A Method for the Selective Hydrolysis of Ketone Hydrazones in the Presence of Acetals

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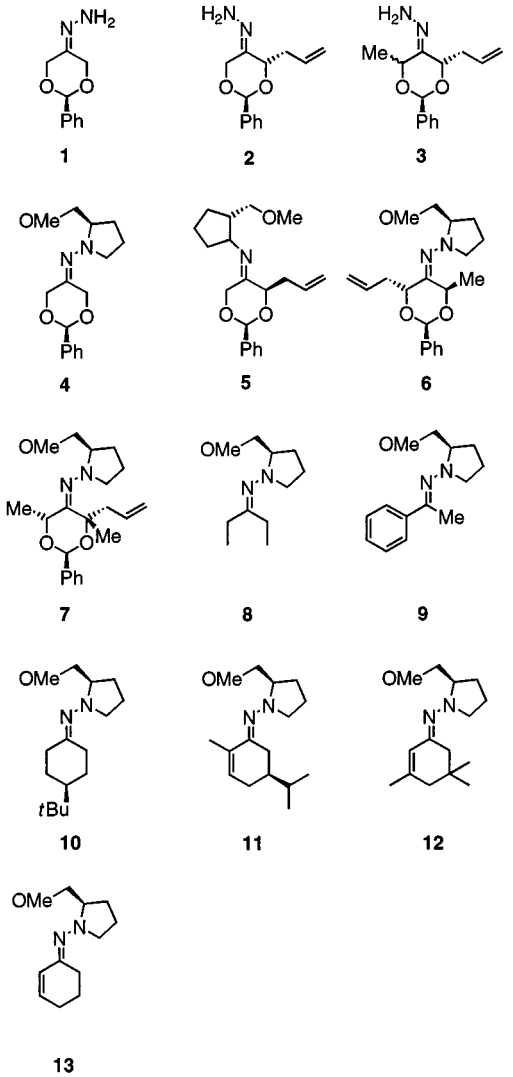
Dimethylhydrazones and RAMP-hydrazones containing acetal or olefin groups were hydrolysed selectively to form the corresponding ketones, by treatment with ammonium dihydrogen phosphate buffer solutions.

Introduction

Asymmetric alkylation of ketones using the SAMP/RAMP auxiliaries have over the last 20 years been developed by Enders and co-workers to become a powerful and versatile tool for alkylation with asymmetric induction.[1] The standard method for cleaving the SAMP/RAMP-hydrazones usually requires ozonolysis. Hydrazones that contain functional groups sensitive to ozonolysis may be cleaved by *N*-methylation and subsequent hydrolysis in an aqueous HCl/pentane mixture.[2] We are currently studying the synthetic application of benzylidenedihydroxyacetone and BDHA, and have encountered problems cleaving the corresponding hydrazones. For example, compounds **1** and **2** were incompatible with acidic reaction conditions and ozonolysis. A search for alternative routes for converting hydrazones into the corresponding ketones was therefore undertaken.

Results and Discussion

Neither of the methods mentioned above[2] worked satisfactorily in converting the *N*,*N*-dimethylhydrazone of the unsaturated acetal **2** to the corresponding ketone. Other published methods were tested, including treatment with aqueous cupric chloride,[3] oxidative cleavage of the hydrazones with sodium perborate,[4] hydrolysis with aqueous buffer (pH = 7.0) at 60 °C[5] or with acetate buffers.[6] These methods all failed for the BDHA derivatives, and hydrolysis of both the hydrazone and the acetal functional group was observed. However, hydrolysis of BDHA-hydrazone **1** with an ammonium phosphate buffer showed promise. Mixtures of aqueous ammonium dihydrogen phosphate (1.6 M, pH = 4.5) and the hydrazones in THF solution (4:1) at room temperature gave satisfactory results. This hydrolytic procedure



was tested for a variety of *N*,*N*-dimethyl- and RAMP-hydrazones. Representative examples are shown in Table 1. Thus, compound **1** was completely hydrolysed in less than 1 h, and compound **2** within 7 h, without detectable amounts of by-products.

In order to elucidate the possible significance of ammonia, hydrolysis of **5** in potassium phosphate solution (1.6 M, pH = 4.5) was studied. The reaction was complete in less

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Table 1. ((AUTHOR: Please insert caption!))

Hydrazone	Reaction time	Conversion (%)[a]	Isolated yield (%)
1	< 60 min	> 99	–
2	7 h	> 99	88[b]
3	< 16 h	> 99	> 99[c]
4	< 7 h	> 99	–
5	7 + 1 h[d]	> 99	97[c]
6	48 + 24 h[d]	> 99	77[e]
7	15 d	30	
8	< 3 h	> 99	–
9	< 14 h	> 99	–
10	< 15 h	> 99	–
11	> 15 h	94	–
12	> 220 h	96	–
13	> 46 d	50	–

[a] Determined by GC. – [b] Purified by recrystallisation. – [c] Crude product. – [d] Two-stage hydrolysis. – [e] Purified by flash-chromatography.

than 48 hours. However, by-products (e.g. benzaldehyde) corresponding to the hydrolysis of the acetal moiety were observed.

Hydrolysis of the dialkylated compound **3** proceeded more slowly but was complete within 16 h. Hydrolysis of the RAMP-hydrazones **5** and **6** stopped at approximately 90% conversion. However, extraction of the ketone and the unchanged hydrazone with dichloromethane and subsequent repeated hydrolysis of the concentrated extract resulted in complete conversion. In neither of these cases were products corresponding to hydrolysis of the acetal group observed. The more substituted RAMP-hydrazone **6**, required longer reaction times. Reaction at room temperature for 48 h, extraction of the partially hydrolysed product, and repeated hydrolysis for an additional 24 h, however, resulted in complete conversion into the ketone. Hydrolysis of the trisubstituted BDHA-hydrazone **7** was slow and only 30% was converted after 15 d at room temperature. To investigate the scope of this method further, the hydrolysis of a number of other hydrazones was investigated. The RAMP-hydrazone **8** of 3-pentanone was hydrolysed in less than 3 h, the acetophenone hydrazone **9** in 15 h, and the 4-*tert*-butylcyclohexanone hydrazone **10** in less than 14 h.

The method is useful for hydrazones of enones, which are incompatible with ozonolysis. Hydrolysis of the RAMP-hydrazone **11** of 2-cyclohexenone, was almost complete within 15 h, but the more substituted hydrazone **12** required 220 h for 96% conversion. Only 50% of compound **13** was converted after 46 d at room temperature.

All experiments described above were performed under nitrogen at room temperature. Under refluxing conditions, the reaction proceeded faster. For example, GC analysis indicated that the reaction of compound **13** was complete in approximately 1 h. The more substituted hydrazones appeared to react sluggishly. This may be due to either steric effects or to differences in solubilities under the potential two-phase conditions. The reaction mixtures appeared to be homogeneous. However, if volumes were reduced too much, two distinct phases were observed and the hydrolysis then proceeded very slowly. The addition of co-solvents, for example, *tert*-butyl alcohol, isopropyl alcohol or acetone, in combination with ultrasound, did not noticeably improve the rate of reaction. Adjusting the pH of the aqueous phase of the reaction to > 12 with sodium hydroxide, and subsequent continuous extraction with diethyl ether, led to the recovery of approximately 70% of the RAMP auxiliary.

Conclusion

A procedure for the hydrolysis of hydrazones containing acid-labile acetal groups and ozone-sensitive olefin moieties, using ammonium phosphate buffers (pH = 4.5) under mild reaction conditions is reported. The method is more suitable for acid-sensitive substrates than the known acetate buffer method, and worked satisfactorily for a series of *N*,*N*-dimethylhydrazones and RAMP-hydrazones, yielding the corresponding ketones in high yields.

Experimental Section

Hydrolysis of Hydrazones. – General Procedure: The hydrazone (1 mmol) was dissolved in THF (6 mL). Aqueous $NH_4H_2PO_4$ (1.6 M, pH = 4.5, 30 mL) was added and the mixture was stirred vigorously at room temperature under nitrogen. When no more hydrazone was detected by GLC and TLC analysis, the reaction mixture was extracted with dichloromethane (5 × 5 mL). The organic phase was washed with brine and dried with anhydrous magnesium sulfate. The solvent was removed under reduced pressure to yield the crude product, which was further purified by recrystallisation, flash chromatography or analysed by GLC.

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