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COMMUNICATION

Nitrous oxide as a primary product in base-mediated β-elimination reactions of diazeniumdiolated benzylamine derivatives†

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We report an unexpected β-elimination pathway by which diazeniumdiolated benzylamines of structure Bn–N(R)–N(O)═N–OR′ undergo base-mediated fragmentation to generate N_2O as the only gaseous product. The reaction is especially rapid for R = 2-hydroxyethyl, in which the hydroxyl group anchimerically assists benzylic proton removal with concomitant expulsion of PhCH═NR and R′OH.

O^2-Derivatized secondary amine diazeniumdiolate prodrugs have emerged as efficient and reliable sources of the bio-effector molecule nitric oxide (NO).[1] Removal of the O^2-protecting groups by hydrolysis or appropriate metabolic triggers furnishes the corresponding diazeniumdiolate anion.[2] This species (**1**, see Fig. 1) under physiological conditions decomposes to yield up to two moles of NO and the nucleophilic secondary amine by initial protonation of the amine nitrogen (Fig. 1).[3] Recently, primary amine diazeniumdiolate IPA/NO[4] was reported to release HNO, which then dimerizes to produce N_2O, at both neutral and alkaline pH. However, N-bound diazeniumdiolates have not been found to release N_2O as a direct decomposition product, although some C-bound diazeniumdiolates are known to furnish only N_2O at neutral pH.[5] Our laboratory has been involved in diazeniumdiolate-based drug discovery focused towards effective site-directed delivery of NO for therapeutic applications.[6] Recently, we began a study of diazeniumdiolated benzylamines as potential NO prodrugs containing aromatic chromophores and have probed into their structure–property relationships. In this effort to develop new *N*-diazeniumdiolates as efficient sources of biomedically useful NO, we have unexpectedly encountered a pathway by which certain members of this family fragment directly to N_2O without the formation of HNO as an initial step. Herein, we report on the base-mediated β-elimination reaction of certain secondary benzylamine diazeniumdiolates.

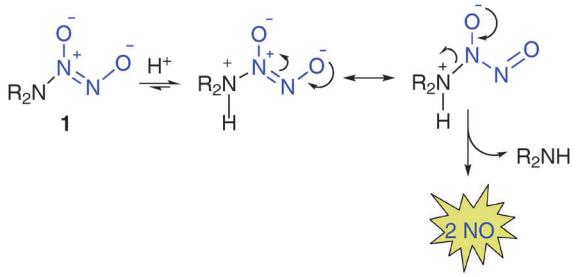
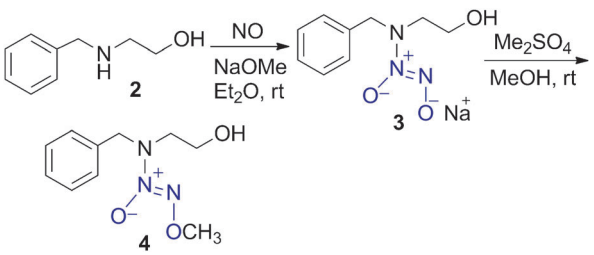


Fig. 1 Decomposition mechanism of secondary amine diazeniumdiolates.

Reaction of 2-benzylaminoethanol (**2**) with NO in the presence of sodium methoxide afforded the corresponding *N*-diazeniumdiolated sodium salt (**3**). Under physiological conditions, in the presence of 7.4 pH phosphate buffer at 37 °C, this sodium salt releases about 1.6 mole of NO per mole of the compound ($t_{1/2}$ = 8.9 min) and can be considered as a new addition to the arsenal of NO-releasing diazeniumdiolates.[6] O^2-Alkylation of diazeniumdiolate salts renders enhanced stability in acidic and alkaline media[7] and accordingly the corresponding methylated derivative (**4**) was prepared by the treatment of **3** with dimethyl sulfate (Scheme 1). This analog, barely soluble in aqueous media, was found to be fairly stable under acidic conditions and showed no signs of decomposition in a solution of 0.5 M HCl in ether at room temperature for over 12 h. However, a surprisingly facile chemical transformation of **4** was observed in the presence of base.

Treating a solution of **4** in THF with Li^{t}BuO at 50 °C was marked with a rapid disappearance of the starting material. Under optimized conditions, the reaction completed in 1.5 h and isolation of the product indicated the formation of Schiff base **5** in 84% isolated yield, whose identity was confirmed by comparing its NMR and HR-MS data with those for an authentic sample prepared as reported.[8] An effort to determine the fate of the diazeniumdiolate nitrogen atoms in **4** using gas



Scheme 1 Preparation of **4**.

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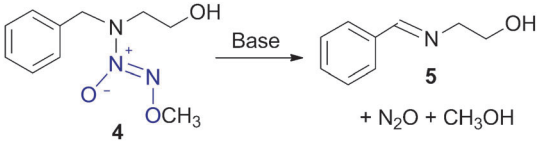
† Electronic supplementary information (ESI) available: Full experimental procedures and spectroscopic data for compounds **3**, **4**, **7a**, **7b**, and **9** are available. See DOI: 10.1039/c2cc32284f

Table 1 Base-mediated fragmentation of **4**



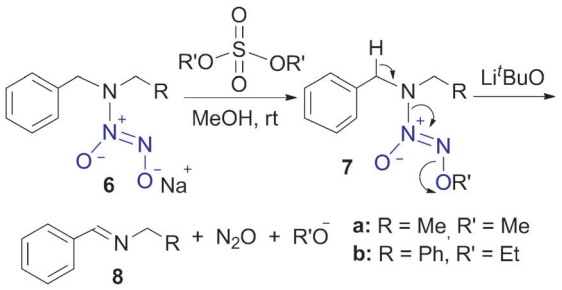
Entry[a]	Base	Solvent	Rxn. time/h	Yield[b] (%)
1	Li^{t}BuO	THF	1.5	84
2	Li^{t}BuO	DMF	2	71
3	LiOH	EtOH	72	—
4	Et_3N	THF	24	<2

[a] All reactions were carried out at 50 °C. [b] Isolated yields.

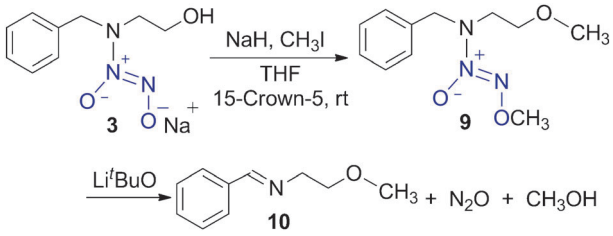
chromatographic analysis of this reaction proved to be futile due to the use of volatile THF as a solvent. However, a careful GC analysis of the reaction of **4** with Li^{t}BuO in DMF for 2 h at 50 °C revealed the release of 64 mol% of N_2O as a reaction product along with the isolation of **5** in 71% yield following an aqueous workup. ^{1}H NMR analysis of an aliquot of this reaction mixture also revealed the formation of methanol as a product. It is also to be noted that the potential fragmentation of **4** in the presence of weak bases was examined and was found to be extremely sluggish (Table 1, entries 3 and 4) in contrast to that of reactions with a strong base, such as Li^{t}BuO (Table 1, entries 1 and 2). These results strongly indicate that the treatment of **4** with a strong base, such as Li^{t}BuO, triggers *in situ* β-elimination of the protected diazeniumdiolate leading to the formation of the corresponding imine, N_2O and methanol in a near stoichiometric ratio. We postulate that the acid–base properties of the hydroxyl group in **4** play a pivotal role in this chemical transformation.

To confirm this, we studied the effect of base on several other protected diazeniumdiolates with structures analogous to that of **4**. Sodium salts of *N*-diazeniumdiolated *N*-benzylethylamine (**6a**) and *N*,*N*-dibenzylamine (**6b**) were prepared following the reported procedure[9] and the corresponding O^2-alkylated derivatives were synthesized. Reaction of **7a** with Li^{t}BuO in THF was found to be extremely sluggish even after reflux for 15 h. ^{1}H NMR analysis of the crude reaction mixture revealed that the majority of the starting material was unreacted. However, formation of the corresponding imine **8a** in only 6% estimated yield was determined by comparing the ^{1}H NMR spectrum of the crude reaction mixture with that of the authentic imine obtained commercially. Also, gas chromatographic examination of the reaction of **7a** with Li^{t}BuO in DMF revealed the release of only 5% N_2O which is consistent with the estimated yield of **8a** as determined by ^{1}H NMR. A similar outcome was also observed for the NMR and GC analyses of the base-mediated reaction of **7b**, indicating the formation of imine **8b** and N_2O in about 2% yield each. Analogs **7a** and **7b**, being devoid of any free *N*-hydroxyethyl functionality, proved to be much less susceptible towards base-induced fragmentation under identical conditions (Scheme 2).

Accordingly, **9**, prepared by the treatment of **3** with iodomethane in the presence of 15-crown-5 ether, when reacted with Li^{t}BuO in THF at 50 °C, afforded only imine **10**, albeit in trace quantity (Scheme 3). Identification of the product was achieved by comparing the NMR and HR-MS data of the crude reaction mixture with an authentic sample of **10**.[10] The anomaly between



Scheme 2 Preparation and fragmentation of **7a** and **7b**.



Scheme 3 Preparation and reaction of **9** in base.

the reactivities of **4** and its above-mentioned analogs **7a**, **7b**, and **9** points towards a key role of the *N*-hydroxyethyl group in initiating a presumably concerted elimination by abstracting one of the benzylic protons in **4** *via in situ* formation of the potentially six-membered cyclic transition state (**11**) and leading to the facile formation of imine **5** (Fig. 2). Based on this tentative mechanism for the proposed β-elimination reaction, we presume that the base-mediated reactivity of the diazeniumdiolated benzylamines with longer *N*-hydroxyalkyl chains will be substantially sluggish due to the formation of potentially unfavorable cyclic transition states.

In summary, we have reported for the first time the preparation of a unique secondary benzylamine diazeniumdiolate, the O^2-protected prodrugs of which can fragment directly to N_2O *via* a novel base-mediated β-elimination reaction triggered by the potential acidity of the benzylic protons. Even though these caged diazeniumdiolates have not been developed as potential N_2O donors in biological systems, this unexpected finding should be borne in mind when working with such prodrugs, especially diazeniumdiolated benzylamine derivatives and other diazeniumdiolates bearing hydroxyl groups with similarly situated acidic protons α to the amino nitrogen.

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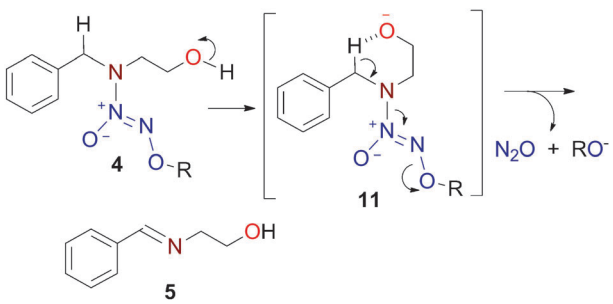

Fig. 2 Mechanism for the formation of imine **5**.

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