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Azo bond hydrogenation with hydrazine, R–$NHNH_2$, and hydrazobenzene

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Abstract

Hydrogenation of azo bonds with hydrazine, mono-substituted hydrazine, and hydrazobenzene was studied with selected diazene compounds under oxygen-free conditions. The reactions proceed rapidly and in high yield in several solvents, utilizing all N–H protons. While the reduction process is accompanied by the evolution of nitrogen gas in the case of N_2H_4, the intermediacy of diimide could not be confirmed by standard trapping experiments.

1. Introduction

The direct reduction of unsaturated bonds in certain carbonyl and nitro functionalities with hydrazine is an established technique.[1,2a] The indirect reduction of the non-polar, unsaturated bonds in olefins is achieved by the decomposition of hydrazine derivatives to diimide (or diazene, HN=NH).[3] In the presence of oxygen or hydrogen peroxide, and with metal salt (e.g., Cu^{2+}) catalysis, hydrazine also reduces olefins.[4–8] This is attributed to diimide formation rather than a direct reduction by hydrazine.[9]

In a recent communication, an apparent direct reduction of azo compounds with hydrazine is reported.[10] The procedure utilizes hydrazine in approximately a 100:1 ratio to the azo compound. The reactions are done in ethanol at 60 °C with no mention of an attempt to exclude exposure to air. In connection with a program to synthesize energetic triazinyl diazenes, we also observed their reduction to hydrazo compounds in the course of using hydrazine to displace leaving groups at the 4,6 positions of the triazine rings linked by azo bonds.[11] We present here the first investigation of the hydrogenation of azo compounds by hydrazine with the exclusion of oxygen or other oxidizing agents. Under these conditions, the reduction appears to occur by a pathway different from that commonly accepted for olefins. An efficient reduction is observed with a minimum quantity of hydrazine, whereas the common practice is to use a substantial excess of hydrazine or hydrazine derivatives. An excess of reducing reagent is used because of the disproportionation of the intermediate diimide, which is assumed to be the actual reducing agent.[3] Our experiments with less than a molar equivalent of hydrazine suggest that all the hydrogens from hydrazine are efficiently utilized. These anaerobic experiments appear to involve a direct reduction with hydrazine, whereas the previous report of azo bond reduction with hydrazine likely involved an indirect reduction through the diimide intermediate.

2. Results

We investigated the reduction reaction with triazinyl diazenes having structural variations, which revealed varying degrees of reactivity, as well as azo compounds with attached alkyl, phenyl, and carbonyl functional groups (Fig. 1). Diazenes that were relatively electron deficient were rapidly reduced in the presence or absence of oxygen, whereas exposure to air was required for the reduction of azobenzene. The effect of using substituted hydrazines as

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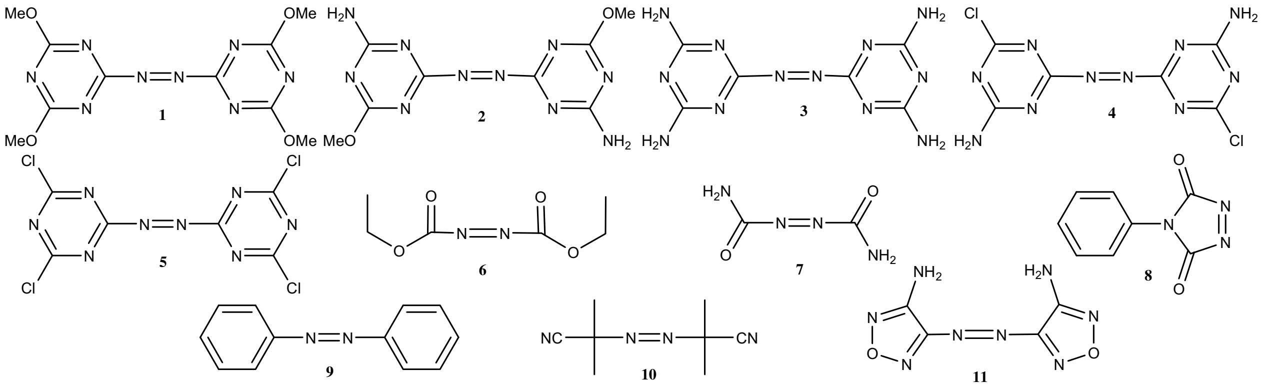

Fig. 1. Synthesized and commercial diazenes used in this study.

reducing agents was also investigated. Although this has not been previously reported, we found that phenylhydrazine, for example, was also an effective reducing agent (Table 1). Hydrazine, substituted hydrazines, and hydrazobenzene react rapidly under anaerobic conditions with electron-deficient azo compounds to convert the colored azo compounds to colorless hydrazo products, accompanied the evolution of gas. The headspace gases produced from the reaction of **1** and hydrazine or phenylhydrazine, when analyzed by gas chromatography/mass spectrometry (GC/MS), confirmed that the effervescence observed was due to the production of nitrogen.

Our reduction experiments were conducted primarily in acetonitrile, but the use of chloroform, alcohols, and toluene afforded the same outcome. Several experiments were conducted in ethanol as a comparison to the reductions reported by Wang.[10] The hydrazine reagent was in some cases pre-dissolved in acetonitrile to enhance its mixing with chloroform solutions of an azo substrate. Several experiments with **1**, **6**, and **7**, done in the absence of ultraviolet light, did not affect the outcome, implying a reaction initiating from a transient *cis*-diazene is not a requirement.

The reduction was accompanied by a rapid loss of the initial color and the evolution of a gas. The color loss is the expected as a result of loss of the π-bond connection between the substituents of the diazene. Depending on the compound, complete reaction was achieved in seconds to many hours. The rate of reduction could not in all the cases be reliably linked to the activation of the azo bond due to the electron-withdrawing properties of the functional group or ring system to which it was bonded because some of the reactants were only marginally soluble in the chosen solvent. The reaction rate, as qualitatively observed by effervescence, remained unchanged when the hydrazine reagent was stoichiometrically limited. The reduction of diazenes achieved full conversion, even when the reaction took several hours, with only one-half an equivalent of hydrazine. Diimide lacks the stability to achieve this efficiency over long reaction times.[3]

The comparison of the homogeneous reductions of azobenzene **9** and tetramethoxy-substituted triazinyl diazene **1** does show a dramatic difference in reactivity. The more electron-deficient azo bond in **1** results in decolorization in minutes at ambient temperature to give a 92% yield of the reduced product. Azobenzene does not react in 18 h, or after 6 h of heating at 60 °C (Table 1). Compounds **2** and **4**, with 1 M equiv of hydrazine, displayed selective reduction of the diazene and no displacement of the chloro or methoxy substituents. Compound **3** was the least reactive of the triazinyl diazenes, which may be chiefly attributable to the deactivating amino groups, but its low solubility would also contribute to the rate of reduction. Compound **5** showed very rapid elimination of its deep red color on the addition of hydrazine at -10 °C. The reduction of the azo bond took place without the displacement of the chloro substituents. Diethyl azodicarboxylate **6** also was reduced rapidly and in high yield. This reduction was observed in 1895 and again in 1957, but the reaction specifics were not detailed.[12,13] Azodicarbonamide **7** also reacted with hydrazine efficiently and quickly to yield biurea. The rate was somewhat slower than **6**. The related cyclic amide **8** presented the shortest reaction time of all the compounds studied. It is the only compound in this study which contains a highly activated azo bond in the cis conformation.

The elimination of oxygen prevents azobenzene, **9**, from reacting with hydrazine. Azobenzene was unreactive with 20 and 100 M equiv of hydrazine, in both ethanol and acetonitrile without atmospheric oxygen, even at elevated temperatures. When the azobenzene reaction is exposed to the atmosphere, it proceeds, and with increasing rate with greater hydrazine concentration. A considerable excess of hydrazine is required to complete the reaction in a few hours, but the reduction of azobenzenes does not require heating in ethanol as done in a previous report.[10] (Contradictory to our findings and those of Wang, Pasha reported that diazene cleavage rather than the reduction that occurred under similar conditions.[14]) Under anaerobic conditions azoisobutyronitrile, **10**, and azo(bis-aminofurozan), **11**, are resistant to hydrazine reduction.

We found that hydrazobenzene could be quickly and efficiently oxidized to azobenzene while reducing diazene compounds. The yield was similar to our other experiments, and the azobenzene produced was also recovered.

Table 1
Summary of the reduction reactions

ID	Hydrazine reagent	M equiv	Solvent	Yield (%)	Time
1	NH_2NH_2	1	ACN	92	20 m
		1	EtOH	97	4 h
		0.5	ACN	90	20 m
		0.5	$CHCl_3$	90	10 m
		0.5	EtOH	93	10 m
	Me–$NHNH_2$	0.66	$CHCl_3$	83	10 m
	Ph–$NHNH_2$	0.5	ACN	63	20 m
		1	ACN	94	15 m
	HOEt–$NHNH_2$	0.66	$CHCl_3$	75	20 m
	Ph–NHNH–Ph	1	ACN	94	15 h
		1	EtOH	94	15 h
2	NH_2NH_2	1	ACN	94	2 h
3	NH_2NH_2	1	ACN	98	7 d
4	NH_2NH_2	1	ACN	100	18 h
5	NH_2NH_2	1	ACN	n/a[a]	2 m
	NH_2NH_2	0.5	ACN	87	2 m
6	NH_2NH_2	1	ACN	100	10 m
		1	Toluene	99	5 m
		0.5	ACN	89	1 m
	Me–$NHNH_2$	0.66	ACN	88	1 m
	Ph–$NHNH_2$	0.66	ACN	74	30 m
	Ph–NHNH–Ph	1	ACN	86	1 h
7	NH_2NH_2	1	ACN	98	1.5 h
		0.5	ACN	98	18 h
		0.5	$CHCl_3$	98	8 h
	Me–$NHNH_2$	0.66	ACN	87	4 h
	Ph–$NHNH_2$	1	ACN	95	8 h
	HOEt–$NHNH_2$	0.66	ACN	81	2 h
		0.66	EtOH	95	15 h
8	NH_2NH_2	1	ACN	99	<1 m
		0.5	ACN	96	1 m
9	NH_2NH_2	100	EtOH	NR	3 d[b]
	NH_2NH_2/O_2	100	EtOH	97	3.5 h
		10	EtOH	94	24 d
	NH_2NH_2	1	ACN	NR	18 h
				NR	6 h[c,d]
	NH_2NH_2	1	EtOH	NR	18 h
				NR	6 h[c]
	NH_2NH_2/O_2	1	EtOH	NR	18 h
				NR	2 d[c]
	Ph–$NHNH_2$	1	ACN	NR	2 h
				NR	18 h[c,d]
10	NH_2NH_2	1	ACN	NR	18 h
		1	ACN	NR	18 h[c]
11	NH_2NH_2	1	ACN	NR	7 d

[a] Excess hydrazine causes rapid polymerization.
[b] Subsequent venting to air gave 94% in 2 h.
[c] Reactions performed at 60 °C.
[d] Subsequent venting to air gave NR.

However, the color loss of the diazene was masked by the color of azobenzene, and no effervescence was observed. It was therefore difficult to qualitatively measure the reaction progress, and the reaction times reported may not reflect the time necessary for full conversion.

3. Discussion

The possible role of oxygen in the hydrazine reductions that we initially observed in our triazinyl diazene synthesis reactions led us to use anaerobic conditions in investigating these reactions so that we could eliminate the complication of possible simultaneous direct and indirect reduction pathways. The autoxidation of hydrazine with oxygen occurs to some degree without catalysis by metal ions, but hydrazine oxidation in synthetically useful procedures is usually done in the presence of catalysts.[2b] It was initially assumed that diimide was the active species in the reduction of the diazenes. However, the elimination of oxygen did not stop the reduction. Furthermore, the stoichiometry suggested that all four hydrogens from hydrazine are available for delivery. These observations led us to believe the published diimide mechanism was not solely operative. To probe for the evidence of diimide generated in situ by the action of the highly electron-deficient azo linkage, the reaction was conducted in the presence of an olefin. However, our diazene reactions conducted with *cis*- or *trans*-stilbene or diphenylacetylene were unaffected even when severe molar excesses were employed. Additionally, the reduction of acetonitrile solvent was not observed offering no evidence for a diimide intermediate.[4] Wang's conditions (hydrazinous ethanol) including a labile olefin,[8] effectively yield the saturated product indicating in situ diimide generation.

An insertion mechanism was considered as a possible route to the overall reduction. Although such a mechanism would be indistinguishable from the reduction when using hydrazine, a two-step insertion and then the ejection of the original linkage are less plausible with substituted hydrazines. Reacting substituted hydrazines with **1**, **6**, or **7** produced the reduced product and effervescence (N_2), but no substituted triazinyl hydrazines that would indicate an insertion of hydrazine into the C–N bond. When phenylhydrazine was used as the reducing agent, azobenzene, benzene, nitrogen, and biphenyl were identified by GC/MS. While these match the expected decay products resulting from the oxidation of phenylhydrazine to phenyldiazene (Ph–N=NH),[15] we were unable to obtain any UV evidence for a phenyldiazene intermediate. Unlike diimide, phenylhydrazine or hydroxyethylhydrazine, when oxidized to substituted diazenes (R–N=NH), show no reaction with olefins,[6] and delivery of the final hydrogen is not adequately described by the published mechanisms. Nevertheless, even in aprotic solvents, reactions with 2/3rd M equiv fully reduced our diazenes even when the reaction took several hours.

The azobenzene experiments suggest that the effectiveness of oxygen in promoting the reduction is greater than would be expected if it is proceeding through the simple oxidation of hydrazine to diimide. The admission of air to a solution that was standing for three days without reaction resulted in the isolation of hydrazobenzene in 94% yield after 2 h exposure. This efficiency in the apparent air oxidation of hydrazine indicates that the azo-bond in azobenzene has an activating effect on hydrazine that facilitates its oxidation to form the diimide (shown to be only slowly generated in air/hydrazine mixes without the help of catalysts). In notably electron poor diazenes, the activation is such that oxygen is not a requirement to yield a reductive species. However, our experiments show that a diimide species, if generated, is not available to susceptible olefins (stilbenes) in the reaction mixture.

4. Conclusions

We have shown that all N–H hydrogens of hydrazine and several substituted hydrazines (methyl-, hydroxyethyl-, and phenyl-hydrazine) and hydrazobenzene are efficiently delivered to highly electron poor diazenes under mild conditions, in a variety of solvents. No evidence was found for diimide generated in situ. The difference in reactivity between these diazenes and azoarenes in the absence of oxygen, coupled with stoichiometry observed when using substituted hydrazines, indicates a previously unstudied mechanism.

While we have discussed the role of hydrazine as a reducing agent, we should also consider our observations in terms of the behavior of diazenes as oxidizing agents. Such reactivity has been observed by Yoneda when using **6** as a hydrogen-abstractor, but a mechanism was not postulated nor the role of oxygen adequately examined.[16,17] Several papers have reported that **8** can be used to remove non-adjacent C–H hydrogens.[18,19] We observed a stark difference between highly electron poor diazenes, requiring no external oxygen for their reaction with hydrazines, and the more electron-rich azoarenes which required the reaction to be conducted under oxygen atmosphere. Indeed, the results suggest some hierarchy of reactivity when comparing olefins, azoarenes, and electron-poor diazenes. This continuum may include a change in mechanism which has yet to be recognized and suggests unstudied chemistry surrounding the azo functionality. It may be that further studies will find that highly electron-poor diazenes may be used as green oxidizers, offering the advantages of atom efficiency, facile workup, and mild reaction conditions.

5. Experimental

A round-bottom flask fitted with a rubber septa was charged with the starting azo compound (0.25–0.1 g) dissolved or suspended in a solvent (25 mL) and appropriate stir bar. The reaction mixture was sonicated for 10 min and then placed on a vacuum line. The reaction was freeze–thaw degassed three times with multiple backfills of inert gas. The reaction mixtures for all the compounds except (**10**) were highly colored. During the third warming of the reaction, after all the solvent ice had melted, the hydrazine compound was added via syringe. The temperature at this point was estimated to be somewhat below the room temperature, but the reaction flask was equilibrated to room temperature in only a few minutes. The hydrazine monohydrate was delivered via syringe from a sonicated 1 M solution in matching solvent where applicable. In some cases, the hydrazine monohydrate was delivered neat in microliter quantities via a gastight syringe in one portion. The reaction proceeded with effervescence over minutes to many hours. The mixture was allowed to stir under the inert gas until the loss of color indicated the reaction complete or unchanging. The resulting hydrazo compounds were typically of lesser solubility and presented themselves as a white precipitate. The solvent was removed under high vacuum and the product isolated. In the cases where the product was highly insoluble, the dry solid was reconstituted with solvent (25 mL) and immediately filtered to retrieve the solid product. Reactions deviating from this general workup are described as necessary. Properties were compared to literature spectra or authentic samples. Nuclear magnetic resonance and melting-point were primarily used for the analysis of the products but at such times when GC/MS was feasible, it was also implemented and the retention time and fragmentation matched with authentic samples.

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Supplementary data

Experimental details and spectral data for unpublished compounds. Instrument settings for chromatographic experiments. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.03.083.

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