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APPLICATIONS OF N, N-DIMETHYLHYDRAZONES TO SYNTHESIS. USE IN EFFICIENT, POSITIONALLY AND STEREOCHEMICALLY SELECTIVE C-C BOND FORMATION; OXIDATIVE HYDROLYSIS TO CARBONYL COMPOUNDS

E. J. Corey* and Dieter Enders

Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138, USA

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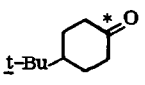
N, N-Dimethylhydrazones (DMH's) have not been regarded as widely useful intermediates in organic synthesis. They have been recommended as advantageous precursors for the preparation of certain hydrazones in pure form (e.g., acetone hydrazone) via exchange with hydrazine[1] and as protected forms of aldehydes and ketones from which the free carbonyl compounds can be regenerated by (a) direct hydrolysis with aqueous acid or (b) N-methylation (CH_3I) followed by hydrolysis in hot water or aqueous base.[2] Even these relatively limited possibilities have been little developed. In this and the accompanying papers it is shown that DMH's, usually available easily and in quantitative yield from the corresponding carbonyl compounds, are amenable to a broad range of valuable synthetic operations.

Our initial concern was to find the mildest possible method for the conversion of DMH derivatives to ketones or aldehydes so that the synthesis of even quite labile carbonyl compounds via DMH's would be efficient and straightforward. The defined objective was quickly attained with the discovery that DMH cleavage to form ketones can be accomplished generally and in high yield by a novel oxidative hydrolysis using aqueous sodium periodate at pH 7 and 20-25°. Methanol, THF or t-butyl alcohol are suitable cosolvents; faster rates are generally observed in the last two. The effectiveness of this method is apparent from the following list of ketones prepared from DMH derivatives by the periodate process. Reaction times and yields are indicated for each product together with the site of the DMH group in the starting material (starred). A darkened bond appearing in a formula reflects the bond created in the synthesis of the DMH derivative for those compounds produced by C-C bond forming reactions (vide infra).



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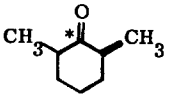

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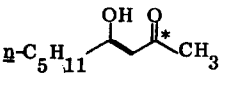

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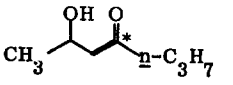

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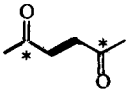

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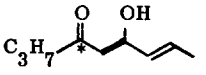

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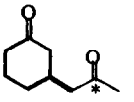
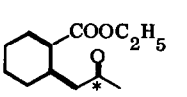


(15 hr, 90%)



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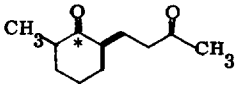

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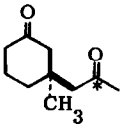

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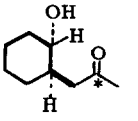
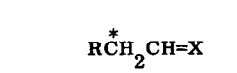


(3 hr, 90%)

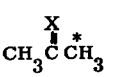
The neutral periodate hydrolysis procedure is not satisfactory for the cleavage of DMH derivatives of aromatic or α,β-unsaturated aldehydes since these usually afford mixtures of aldehydes and nitriles. This finding is consistent with a previous report that the reaction of DMH derivatives of aldehydes with hydrogen peroxide constitutes a synthetic route to nitriles.[3] However, under modified conditions, non-conjugated aldehydes can be obtained in high yield from the corresponding DMH's. Thus, cyclohexane carboxaldehyde and 1-dodecanal were formed in >90% isolated yield (<1% of corresponding nitrile) from the corresponding DMH's using 1 equiv of periodic acid in 1:1 THF-water, buffered to pH 4.5 with sodium acetate-acetic acid, at 25° for 3 hr. In general the production of nitrile at the expense of aldehyde is favored at higher pH in periodate cleavage. Hydrolysis of aldehyde DMH's via the methiodides[2] leads to formation of much nitrile even in aqueous bicarbonate solution (the ratio of RCN to RCHO again increases with pH). At pH<2, hydrolysis is rapid and affords simple aldehydes or α,β-unsaturated aldehydes cleanly in yields of 90% or better (25°, 2 phase system of 5% aq. HCl and ether).

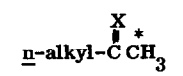
The mechanism of the periodate induced hydrolysis of DMH derivatives to carbonyl compounds will be dealt with later. Carbonyl compounds have been observed previously as products in the ozonolysis[4] or peracetic acid oxidation[5] of DMH derivatives.

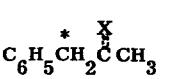
DMH derivatives of "enolizable" aldehydes and ketones can be metallated cleanly by lithium diisopropylamide (LDA) in THF at 0°. For DMH's of type $R-\overset{X}{\underset{|}{C}}-CH_3$ complete metallation was accomplished to form $R-\overset{X}{\underset{|}{C}}-CH_2Li$ using 1 equiv of LDA (from diisopropylamine and 1 equiv of n-butyllithium) at 0° for 20 min (conc = 0.3M);[6] for DMH's of type $R-\overset{X}{\underset{|}{C}}-CH_2-C-$ complete metallation was observed under the same conditions usually (but not always) after 2 hr. Alternatively DMH's of type $R-\overset{X}{\underset{|}{C}}-CH_3$ could be metallated by n-butyllithium in THF at -78° for 20 min. The following DMH's were deprotonated at the starred positions to form lithio derivatives in 90-100% yield (as ascertained from quenching experiments with reagents such as methyl iodide, benzaldehyde or trimethylchlorosilane).

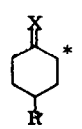


R = H or CH_3









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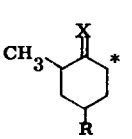
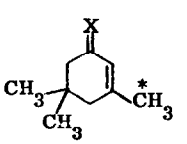
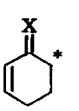
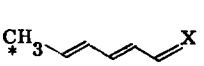
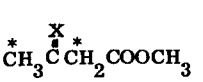


R = H or t-Bu

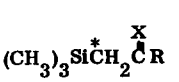




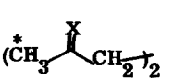




(2 equiv LDA)



R = H or CH_3



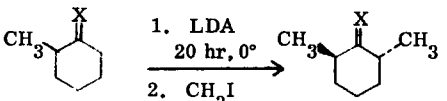
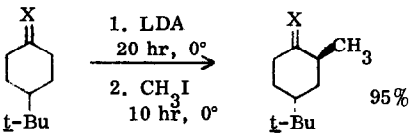
X = N-N(CH$_3$)$_2$

Obviously α-lithiated DMH's can serve as equivalents of enolate ions in synthesis. In fact they possess several advantages which can be of crucial importance: (1) efficiency of formation and lack of side reactions observed with enolate generation from free carbonyl compounds (aldol type self condensation, C=O addition), (2) stability (in absence of O_2, CO_2, H_2O, etc.) even at 25°, (3) much higher reactivity than enolates toward electrophiles such as halides, oxiranes and carbonyl compounds, (4) formation with high positional (regio) specificity, (5) formation of only monosubstitution products with electrophiles (as compared to di- and poly-alkylation of enolates) and (6) unique stereoselectivity.

Generally, metallation of ketones occurs very selectively at the less alkylated carbon (see examples a-d) (yields refer to distilled product)[7]. No position isomeric or polyalkylation products could be detected by nmr

(a) $\underline{n}\text{-}C_5H_{11}\overset{X}{\underset{\|}{C}}CH_2\underline{i}\text{-}Pr$ (83%) $\xleftarrow[2.\ \underline{i}\text{-}Pr\text{-}I,\ 15\ hr,\ 0°]{1.\ LDA}$ $\underline{n}\text{-}C_5H_{11}\overset{X}{\underset{\|}{C}}CH_3$ $\xrightarrow[2.\ CH_3I,\ 15\ hr,\ 0°]{1.\ LDA}$ $\underline{n}\text{-}C_5H_{11}\overset{X}{\underset{\|}{C}}CH_2CH_3$ (95%) (b)

$X = NN(CH_3)_2$

(c)  (d) 

or tlc analysis of the DMH's formed in cases a-d above or by analysis of the corresponding ketones derived therefrom by oxidative hydrolysis. In the case of cyclohexanone derivatives (cases c and d) axial methylation is highly favored; e.g. periodate hydrolysis (pH 7) of the product of case c gave trans-2,6-dimethylcyclohexanone (97% by vpc analysis) contaminated by only 3% of the more stable cis isomer.

Lithiation of the DMH of methyl benzyl ketone and subsequent methylation occurs cleanly by path (e), a

$C_6H_5CH_2\overset{X}{\underset{\|}{C}}CH_3 \xrightarrow[2.\ CH_3I]{1.\ LDA} C_6H_5\underset{CH_3}{\diagup}CH\overset{X}{\underset{\|}{C}}CH_3$ 95% (e)

result which is understandable in view of the charge delocalizing capability of the phenyl substituent.

The following general and specific experimental procedures are provided.

Oxidative Hydrolysis of Ketone DMH's. The DMH (1 mmole) (for preparation in 95-100% yield see ref. 1) was dissolved in 15 ml of methanol and 3 ml of 1.0N pH 7 phosphate buffer and a solution of 2.2 equiv of sodium periodate in 5 ml of water was added at 25° with stirring. Gas evolution and precipitation of sodium iodate ensued rapidly. After completion of the hydrolysis as determined by tlc analysis (usually 2-3 hr), the reaction mixture was filtered, diluted with water and extracted with methylene chloride. The ketone was obtained by drying and vacuum concentration of the extract. Other media including 3:1 t-butyl alcohol-water and 4:1 to 1:1 THF-water can be used (the reaction is usually fastest in 4:1 THF-water). In cases where the oxidative hydrolysis becomes undesireably slow before completion additional sodium periodate serves to speed hydrolysis of any remaining DMH.

Alternatively, cleavage of DMH's can be accomplished after conversion to the methiodide (excess CH_3I, reflux 3-5 hr) and stirring with 0.1N sodium bicarbonate (pH 8.4) at 25°.

DMH derivatives of aldehydes were cleaved at 25° using 1 equiv periodic acid in 1:1 THF-water buffered with a little acetic acid-sodium acetate to pH 4.5 using a reaction time of 2-3 hr.

trans-2,6-Dimethylcyclohexanone. A solution of 0.86 g (5.6 mmole) of the 2-methylcyclohexanone DMH in 15 ml of dry THF under nitrogen was metallated with 6.2 mmole of lithium diisopropylamide in 15 ml of THF (LDA freshly generated from the amine and 1.4 N n-butyllithium) at 0° for 20 hr. The resulting solution was cooled to -78° and treated with 0.39 ml (6.2 mmole) of methyl iodide. After 1 hr at -78° the reaction mixture was allowed to warm to 0° and poured into 3:1 water-methylene chloride. Separation of the organic phase, two further extractions of the aqueous part, drying of the organic extract (Na_2SO_4) and concentration gave 0.95 g of DMH as a yellow oil. Hydrolysis by the periodate procedure detailed above gave 0.67 g (95%) of 2,6-dimethylcyclohexanone which was found by vpc analysis (10', 10% diethylene glycol succinate at 110°) to consist of 97% trans isomer and 3% cis isomer (a commercial, Aldrich Co., sample contained 15% trans- and 85% cis-2,6-dimethylcyclohexanone); no 2,2-dimethylcyclohexanone or trimethylcyclohexanone could be detected. The nmr spectrum of the synthetic product in CCl_4 solution confirmed the trans stereochemistry and 2,6-dimethyl substitution: (shifts in ppm downfield from tetramethylsilane) 1.07 (d, 6H, CH_3, J = 7 Hz), 1.3-2.2 (m, 6H, ring CH_2), and 2.3-2.8 ppm (m, 2H, ring CH).

Many of the reactions of α-lithiated DMH's parallel those reported earlier by Wittig, Stork and their coworkers[8-11] for α-metallated N-alkylimines. Nonetheless, there seem to be several unique advantages of the DMH's including (1) quantitative formation even from quite hindered ketones, (2) greater stability, (3) higher reactivity of metallated derivatives, (4) availability of corresponding cuprates and (5) stereospecificity and significantly higher yields in C-C bond forming reactions.[12]

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5. L. Horner and H. Fernekess, Chem. Ber., 94, 712 (1961).
6. Lithiation of DMH's to form RCCuLi reagents can also be effected cleanly by 1 equiv n-BuLi in THF at -78°
7. Structures of all new compounds reported herein were confirmed by ir, nmr and mass spectral data on distilled or chromatographically purified samples.
8. G. Wittig and H. Reiff, Angew. Chem. Int. Ed., 7, 7 (1968).
9. G. Stork and S. Dowd, J. Amer. Chem. Soc., 85, 2178 (1963).
10. G. Stork and J. Benaim, ibid., 93, 5938 (1971), describe monoalkylation of α,β-unsaturated ketimines and two instances with N, N-dimethylhydrazones.
11. See also G. Stork, G. A. Kraus and G. A. Garcia, J. Org. Chem., 39, 3459 (1974) for position-selective enolate formation from methyl ketones.

12. This research was assisted by grants from the Studienstiftung des deutschen Volk and the U. S. National Science Foundation.