** bearing a $BpqCH_2$ group was prepared by the route shown in Scheme 1, in which the *m*-phenylene framework of the Bpq group was constructed via a Suzuki–Miyaura coupling reaction of the terphenylboronic acid and 2,6-dibromobenzaldehyde.



Scheme 1

Sulfenyl iodides have been recognized as important intermediates in various types of modification of protein thiols.[4] However, they are usually very unstable because of the ready disproportionation reaction to give disulfide and iodine. While we previously reported the synthesis of stable sulfenyl iodides bearing an aromatic substituent,[2a,5] isolation of a primary alkyl derivative is only limited to that bearing a poly(benzyl ether) dendrimer-type framework reported by Takaguchi et al.,[6] and its crystal structure has not been determined. The reaction of thiol **1** with *N*-iodosuccinimide (NIS) afforded sulfenyl iodide **2**, which was successfully isolated as red crystals in 96% yield (Scheme 2). The structure of **2** was established by X-ray crystallographic analysis (Figure 2). This is the first example of a crystallographic analysis of a primary-alkyl-substituted sulfenyl iodide. The S—I bond length of **2** is 2.3743(17) Å, which is comparable to those of the arenesulfenyl iodides we

$$\underset{\mathbf{1}}{BpqCH_2SH} \xrightarrow[CCl_4,\ rt,\ 2\ h]{NIS\ (2.7\ equiv.)} \underset{\mathbf{2}\ (96\%)}{BpqCH_2SI}$$

Scheme 2

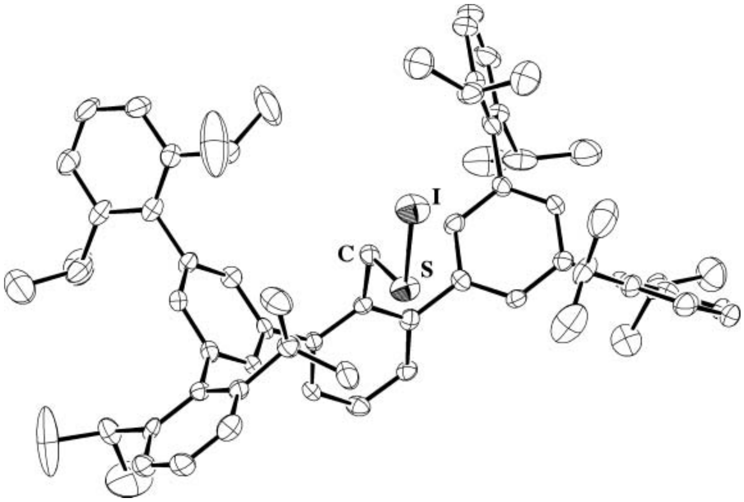
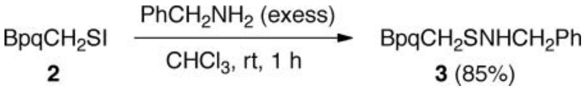


Figure 2 ORTEP drawing of **2** (50% probability). Hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and bond angle (deg): S—I, 2.3743(17); C—S, 1.808(6); C—S—I, 101.62(18).

reported previously.[2a,5] The shortest intermolecular S· · ·I distance is 8.79 Å, indicating that **2** is monomeric in the crystalline state. The $-CH_2SI$ moiety is incorporated in the large cavity of the Bpq group, and it is expected that disulfide formation by disproportionation of **2** would be difficult due to the peripheral steric protection by the cavity-shaped framework. In fact, sulfenyl iodide **2** exhibited remarkably high thermal stability. Heating of **2** in toluene-d_8 at 80°C for 9 days resulted in no decomposition, indicating the effectiveness of the $BpqCH_2$ group.

Treatment of **2** with benzylamine readily afforded sulfenamide **3** in a good yield (Scheme 3). This is in sharp contrast to the result reported by Takaguchi et al. that the sulfenyl iodide bearing a poly(benzyl ether) dendrimer-type framework does not react with the same nucleophile.[6] These results demonstrate that there is a space around the central functional group of **2**, which is large enough to allow the reaction with a relatively small reagent.



$$\underset{\mathbf{2}}{BpqCH_2SI} \xrightarrow[CHCl_3,\ rt,\ 1\ h]{PhCH_2NH_2\ (exess)} \underset{\mathbf{3}\ (85\%)}{BpqCH_2SNHCH_2Ph}$$

Scheme 3

The application of this novel primary alkyl steric protection group to the synthesis of other reactive species is currently in progress.

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