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Lithium Aluminum Hydride Reduction of N-Aziridinylimines to Hydrocarbons

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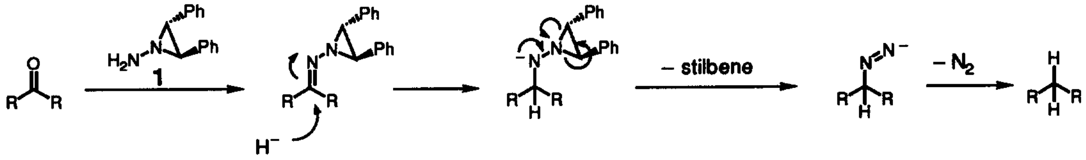
Summary: *The hydride reduction of ketone and aldehyde N-aziridinylimines is reported. Unlike most other hydrazone reductions, the reaction proceeds at room temperature under non-acidic conditions, providing an unusually mild carbonyl-to-methylene conversion.*

Methods for the deoxygenation of ketones and aldehydes under conditions that are compatible with highly functionalized substrates have been sought for many years. The classical Clemmensen[1] and Wolff-Kishner[2] reductions have been successfully applied to many alkyl and aryl ketones and aldehydes, but these procedures and their modifications employ strongly acidic or basic conditions, which can limit their applicability in functionally complex molecules.

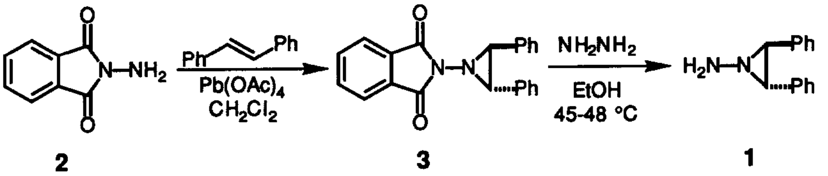
The need to accomplish this important synthetic transformation under milder conditions has led to the exploration of a variety of indirect methods. For example, ketones or aldehydes can first be reduced to the corresponding alcohol, followed by conversion to a halide or sulfonate ester and subsequent hydride reduction to the corresponding hydrocarbon.[3] Thioacetals and thioketals offer an appealing alternative; desulfurization can be achieved by a variety of methods,[4] the most common being hydrogenolysis with Raney nickel,[5] alkali metals,[6] or tri-*n*-butyl tin hydride.[7] Organosilanes and gaseous boron trifluoride have also been employed to convert ketones into methylene groups,[8] but this method, which involves hydride transfer from the silane to a carbenium ion, affords the primary alcohol with aldehydes.

Since Cagliotti first communicated successful hydride reductions of tosyl hydrazones in 1963,[9] a number of variants of that procedure have been reported for ketone-to-methylene conversion. Hutchins found that the use of $NaBH_3CN$ allows the *in situ* generation of the tosylhydrazone and subsequent reduction to the hydrocarbon.[10] Functional groups such as esters, nitriles, amides, and chlorides are unaffected, but relatively high temperatures (100°C) and strong acid are required. It was later reported that higher overall yields of hydrocarbons are obtained if the hydrazones are isolated, rather than generated *in situ*, prior to reduction with sodium cyanoborohydride[11] or sodium borohydride[12] in acidic media. The nucleophilic reagent bis(triphenylphosphine) copper (I) tetrahydroborate,[13] as well as electrophilic agents such as catechol borane[14] or bis(benzyloxy)borane,[15] have also been employed with some success to reduce tosylhydrazones.

We sought a variant of these reactions that would proceed at relatively low temperature under non-acidic conditions, produce easily separable by-products, and require only a simple readily available hydride source. Reports that the thermolysis of the aziridinylimines derived from β-epoxy ketones undergo the Eschenmoser fragmentation[16] prompted us to consider the use of such hydrazones for this purpose. Further evidence that these derivatives should behave similarly to tosylhydrazones—but react at lower temperatures—was provided by reports that hydrazones formed from N-amino aziridines undergo the Shapiro elimination[17] and the Bamford-Stevens reaction.[18] Based on these precedents, aziridinylimines should also be susceptible to hydride reduction. For example, reduction of *trans*-1-amino-2,3-diphenyl aziridine-derived hydrazones under neutral conditions would be expected to afford the corresponding hydrocarbon, gaseous nitrogen, and *trans*-stilbene.

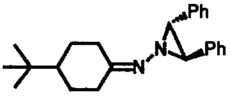
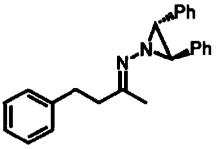
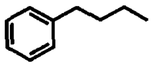
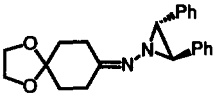
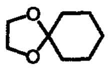
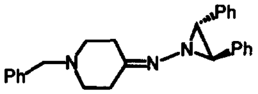
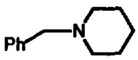
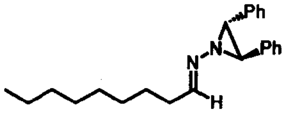


To test this scheme, the hydrazine derivative **1** was prepared following modifications of procedures previously published by Eschenmoser.[16a] Although it can be purchased commercially, the N-aminophthalimide **2** was prepared on large scale from phthalimide. Generation of the phthalimido nitrene by treatment of **2** with lead tetraacetate in the presence of *trans*-stilbene afforded the N-phthalimido aziridine **3** in moderate yield. Hydrazinolysis then yielded the *trans*-2,3-diphenyl N-amino aziridine **1** as white crystals. This product undergoes decomposition at room temperature, and must be stored at -20 °C.



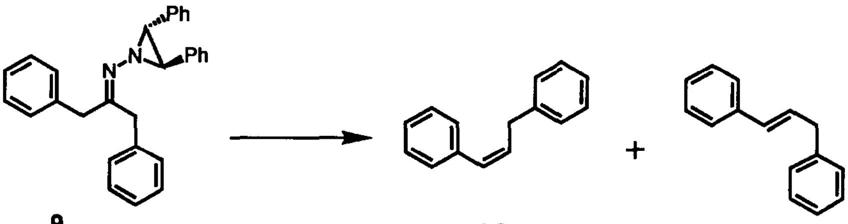
To test the proposed reduction, several representative hydrazones, **4-8** (Table), were prepared by condensation of the N-amino aziridine **1** with ketones or aldehydes in dichloromethane at 0 °C. The ketone derivatives shown could be purified by radial chromatography in yields ranging from 82-97%. The aldehyde gave a slightly lower yield (68%). Reductions were attempted with a number of hydride sources, but lithium aluminum hydride at room temperature proved to be the most satisfactory. Reactions were conducted on a small scale and analyzed by gas chromatographic comparison with authentic samples of each product. The hydrazones of t-butylcyclohexanone (**4**), benzyl acetone (**5**), and nonyl aldehyde (**8**), afforded the highest yields of reduced products, while yields for the more highly functionalized substrates derived from benzyl piperidone (**6**) and cyclohexadione monoethylene ketal (**7**) were somewhat lower. These yields, while modest, parallel those reported for tosyl hydrazone reductions.

Table 6. Reduction of Hydrazones with $LiAlH_4$

Hydrazone	No.	Product	%Yield[a]
	4		81
	5		59
	6		48
	7		44
	8		65

a. Yields were determined using an internal standard and detector response factors

For all of the examples shown in the Table, GC/MS analysis revealed only traces of the corresponding alkene products, which can be formed by competing Shapiro elimination.[19] However, treatment of the hydrazone of diphenyl acetone, **9**, with lithium aluminum hydride afforded predominently the elimination product as a mixture of isomers **10** and **11**, presumably because of the relatively acidic α-protons.



9 **10** **11**

In conclusion, we believe that this procedure is a useful alternative to existing hydrazone reductions. Reduction yields are moderate but compare well with those observed for related reactions under more drastic conditions. The precursors are easily prepared, and the reaction proceeds under non-acidic conditions to give hydrocarbons without the need of specialized reducing agents or elevated temperatures.

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