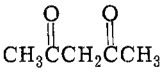
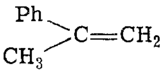
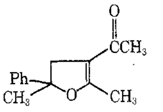
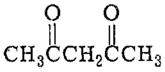
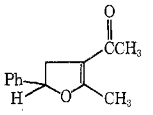
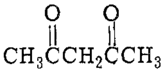
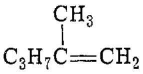
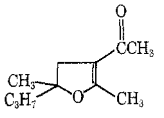
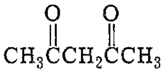
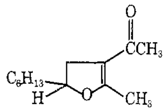
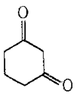
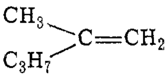
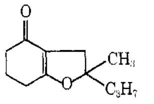
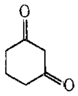
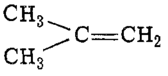
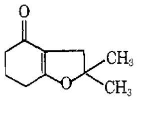
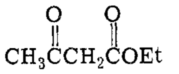
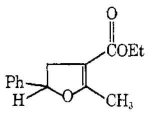
Table I
Synthesis of Dihydrofurans

Ketone	Olefin	Dihydrofuran	Yield,[a] %
 $CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}CH_3$			100
 $CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}CH_3$	$PhCH{=}CH_2$		30
 $CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}CH_3$	 $C_3H_7\overset{CH_3}{\overset{\vert}{C}}{=}CH_2$		40
 $CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}CH_3$	$C_6H_{13}CH{=}CH_2$		10 (33)[b]
			74
			>40
 $CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}OEt$	$PhCH{=}CH_2$		57

[a] Yields are based on Mn^{3+} consumed, assuming 2 equiv/mol of product. [b] In the presence of trifluoroacetic acid as cosolvent.

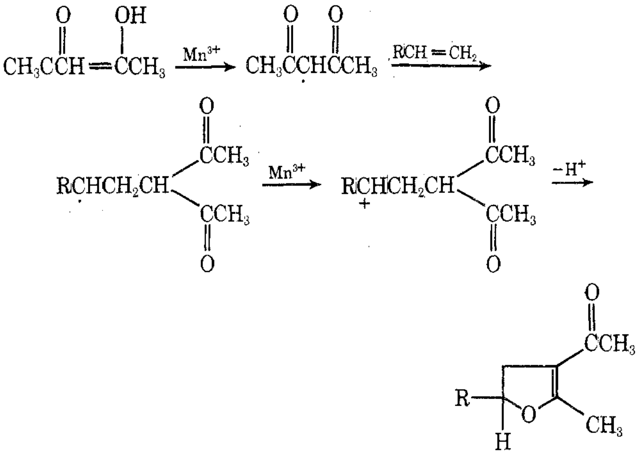
the case of simple ketones (2-methyl-5-phenyl-4,5-dihydrofuran was obtained as a very minor product in the reaction of acetone with styrene). This can be rationalized on the basis of the more rapid cyclization of the carbonium ion intermediate due to the greater enol content of these dicarbonyl compounds, as well as the greater stability of the resulting carbonyl-stabilized dihydrofuran products toward acid-catalyzed ring opening under reaction and work-up conditions.[5]

The dihydrofurans produced in the manganic acetate reaction of acetylacetone with terminal olefins have in all cases consisted of only one isomer, namely, the 5-substituted 2-methyl-3-acetyl-4,5-dihydrofuran. This stands in sharp contrast to the dihydrofuran reported in the thallic acetate reaction of acetylacetone with styrene,[6] where only the 4-substituted isomer was observed. The corresponding reaction of lead tetraacetate led to either one or both isomers, depending on the solvent employed.[7] At that time, two competing ionic mechanisms were proposed,[7] although the controlling factors for these two paths remained unexplained.

Our experience with manganic acetate now suggests that the 5 isomer is produced exclusively *via* a free-radical mechanism as depicted in Scheme I. The formation of the 4 isomer can then be rationalized by an ionic mechanism similar to that suggested,[6,7] in which a benzylic carbonium ion is produced by attack of the electrophilic metal acetate, which then, in turn, adds to the diketone.

The effect of solvent on the $Pb(OAc)_4$ reaction can be understood in terms of the well-established competition between ionic and free-radical pathways characteristic of

Scheme I



lead tetraacetate,[8] both of which occur in the polar acetic acid solvent, whereas only the free-radical product is observed in benzene. This mechanistic explanation is consistent with the reported formation of the 5-substituted dihydrofuran in the electrochemical oxidative addition of sodium acetylacetonate to olefins,[9] which presumably is a free-radical reaction similar to that of manganic acetate.

The simple one-step synthesis of dihydrofurans presented in this communication represents one more example of syntheses based on the selective generation and oxidation of organic free radicals. Further examples of such syntheses will be presented in forthcoming publications.

Acknowledgment. The skillful technical assistance of George Stead is gratefully acknowledged.

References and Notes

(1) E. I. Heiba and R. M. Dessau, *J. Amer. Chem. Soc.*, **93**, 524 (1971).

(2) The dihydrofuran analyzed for $C_{14}H_{16}O_2$: mol wt (mass spectrum) 216; ir peaks at 5.96, 6.15, 6.24, 7.22, and 8.02 μ; nmr τ 8.35 (3 H, s), 7.85 (3 H, s), 7.7 (3 H, tr, J = 1.4 Hz), 6.9 (2 H, m), 2.7 (5 H, m).

(3) E. I. Heiba, R. M. Dessau, and W. J. Koehl, Jr., *J. Amer. Chem. Soc.*, **91**, 138 (1969).

(4) E. I. Heiba and R. M. Dessau, *J. Amer. Chem. Soc.*, **94**, 2888 (1972).

(5) L. H. Brannigan and D. S. Tarbell, *J. Org. Chem.*, **35**, 639 (1970).

(6) K. Ichikawa, S. Uemura, and T. Sugita, *Tetrahedron*, **22**, 407 (1966).

(7) K. Ichikawa and S. Uemura, *J. Org. Chem.*, **32**, 493 (1967).

(8) E. I. Heiba, R. M. Dessau, and W. J. Koehl, Jr., *J. Amer. Chem. Soc.*, **90**, 2706 (1968); R. O. C. Norman and C. B. Thomas, *J. Chem. Soc. B*, 771 (1967).

(9) H. Schafer and A. Alazrak, *Angew. Chem., Int. Ed. Engl.*, **7**, 474 (1968).

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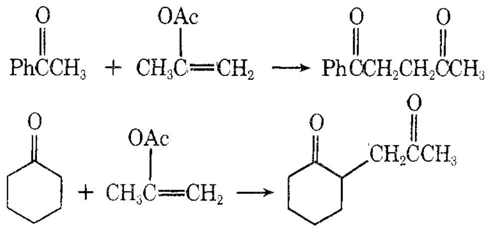
Oxidation by Metal Salts. XII.
A Novel One-Step Synthesis of 1,4 Diketones

Summary: A convenient one-step synthesis of 1,4 diketones by the reaction of enol esters with ketones in the presence of manganic acetate is presented.

Sir: As a continuation of our interest in the development of new synthetic methods based on the selective generation and oxidation of organic free radicals,[1] we wish to report a convenient one-step synthesis of 1,4 diketones from readily available starting materials. The development of new synthetic routes to 1,4 diketones has received considerable interest during the past few years, in view of their value as cyclopentenone precursors.[2]

We have previously demonstrated[1b,c] that ketones could be added to olefins in the presence of an oxidant such as manganic acetate to give a variety of products. We now wish to report the formation of 1,4 diketones as the predominant nonpolymeric reaction product when an enol ester is treated with a ketone and manganic acetate. Thus, the reaction of acetophenone with isopropenyl acetate and manganic acetate produced 1-phenylpentane-1,4-dione, while the corresponding reaction with cyclohexanone gave 2-(2-oxopropyl)-cyclohexanone.

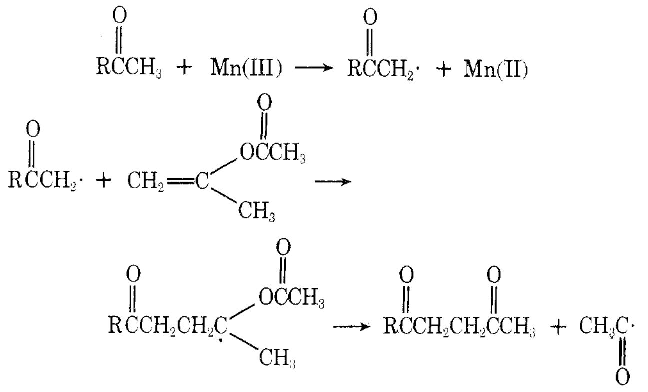


Reactions were generally conducted at 50–70°, with reaction times on the order of 1 hr or less. Yields of 1,4 diketones were 20–35% based on the manganic ion consumed, assuming 2 equiv/mol of diketone produced.[3] Despite the modest yield obtained, this method is well suited for the laboratory preparation of 1,4 diketones in a single step from readily available reagents, especially since manganic acetate can be prepared *in situ* by the addition of potassium permanganate to a solution of manganous acetate in acetic acid.

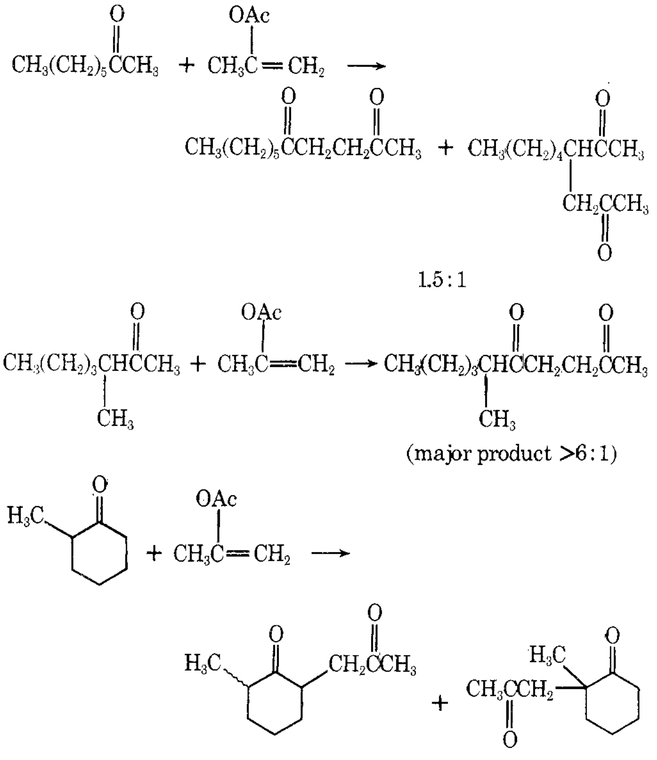
In a typical experiment, 0.5 mol of cyclohexanone and 0.5 mol of isopropenyl acetate were added together to 0.5 mol of a manganic acetate–acetic acid solution at 70°. The reaction, which was over in ~10 min, yielded 8 g (22% yielded based on manganic ion) of 1,4 diketone as the predominant product after extraction and distillation.

A reasonable mechanism for the formation of 1,4-diketones using manganic acetate is shown in Scheme I. The success of this synthesis as shown in Scheme I is due to three factors: (1) the selective oxidation of enolizable ketones by manganic ions to generate α-keto radicals exclusively, (2) the facile elimination of acetyl radical from the α-acetoxyalkyl adduct radical, and (3) the resistance of the initially formed α-keto radical to oxidation by manganic ion due to the electron-withdrawing character of the carbonyl group. Since the initial formation of the α-keto radical involves attack by manganic ion on either the enol or enolate ion of the ketone,[1b] unsymmetrical ketones having two different enolizable hydrogens would be expected to lead to mixture of products. This was indeed observed; the predominant diketone product in each case was that derived from the less substituted α-keto radical, as shown in Scheme II. The preferential formation of the least substituted α-keto radical from unsymmetrical ketones is consistent with a base-catalyzed enolization mechanism, evidence for which has been presented earlier.[1b]

Scheme I



Scheme II

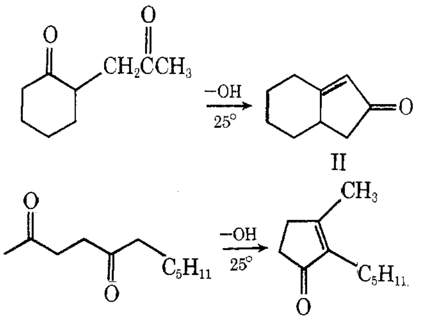


1.5:1

(major product >6:1)

(6:1 cis: trans)

1,4 diketones are useful intermediates in that they can be readily transformgd into cyclopentenone derivatives by treatment with dilute base.[4] Thus, 2-(2-oxopropyl)cyclohexanone (I) was converted in high yield to hydrindenone (II) [bp 70° (0.1 mm); ir 1718, 1626 cm^{-1}; pmr τ 4.2 (1 vinyl H); uv λ_{max} (EtOH) 230 mμ (ϵ 14,000)], and undecadione-2,5 was transformed into dihydrojasmone.



The relatively simple one-step synthesis of 1,4 diketones presented in this communication represents one more example of syntheses based on the selective generation and oxidation of organic free radicals. Further examples of such syntheses will be presented in forthcoming publications.

Acknowledgment. The skillful technical assistance of Ms. M. Zikos is gratefully acknowledged.

Supplementary Material Available. A detailed experimental procedure will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-3457.

References and Notes

(1) (a) E. I. Heiba, R. M. Dessau, and W. J. Koehl, Jr., *J. Amer. Chem. Soc.*, **90**, 5905 (1968); (b) E. I. Heiba and R. M. Dessau, *ibid.*, **93**, 524 (1971); (c) E. I. Heiba and R. M. Dessau, *ibid.*, **94**, 2888 (1972).

(2) G. Stork and R. Borch, *J. Amer. Chem. Soc.*, **86**, 935 (1964); G. Büchi and H. Wüest, *J. Org. Chem.*, **31**, 977 (1966); E. J. Corey and L. S. Hegedus, *J. Amer. Chem. Soc.*, **91**, 4926 (1969); E. Wenkert, R. A. Mueller, E. J. Reardon, Jr., S. S. Sathe, D. J. Scharf, and G. Tosi, *ibid.*, **92**, 7428 (1970); J. E. McMurry and T. E. Glass, *Tetrahedron Lett.*, 2575 (1971); J. E. McMurry and J. Melton, *J. Amer. Chem. Soc.*, **93**, 5309 (1971); T. Mukaiyama, K. Narasaka, and M. Furusato, *ibid.*, **94**, 8641 (1972); P. A. Grieco and C. S. Pogonowski, *J. Org. Chem.*, **39**, 733 (1974).

(3) Two equivalents of manganic ion are required since the acetyl radical eliminated undoubtedly is quantitatively oxidized to the carbonium ion by manganese(III).

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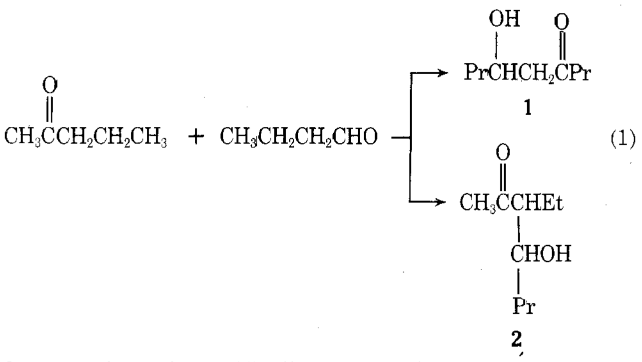
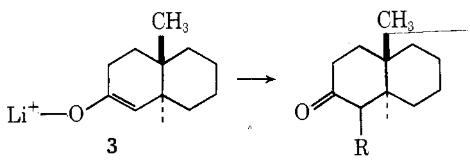
Regiospecific Aldol Condensations of the Kinetic Lithium Enolates of Methyl Ketones

Summary: The aldol condensation can be carried out regiospecifically and in good yield at the methyl group of methyl ketones *via* their kinetic lithium enolates generated in tetrahydrofuran at −78°.

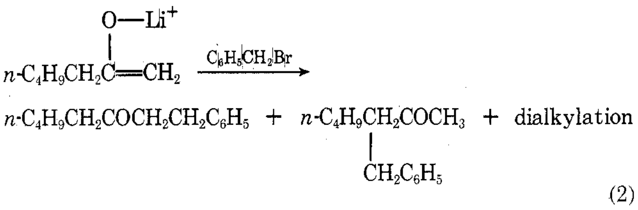
Sir: The aldol condensation is one of the fundamental reactions for the formation of carbon–carbon bonds. It has established itself as one of the most important methods for the formation of five- and six-membered rings.[1] In contrast, directed intermolecular aldol condensation has not been a generally feasible synthetic method[2] because of rapid equilibration of the anions especially of methyl ketones, during their formation. Two recent examples[3,4] illustrate this difficulty (eq 1). We demonstrated 13 years ago[5] that certain regiospecifically generated, thermodynamically unstable *lithium* enolates can be alkylated with reactive alkyl halides more rapidly than they undergo equilibration (*cf.* 3 → 4).





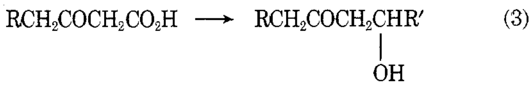
3 4

Efforts to apply this technique to the kinetic primary ion derived from a methyl ketone have, however, not met with success, even with halides which proved satisfactory with 3.[6,7] For instance, the alkylation of enolates such as $RCHCH_2C(O^-){=}CH_2Li^+$ with benzyl bromide gave relatively low yields of mixtures of alkylation at the terminal and internal positions[8] (eq 2).



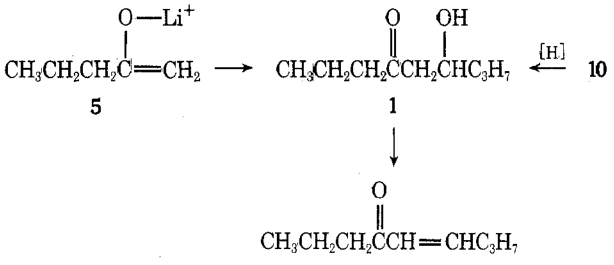
$$n\text{-}C_4H_9CH_2C(OLi^+){=}CH_2 \xrightarrow{C_6H_5CH_2Br} n\text{-}C_4H_9CH_2COCH_2CH_2C_6H_5 + n\text{-}C_4H_9CH_2COCH_3(CH_2C_6H_5) + \text{dialkylation} \quad (2)$$

An ingenious solution to the synthesis of regiospecific aldols, including the linear aldols from methyl ketones, was provided by Schöpf[9] who used β-keto acids to achieve the desired regiospecificity, as shown in eq 3. The overall yields are, however, only fair to moderate.

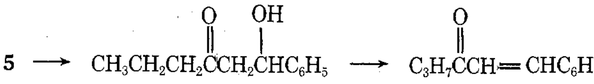


$$RCH_2COCH_2CO_2H \longrightarrow RCH_2COCH_2CHR'(OH) \quad (3)$$

It occurred to us that the difficulty in trapping the kinetic anions of simple methyl ketones with alkyl halides might not be encountered with a more reactive nucleophile such as an aldehyde. This has indeed proved to be the case.[10] To the kinetic enolate 5 prepared from 2-pentanone and 1.1 equiv of lithium diisopropylamide in dry tetrahydrofuran at −78° was added, dropwise, a solution of butyraldehyde in tetrahydrofuran. After 15 min, the cooling was removed and the solution was immediately neutralized with 1.1 equiv of acetic acid in ether. Isolation and distillation (Kugelrohr, 100° (10 mm)) gave in 65% yield the aldol 1: ir (film) 5.81, 2.93 μ; nmr ($CDCl_3$) δ 0.9–1.8 (m, 13 H), 2.2–2.6 (m, 4 H, $\mathbf{CH_2}C({=}O)\mathbf{CH_2}$), 4.1 (m, 1 H **H**COH); *m/e* 140 ($M+ - H_2O$), 97 ($PrCH{=}CH{-}C({=}O)^+$). The absorption in the nmr at δ 2.3, which is characteristic of the acetyl group of 2, was very small, suggesting that the aldol 1 was at least 90% pure. The structure was established further (a) by comparison with an authentic mixture of 1 and 2 (separable[11] on 5% QF_1 at 150°), (b) by showing the identity of 1 with the product of hydrogenation (Pd–C in ethanol) of the hydroxydienone 10, (c) by dehydration (*p*-toluenesulfonic acid, benzene, 1 hr reflux, 72% yield) to the α,β-unsaturated ketone 6 identical with an unambiguously synthesized[12] sample. These results show that lithium enolates of methyl ketones can retain their integrity in the aldol condensation.[13]



Under similar conditions, the kinetic lithium enolate 5 was condensed with benzaldehyde to give the aldol 7 in 75–80% yield (Kugelrohr, bp 95–100° (0.025 mm)). The structure followed from the nmr ($CDCl_3$): δ 7.3 (C_6H_5, s), 5.1 (d of d, **H**COH), 2.6 ($HOCC\mathbf{H_2}C{=}O$), 2.2 (q, $Et\text{-}\mathbf{CH_2}C{=}O$), 0.9–1.8 (m, C_2H_5). It was further confirmed (a) by oxidation (MnO_2–$CHCl_3$, room temp) to 1-phenyl-1,3-hexanedione, identical with a sample made from the dianion of 1-phenyl-1,3-butanedione (2 equiv of $LiN(i\text{-}Pr)_2$



7 8

$$5 \longrightarrow CH_3CH_2CH_2C({=}O)CH_2CH(OH)C_6H_5 \longrightarrow C_3H_7C({=}O)CH{=}CHC_6H_5$$