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Cover Letter

8 February 2008

Gentlemen:

We wish to submit the manuscript entitled, "Azo Bond Hydrogenation with Hydrazine, R-NHNH$_2$, and Hydrazobenzene" by William M. Koppes, Jesse S. Moran, Jimmie C. Oxley, and James L. Smith for consideration as a publication in Tetrahedron Letters. This study is the first to investigate the hydrogenation of azo compounds by hydrazine with the exclusion of oxygen or other oxidizing agents. Oxygen elimination indicates the reaction proceeds through a pathway different from that commonly accepted for olefins (diimide). We have found that substituted hydrazines behave similarly and that there is a disparity between highly electron poor diazenes and azobenezenes. Several mechanistic implications are explored. We would be pleased to have this material published in Tetrahedron Letters. Thank you for your time and consideration.

Sincerely,
Jimmie C Oxley

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Graphical Abstract

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Azo Bond Hydrogenation with Hydrazine, R-NHNH$_2$, and Hydrazobenzene

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William M. Koppes[a], Jesse S. Moran[b]
Jimmie C. Oxley[b], James L. Smith[b]
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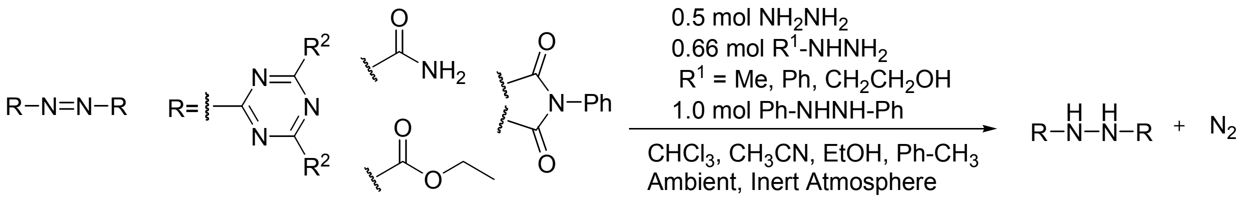
Hydrogenation of azo bonds with hydrazine, mono-substituted hydrazine, and hydrazobenzene was studied with selected diazene compounds under oxygen-free conditions. The reactions proceed rapidly and in high yield in several solvents, utilizing all N-H protons. While the reduction process is accompanied 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.



Graphical Abstract

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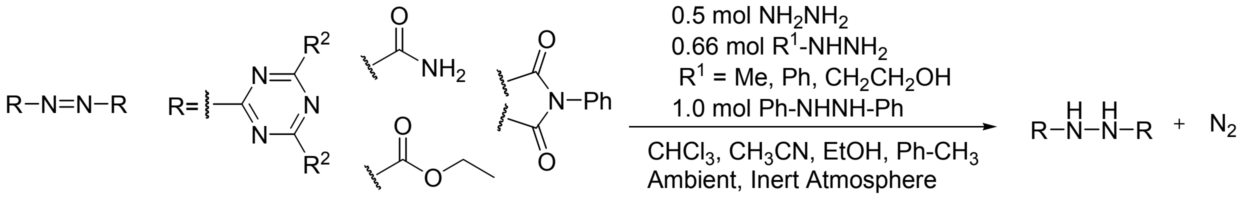

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LETTERS

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.

Direct reduction of unsaturated bonds in certain carbonyl and nitro functionalities with hydrazine is an established technique.[1,2] 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^{++}) 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 exlude 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 investigaton 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. 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 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.

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 (Figure 1). Diazenes that were relatively electron deficient were rapidly reduced in the presence or absence of oxygen, whereas, exposure to air was required for reduction of azobenzene. The effect of using substituted hydrazines as 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 and substituted hydrazines react rapidly under anerobic 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 the effervescence observed was due to the production of nitrogen.

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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] Hydrazine reagent was in some cases pre-dissolved in acetonitrile to enhance its mixing with chloroform solutions of an azo substrate.

Reduction was accompanied by rapid loss of the initial color and the evolution of a gas. The color loss is the expected result of loss of the π–bond connection between the substiutents of the diazene. Depending on the compound, complete reaction was achieved in seconds to many hours. The rate of reduction could not in all cases be reliably linked to 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.

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 reduced product. Azobenzene does not react in 18 h, or after 6 h of heating at 60^{o}C (Table 1). Compounds **2** and **4**, with one molar equivalent 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 contribute also to the rate of reduction. Compound **5** showed very rapid elimination of its deep red color on addition of hydrazine at -10^{o}C. Reduction of the azo bond took place without 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 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.[2a] Wang reported the reduction of a series of azobenzene derivatives using an excess of hydrazine with no mention of an attempt to exlude exposure to air.[10] Replication of those conditions in the absence of oxygen prevents azobenzene, **9**, from reacting with hydrazine. Azobenzene was unreactive with 20 and 100 molar equivalents of hydrazine, in both ethanol and acetonitrile without atmospheric oxygen, even at elevated temperatures. [Under anaerobic conditions azoisobutyronitrile, **10**, and azo(bis-aminofurozan), **11**, are resistant to hydrazine reduction.] However, 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 the previous report. Wang's conditions (hydrazinous ethanol) including a labile olefin[8], effectivily yields the saturated product indicating *in situ* diimide generation. 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]

When using phenylhydrazine, no UV-Vis evidence of a long lived phenyldiazene (Ph-N=NH) was found but its decay products (azobenzene and biphenyl) described by Huang were evident by GC/MS analysis of the reaction mixture.[14] 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 adquately described by published mechanisms. Nevertheless, reactions with 2/3rd molar equivalents fully reduced our diazenes. The initial transfer from phenylhydrazine may be the rate-determining step, owing to a fleeting presence of phenyldiazene. Reactions with excess phenylhydrazine yield similar effervesence, indicating the nitrogen containing intermediate is short lived. Reacting subsituted hydrazines with **1**, **6**, or **7** produced the reduced product and effervesence (N_2), but no substituted triazinyl hydrazines that would indicate an insertion of hydrazine into the C-N bond. Under conditions similar to Wang, Pasha reports fission of the diazene linkage of azobenzenes.[15] However, when azoxybenzene is subjected to an Al or Sn/NH_2NH_2 mixture refluxing in ethanol, azobenzene is returned with no hydrazobenzene or fission products.[16,17] Again, both reports do no limit atmospheric oxygen but starkly disaggree on the reduction potential of the hydrazine reagent.

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. Admission of air to a solution that was standing for three days without reaction resulted in the isolation of hydrazobenzene in 94% yield after two hours exposure. This efficiency in the apparent air oxidation of hydrazine may be explained by an initial complex formed between azobenzene and hydrazine that facilitates the oxidation of the hydrazine to form the diimide reducing agent (Scheme 1 A). The strength of this complex may be dependent on the electronegativity of the diazene and determine the succeptibility of hydrazine oxidation. Highly electron poor diazenes could permit their role as the oxidizing agent for hydrazine and therefore not require oxygen (Scheme 1 B). The attraction of two diazene molecules to one hydrazine species would lead to "sandwich" system which would prevent a diimide species from being available to "external" olefins. Several experiments with **1**, **6**, and **7**, done in the absence of ultraviolet light, did not effect the outcome, implying a reaction initiating from a transient *cis*-diazene is not a requirement.

Finally, hydrazobenzene could be quickly and efficiently oxidized to azobenzene while reducing diazene compounds. Such reactivity has been observed by Yoneda when using **6** as a hydrogen-abstractor, but a mechansim was not postulated nor the role of oxygen adquately examined.[18,19] Recently, Klindert and Christoforou have exposed the similar dehydrogenating properties of **8**.[20,21] These reactions are interesting as they proceed from non-adjacent C-H hydrogens. While have shown that all four hydrogens of hydrazine are deliverable, the reactions with substituted hydrazines do not lend themselves easily to traditional insertion or hydrogen transfer mechanisms. No evidence was found for diimide generated *in situ* or rapid rearrangment of radical intermediates to "diimide-like" species. An initial diazene-hydrazine complex is postulated to promote the oxidation and hydrogen transfer from hydrazine through a mechanism that explains differences in reactivty but will necessitate further work.

Experimental

A round bottom flask fitted with rubber septa was charged with the starting azo compound (0.25-0.1 g) dissolved or suspended in solvent (25 mL) and appropriate stir bar. The reaction mixture was sonicated for ten minutes 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 compounds except (10) were highly colored. During the third warming of the reaction, after all solvent ice had melted, the hydrazine compound was added via syringe. The temperature at this point was estimated to be somewhat below room temperature but the reaction flask was equilibrated to room temperature in only a few minutes. The hydrazine monohydrate delivered via syringe from a sonicated one molar 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 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 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. The use of 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.

Acknowledgement

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Supplementary Material

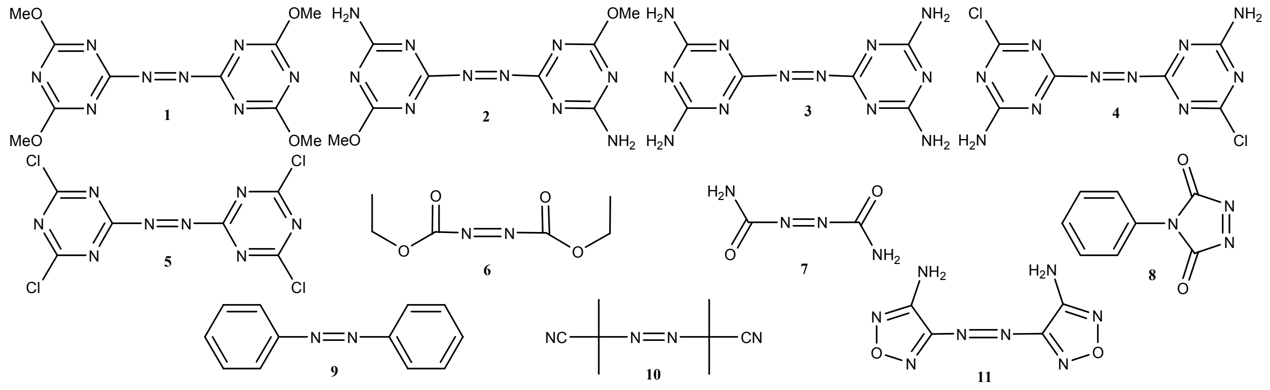
Experimental details and spectral data for unpublished compounds. Instrument settings for chromatographic experiments.

Table 1. Summary of the Reduction Reactions

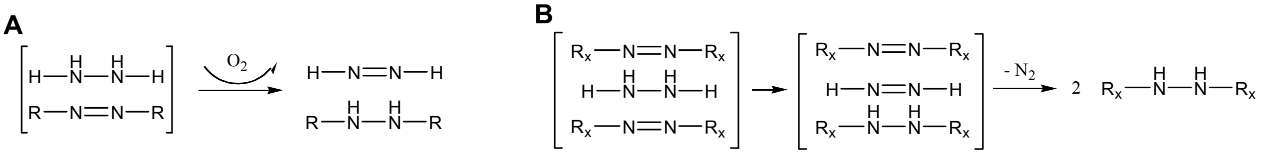
ID	hydrazine reagent	molar equiv.	solvent	yield (%)	time
1	NH_2NH_2	1	ACN	92	20 m
		1	EtOH	97	4 h
		0.5	ACN	90	20 m
		0.5	$CHCl_3$	90	10 m
		0.5	EtOH	93	10 m
	Me-$NHNH_2$	0.66	$CHCl_3$	83	10 m
	Ph-$NHNH_2$	0.5	ACN	63	20 m
		1	ACN	94	15 m
	HOEt-$NHNH_2$	0.66	$CHCl_3$	75	20 m
	Ph-NHNH-Ph	1	ACN	94	15 h
		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 hr
	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

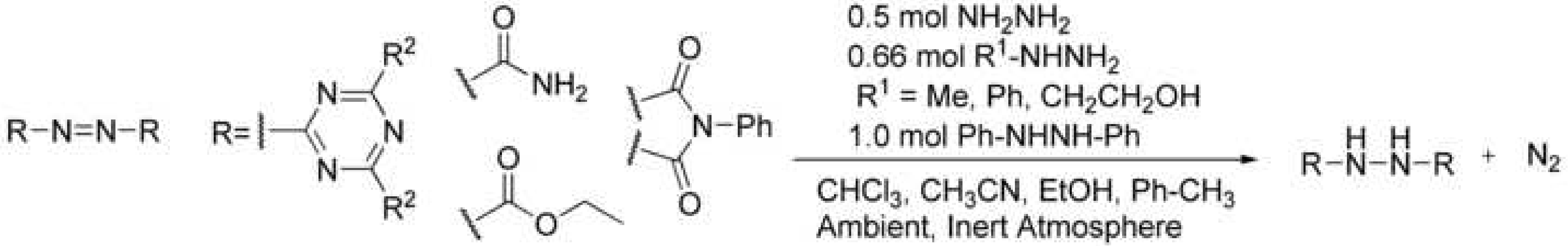
[a] Excess hydrazine causes rapid polymerization. [b] Subsequent venting to air gave 94% in 2 hr. [c] Reactions performed at 60°C. [d] Subsequent venting to air gave NR.

Figure 1. Synthesized and commercial diazenes used in this study



Scheme 1. Reductions on R-N=N-R where the R group is more electropositive (A) or where the Rx group is more electronegative (B)




R−N=N−R
R=
R²
N
N
N
R²
O
NH₂
O
O
O
N−Ph
O
0.5 mol NH₂NH₂
0.66 mol R¹-NHNH₂
R¹ = Me, Ph, CH₂CH₂OH
1.0 mol Ph-NHNH-Ph
CHCl₃, CH₃CN, EtOH, Ph-CH₃
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+
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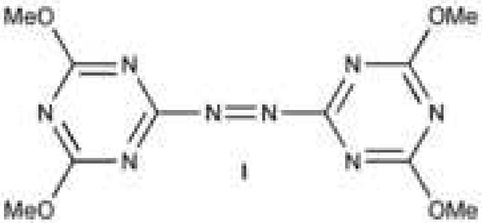
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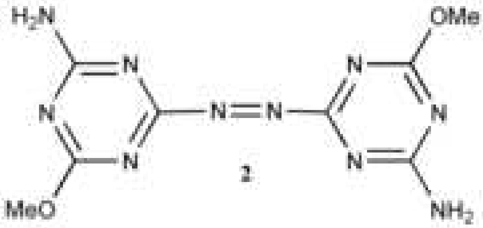
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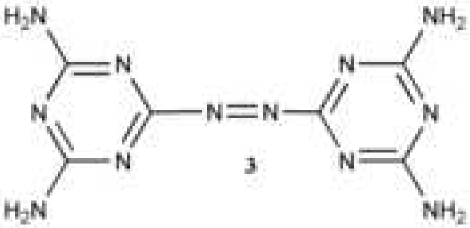
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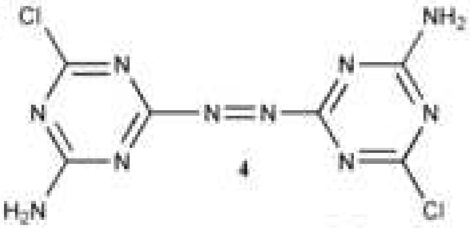
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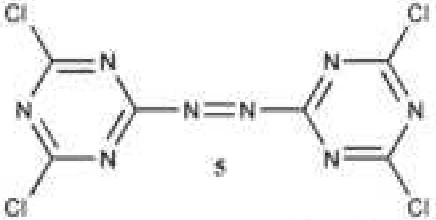
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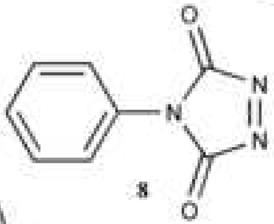
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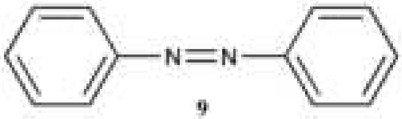
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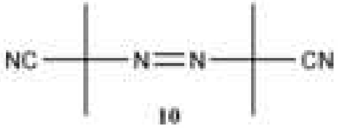
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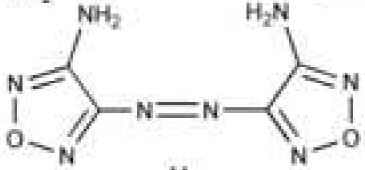
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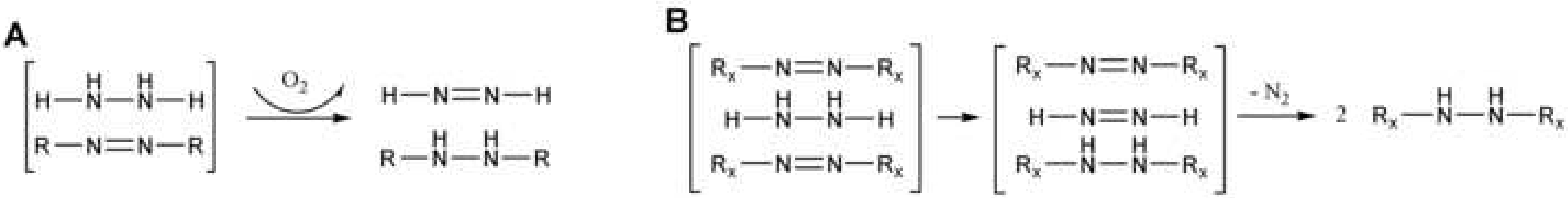
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