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SYNTHETIC ROUTES TO POLYFUNCTIONAL MOLECULES VIA METALLATED N, N-DIMETHYLHYDRAZONES

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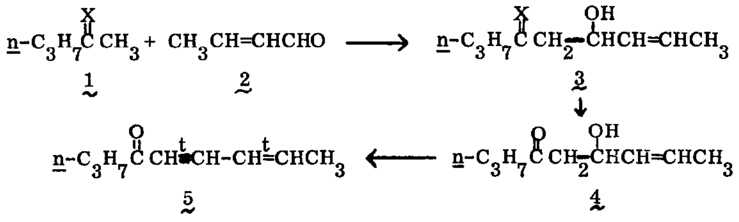
In the foregoing paper[1] we described the efficient metallation and alkylation of N, N-dimethylhydrazones (DMH's) and also effective and mild cleavage of DMH's to carbonyl compounds. This Letter is primarily concerned with reactions of metallated DMH's which lead to a wide variety of polyfunctional molecules.

I. <u>β-Hydroxycarbonyl Compounds</u>. α-Lithiated DMH's undergo 1, 2-addition to aldehydes and ketones to form β-hydroxy DMH's in generally high yield.[2] The process may be typified by the sequence **1**→**5**. 2-Pentanone DMH (**1**) was metallated[1] with n-butyllithium (1 equiv) in THF at -78° for 20 min, 1 equiv of crotonaldehyde (**2**) was added and after 3 hr at -78° and 12 hr warming to 0°, neutralization with acetic acid and extractive workup ($CH_2Cl_2-H_2O$) afforded the hydroxy DMH **3**, homogeneous by tlc and pmr analysis, in >98% yield. Treatment directly with sodium periodate in methanol at pH 7 and isolation as previously described afforded 7-nonen-4-on-6-ol (**4**) in >98% yield (pure by pmr and tlc analysis). Short-path distillation (70° and 0.05 mm) was accomplished with no appreciable loss of material giving distilled **4** in >95% yield overall from **1**.[3] Dehydration of **4** with methanesulfonyl chloride-triethylamine furnished after isolation and distillation (50°, 0.1 mm) 85% of pure <u>trans</u>, <u>trans</u>-5, 7-nonadiene-4-one (**5**).



$$n\text{-}C_3H_7\overset{X}{\overset{\|}{C}}CH_3 + CH_3CH{=}CHCHO \longrightarrow n\text{-}C_3H_7\overset{X}{\overset{\|}{C}}CH_2\text{—}\overset{OH}{\overset{|}{C}}HCH{=}CHCH_3$$

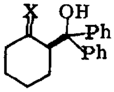
$$\mathbf{1} \qquad \mathbf{2} \qquad \mathbf{3}$$

$$n\text{-}C_3H_7\overset{O}{\overset{\|}{C}}CH\overset{t}{=}CH\text{-}CH\overset{t}{=}CHCH_3 \longleftarrow n\text{-}C_3H_7\overset{O}{\overset{\|}{C}}CH_2\text{—}\overset{OH}{\overset{|}{C}}HCH{=}CHCH_3$$

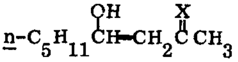
$$\mathbf{5} \qquad \mathbf{4}$$

X = $NN(CH_3)_2$

Similarly, metallation of cyclohexanone DMH using lithium diisopropylamide at 0° in THF for 2 hr,[1] cooling to -78° and reaction with 1 equiv of benzophenone (10 hr at -78° to 0°) afforded 90% yield of the carbonyl adduct **6**, m.p. 140°. Ten other β-hydroxy DMH's (**7**-**16**) were prepared in an analogous manner (yields of pure isolated product and m.p., if solid, as indicated). In each formula the C-C bond created in the condensation is darkened.

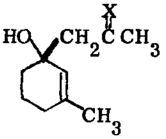


6 (90%)

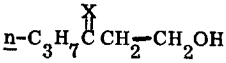


$n\text{-}C_5H_{11}\overset{OH}{C}H\text{-}CH_2\overset{X}{\overset{\|}{C}}CH_3$

7 (90%)

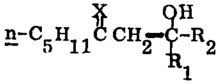


8 (99%, m.p. 65°)



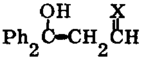
$n\text{-}C_3H_7\overset{X}{\overset{\|}{C}}CH_2\text{-}CH_2OH$

9 (90%)



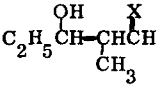
$n\text{-}C_5H_{11}\overset{X}{\overset{\|}{C}}CH_2\text{-}\underset{R_1}{\overset{OH}{C}}\text{-}R_2$

10 $R_1 = R_2 = Ph$ (85%, m.p. 86°)
11 $R_1 = Ph$, $R_2 = H$ (95%)
12 $R_1 = Ph$, $R_2 = CH_3$ (80%)



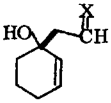
$Ph_2\overset{OH}{C}\text{-}CH_2\overset{X}{\overset{\|}{C}}H$

13 (81%, m.p. 65°)

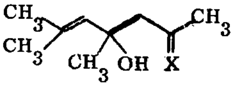


$C_2H_5\overset{OH}{C}H\text{-}\underset{CH_3}{C}H\overset{X}{\overset{\|}{C}}H$

14 (80%)
(2 diastereomers, 2:1)



15 (95%)

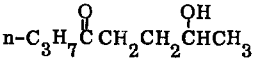


16 (95%)

$X = NN(CH_3)_2$

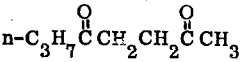
In the case of 9 dry paraformaldehyde was used.[4] Hydrolysis to the free β-hydroxy carbonyl compounds could be effected in these cases in high yield as described[1] without the occurrence of dehydration.[5]

II. γ-Hydroxycarbonyl, 1,4-Dicarbonyl Compounds. Reaction of the lithio derivative of 2-pentanone DMH with 2 equiv of propylene oxide in THF for 18 hr at 0–10° followed by isolation of product and periodate hydrolysis gave specifically the γ-hydroxy ketone 17 in 98% yield after short path distillation at 50°, 0.03 mm. Oxidation of 17 in methylene chloride with pyridinium chlorochromate[6] afforded spectroscopically pure 2,5-octadione 18 in 96% yield. The facility, position-specificity and high efficiency of the metallated DMH-oxirane reaction are noteworthy, and the utility of these operations in the synthesis of 1,4-dicarbonyl compounds[7] from standard precursors is apparent. A further indication of scope is provided by the reaction of the lithio DMH derivatives of acetone and acetaldehyde with cyclohexene oxide to give after hydrolysis pure 19 (87%) and 20 (80%) (as the cyclic hemiacetal), respectively.



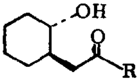
$n\text{-}C_3H_7\overset{O}{\overset{\|}{C}}CH_2CH_2\overset{OH}{C}HCH_3$

17



$n\text{-}C_3H_7\overset{O}{\overset{\|}{C}}CH_2CH_2\overset{O}{\overset{\|}{C}}CH_3$

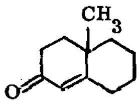
18



19 $R = CH_3$
20 $R = H$

Symmetrical 1,4-dicarbonyl compounds are formed cleanly by reaction of α-lithio DMH's with iodine (1 equiv consumed) at -78°. Thus, from the α-lithiated DMH derivative of acetone after treatment with 1 equiv of iodine at -78° (2 hr) and -78° to 0° for 5 hr and subsequent isolation and periodate hydrolysis, hexan-2,5-dione could be isolated in 90% yield.

III. 1,5-Dicarbonyl Compounds; DMH Modification of the Robinson Annelation. The use of organocopper DMH derivatives opens a wide range of new possibilities for C-C coupling and ring-forming operations in synthesis. For example, the various techniques for Robinson annelation of 2-methylcyclohexanone all lead to attachment of the methyl vinyl ketone (MVK) equivalent at C-(2) and eventual formation of 21 (in yields no better than 50%).[8] In contrast, metallation of the DMH derivative of 2-methylcyclohexane (LDA procedure[1]) in THF and subsequent reaction with 1:1 cuprous iodide-isopropylsulfide complex at -30° (0.5 equiv, 1 hr), and then with MVK (0.5 equiv initially at -30°, gradual warming over 12 hr to 0°), followed by isolation and oxidative hydrolysis gave the 1,5-diketone 22[9] (90-95%), treatment of which with ethanolic base afforded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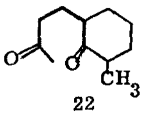
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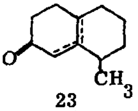
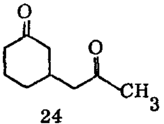

23

quantitatively the octalones 23. The possibility of forming and using cuprate reagents derived from α-lithiated DMH's represents still another advantage vis a vis enolate intermediates. It now seems probable that many of the limitations which have plagued the Robinson annelation can be avoided.

The orange cuprate derivative of acetone DMH (formed as above at -30°) underwent clean 1,4-addition to 2-cyclohexenone and methyl 1-cyclohexenecarboxylate to give after periodate hydrolysis diketone 24 (90%) and keto ester 25 (80%) respectively. Similarly the keto aldehyde 26[10] was obtained in ca. 75% yield from the cuprate of acetaldehyde DMH and 2-cyclohexenone. As expected only 1,2-addition is observed with enones and α-lithiated DMH's; for example, α-lithiated acetone DMH and 2-cyclohexenone affords exclusively the DMH of 1-acetonyl-2-cyclohexen-1-ol.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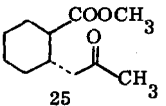
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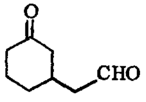
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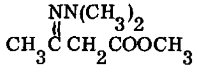
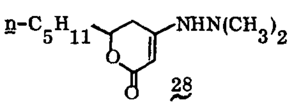
IV. Polyfunctional Compounds from Bis-metallated DMH Derivatives. Formation of doubly metallated DMH's can broaden further the range of useful synthetic operations. Thus, the bis-DMH of hexane-2,5-dione reacts with 2 equiv of n-butyllithium in THF at -78° (1 hr) and -20° (20 min), forming a dianion as shown by reaction with methyl iodide to form the bis-DMH of octane-3,6-dione (91%, isolated). The DMH of methylacetoacetate (27) undergoes double metallation (2 equiv LDA at 0° or 2 equiv NaH at -20° or 2 equiv n-butyllithium at -78°) and further reaction with 1-hexanal to form the lactone 28, m.p. 85° (75% yield), which undergoes hydrolysis with 5% aq. HCl at 25° for 15 hr to give the hydroxy keto acid 29 in 80% yield.[11]


$CH_3\overset{NN(CH_3)_2}{\overset{\|}{C}}CH_2COOCH_3$

27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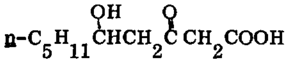
$n\text{-}C_5H_{11}\overset{OH}{C}HCH_2\overset{O}{\overset{\|}{C}}CH_2COOH$

29

References

1. E. J. Corey and D. Enders, *Tetrahedron Letters,* preceding paper.
2. For a summary of analogous "directed aldol" condensations using aldimines or ketimines see, G. Wittig and H. Reiff, *Angew. Chem. Int. Ed.*, **7**, 7 (1968).
3. Satisfactory infrared, pmr and mass spectra were obtained on purified samples of reaction products described herein.
4. This is much more convenient (especially on a large scale) than the use of gaseous monomeric formaldehyde which is recommended for enolates; see G. Stork and J. d'Angelo, *J. Amer. Chem. Soc.*, **96**, 7114 (1974). The hydrolysis of **9** to the corresponding β-hydroxy ketone is so facile that it occurred during work-up if excess acetic acid (2 equiv) was used.
5. The very sensitive aldol **14** could only be obtained in ethereal or methylene chloride solution since bimolecular condensation ensued rapidly after concentration.
6. E. J. Corey and J. W. Suggs, *Tetrahedron Letters*, 2647 (1975).
7. For a review of this unusually active area of synthetic endeavor see, T-L. Ho, *Synthetic Comm.*, **4**, 265 (1974).
8. See (a) C. H. Heathcock, J. E. Ellis, J. E. McMurry and A. Coppolino, *Tetrahedron Letters*, 4995 (1971) and (b) J. A. Marshall and W. I. Fanta, *J. Org. Chem.*, **29**, 2501 (1964).
9. J. A. Marshall and D. J. Schaeffer, *J. Org. Chem.*, **30**, 3642 (1965).
10. Previously prepared using divinylcuprate as the "acetaldehyde" cuprate equivalent; see, E. J. Corey and R. L. Carney, *J. Amer. Chem. Soc.*, **93**, 7318 (1971).
11. This research was assisted by grants from the Studienstiftung des deutschen Volk and the U. S. National Science Foundation.