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Investigating the Reaction of *N*-Carbobenzoxy-*O*-carbobenzoxyhydroxylamine with Dimethyl Sulfoxide: Formation of *S,S*-Dimethyl-*N*-[(phenylmethoxy)carbonyl]sulfoximine

Ron W. Darbeau,*,§ Noe T. Alvarez,§ Gregory A. Trahan,† and Frank R. Fronczek‡

Department of Chemistry, McNeese State University, Lake Charles, Louisiana 70609, Department of Chemistry, Louisiana State University, Baton Rouge, Louisiana 70803, and Research & Development Division, Sasol North America Inc., 2201 Old Spanish Trail, Westlake, Louisiana 70669

rdarbeau@mail.mcneese.edu

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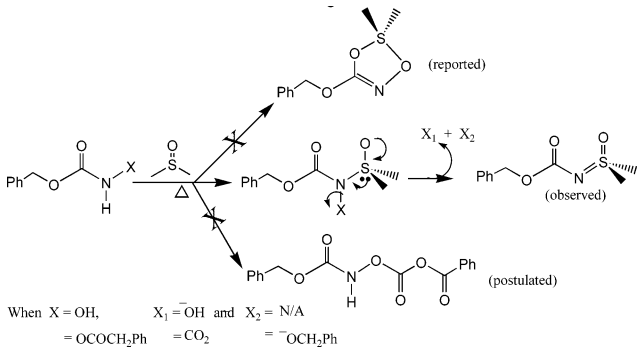

N-Carbobenzoxy-*O*-carbobenzoxyhydroxylamine (**1a)** underwent a thermally induced reaction in DMSO in which there is net *N*-α-eliminative oxidation with tandem oxidative incorporation of DMSO to yield *S,S*-dimethyl-*N*-[(phenylmethoxy)carbonyl]sulfoximine. Mechanisms for the formation of the sulfoximine are presented as well as the product characterizations, including the X-ray crystal structure.

We recently reported[1] the synthesis and characterization of *N*-carbobenzoxy-*O*-carbobenzoxyhydroxylamine (**1a**), whose nitrosation and subsequent decomposition yields carbocations in multiple spacer-molecule separated ion pairs,[1,2] with reactivities and lifetimes significantly larger than those of their standard deaminative counterparts.[1,2] Such hyperdeaminatively generated benzyl cations react nearly quantitatively with arenes,[2] and disobey the Brown Selectivity Relationship.[3]

In the present work, **1a** underwent an unknown reaction in DMSO-d_6 at elevated temperatures. Hydrolysis of **1a** is not the operative route because, although benzyl alcohol was formed, only traces of *N*-carbobenzoxyhydroxylamine[4a] (**1b**) were detected. Other unknown trace minor products were formed; however, the unidentified product (δ 5.01 in DMSO-d_6) and benzyl alcohol were the only major products. Interestingly, when **1a** was heated in methylene chloride (at 60 °C) and toluene (at 100 °C), no corresponding reaction occurred. The reaction was originally thought to be a thermal isomerization in which *N,N*-dicarbobenzoxyhydroxylamine (**1c**) was produced from **1a** (Scheme 1) via the charge-separated

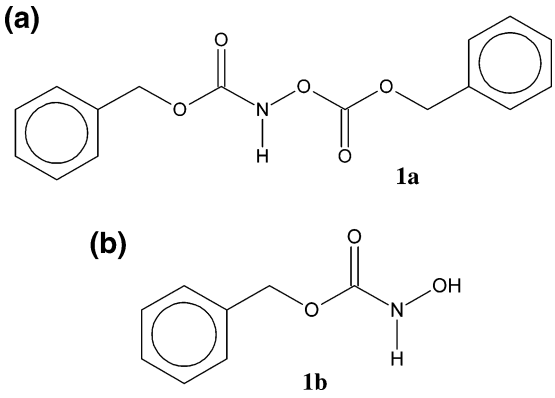

FIGURE 1. (a) *N*-Carbobenzoxy-*O*-carbobenzoxyhydroxylamine (**1a**). (b) *N*-Carbobenzoxyhydroxylamine (**1b**).

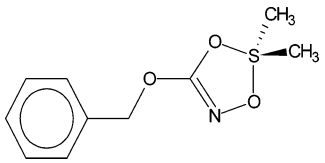

FIGURE 2. 5-(Benzyloxy)-2,2-dimethyl-1,3,2λ^4,4-dioxathiazole (**2**).

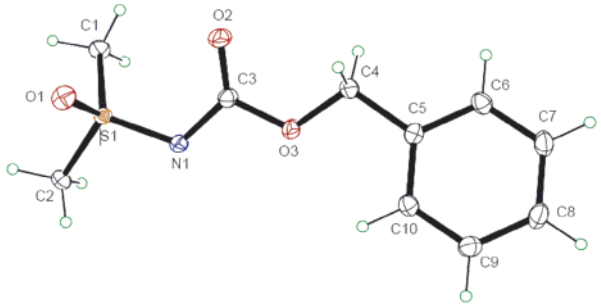

FIGURE 3. Crystal structure of *S,S*-dimethyl-*N*-[(phenylmethoxy)carbonyl]sulfoximine.

* To whom correspondence should be addressed.
§ McNeese State University.
† Research & Development Division, Sasol North America Inc.
‡ Louisiana State University.

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(4) Benzyl *N*-hydroxycarbamate or *N*-(benzyloxycarbonyl)hydroxylamine.

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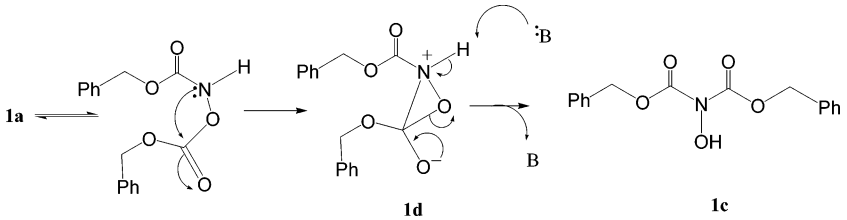
SCHEME 1. Proposed Mechanism for the Thermal Isomerization of 1a to 1c



transition state **1d**. This putative reaction would proceed in DMSO (ϵ = 46.7),[5a,b] but not in the low-polarity/polarizability solvents CH_2Cl_2 (ϵ = 8.9)[5a,b] and toluene (ϵ = 2.4).[5a,b] We investigated this reaction and its kinetics to test our hypothesis.

A 20 mg sample of **1a** was heated in 750 μL of DMSO-d_6 at 70 °C for 4 days. Removal of the solvent in vacuo followed by washing the residue with 3 × 1 mL aliquots of ether afforded a pure white solid (mp 99.5−100.5 °C) that gave a single peak in the aliphatic region of the ^{1}H NMR spectrum at δ 5.01. Elemental analysis (C, H, N, and O) of the unknown revealed that 17.35% of its mass was unaccounted for, indicating the incorporation of sulfur and perhaps deuterium from DMSO-d_6. The reaction was rerun in dry DMSO-h_6, and the product was isolated and characterized via ^{1}H and ^{13}C NMR, FT-IR, UV−vis, and elemental analysis (C, H, N, O, and S).

A new singlet was observed at δ 3.25, which corresponded to H atoms previously replaced by D atoms in the preceding synthesis. This latter peak bore a 6:5 integral ratio with the aromatic signal, and a 3:1 ratio with the benzylic proton signal (δ 5.01), indicating that it corresponded to 6 equivalent methyl protons via the incorporation of DMSO into the new compound. No heteroatom (broad, D_2O-exchangeable) peak was observed. The FT-IR indicated the lack of an imidodicarbonyl doublet in the approximate region 1840−1740 cm^{-1}. Percentage composition from elemental analysis of the product yielded an empirical formula of $C_{10}H_{13}NO_3S$, confirming that the product is not **1c**. From the molecular formula and spectral data, we proposed[1c,d] structure **2**, and reported the reaction as a decarboxylative [3+2] cycloaddition of DMSO across the amido unit of **1a**.[1c,d]

X-ray Diffraction Study on the Unknown. Structure determination of a crystal grown by evaporation of an ethyl acetate-based solution of the unknown compound showed that it is **not** heterocyclic,[1c,d] but possesses a S=N bond[6a−c] and is, in fact, *S,S*-dimethyl-*N*-[(phenylmethoxy)carbonyl]sulfoximine (**3**). We have found only one reference to this compound[6b] (but no crystal structure (Figure 3)). Interestingly, only one other compound in the Cambridge Crystallographic Database contains the N=S(Me_2)=O moiety.[6c]

FT-IR Spectrum of 3. A key feature of the spectrum of **3** is the intense peak at 1657 cm^{-1} attributable to the carbamate moiety. Bands at 1264, 1195, and 1019 cm^{-1} are characteristic of the −N=S=O moiety;[7] those at 1456 cm^{-1} and at 1380 and 1329 cm^{-1} likely correspond to CH_2 scissoring and C−H bending of the gem dimethyl groups of **3**.

^{1}H NMR Spectrum of 3. Compound **3** gives rise to an aromatic multiplet at δ 7.34 (5H), a benzylic singlet at δ 5.12 (2H), and the methyl singlet at δ 3.25 (6H).

^{13}C NMR Spectrum of 3. There are four types of aromatic carbons assigned by their proximity to the oxygen of the benzyloxy group. The ipso carbon appears at δ 136.2, the para carbon (also the least intense) at δ 128.1. The meta carbons arise at δ 128.3, and the ortho carbons at δ 128.5. The three types of nonaromatic carbons are the carbamate C at δ 159.0, the methyl carbons at δ 41.9, and the benzyl carbon at δ 67.9.

Potential Mechanisms for the Formation of 3. Interestingly, there are three reasonable mechanisms (Scheme 2) for the formation of **3** that differ in the roles of DMSO and the intermediacy of a labile dioxathiazolone (**5**) along the reaction pathway. There are several noteworthy points regarding Scheme 2. In mechanism A, DMSO acts as an electrophile,[6d] and suffers attack by the N of **1a** so that S−N bond formation is the first step. Deprotonation of the first-formed intermediate yields a species (**4a**) capable of eliminating the elements of the benzyl carbonate ion as CO_2 and $PhCH_2O^-$ to form **3** directly (path A1). Alternatively, in path A2, **4a** may undergo a conformational change and then cyclization to **5**, from which decarboxylative fragmentation yields **3.**

In mechanism B (Scheme 2), DMSO functions as a nucleophile,[6e] attacking the carbonate group of **1a** with the expulsion of $PhCH_2O^-$ to form the cationic species **4b.** The latter cyclizes by formation of the S−N bond to form **5**, which decomposes, as in the previous case. Regardless of the operative mechanism(s), however, the overall reaction may be viewed as a net *N*-α-eliminative oxidation with tandem oxidative incorporation of DMSO or as a decarboxylative sulfoximation to yield **3**.

Determination of Activation Parameters for Sulfoximine Formation. We investigated the kinetics of the formation of **3** by heating a solution of **1a** in DMSO-d_6 at 80, 90, and 95 °C in the NMR probe and taking spectra at regular intervals. From the integrals as a function of time,[6f] we made plots of the ln(% **3**) versus

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SCHEME 2. Potential Routes for the Reaction of *N*-Carbobenzoxy-*O*-carbobenzoxyhydroxylamine with DMSO To Form *S,S*-Dimethyl-*N*-[(phenylmethoxy)carbonyl]sulfoximine

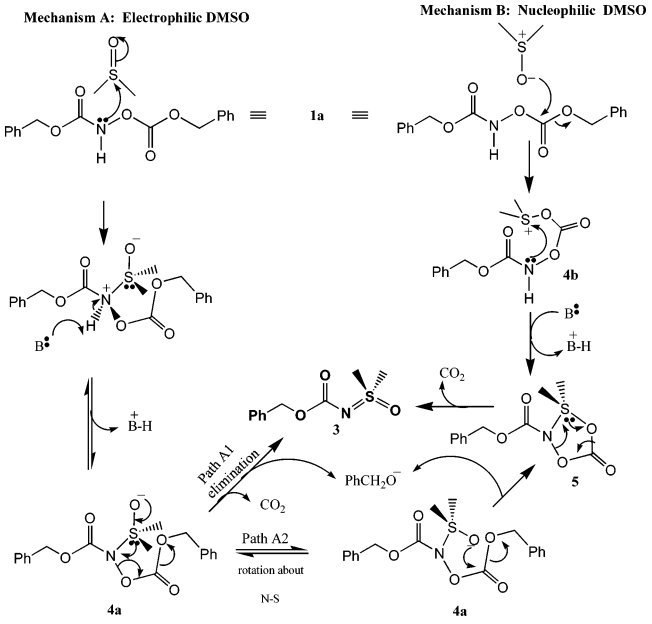


TABLE 1.

Kinetic Data[a] for Thermolyses of **1a** in DMSO			
temperature (°C)	85	90	95
rate constant ($\times 10^{-2}$ s^{-1})	2.3	3.9	6.2

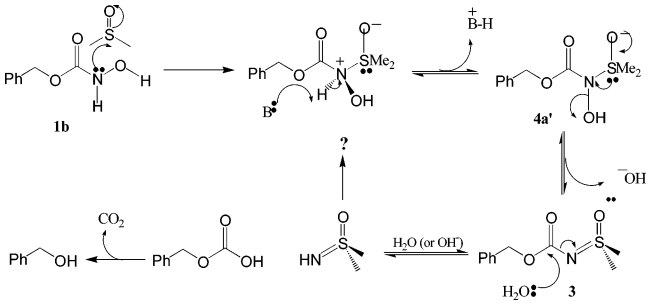
Activation Parameters[b] for Thermolyses of **1a** in DMSO

parameter	A	E_a (kJ mol^{-1})	ΔH^* (kJ mol^{-1})	ΔS^* (J mol^{-1} K^{-1})
value	1.21×10^{14}	107.7	104.7	14.7

[a] Data are averages of at least duplicate runs; max. std. dev. = 2×10^{-4}. [b] Data are averages of at least duplicate runs; max. std. dev. = 2×10^{-2}.

time (R^2 values ranged from 0.93 to 0.97). From these plots, we determined the rate constants (equal to the slopes) for each temperature (Table 1a), and Arrhenius ($R = 0.9997$)[6f] and Eyring ($R = 0.9996$)[6f] plots were made. The data (Table 1b) show a very large preexponential factor consistent with a first-order reaction or, as postulated here, a pseudo-first-order one in which DMSO functions as both the solvent and reagent. Additionally, the positive ΔS^* value indicates that decarboxylation is an event that occurs up to or including the rate-determining step (RDS). Hence one of the following takes place: (1) decarboxylation (in which $\Delta S^* > 0$) precedes cyclization (in which $\Delta S^* < 0$), and the latter occurs after the RDS; (2) decarboxylation but not cyclization occurs along the reaction profile (path A1; Scheme 2); or (3) decarboxylation and cyclization are concurrent processes (paths A2 and B; Scheme 2). Option (1) appears unlikely, given that the formation of **5** would be expected to be somewhat difficult because of the stereochemical demands of an sp^2-hybridized N, a C, and a T-shaped S. Thus, the E_a for cyclization would probably be too high for the cyclization to not be involved in the RDS. Also, if the cyclization is indeed difficult, the reaction path may

SCHEME 3. Proposed Mechanism for the Reaction of 1b with DMSO To Form 3, and Subsequent Hydrolysis of the Latter to Benzyl Alcohol



circumvent the formation of **5** and proceed as in path A1, for example.

Relative Stability of 1b in DMSO. When **1b** is incubated with DMSO, trace formation of **3** is detected under only the more extreme conditions of 110 °C for 2 days. In contrast, with **1a**, the reaction is complete after 11 h at 110 °C. This observation is interesting for several reasons. (1) **1b** being devoid of the benzyl carbonate moiety would make it incapable of proceeding through either the B or A2 pathway (Scheme 2). Consequently, if **1a** and **1b** follow analogous pathways to **3** (probable, given the unusual nature of both the reagents and product), then pathway A1 would appear to be more likely than pathways B and A2. (2) The N in **1b** should be more nucleophilic than that in **1a** because the lone pairs on the O of the adjacent O−H are not in resonance with a carbonate carbonyl as in **1a**. Thus, a full α-effect is felt by the lone pair on the nitrogen of **1b**. Consequently, nucleophilic attack by **1b** on DMSO should be more facile than the parallel attack by **1a**. (3) However, decarboxylative elimination from **1a** (a relatively facile process because of the positive ΔS^* associated with one particle forming three, including a gas) is replaced, in **1b**, by the loss of OH^-, a relatively poor nucleofuge, without the benefit of a tandem decarboxylative event.

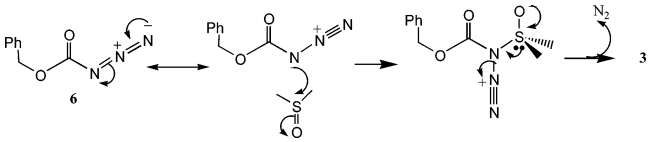
We postulate that the mechanisms for the thermal reactions of **1a** and **1b** in DMSO both involve nucleophilic attack by N on DMSO. This forms a zwitterionic entity whose rapid deprotonation yields an anion that eliminates either OH^- (**1b**) or CO_2 and $PhCH_2O^-$ (**1a**) in the RDS. This step is accompanied by increases in entropy on going from the intermediate **4a** (or **4a′** for **1b**; Scheme 3) to the activated complex. The large ΔS^* in the case of **1a** is apparently critical for keeping the ΔG^* low enough for observable chemistry under less strenuous conditions. As observed in the case of **1b**, in which no decarboxylation occurs, the ΔS^* is only slightly positive, and the ΔG^* rises, making the reaction more difficult,.

Kinetics of 1b + DMSO → 3. We attempted to determine the kinetics of the formation of **3** from **1b** and DMSO. However, the reaction occurs only at observable rates at ~135 °C. Unfortunately, although some **3** is observed, benzyl alcohol dominates the reaction product, even when the reactions are carried out in sealed tubes in extensively dried DMSO. We have accounted for this event by the mechanism shown in Scheme 3. Thus, the generation of **3** from **1b** requires the tandem formation of 1 equiv of water. At the elevated temperature, this (in

situ) water evidently hydrolyzes **3** into benzyl alcohol and a sulfonyl derivative(s). This conclusion is supported by the fact that the sum of the % composition of **1a**, **3**, and benzyl alcohol approximates 100% throughout the reaction (see Table 2, Supporting Information). The hydrolysis of **3** makes determining the kinetics of its formation difficult. Nonetheless, the requirement of more strenuous conditions for the initiation of the reaction from **1b** as compared to **1a** lends strong support to our proposal.

A Brief Look at Sulfoximines. Sulfoximines are an interesting class of compounds that have been generated via reactions of azidopentafluorobenzene with DMSO,[7a] oxidation of sulfilimines,[7b] treatment of amines with a DMSO−*tert*-butyl hypochlorite complex,[7c] reaction of *o*-quinone monoimides with sulfoxides,[6c] and reaction of alkoxycarbonyl azides with DMSO (vide infra).[6b] They are biologically active compounds with roles such as inhibition of GSH synthesis, which has implications in the background resistance of cancer cells to chemotherapeutic agents,[8a] protection of the mitochondrial electron transport chain from damage by oxidative stress in astrocytes and neurons,[8b] and survival of U937 cells via inhibition of the apoptotic program downstream of the release of cytochrome *c*.[8c] They also play roles in medicine by decreasing blood−brain, large−neutral amino acid transport in adults,[8d] and in agriculture by inhibiting phytochelatin synthesis.[8e] Reviews of sulfoximine chemistry are available.[9]

General Mechanism for Sulfoximine Formation from Alkoxycarbonyls. Nitrogen atoms of alkoxycarbonyl compounds are evidently sufficiently nucleophilic to attack even the relatively weakly electrophilic DMSO. The reaction presented in this work appears to be a variant of a side reaction observed by Kirby et al.,[6d] in which an alkoxycarbonyl azide undergoes deaminative sulfoximination to yield **3**.[6d] It is noteworthy that the carbamyl nitrogen in all three cases (**1a**, **1b**, and **6**) is activated by either the α-effect (**1a**, **1b**) or resonance (**6**) to offset the drain of electron density from the adjacent carbonyl (although that drain is somewhat diminished by the carbamyl O).



The reaction of **6** with DMSO, and its mechanism, is consistent with our observations and postulates (vide supra).

Experimental Section

***N*-Carbobenzoxy-*O*-carbobenzoxyhydroxylamine (1a). 1b** (2.8 g) and dry $NaHCO_3$ (9.8 g) were placed in 200 mL of methylene chloride, and 3.1 g (1.1 equiv) of benzyl chloroformate was added dropwise with stirring. The flask was charged with Ar and sealed with a rubber septum, and a syringe needle attached to a balloon of Ar was placed. The reaction was run for 24 h at 20 °C with vigorous stirring. The suspension was filtered, and the filtrate was evaporated in vacuo. The residue was recrystallized from 1:3 ether:hexane in 52% yield:[10] mp 72−74 °C; IR (KBr) 3221, 1805, 1716, 1506, 1244, 1146 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.23 (s, 2H), 5.26 (s, 2H), 7.35 (s, 5H), 7.37 (s, 5H), 7.83 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 68.5, 71.6, 128.4, 128.6, 128.7, 128.8, 128.9, 129.1, 134.3, 135.2, 155.5, 156.8; UV (CD_3CN) λ_{max} 252 (ϵ = 368), 257 (ϵ = 487), 262 (ϵ = 445), 268 nm (ϵ = 292). Anal. Calcd for $C_{16}H_{15}NO_5$: C, 63.78; H, 5.02; N, 4.65; O, 26.55; Found: C, 63.69; H, 4.88; N, 4.63; O, 26.43.

***S, S*-Dimethyl-*N*-[(phenylmethoxy)carbonyl]sulfoximine (3). 1a** (180 mg) was dissolved in 5 mL of dry DMSO in a pressure vial, and the vial was then sealed with a Teflon-lined cap. The solution was placed at 80 °C for 2 days, after which the DMSO was removed in vacuo. The remaining viscous liquid was washed twice with 3 mL of boiling ether, after which precipitation of a white solid occurred. The precipitate was then pumped for 1 h to yield pure **3** in 16% yield:[10] mp 99.5−100.5 °C; IR (KBr) 3052, 3024, 2939, 1657, 1264, 1195, 1019, 994, 896, 790, 739, 696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.25 (s, 6H), 5.12 (s, 2H), 7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 41.9, 67.9, 128.1, 128.3, 128.5, 136.2, 159.0; UV (Acetonitrile) λ_{max} 252 (ϵ = 286), 258 (ϵ = 354), 268 nm (ϵ = 196). Anal. Calcd for $C_{10}H_{13}NO_3S$: C, 52.85; H, 5.77; N, 6.16; O, 21.12; S, 14.11. Found: C, 52.75; H, 5.64; N, 6.03; O, 21.13; S, 13.83.

Acknowledgment. Acknowledgment is given to the Louisiana Education Quality Support Fund, Grants LEQSF(1999-2000)-ENH-TR-13, LEQSF-(2001-04)-RD-A-23, and LEQSF-(2003-05)-RD-B-06, the Calcasieu Parish Industrial and Development Board Endowed Professorship, the Pinnacle Corporation, and the McNeese State University Chemistry Department. The authors also thank Prof. Kenton H. Whitmire, Prof. Peter Loos, and Teyeb O. Ely of the Rice University Chemistry Department for their kind assistance in this project.

Supporting Information Available: Crystallographic information file (CIF) for compound **3**. Kinetics tables and Arrhenius and Eyring plots for thermolysis of **1a** in DMSO**.** This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Nonoptimized yield.