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).

(4) H. Hunsdiecker, *Chem. Ber.*, **75**, 455 (1942).

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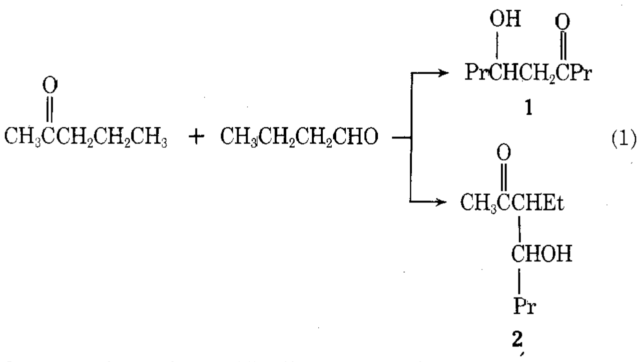
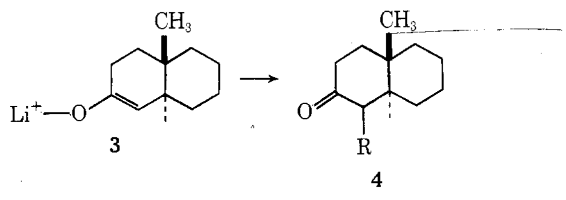
Received August 8, 1974

Regiospecific Aldol Condensations of the Kinetic Lithium Enolates of Methyl Ketones

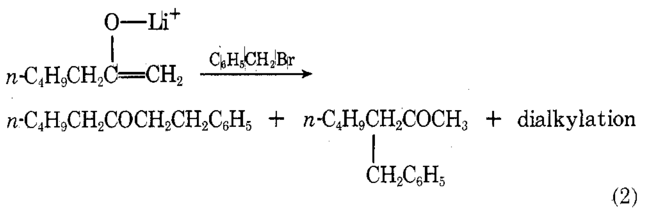
Summary: The aldol condensation can be carried out regiospecifically and in good yield at the methyl group of methyl ketones *via* their kinetic lithium enolates generated in tetrahydrofuran at −78°.

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).



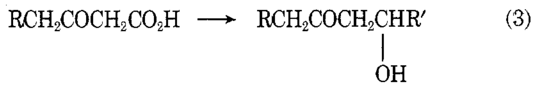


Efforts to apply this technique to the kinetic primary ion derived from a methyl ketone have, however, not met with success, even with halides which proved satisfactory with 3.[6,7] For instance, the alkylation of enolates such as $RCHCH_2C(O^-){=}CH_2Li^+$ with benzyl bromide gave relatively low yields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



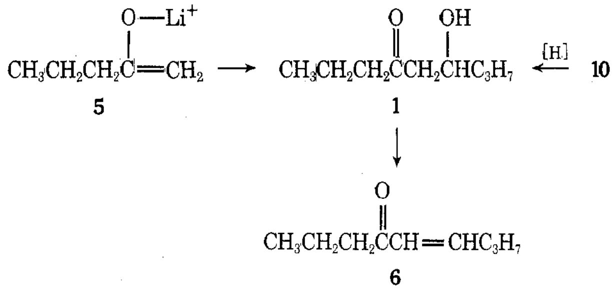
$$n\text{-}C_4H_9CH_2\overset{\overset{\displaystyle O{-}Li^+}{|}}{C}{=}CH_2 \xrightarrow{C_6H_5CH_2Br} n\text{-}C_4H_9CH_2COCH_2CH_2C_6H_5 + n\text{-}C_4H_9CH_2CO\underset{\underset{\displaystyle CH_2C_6H_5}{|}}{C}H_3 + \text{dialkylation} \qquad (2)$$

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.

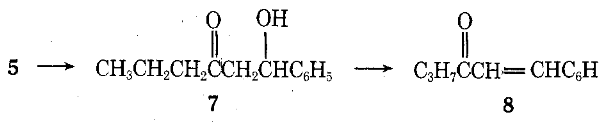


$$RCH_2COCH_2CO_2H \longrightarrow RCH_2COCH_2\underset{\underset{\displaystyle OH}{|}}{C}HR' \qquad (3)$$

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, $C\mathbf{H}_2C({=}O)C\mathbf{H}_2$), 4.1 (m, 1 H **H**COH); *m/e* 140 (M+ − H_2O), 97 ($PrCH{=}CH\text{-}C({=}O)^+$). 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 ($HOCC\mathbf{H}_2C{=}O$), 2.2 (q, $Et\text{-}C\mathbf{H}_2C{=}O$), 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 $LiN(i\text{-}Pr)_2$

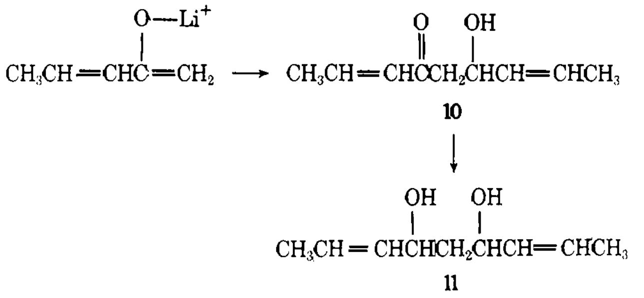


$$5 \longrightarrow CH_3CH_2CH_2\overset{\overset{\displaystyle O}{\|}}{C}CH_2\overset{\overset{\displaystyle OH}{|}}{C}HC_6H_5 \longrightarrow C_3H_7\overset{\overset{\displaystyle O}{\|}}{C}CH{=}CHC_6H_5$$

7 8

in THF) with ethyl iodide; and (b) by dehydration (p-toluenesulfonic acid, refluxing benzene) to the known[14] unsaturated ketone **8**.

The kinetic lithium enolates of α,β-unsaturated ketones[15] can also be used in regiospecific aldol condensation. The lithium enolate from 3-penten-2-one was prepared and condensed, as described above, with crotonaldehyde to give the dienolone **10** in 70% yield (after preparative tlc on silica gel with 4:1 methylene chloride–ether): ir (film) 3.0, 5.9 μ; nmr ($CDCl_3$) δ 5.9–7.1 (m, $CH_3CH{=}CH{=}C{=}O$) 5.5–5.7 (m, $CH_2CH{=}CHCHOH{-}$), 4.4–4.6 (m, HCOH), 2.6 (d, J = 6 Hz, $-CH_2C{=}O$), 1.98 (d, b, J = 6 Hz, $O{=}CC{=}CCH_3$), 1.85 (d, J = 5 Hz $CH_3C{=}CCHOH$). Analysis was performed on the bis(trimethylsilyl) ether of the doubly unsaturated diol **11** from reduction (bis(2-methoxyethoxy)aluminum hydride in benzene): m/e 300.1938 (calcd 300.1940). Catalytic hydgenation of **10** gave the saturated aldol **1** identical (*vide supra*) with the product of the aldol condensation of butyraldehyde and the kinetic lithium enolate of 2-pentanone.



$$\mathrm{CH_3CH{=}CH\overset{O-Li^+}{\overset{|}{C}}{=}CH_2} \longrightarrow \mathrm{CH_3CH{=}CH\overset{O}{\overset{\|}{C}}CH_2\overset{OH}{\overset{|}{C}}HCH{=}CHCH_3}$$

10

$$\downarrow$$

$$\mathrm{CH_3CH{=}CH\overset{OH}{\overset{|}{C}}HCH_2\overset{OH}{\overset{|}{C}}HCH{=}CHCH_3}$$

11

The ability of regiospecifically produced lithium enolates to maintain their integrity in aldol condensations should greatly extend the usefulness of the reaction.[16,17]

References and Notes

(1) *Cf.* H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Menlo Park, Calif., 1972.

(2) "No examples (of successful aldol condensation under nonequilibrating conditions) involving methyl ketones are known": A. T. Nielsen, *Org. React.*, **16**, 37 (1968).

(3) M. Gaudemar, *C. R. Acad. Sci.*, **270**, 533 (1974).

(4) C. A. Brown, *J. Org. Chem.*, **39**, 1324 (1974).

(5) G. Stork, P. Rosen, and N. L. Goldman, *J. Amer. Chem. Soc.*, **83** 2965 (1961); G. Stork, P. Rosen, N. L. Goldman, R. Coombs, and J. Tsuji, *ibid.*, **87**, 275 (1965).

(6) Except, of course, when the kinetic enolate is also the more stable one.

(7) For the structure of the kinetic enolates of methyl ketones, see H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 1341 (1965); H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *ibid.*, **34**, 2324 (1969).

(8) "Selective alkylation of the methyl group of ketones RCH_2COCH_3 by any method which involves generation of the enolate $RCH_2C(O^-){=}CH_2Li^+$ in an ethereal solvent will not be a good synthetic procedure": H. O. House, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **36**, 2361 (1971).

(9) C. Schöpf and K. Thierfelder, *Justus Liebigs Ann. Chem.*, **518**, 127 (1935). For a more recent application to a mechanistic problem, *cf.* M. Stiles, D. Wolf, and G. V. Hudson, *J. Amer. Chem. Soc.*, **81**, 628 (1959).

(10) H. O. House, D. S. Crumrine, A. Y. Teranishi, and H. D. Olmstead, *J. Amer. Chem. Soc.*, **95**, 3310 (1973), recently reported on the aldol condensation of acetophenone and of acetomesitylene with benzaldehyde, using the lithium, magnesium, or zinc enolates. The question of regiospecificity obviously does not arise in the case of these particular methyl ketones.

(11) The linear isomer had the longer retention time.

(12) By reduction of the enol ether of 4,6-nonanedione with bis(2-methoxyethoxy)aluminum hydride in benzene, followed by aqueous acid hydrolysis.

(13) In a paper (ref 3) which was published after the completion of our own work, the statement is made (without experimental details) that direct preparation of lithium enolates with lithium diisopropylamide in tetrahydrofuran had not given satisfactory results. In the absence of experimental details, the reason for this difference with our own results is unclear.

(14) C. Harres and P. Bromberger, *Ber.*, **35**, 3088 (1902).

(15) For the structure of the kinetic enolates of *cyclic* α,β-unsaturated ketones, see R. A. Lee, C. McAndrews, K. M. Patel, and W. Reusch, *Tetrahedron Lett.*, 965 (1973); G. Stork and R. L. Danheiser, *J. Org. Chem.*, **38**, 1775 (1973).

(16) We have, for instance (G. Stork and J. D'Angelo, in preparation), shown that the synthetically versatile α-hydroxymethyl ketones can be produced regiospecifically by trapping enolate ions with formaldehyde.

(17) We thank the National Institutes of Health and the National Science Foundation for their support of this work.

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Received August 23, 1974

Capillary Techniques in Organic Synthesis

Summary: Some reactions such as nucleophilic displacements and additions have been found to be considerably accelerated if allowed to take place inside the pores of high surface area materials (silica gel, aluminum oxide and others).

Sir: Solids such as activated charcoal, silica gel, and aluminum oxide having high surface areas promote reactions which would otherwise require much higher temperatures or would not take place at all. Innumerable examples of such reactions in the vapor phase are well known.

In the liquid phase, catalytic effects of the adsorbent were frequently observed during adsorption chromatography when polymerization, isomerization, hydrolysis, dehydration,[1] dehydrohalogenation,[2] reduction,[3] and similar alterations[1] of the chromatographed substances were occasionally recorded. In some instances, the adsorbent was pretreated with certain chemicals to achieve reactions which would not occur over the pure adsorbent.[4]

In all these instances, the reactions take place between the compound and the adsorbent which reacts by virtue of its chemical properties (acidity, dehydrating power, etc.).

It was of interest to find out whether porous materials could be used just to bring two or more compounds together in the liquid phase inside the pores where the minimum pore size is of the order of several molecular diameters. For this purpose, several displacement and addition reactions have been carried out.

When a column of acid aluminum oxide was soaked with a solution of benzyl chloride in chloroform containing hydrazoic acid, and after 16 hr at room temperature the column was eluted with hexane and ether, 49.5% conversion and 68.5% yield of benzyl azide was obtained.

Similar treatment of dialkyl α-bromo-α'-fluorosuccinate or α,α'-dibromosuccinate with a solution of hydrazoic acid gave dialkyl azidofumarate. Preparation of the same compound required refluxing of the halogenated esters with sodium azide in methanol for 12 hr.[5]

The Diels–Alder reaction between 1-acetoxy-1,3-butadiene and fluoranil (tetrafluoro-p-benzoquinone) requires heating of the benzene solution of the two compounds at 98° for several hours.[6] When the same solution was placed in a column of silica gel at room temperature for 60 hr, the product, 5-acetoxy-2,3,4a,8a-tetrafluoro-4a,5,8,8a-tetrahydro-1,4-naphthoquinone, was obtained by chloroform elution in 49.5% conversion and 67–78% yield.

Similar reaction of 1-acetoxy-1,3-butadiene with p-benzoquinone was described taking place at a reflux temperature of carbon tetrachloride and diisopropyl ether after at least 1 hr.[7] When a solution of 1-acetoxy-1,3-butadiene and p-benzoquinone in benzene was allowed to react for 40 hr at room temperature in a column of silica gel presoaked with hexane, not only did the addition occur, but the product, 5-acetoxy-4a,5,8,8a-tetrahydro-1,4-naphthoquinone, eliminated acetic acid, and the intermediate dihydro com-