Pergamon

Tetrahedron Letters, Vol. 38, No. 37, pp. 6569-6572, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01497-4

Mechanistic Studies of the Free-Radical Fragmentation of Monoalkyl Diazenes

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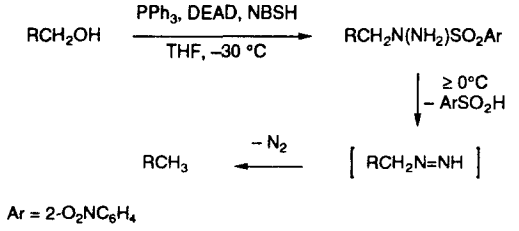
Abstract: Mechanistic studies of the deoxygenation of primary alcohols by Mitsunobu displacement with *o*-nitrobenzenesulfonylhydrazine (NBSH) reveal that the monoalkyl diazene intermediates formed in this process are exceedingly good hydrogen-atom donors toward alkyl radicals, exceeding tri-*n*-butyltin hydride in reactivity. Competition experiments are described wherein the radical intermediates are trapped by intra- and intermolecular addition to carbon-carbon double bonds, to dioxygen, and to the free radical 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO). © 1997 Elsevier Science Ltd.

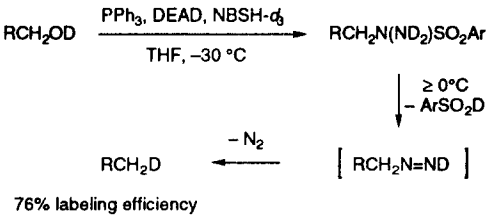
We recently described a new method for the deoxygenation of unhindered alcohols that proceeds in a single step without using heavy metal hydride reagents. The method involves the Mitsunobu displacement of an alcohol with *o*-nitrobenzenesulfonylhydrazine (NBSH) followed by in situ elimination of nitrobenzenesulfinic acid to form a monoalkyl diazene as an intermediate.[1] The diazene does not persist in solution, but undergoes fragmentation by a free-radical mechanism to form dinitrogen and an alkane, in accord with literature precedent.[2] The new method for diazene preparation has facilitated mechanistic studies, described herein, that have elucidated details of the fragmentation pathway. Of particular interest, we find that monoalkyl diazenes are more reactive as hydrogen-atom donors toward alkyl radicals than tri-*n*-butyltin hydride.



The transformation of 2-(2-naphthalenyl)ethanol to 2-ethylnaphthalene exemplifies the method of diazene formation and fragmentation. Diethylazodicarboxylate (DEAD, 2.0 equiv) was added to a deoxygenated solution of 2-(2-naphthalenyl)ethanol (1 equiv) and triphenylphosphine (2.0 equiv) in tetrahydrofuran (THF) at –30 °C. After 20 min, a solution of NBSH (3.0 equiv) in THF was added, the mixture was stirred for 2 h at –30 °C, then was warmed to 23 °C where 2-ethylnaphthalene was formed (83% yield as determined by capillary GC analysis). Monitoring of the latter reaction (conducted in THF-d_8) by ^{1}H NMR spectroscopy revealed that the Mitsunobu displacement occurred at –30 °C and that the resulting *N*-alkyl sulfonylhydrazine intermediate was stable below

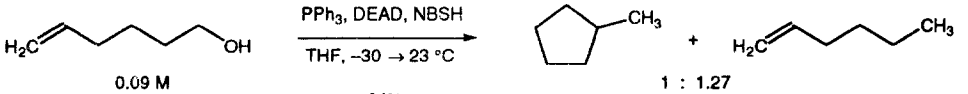
−15 °C. At 0 °C slow elimination of *o*-nitrobenzenesulfinic acid took place ($t_{1/2}$ >1 h) to form the monoalkyldiazene intermediate, characterized by a diagnostic ^{1}H NMR signal at δ 15.6 ppm for the diazenyl proton. Elimination of *o*-nitrobenzenesulfinic acid was much more rapid at 20 °C. At this temperature the diazene intermediate was observed to fragment as it was formed, such that the diazene did not accumulate in solution. After 10 min at 20 °C the distribution of diazene, Mitsunobu adduct, and 2-ethylnaphthalene in solution was approximately 1:2:2, respectively, and after 40 min at 20 °C the deoxygenation was complete.

The mechanism of the deoxygenation reaction was shown unequivocally to involve free-radical intermediates by both radical fragmentation and cyclization experiments.[1a] Kosower has proposed a straightforward pathway for the free-radical decomposition of monoalkyl diazenes in which the key propagating step involves hydrogen-atom transfer from the monoalkyl diazene to the alkyl radical intermediate.[2] Because the concentration of monoalkyl diazene is not high under the conditions of our experiments, we conducted labeling experiments in order to verify that the diazene N-H bond was, in fact, the hydrogen-atom donor in the transfer reaction as opposed to, e.g., the solvent tetrahydrofuran. The latter possibility was discounted by the observation that <2% of deuterium was incorporated into the product 2-ethylnaphthalene when 2-(2-naphthalenyl)ethanol was deoxygenated in THF-d_8. Evidence that the diazene intermediate was the direct hydrogen-atom donor was obtained by deuteration of both the hydroxylic proton of the substrate and the amino



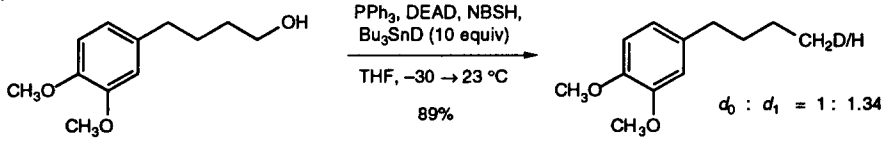
protons of NBSH. Although quantitative deuteration of these reactants was difficult to achieve (because of the sensitivity of the experiment to adventitious moisture), in the most favorable case 76% of deuterium was incorporated within the product, 2-ethylnaphthalene, supporting the direct hydrogen-atom transfer mechanism of Kosower.[2]

Several lines of evidence suggest that monoalkyl diazenes are exceptionally reactive as hydrogen-atom donors toward alkyl radicals, even surpassing tri-*n*-butyltin hydride in reactivity. A classic "radical clock" experiment was conducted to measure the rate of hydrogen-atom transfer (k_H).[3,4] Deoxygenation of 5-hexen-1-ol, as described above, afforded a 1.27:1 mixture of 1-hexene and methylcyclopentane, respectively, in 64%

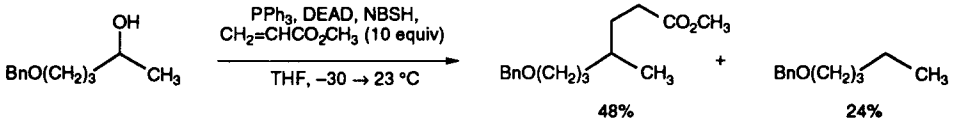


combined yield. The value of k_H can be approximated using the equation k_H = observed ratio × 2.3 × 10^5 s^{-1}/[RN=NH], provided that the concentration of the hydrogen-atom donor (monoalkyl diazene) in solution is known.[3,4] The maximum theoretical value of monoalkyldiazene in solution under the conditions of this

experiment is the same as the concentration of substrate at time zero (0.09 M), providing a lower limit for the value of k_H (3.2×10^6 M^{-1} s^{-1} at 23 °C). For comparison, the rate of hydrogen-atom transfer from tri-*n*-butyltin hydride to the *n*-butyl radical is 2.4×10^6 M^{-1} s^{-1} at 27 °C.[4] This ordering of rate constants was corroborated in a competition experiment in which the deoxygenation of 4-(3,4-dimethoxyphenyl)-1-butanol was conducted in the presence of tri-*n*-butyltin deuteride ($k_D = 1.2 \times 10^6$ M^{-1} s^{-1} for *n*-butyl radical at 27 °C).[4] For competitive deuteration to occur it was necessary to use a 10-fold excess (0.94 M) of *n*-Bu_3SnD (ratio of d_1:d_0 = 1.34:1, 89% yield).



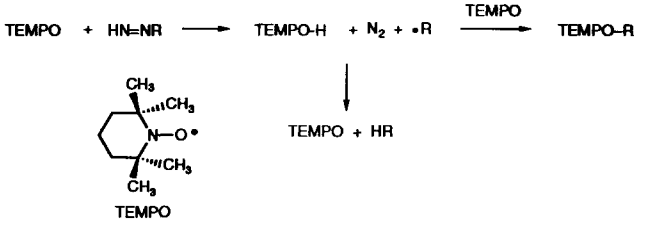
Further confirmation of the reactivity of monoalkyl diazenes as hydrogen-atom donors was obtained in competition experiments with methyl acrylate. Deoxygenation of the secondary alcohol 5-benzyloxy-2-pentanol in the presence of methyl acrylate required 10 equiv of the latter reagent for appreciable trapping by acrylate to



occur. Under these conditions the yield of the simple deoxygenation product, 1-benzyloxypentane, was 24% and the yield of acrylate monoadduct, methyl 7-benzyloxy-4-methylheptanoate, was 48%. For comparison, the rate of addition of the primary radical 5-hexen-1-yl to methyl acrylate is 2.1×10^5 M^{-1} s^{-1} at 25 °C,[5] and for cyclohexyl radical $k = 2.68 \times 10^5$ M^{-1} s^{-1} at 20 °C.[6]

In the presence of 1 atmosphere of dioxygen (~ 0.01 M,[7] $k_{lit} = 4.15 \times 10^9$ M^{-1} s^{-1} at 22 °C for combination of O_2 with ethyl radical)[8] hydrogen-atom transfer to alkyl radical intermediates was supressed completely; trapping by molecular oxygen occurred exclusively,[1a] as anticipated by comparison of the respective rate constants. Surprisingly, such was not the case for deoxygenation reactions conducted in the presence of the "stable" free radical 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO, $k_{lit} = 1.23 \times 10^9$ M^{-1} s^{-1} at 20 °C for combination with *n*-nonyl radical).[9] For example, deoxygenation of 4-(3,4-dimethoxyphenyl)-1-butanol (0.10 M) in the presence of 1 equiv of TEMPO led to almost equal amounts of the TEMPO adduct (49% yield) and the deoxygenation product, 1-(3,4-dimethoxyphenyl)-butane (45% yield). With a 10-fold excess of TEMPO the yield of the TEMPO adduct was 93% and only 4% of the deoxygenated product was obtained. The observed product ratios are inconsistent with a simple competition for the alkyl radical between trapping with TEMPO and hydrogen-atom transfer from the diazene intermediate, given the proposed rate of hydrogen-atom transfer (~1000-fold slower than trapping by TEMPO). We propose a different mechanism for hydrocarbon formation in the presence of TEMPO, one involving hydrogen-atom transfer from the monoalkyl diazene intermediate to TEMPO followed by loss of dinitrogen and re-abstraction of hydrogen by the alkyl radical from *N*-hydroxy-2,2,6,6-tetramethylpiperidine. In essence, it is proposed that TEMPO is not an inert free radical in the presence of monoalkyl diazenes, rather, that it catalyzes their decomposition.[10] Consistent with this view, it is observed

that the presence of TEMPO in the deoxygenation reaction greatly accelerates the rate of diazene decomposition in solution versus reactions lacking TEMPO.



The results presented herein provide strong evidence that the rate of hydrogen-atom transfer from the monoalkyl diazenes that we have studied to the corresponding alkyl radicals is on the order of 3.2×10^6 M^{-1} s^{-1}, or slightly greater. We suggest that the facility of this transfer reaction reflects the fact that dinitrogen is appreciably formed in the transition state for hydrogen-atom transfer. That is to say, the loss of dinitrogen is concerted or nearly concerted with hydrogen-atom transfer. This need not be the case with less stable radicals such as methyl or cyclopropyl.[11] The apparent stability of methyldiazene and cyclopropyldiazene, as described by Kosower, when compared to the monoalkyl diazenes that we have studied may be reflective of this.

Acknowledgment Generous support from the National Science Foundation is gratefully acknowleged.

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(*Received in USA* 17 *June* 1997; *accepted* 17 *July* 1997)