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Preparation and Reactivity of O^2-Sulfonated Diazeniumdiolates

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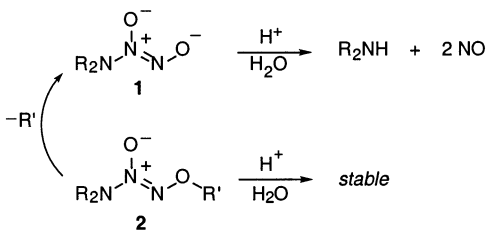
Abstract: We report the facile preparation of O^2-sulfonated diazeniumdiolates and mechanistic investigation of their reactions with representative nucleophiles. This new class of compounds extends the range of O^2-substituted diazeniumdiolates available for potential applications in research and medicine.

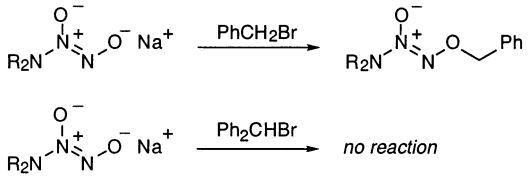
Anions such as 1-(*N*,*N*-dialkylamino)diazen-1-ium-1,2-diolates (**1**) are stable as solid salts, but release up to 2 mol of the important bioregulatory molecule nitric oxide (NO) when dissolved in aqueous solution at physiologically relevant conditions.[1] These compounds have been converted to hydrolytically stable prodrug forms **2** by reacting them with a variety of alkylating and arylating agents to affix electrophilic[1] or photosensitive[2] groups to the terminal oxygen (Scheme 1). Thus, extending the range of synthetically accessible O^2-substituted diazeniumdiolates is of significant interest to researchers involved in the design of compounds for the controlled release of NO.[3]

Reaction of primary alkyl halides with **1** is facile. For example, O^2-benzyl-substituted diazeniumdiolates can be prepared in near quantitative yield by reaction of the appropriate benzyl bromide with 1 equiv of diazeniumdiolate salt (Scheme 2). Problems arise, however, when the alkyl halide is more sterically crowded. Indeed, we found that the analogous reaction failed with *tert*-butyl halides or benzhydryl halides (Scheme 2).

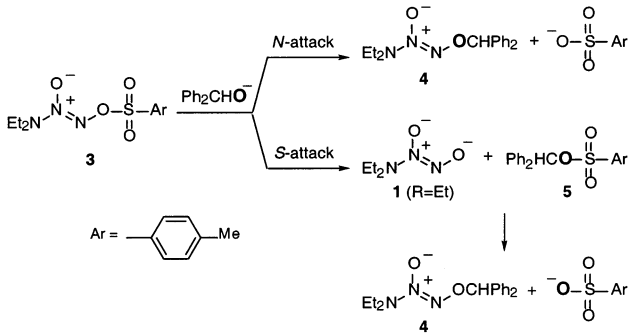
SCHEME 1



SCHEME 2



SCHEME 3



Because of this deficiency we have begun to investigate other synthetic methodologies for the preparation of hindered O^2-substituted diazeniumdiolates. Herein, we report the preparation and initial investigations concerning the reactivity of O^2-tosylated diazeniumdiolate **3**.

Treatment of **1** (R = Et) with *p*-toluenesulfonyl chloride gave O^2-tosylated diazeniumdiolate **3** in good yield. Purification was easily achieved by column chromatography. The corresponding mesylated derivative can be similarly prepared. (See Supporting Information.)

We first examined the reaction of the sodium or potassium salt of benzhydrol with **3** in 5:1 THF/DMF. Unlike the unsuccessful reaction of **1** with benzhydryl bromide described above, we obtained the desired coupled product **4** in small (ca. 10%), but adequate, yield. Our initial rationale to explain this result was simple nucleophilic attack at nitrogen and displacement of the tosylate group (Scheme 3, *N*-attack). However, an alternate mechanism, involving initial nucleophilic attack at sulfur to produce **1** (R = Et) and an intermediate tosyl ester **5** that subsequently alkylates the newly formed **1** ion, is also possible (Scheme 3, *S*-attack).

To differentiate between these two possible mechanisms, the reaction was repeated with ^{18}O-labeled benzhydrol. As indicated in Scheme 3, the direct *N*-attack pathway would lead to incorporation of the ^{18}O-label in

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(1) For a recent review of the chemistry of diazeniumdiolate derivatives, see: Hrabie, J. A.; Keefer, L. K. *Chem. Rev.* **2002**, *102*, 1135−1154.

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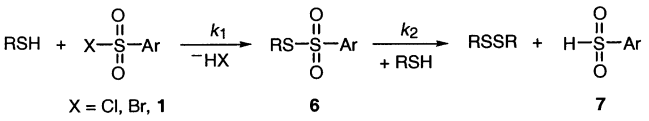
SCHEME 4



the coupled product **4**. Mass spectral analysis, however, revealed no evidence for ^{18}O-incorporation, indicating that attack of the nucleophile on compound **2** proceeds exclusively at sulfur. (Mass spectral data are included as Supporting Information.)

With this information in hand, we prepared tosyl ester **5** and reacted it directly with **1** (R = Et). The observed yield of adduct **4** approximately doubled when compared to the reaction of Scheme 3.

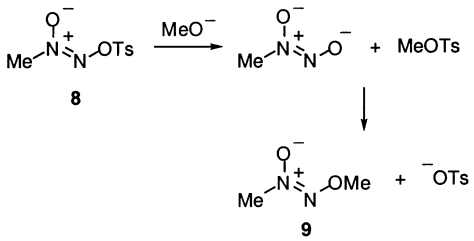
Similarly, coupling of methoxide ion with O^2-tosylated diazeniumdiolate **3**, again in 5:1 THF/DMF, led to only trace amounts of O^2-methyl-substituted diazeniumdiolate **2** (R = Et, R′ = Me); however, a 78% yield was obtained when diazeniumdiolate **1** (R = Et) was directly coupled with methyl tosylate. Presumably, in the reaction of methoxide with **3**, the initially produced methyl tosylate reacted with excess methoxide to generate dimethyl ether.

Further evidence in support of a general *S*-attack pathway was obtained when the reaction of phenoxide and 2,4,6-trimethylphenoxide anions with **3** gave the tosyl esters in high yield with no production of the corresponding O^2-aryl-substituted diazeniumdiolates **2** (R = Et, R′ = Ar).

Mechanistic investigations with thiols as the nucleophile were also carried out. O^2-Tosylated diazeniumdiolate **3** was treated in dimethyl sulfoxide-d_6 with ethyl, *tert*-butyl, and phenyl thiolate, respectively, and the reaction was followed in situ by ^{1}H NMR spectroscopy. Sulfinic acid **7** was observed (and its identity confirmed by spiking with an authentic sample), consistent with an *S*-attack mechanism (Schemes 3 and 4) as described below. The sulfinic acid was completely transformed in a slow oxidation step to the more stable tosic acid over the course of a 24-h period.

Sulfonyl halides are known to react with thiols to afford disulfides and sulfinic acids **7**; thiosulfonic esters **6** have been identified as intermediates.[4] As indicated in Scheme 4, the product disulfides are produced at the expense of the initially formed thiosulfonic esters **6** and the observation of **6** will be dependent on the relative magnitudes of the two rate constants k_1 and k_2 shown. Since sulfonyl chlorides are less reactive with thiols than thiosulfonic esters ($k_1 < k_2$), **6** is not observed in the reaction of *p*-toluenesulfonyl chloride with thiols.[4] On the other hand, analogous transformations with the more reactive *p*-toluenesulfonyl bromide give thiosulfonic esters **6** in high yield without appreciable formation of disulfides ($k_1 > k_2$).[4c]

SCHEME 5



The leaving group ability of diazeniumdiolates has previously been demonstrated to be intermediate between that of chloride and fluoride.[5] The rate constants, therefore, in Scheme 4 for the reaction of **3** with thiols should more closely resemble those of sulfonyl chlorides (i.e., $k_1 < k_2$), consistent with our lack of observation of intermediate **6**.

No evidence has been obtained for the *N*-attack mechanism. The use of bulkier thiols such as diphenylmethanethiol and triphenylmethanethiol resulted in no reaction.

These results are also consistent with the report by Stevens[6,7] that tosylated carbon-bound diazeniumdiolate **8** reacts with methoxide to give ultimately compound **9**, produced by an analogous *S*-attack mechanism (Scheme 5).

In summary, we have reported the facile preparation of O^2-sulfonated diazeniumdiolates. Mechanistic investigations with a variety of nucleophiles have revealed that this class of compounds reacts by an *S*-attack pathway. We have used O^2-tosylated diazeniumdiolate **3** to synthesize benzhydryl derivative **4**, which had been previously inaccessible by standard halide coupling reactions. Further use of O^2-sulfonated diazeniumdiolates should extend the range of synthetically accessible O^2-substituted diazeniumdiolates for potential applications in research and medicine.

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Supporting Information Available: General experimental procedures and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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