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α-FUNCTIONALIZATION OF KETONES VIA N, N-DIMETHYLHYDRAZONES

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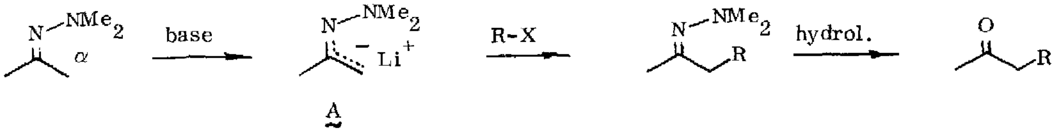
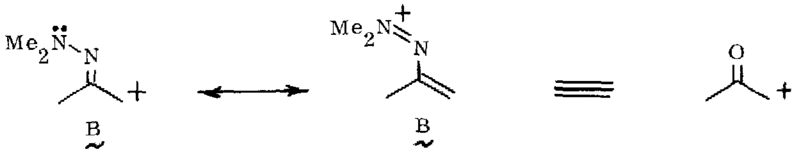
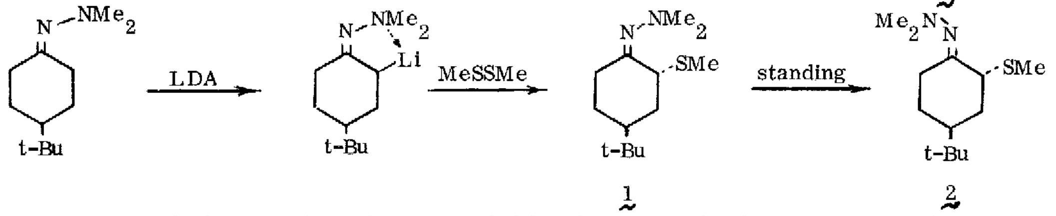
We have previously shown that N, N-dimethylhydrazones (DMH's) can be efficiently metallated at the α-carbon,[1] that these reagents (enolate equivalents **A**) participate in a variety of useful carbon-carbon bond forming reactions,[1,2,3] and that hydrolysis of the DMH's to carbonyl compounds may be accomplished under mild conditions using aqueous sodium periodate[1] or cupric ion.[4] The α-carbon might also support a *positive* charge (**B**) because of n-electron delocalization from the DMH group, and this cation could be synthetically equivalent to an acylcarbonium ion $(\mathrm{R}\overset{\mathrm{O}+}{\overset{\|}{\mathrm{C}}}\mathrm{C}\lessdot)$.[5] In this paper we describe methodology for the conversion of DMH's into various α-functionalized ketones *via* reactive intermediates of both type **A** and **B**, employing 4-*tert*-butylcyclohexanone-DMH as the model compound.

Metallation of 4-*tert*-butylcyclohexanone-DMH was effected by a 0.33M solution of 1 equiv of lithium diisopropylamide (LDA) in tetrahydrofuran (THF) in 2 hr at 0°. The resulting lithio derivative reacted with 1 equiv of dimethyldisulfide within 1 hr at -78°, giving the methylthio-DMH in quantitative yield. The *Z*-isomer (higher R_f, 1:1 ether: hexane on silica gel) (**1**) is formed initially, presumably due to chelation of nitrogen of the dimethylamino group with the lithium atom in the metallated intermediate. Isomerization of



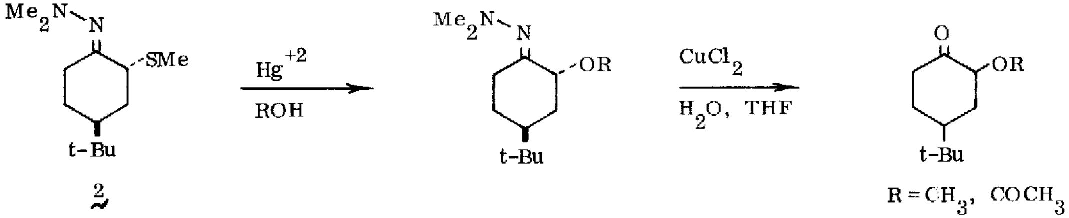


the product occurred upon standing to the more stable, crystalline (mp 47-48°) *E*-isomer (2).[6] We have also

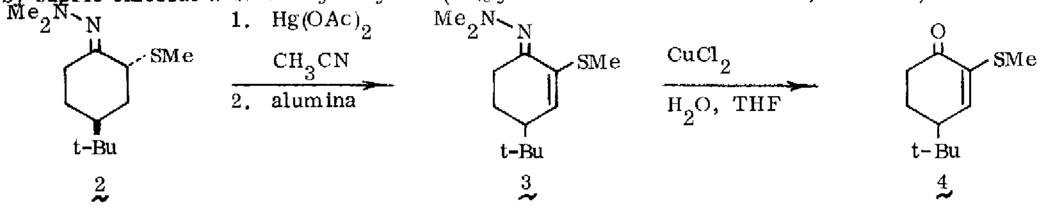


converted a variety of other DMH's to their α-methylthio derivatives by this procedure, which, when followed by cupric ion assisted hydrolysis of the DMH[4], constitutes a highly effective general synthesis of 2-methylthio-ketones.[7]

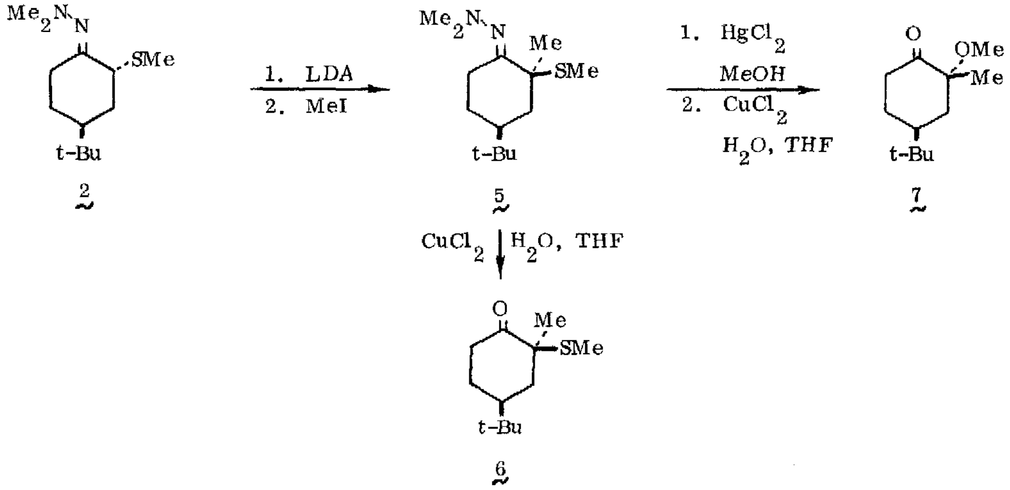
The methylthio-DMH can be converted to a reactive intermediate of type A (masked enolate ion) or type B (masked $\mathrm{RCOC}^{+}\!<$). Treatment of a 0.2M solution of 4-*tert*-butyl-2-methylthiocyclohexanone-DMH in methanol with 1.1 equiv of mercuric chloride at 23° for 30 min with vigorous stirring gave the α-methoxy-DMH, which was converted to 4-*tert*-butyl-2-methoxycyclohexanone (90% yield for two steps, 83:17 trans:cis) by cupric chloride assisted hydrolysis[4] for 3 hr at 23°, followed by bulb to bulb distillation[8] (70° bath, 0.1 torr). Similarly, the α-acetoxyketone[9] (75:25 trans:cis) was obtained in 97% overall yield by treatment of the methylthio-DMH with 1.1 equiv of mercuric acetate in acetic acid (0.2M) for 30 min at 23°, followed by cupric chloride assisted hydrolysis[4] for 3 hr at 23° and distillation (90°, 0.8 torr). The sequences provide a new method for the introduction of alkoxy and acetoxy groups at a carbon alpha to ketonic carbonyl.



The methylthio-DMH 2 underwent a novel dehydrogenation reaction when treated with 0.2*M* mercuric acetate (1.1 equiv) in acetonitrile for 15 min at 23° followed by passage of the product through basic alumina. The unsaturated DMH 3, obtained in 73% yield, was converted to 4-*tert*-butyl-2-methylthiocyclohex-2-enone (4) by cupric chloride assisted hydrolysis[4] (99% yield after distillation at 60°, 0.1 torr).

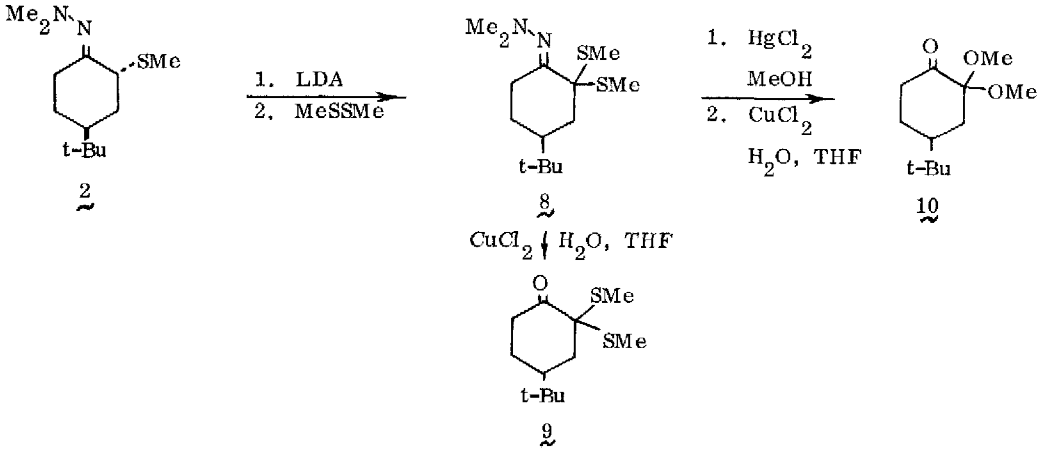


Further transformations have been realized using various combinations of the above described alkylation, sulfenylation, and solvolysis reactions of DMH's. One equiv of LDA in THF (0.33M, 20 min, 0°) converted the methylthio-DMH 2 to a lithio derivative, which was methylated using 1 equiv of iodomethane at 0° for 15 min to give after distillation (90°, 0.6 torr) the methylthio-DMH 5 in 93% yield. This substrate underwent hydrolysis to the corresponding ketone (6) when treated with 2.2 equiv of cupric chloride in 2:1 THF: water (0.04M) for 4 hr at 0°. After distillation (90°, 0.6 torr) 6 was isolated as a single isomer containing an axial methyl group[10] (98% yield). Alternatively, the thiomethyl group could be exchanged for methoxy prior to DMH hydrolysis by treatment of 5 with 1.1 equiv of mercuric chloride in methanol (0.2M) for 1 hr, and then 1.1 equiv of cupric chloride in 2:1 THF: water (0.04M) for 4 hr. The α-methoxyketone 7 was obtained in 87% overall yield after distillation (70°, 0.15 torr) as a single isomer containing an equatorial methyl group.[11] These sequences and previous results[1] demonstrate that the alkylation, sulfenylation, and methanolysis reactions place the unit being introduced in an axial position with respect to the conformationally anchored 4-*tert*-butylcyclohexanone ring.



The lithio derivative of 4-*tert*-butyl-2-methylthiocyclohexanone-DMH (2) reacted with dimethyldisulfide in 15 min at 0° to give the *bis*-methylthio-DMH 8 (mp 56-57°) in 90% yield (distilled at 95°, 0.6 torr). Two 1,2-dicarbonyl derivatives were prepared from this compound. Hydrolysis using 10 equiv of cupric chloride in 1:1 THF: water at 0° for 30 hr and distillation (105°, 0.6 torr) gave 4-*tert*-butyl-2,2-*bis*-methylthiocyclohexanone 9 in 98% yield. The use of higher temperature in this reaction led to the formation of substantial amounts of 4-*tert*-butyl-2-methylthiocyclohex-2-enone-DMH, a side product which results from elimination of methylmercaptan. Finally, treatment of the *bis*-methylthio-DMH 8 with 5 equiv of mercuric chloride in methanol (0.2M) for 10 hr at -20°, followed by hydrolysis using 1.1 equiv of cupric chloride in 2:1 THF: water (0.04M) for 2 hr at 23° and distillation (95°, 0.5 torr) gave 4-*tert*-butyl-2,2-dimethoxycyclohexanone (10) in 89% overall yield.

It seems clear that the methodology described herein can encompass a variety of ketonic substrates and a wide range of alkylating and solvolytic reagents. These processes should be especially useful for the introduction of functionality in complex ketonic molecules where site selectivity[13] and stereochemical control are crucial constraints.[14]



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2. E. J. Corey and D. Enders, *ibid.*, 11 (1976).
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5. (a) E. J. Corey, L. S. Melvin, Jr., and M. Haslanger, *ibid.*, 3117 (1975); (b) E. J. Corey, M. Petrzilka and Y. Ueda, *ibid.*, 4343 (1975); and (c) C. E. Sacks and P. L. Fuchs, *J. Amer. Chem. Soc.*, **97**, 7372 (1975).
6. The same phenomenon is commonly observed after alkylation reactions of lithio-DMH's; E. J. Corey and D. Enders, unpublished results.
7. D. Seebach and M. Teschner, *Chem. Ber.*, **109**, 1601 (1976).
8. Compounds described herein were purified by evaporative bulb to bulb distillation using a Buchi Kugelrohrofen at the bath temperature and pressure indicated and were spectrally (pmr, ir) and chromatographically homogeneous.
9. A known compound. M. E. Kuehne and T. J. Giacobbe, *J. Org. Chem.*, **33**, 3359 (1968).
10. Methylation of 4-*tert*-butyl-2-lithiocyclohexanone-DMH also gives a product with an axial methyl group. See reference 1.
11. The stereochemistry shown is assigned based on the downfield position (1.17 ppm) of the C-methyl signal in the pmr spectrum relative to that of *cis*-and *trans*-4-*tert*-butyl-2-methylcyclohexanone (1.02 and 1.15 ppm, respectively). Replacement of the methine at C-2 with methoxy should give a chemical shift difference of about 0.15 ppm for the C-methyl protons.[12] Note also the chemical shift (1.42 ppm) in 4-*tert*-butyl-2-methyl-2-methylthiocyclohexanone, which has an axial C-methyl.
12. R. M. Silverstein and G. P. Bassler, "Spectrometric Identification of Organic Compounds", John Wiley and Sons, New York, 1967, p. 136.
13. Lithiation of a DMH generally occurs at the least substituted α-carbon. See reference 1.
14. This work was assisted financially by a grant from the National Science Foundation.