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Conversion of hydrazones to alkyl chlorides under Swern oxidation conditions

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Abstract—The unsubstituted hydrazones derived from aromatic ketones and aldehydes were converted in high yield to the corresponding alkyl chlorides under Swern oxidation conditions. In this unusual oxidation/reduction sequence the substrate undergoes a net reduction under the well established Swern oxidation conditions. Unsubstituted hydrazones derived from cyclohexyl ketones returned elimination products.

Unsubstituted hydrazones are versatile synthetic intermediates used in the preparation of diazo compounds,[1–3] vinyl iodides,[4,5] vinyl selenides,[6] gem dihalides,[7,8] and are substrates for the Wolff–Kishner[9] reduction. This letter details the previously undescribed reactivity of N-unsubstituted hydrazones under Swern oxidation conditions.[10] Of note, hydrazones derived from aryl ketones or aryl aldehydes are converted in high yields to alkyl chlorides. This is an interesting oxidation/reduction sequence as the substrate hydrazone undergoes net reduction to provide an alkyl chloride under the well established Swern oxidation conditions.

In this procedure, a dichloromethane solution of the hydrazone and 1 M equiv of triethylamine was added to a cooled (−78 °C) dichloromethane solution of dimethylsulfoxide previously activated with oxalyl chloride. Upon removing the solution from the cold bath, a gas evolution ensued. In each case the reaction was complete before reaching the room temperature. A simple extractive work-up provided high product yields typically in greater than 95% purity as determined by NMR and GC analysis.[11,12]

The results for various hydrazones subjected to these conditions are compiled in Table 1. The hydrazones derived from aryl ketones and aldehydes were efficiently converted to alkyl chlorides in uniformly high yields. Benzophenone hydrazone was converted to chlorodiphenylmethane in a 93% yield and the hydrazone derived from 9-anthraldehyde was converted to 9-chloromethyl anthracene in a 98% yield. When acetophenone hydrazone was subjected to these conditions 1-chloroethyl benzene was formed in a 92% yield along with a 6% yield of styrene as a side product. Finally, an α-keto hydrazone, benzyl monohydrazone, also proved to be a suitable reactant and provided desyl chloride in a 95% yield.

Hydrazones derived from cyclohexyl ketones proved unsuitable as substrates. Subjecting 4-*tert*-butyl cyclohexanone hydrazone to the reaction conditions provided the expected gas evolution, but no alkyl chloride was isolated. Instead, a mixture of 4-*tert*-butylcyclohex-1-ene, 1-*tert*-butylcyclohex-1-ene, and 4-*tert*-butyl cyclohexanone was recovered. The hydrazone of 4-cholesterone also returned only elimination products and ketone.

A mechanistic hypothesis that accounts for these results is presented in Scheme 1. Hydrazone **1** would react with the dimethylchlorosulphonium ion (generated by the action of oxalyl chloride on DMSO) to provide diazosulphonium ion **2** upon deprotonation with Et_3N.[13] A lone pair donation by the α-nitrogen would result in the elimination of dimethyl sulfide to provide N-protonated diazonium ion **3**. The migration of a proton from nitrogen to carbon would provide diazonium ion **4**, which the could provide alkyl chloride **6** either directly via S_N2 substitution of nitrogen by chloride, or through an S_N1 mechanism in which loss of nitrogen provides carbenium ion **5** as an intermediate.[14] Due to the high

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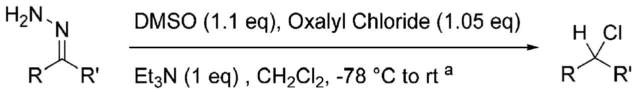
Table 1. Table of results



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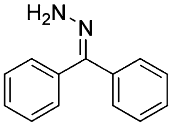
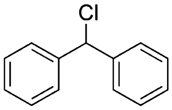
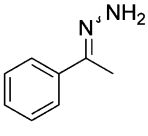
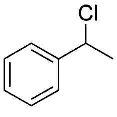
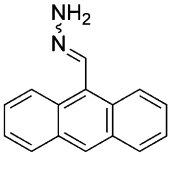
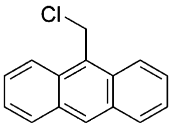
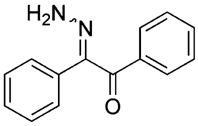
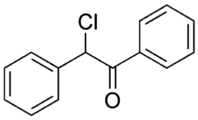
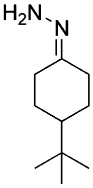
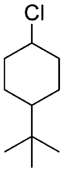
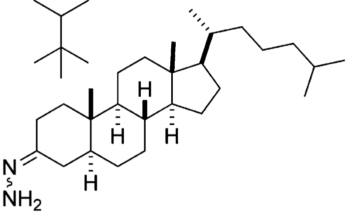
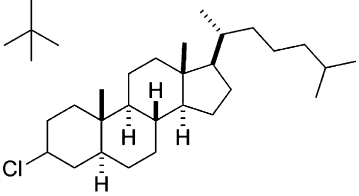
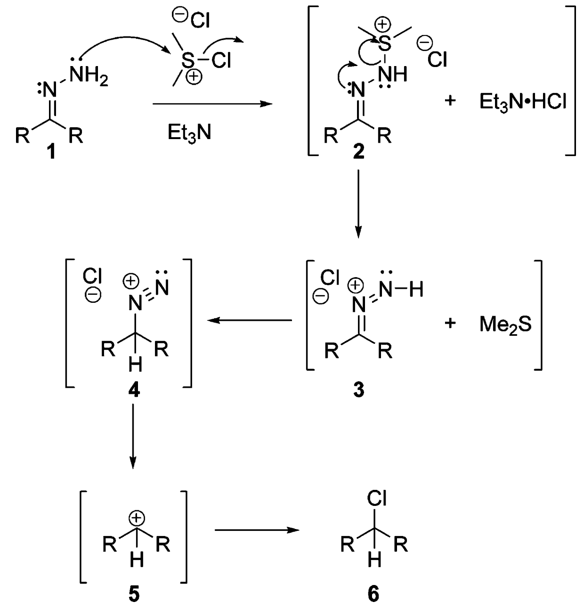
1			93
2			92[b]
3			98
4			95
5			0[c]
6			0[c]

[a] Detailed experimental conditions are provided in Ref. 11.

[b] Styrene (6%) was obtained as side product.

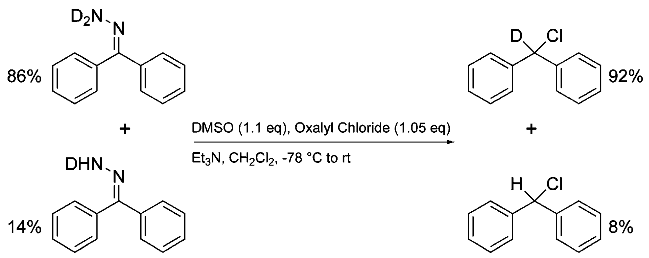
[c] Products derived from elimination were obtained.



Scheme 1.

instability of secondary diazonium ions, it is not surprising that the elimination products predominate in the reactions of 4-*tert*-butyl cyclohexanone hydrazone and the hydrazone of 4-cholesterone. In fact, the acid catalyzed decomposition of 1-diazo-4-*tert*-butylcyclohexane and steroidal diazo compounds is known to provide similar product mixtures to those observed here.[15,16] The origin of the recovered ketone could be accounted for by invoking a rapid elimination step that would result in the generation of a second equivalent of HCl. This acid could then protonate the unreacted hydrazone and thus inhibit subsequent diazo formation. The hydrolysis of the hydrazone hydrochloride salt during purification would return ketone.

To broaden the utility and to further test the proposed mechanism of this transformation, the reaction was repeated on a sample of deuterium enriched benzophenone hydrazone (Scheme 2). This sample was generated by simply dissolving benzophenone hydrazone in a mixture of dichloromethane and deuterated methanol and then removing the solvents in vacuo.



Scheme 2.

The proton NMR spectrum of this material revealed that 93% of the protons on nitrogen had exchanged for deuterium. Upon subjecting this material to the above reaction conditions, a 92:8 mixture of chlorodeutrodiphenylmethane and chlorodiphenylmethane was isolated in a 90% yield. This ratio is consistent with the proposed mechanism and unambiguously shows the origin of the transferred proton. This also highlights the utility of this methodology as a facile means to incorporate deuterium into organic substrates.

We are currently working to develop these reaction conditions into a method for the preparation and isolation of diazo compounds.

Acknowledgements

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11. A typical experimental procedure follows: oxalyl chloride (0.18 mL, 2.1 mmol, 1.05 equiv) was added to a −55 °C solution of dimethyl sulfoxide (0.16 mL, 2.2 mmol, 1.10 equiv) in dichloromethane (15 mL) and the reaction was maintained at this temperature until gas evolution had ceased. The solution was then cooled to −78 °C and a mixture of benzophenone hydrazone (0.39 g, 2.0 mmol, 1 equiv) and triethylamine (0.28 mL, 2.0 mmol, 1 equiv) in dichloromethane (5 mL) was added in a dropwise manner. The cooling bath was removed and the reaction was allowed to warm to room temperature over which time gas evolution was noted. The reaction was washed with water (20 mL), the aqueous layer was extracted with fresh dichloromethane (10 mL), the organics were combined, washed with aqueous 10% HCl (10 mL), brine (10 mL), dried ($MgSO_4$), and concentrated to provide 0.38 g (93% yield) of chlorodiphenylmethane in greater than 95% purity as determined by proton NMR and GC analysis.
12. All products display characterization data identical to literature values.
13. An alternative, but similar, mechanism can be written in which the internal nitrogen of the hydrazone acts as the initial site of reactivity.
14. Pross and Sternhell reported the formation of 2-chloro-1-phenylpropane in a 9% yield upon treatment of the hydrazone of benzyl methyl ketone with chlorine. [Pross, A.; Sternhell, S. *Aust. J. Chem.* **1971**, *24*, 1437–1447.] They propose a mechanism in which an electrophilic addition of chlorine to the carbon–nitrogen double bond leads to a diimide derivative that reacts further to provide the alkyl chloride. I would like to thank a reviewer for noting that in the present work an alternative mechanism (similar to that proposed by Pross and Sternhell) could be written in which the dimethylchlorosulphonium ion adds chlorine to the carbon–nitrogen double bond.
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