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On the Mechanism of the Wolff-Kishner Reduction#

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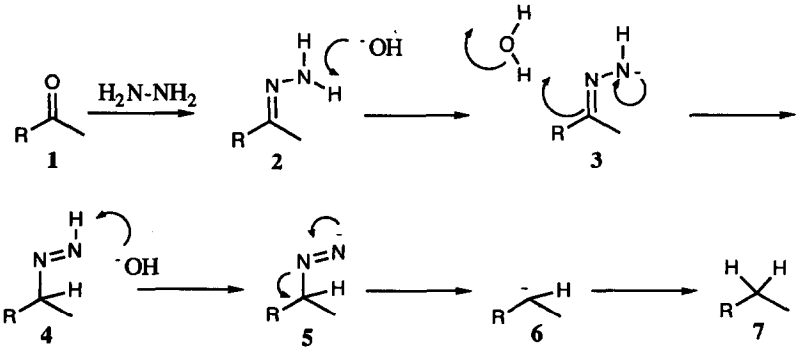
Abstract: *The observation that Wolff-Kishner reduction of a δ,ε-unsaturated ketone leads to the trans cyclized product supports the proposed intermediacy of a carbanion in this reaction.*

The hydrazine/KOH reduction of a ketone to a methylene, developed by Wolff and Kishner [1] and modified by Huang-Minlon,[2] is one of the most commonly used procedures of organic synthesis. The demonstration by Szmant [3] that this reaction is first order in both hydroxide ion and ketone hydrazone led to a mechanistic proposal that is now faithfully reproduced in every introductory organic chemistry textbook.

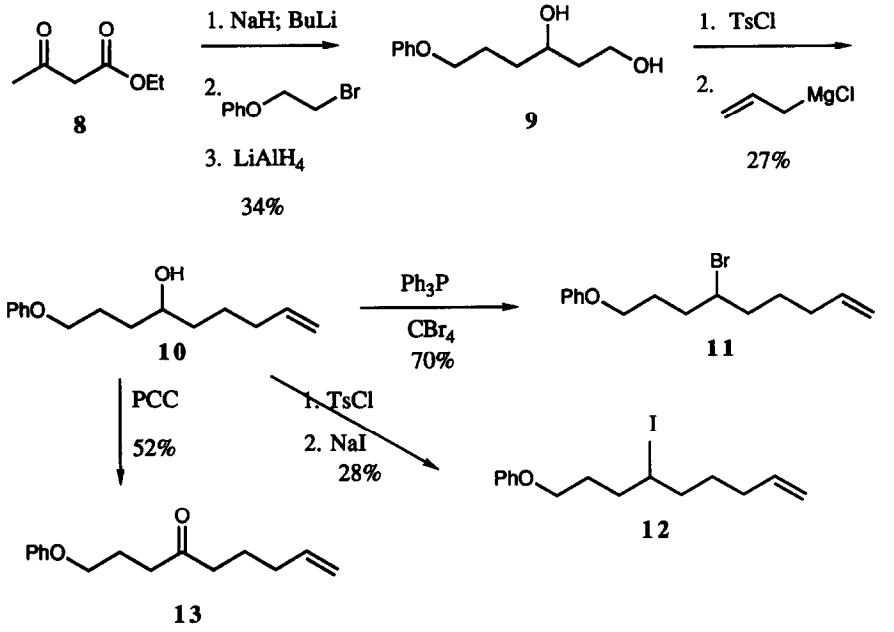


It seemed likely to us that tautomerization of **2** to **4** is the rate-determining step in this reduction. This would suffice to explain Szmant's kinetic observations. The mechanism of N_2 loss, **4** -> **7**, was thus still open.

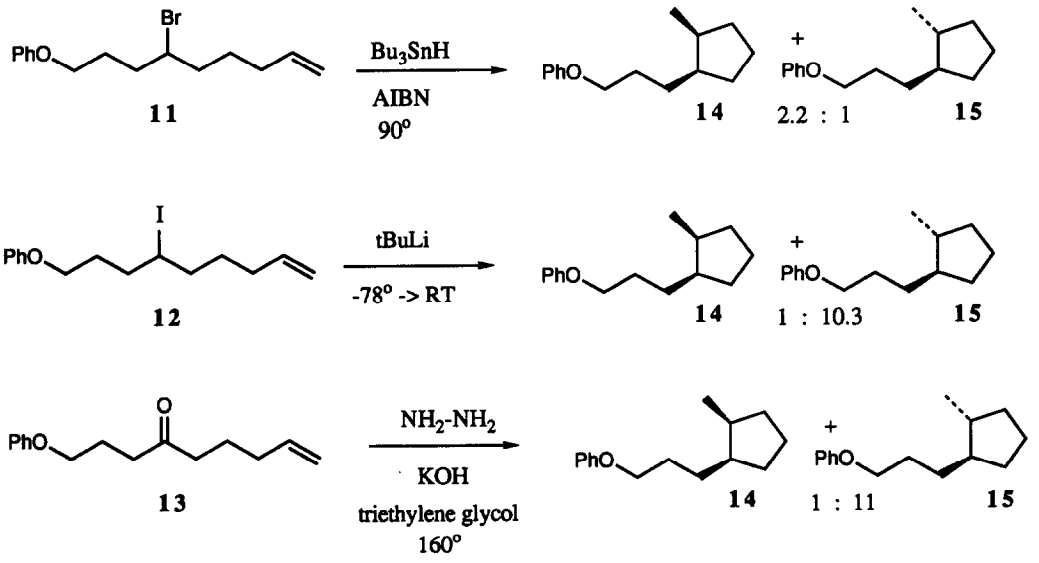
Loss of N_2 from monoalkyl diimides under neutral conditions [4] apparently occurs via a free radical mechanism. It seemed possible that **4** also was losing N_2 by a radical mechanism. To distinguish between these two possibilities, we have prepared (**Scheme 1**) and cyclized (**Scheme 2**) bromide **11**, iodide **12**, and ketone **13**.

Dedicated to Professor Gilbert Stork on the occasion of his 70th birthday.

Scheme 1



Scheme 2



The cyclization substrates were prepared (**Scheme 1**) by alkylation [5] of the dianion of ethyl acetoacetate with 2-bromophenetole, followed by reduction. Coupling [6] of the monotosylate of diol **9** with allylmagnesium chloride provided **10**, the immediate precursor to each of the three cyclization substrates. Bromination [7] converted **10** to **11**, heating of the monotosylate of **10** with sodium iodide gave **12**, and oxidation of **10** gave **13**. All intermediates were characterized fully (^{1}H NMR, ^{13}C NMR, MS, IR), but no attempt was made to optimize the yields of any of these transformations.

Free radical reduction of secondary halides such as **11** was reported by Beckwith [8] to give significantly more of the cis than the trans 1,2-dialkyl cyclopentane. In contrast, cyclization of secondary lithium alkyls was reported by Bailey and by Ashby [9] to give, in each case, a preponderance of the trans 1,2-dialkyl cyclopentane. To establish procedures for the analytical separation of the two cyclopentane diastereomers, we first cyclized bromide **11** and iodide **12**.

We found that the product from tributyltin hydride reduction of **11** was, even after silica gel chromatography, substantially contaminated with a tin-containing byproduct. Exposure of this mixture to NaF in refluxing ethanol, followed again by silica gel chromatography, proved sufficient to give the pure mixture of diastereomeric cyclopentanes, which were not separable from each other under these chromatography conditions. The major component of this mixture, assumed to be the cis diastereomer **14**, showed a methyl doublet at 0.80 ppm by ^{1}H magnetic resonance, and methines at 35.9 and 43.1 ppm by ^{13}C magnetic resonance. The minor product, presumed to be **15**, showed a methyl doublet at 0.98 ppm, and methines at 40.7 and 47.4 ppm. The ratio of **14** to **15**, 2.2 : 1, was established by capillary GC/MS.

In contrast, cyclization of secondary lithium alkyls was reported by Bailey and by Ashby [9] to give, in each case, a preponderance of the trans 1,2-dialkyl cyclopentane. Secondary bromides are, however, reported [9] to undergo one electron transfer with t-BuLi, to give free radical-derived cyclization products. It was therefore necessary to carry out the two-electron reduction on iodide **12**. Indeed, addition of iodide **12** to tBuLi at -78°, followed by warming to room temperature before quenching, again gave **14** and **15**, but now in a ratio of 1:10.3. In this case, unlike the cyclization of **11**, almost an equal quantity of the reduced but not cyclized product was observed.

With these results in hand, we were prepared to carry out the Wolff-Kishner reduction of ketone **13**. In fact, application of the standard procedure [2] to **13** gave largely the reduced but uncyclized product. By careful capillary GC/MS, however, we were able to detect about 5% conversion to cyclopentanes **14** and **15**, in a ratio of 1:11.

The mechanism of the Wolff-Kishner reduction has long been of interest. The detailed studies by Szmant [3] and Kossower [10] amply support the intermediacy of a monoalkyl diimide such as **4**. The work described here is significant in offering the first experimental support for the actual intermediacy in the Wolff-Kishner reduction of an sp^3-hybridized carbanion such as **6**.[11]

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11. We have recently observed that $NaBH_4$/acetic acid reduction [12] of the tosylhydrazone derived from **13** gives cyclized products **14** and **15** in a ratio of 3:1. These results strongly suggest that under these milder conditions, N_2 loss (**4** -> **6**) is proceeding via a free radical mechanism.

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