Reactions of β-Diketones with Aromatic Aldehydes and Ketones in the Presence of Potassium Hydride[1a]

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Received July 10, 1979

Reaction of benzoylacetone (**1a**) and acetylacetone (**1b**) with benzophenone in the presence of excess potassium hydride affords terminal aldol condensation products 5-hydroxy-1,5,5-triphenyl-1,3-pentanedione (**3**) and 6-hydroxy-6,6-diphenyl-2,4-hexanedione (**9**), respectively. Potassium hydride promoted reactions of **1a** with *p*-anisaldehyde and *p*-tolualdehyde result in formation of tetraketones 1,9-diphenyl-5-(*p*-methoxyphenyl)-1,3,7,9-nonanetetrone (**5a**) and 1,9-diphenyl-5-(*p*-tolyl)-1,3,7,9-nonanetetrone (**5b**), respectively. Evidence is presented to support formation of **5a** and **5b** via a sequence of reactions involving Michael addition of the dianion of **1a** to the monoanion of the unsaturated β-diketones derived from terminal aldol condensation of the respective aldehydes with the dianion of **1a**. Reaction of **1b** with *p*-tolualdehyde under similar conditions yields mainly 1,7-bis(*p*-tolyl)-1,6-heptadiene-3,5-dione (**10**). Reaction of **1b** with the monoanion of 1-phenyl-5-(*p*-methoxyphenyl)-4-pentene-1,3-dione (**2b**) in the presence of excess potassium hydride affords the novel hexaketone 1,15-diphenyl-5,11-bis(*p*-methoxyphenyl)-1,3,7,9,13,15-pentadecanehexone (**18**).

In a study of the efficacy of sodium hydride (NaH) as a base for anion formation, Miles, Harris, and Hauser[2] reported that condensation of benzoylacetone (**1a**) with aromatic aldehydes and ketones, using this base in refluxing 1,2-dimethoxyethane (DME), afforded unsaturated β-diketones **2a–b** in modest yields. Although formation

$$\underset{\substack{\mathbf{1a},\ R = C_6H_5\\ \mathbf{1b},\ R = CH_3}}{RCOCH_2COCH_3} \qquad \underset{\substack{\mathbf{2a},\ R_1 = R_2 = C_6H_5\\ \mathbf{2b},\ R_1 = H;\\ R_2 = p\text{-}CH_3OCH_6H_4}}{C_6H_5COCH_2COCH{=}CR_1R_2}$$

of **2a–b** suggests the intermediacy of the 1,3-dianion of **1a**, these authors presented evidence that **1a** was converted only to its monoanion by NaH. Thus, the mechanism of formation of **2a,b** was not evident. Accepted mechanistic ideas would suggest that these products arise from an aldol-type condensation at the terminal site of **1a**. However, this would require that sometime during the reaction **1a** acquire carbanion character at the terminal methyl group. Even if this were to occur, it is difficult to rationalize the elimination process that leads to **2b** in the aprotic reaction medium.

Recently, the superior properties of potassium hydride (KH) as a kinetic base, as compared to NaH, have been demonstrated with a variety of active hydrogen compounds.[3] We thought that the mild conditions which can be used with KH (tetrahydrofuran (THF) at 25 °C) might allow isolation of aldol products derived from **1a**. In addition to providing a convenient synthesis of the resulting hydroxy β-diketones, it was anticipated that such reactions might also provide some insight into the pathway by which terminal condensation products **2a,b** are formed. Accordingly, we undertook an investigation of the reactions of **1a** and **1b** with benzophenone, *p*-anisaldehyde, and *p*-tolualdehyde using KH as the base.

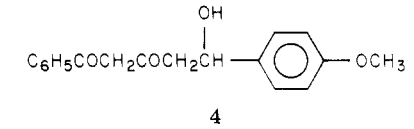
Results and Discussion

When a suspension of 40 mmol of KH in anhydrous THF was treated with 10 mmol of benzoylacetone (**1a**) at 25 °C, the amount of hydrogen evolved (11 mmol) indicated only about 10% dianion formation. Surprisingly, addition of benzophenone to this suspension of excess KH and the monoanion of **1a** led to evolution of an additional 0.8–0.9 equiv of hydrogen. Thus, the total hydrogen supports twofold ionization of **1a**. Careful acidification permitted isolation of the known aldol condensation product **3**[4] in 66% yield. The liberation of hydrogen upon

$$\mathbf{1a} + (C_6H_5)_2CO \xrightarrow[THF]{KH} \underset{\mathbf{3}}{C_6H_5COCH_2COCH_2C(C_6H_5)_2OH}$$

addition of benzophenone parallels the results reported by Miles, Harris, and Hauser,[2] when esters were added to the monoanion of **1a** in the presence of excess NaH.

The excellent result obtained in the KH experiment with benzophenone prompted us to attempt preparation of other aldol products, using aromatic aldehydes. Vigorous hydrogen evolution occurred when *p*-anisaldehyde (10 mmol) was added to the monoanion of **1a** (10 mmol) in THF containing excess KH. Acidification and solvent removal led to a pasty mass from which *p*-anisic acid (38% based on *p*-anisaldehyde) was isolated by bicarbonate extraction. Crystallization yielded a pale yellow solid whose melting point was close to that of the reported carbinol **4**.[4] However, its ^1H NMR spectrum could not be reconciled with this structure.



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The absence of any absorption for an alcohol and the number of absorptions (and their relative intensities) suggested a molecule more symmetric than **4**. The large absorption in the aromatic region required a structure containing two C_6H_5 groups for each *p*-$CH_3OC_6H_4$ group.

(1) (a) Supported by NSF Grant No. CHE 77-13317 and NASA Grant No. NSG 1524. (b) Taken in part from the Ph.D. dissertation of T. L. Rathman, Virginia Polytechnic Institute and State University, July 1976. (c) Department of Chemistry, King College, Bristol, TN 37620.

(2) M. L. Miles, T. M. Harris, and C. R. Hauser, *J. Org. Chem.*, **30**, 1007 (1965).

(3) C. A. Brown, *J. Org. Chem.*, **39**, 3913 (1974).

(4) R. J. Light and C. R. Hauser, *J. Org. Chem.*, **26**, 1716 (1961).

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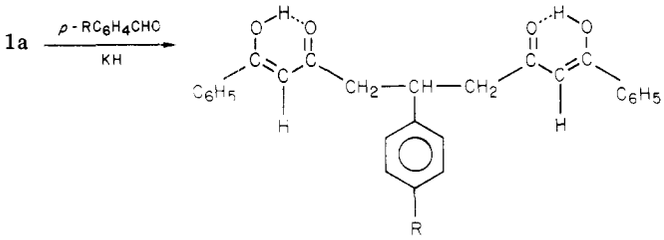
Table I. ^{1}H NMR Spectra of Tetraketones 5a-b, Cyclohexenones 6a-b, and Hexaketone 18

compd.	types of hydrogens and chemical shifts[a]								
	enol	C_6H_5	RC_6H_4	vinyl	methine	methylene	R	C=CCH$_2$	other CH$_2$
5a	15.8, br s	7.75, m 7.39, m	7.13, d 6.79, d	6.02, s		2.85, m	3.70, s		3.99[b]
5b	16.0, br s	7.74, m 7.40, m	7.10, s	6.03, s	3.76, q	2.81, m	2.29, s		3.97[b]
6a		7.76, m 7.36, m	7.14, d 6.82, d		3.50, m		3.80, s	3.96, s	2.80, br s
6b		7.72 7.32, m	7.06, s		3.50		2.33, s	3.92, s	2.79, d
18	16.0, br s 15.3, br s	7.76, m 7.43, m	7.10, d 6.78, d	6.00, s 5.28, s	3.60, s	2.62, m	3.73, s		

[a] The integrals were correct for the number of hydrogens of each type. Multiplicities are designated as follows: m = multiplet, s = singlet, d = doublet, br s = broad singlet, q = quintet. [b] Absorptions for keto form (<10%).

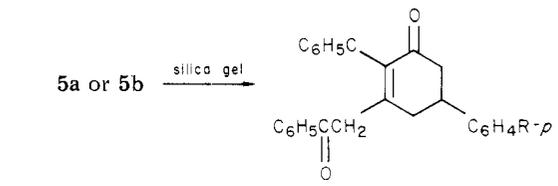
The spectrum was reconcilable with tetraketone structure **5a**. Since the expected quintet for the methine hydrogen



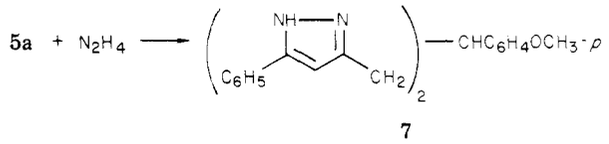
5a, R = OCH_3
5b, R = CH_3

of **5a** was apparently masked by the CH_3O absorption, we repeated the reaction of **1a** with *p*-tolualdehyde in order to obtain a system with a more clearly defined spectrum. This reaction resulted in isolation of *p*-toluic acid and 62% of tetraketone **5b**, possessing the expected *p*-CH_3 singlet at 2.29 ppm and methine quintet at 3.76 ppm. The ^{1}H NMR spectra of **5a** and **5b** are tabulated in Table I.

Further support for structural assignments **5a** and **5b** was obtained by ring closure to form cyclohexenones **6a** and **6b** and by conversion of **5a** to bispyrazole **7** with excess hydrazine. Elemental analyses and ^{1}H NMR spectra (Table I) support the structures of **6a**, **6b**, and **7**.



6a, R = OCH_3
6b, R = CH_3



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In an attempt to determine the possible role of the expected (but unobserved) aldol product **4** in the formation of **5a** we studied the reaction of **4** and KH, with and without *p*-anisaldehyde. Exposure of **4** to excess KH in THF, with no *p*-anisaldehyde present, afforded tetraketone **5a** and *p*-anisic acid. None of the unsaturated β-diketone **2b** was detectable, even by TLC. Reaction of **4** with excess KH, along with 1 equiv of *p*-anisaldehyde, led to formation of **2b** and *p*-anisic acid. This result suggested that enedione **2b**, rather than tetraketone **5a**, might become the major product if the KH-promoted reaction of **1a** were carried out with 2 equiv of *p*-anisaldehyde. This proved to be the case, as simultaneous addition of **1a** (1 equiv) and *p*-anisaldehyde (2 equiv) to 2.3 equiv of KH in THF yielded **2b** (66%) and *p*-anisic acid (61%).

Next, a series of experiments, similar to those described above, was conducted using acetylacetone (**1b**). Treatment of **1b** with excess KH at 25 °C in THF resulted in liberation of 1.1–1.2 equiv of hydrogen. An additional 4 h of reflux led to evolution of another 0.4 equiv of hydrogen. Addition of benzyl chloride *was not* accompanied by hydrogen evolution, and 6-phenyl-2,4-hexanedione (**8**)[5] was produced in only 19% yield.

$$\mathbf{1a} + C_6H_5CH_2Cl \xrightarrow[THF]{KH} \underset{\mathbf{8}}{CH_3COCH_2COCH_2CH_2C_6H_5}$$

As was observed with **1a**, reaction of **1b** with benzophenone in the presence of excess KH at 25 °C yielded the corresponding aldol product **9**[4] in 81% yield. Again, vigorous hydrogen evolution (0.9 equiv) accompanied addition of the ketone.

$$\mathbf{1b} + (C_6H_5)_2CO \xrightarrow[THF]{KH} \underset{\mathbf{9}}{CH_3COCH_2COCH_2C(C_6H_5)_2OH}$$

In contrast to KH-promoted reactions of **1a** with aryl aldehydes, no tetraketone was detected when **1b** was treated with *p*-tolualdehyde in the presence of excess KH. The only product isolated from this reaction was a yellow solid, the ^{1}H NMR spectrum of which was consistent with structure **10** (see Experimental Section).

$$\underset{\mathbf{10}}{p\text{-}CH_3C_6H_4CH{=}CHCOCH_2COCH{=}CHC_6H_4CH_3\text{-}p}$$

Finally, we have duplicated the result obtained by Miles, Harris, and Hauser[2] using NaH in refluxing DME to promote condensation of **1a** with *p*-anisaldehyde. No tetraketone was detectable. The product was a cis/trans mixture of the enediones **2b**.

All of the reactions detailed above can be explained via the dianions of 1,3-diketones **1a** and **1b**. However, hydrogen evolution prior to addition of the carbonyl electrophile indicates only a minimal concentration of the dianion at this point. Thus, any viable mechanistic proposals must accommodate gradual, yet continuous, formation of the requisite dianion upon addition of the aryl aldehyde or ketone. Several mechanisms for dianion formation in the NaH-promoted reactions involving diketones **1a,b** have been proposed.[2] Although we are currently unable to distinguish among these suggestions, we have ruled out the possibility that equilibrating monoanions would explain our results with benzophenone.

(5) C. R. Hauser and T. M. Harris, *J. Am. Chem. Soc.*, **80**, 6360 (1958).

Scheme I

$$\mathbf{1b} + KH \rightarrow CH_3COCHCOCH_3 \rightleftarrows \underset{\mathbf{12}}{CH_3COCH_2COCH_2^-}$$

$$\mathbf{12} + (C_6H_5)_2C{=}O \rightleftarrows \underset{\mathbf{13}}{CH_3COCH_2COCH_2C(C_6H_5)_2O^-} \xrightarrow{NaH}$$

$$CH_3COCHCOCH_2C(C_6H_5)_2O^- + H_2 \xrightarrow{H_3O^+} \underset{\mathbf{9}}{CH_3COCH_2COCH_2C(C_6H_5)_2OH}$$

The experiment outlined in Scheme I was performed to address the question of the possibility that aldol condensation was occurring via an equilibrium of monoanions to attain the necessary carbanion at the terminal methyl group of **1b**. First, the monoanion of **1b** was prepared with 1 equiv of KH. Then benzophenone and 1 equiv of NaH were added simultaneously to the reaction mixture. If terminal anion **12** were present and did condense with benzophenone to yield alkoxide **13**, NaH should ionize a methylene hydrogen of this intermediate, liberating hydrogen and forming the dianion of aldol product **9**. This would shift the overall equilibrium, promoting the aldol condensation. However, no hydrogen was evolved and only starting materials were isolated from this experiment. Thus, aldol product **9** must arise via the dianion of **1b**, which requires KH in THF at ambient temperature. These results also suggest that condensations of **1a** with esters, ketones, and aldehydes in DME also involve the dianion of **1a**. The use of higher temperature and/or acidification following the NaH reactions may explain the isolation of unsaturated β-diketone **2a**, rather than the expected hydroxy β-diketone **3**, which is isolated in good yield under the milder conditions permitted with KH.

The most striking feature of the present study was the formation of tetraketones **5a** and **5b** and aromatic acids in the reaction of **1a** with excess KH and aryl aldehydes. No aldol product **4** or elimination product **2b** was observed in the reaction of equimolar quantities of **1a** with *p*-anisaldehyde. Clearly, these results required further study.

A series of experiments was performed to establish the behavior of expected intermediates in the overall reaction. Since we could not obtain alcohol **4** in the KH-promoted reaction, we prepared **4** and its dehydration product **2b** by the method of Light and Hauser.[4] Treatment of **4** with KH (with no added aldehyde) led to tetraketone **5a** and *p*-anisic acid. Although this supports the intermediacy of **4** in the overall reaction leading to **5a**, the formation of *p*-anisic acid was perplexing.

$$\mathbf{4} \xrightarrow{KH} \mathbf{5a} + p\text{-}CH_6H_4COOH$$

A process involving oxidation of aldehyde formed by a reverse aldol reaction in KH was not expected. However, Lewis[6] has shown that aromatic aldehydes in the presence of NaH can lead to high yields of aromatic acids. This process was shown to involve a Tishchenko reaction, requiring at least catalytic amounts of an alkoxide. Although **4** plus KH could yield alkoxide (by abstraction of the OH proton) and aldehyde (by a reverse aldol condensation), such reactions would not help to explain the route to the observed tetraketones **5a** and **5b**. If the aromatic acid were indeed arising by a Tishchenko reaction, the product should have been β-diketone **1a**. Moreover, addition of *p*-anisaldehyde to a mixture of **4** and KH should increase the amount of *p*-anisic acid produced. When equimolar quantities of **4** and *p*-anisaldehyde were reacted with excess KH, *p*-anisic acid was a product. However, tetraketone **5a** was not formed. The other product was the unsaturated β-diketone **2b**.

$$\mathbf{4} + p\text{-}CH_3OC_6H_4CHO \xrightarrow{KH} \mathbf{2b} + p\text{-}CH_3OC_6H_4COOH$$

The results of the preceding two experiments suggest the remarkable sequence of events outlined in Scheme II. Two new reactions are postulated as follows: (1) an elimination process accomplished by hydride explusion and (2) a Michael reaction in which a dianion adds to a monoanion. We are not aware of a precedent for either of these reactions.

Scheme II

$$\mathbf{1a} + KH \rightarrow \underset{\mathbf{14}}{C_6H_5COCHCOCH_3} + H_2$$

$$\mathbf{14} + ArCHO \xrightarrow{KH} \underset{\substack{\mathbf{15a},\ Ar = p\text{-}CH_3OC_6H_4 \\ \mathbf{15b},\ Ar = p\text{-}CH_3C_6H_4}}{C_6H_5\bar{C}OCHCOCH_2{-}CHArO^-} + H_2$$

$$\mathbf{15a} + ArCHO \xrightarrow{KH} \underset{\mathbf{16}}{C_6H_5\bar{C}OCHCOCH{=}CHAr} + ArCOO^- + H_2$$

$$\mathbf{16} + C_6H_5\bar{C}OCHCOCH_2 \rightarrow \underset{\mathbf{17}}{C_6H_5\bar{C}OCHCO\bar{C}HCH(Ar)CH_2\bar{C}OCHCOC_6H_5}$$

$$\mathbf{17} + \mathbf{14} \rightarrow \mathbf{5a}\ (\text{dianion}) + C_6H_5\bar{C}OCHCOCH_2$$

Support for the reactions in Scheme II was gained by the following two experiments. First, tetraketone **5a** was isolated in 77% yield when equimolar quantities of **1a** and unsaturated β-diketone **2b** were treated with excess KH in THF. Thus, the Michael reaction between the dianion of **1a** and the monoanion of **2b** is an established fact. Secondly, when **1a** was treated with 2 equiv of *p*-anisaldehyde, a 66% yield of **2b** was obtained; tetraketone **5a** could not be detected.

Trianion **17** is given a key role in Scheme II by acting as a base for generation of the dianion of **1a** (from monoanion **14**). In this process **17** is converted into the stable dianion of tetraketone **5a**. This would tend to overcome the potential reversibility of the Michael reaction,[7] since the dianion of **5a** could not revert to its predecessors, **16** and the dianion of **1a**, without first being converted to trianion **17**. It should be noted that hydrogen evolution data for the reaction is consistent with the series of steps in Scheme II.

We suggest the mechanism in Scheme III for the aldehyde promoted elimination process leading from aldol dianion **15a** to aromatic carboxylate ion and alkene anion **16**. The mechanism bears some resemblance to the accepted mechanism for the Cannizzaro reaction.[8] However, we believe that the hydride eliminated here becomes part of the bulk hydride in the reaction medium rather than being transferred to the aldehyde. The absence of aryl alcohol in the product mixture supports this proposal. Since benzophenone cannot participate in the elimination sequence shown in Scheme III, carbinols **3** and **9**, rather

(6) G. E. Lewis, *J. Org. Chem.*, **30**, 2433 (1965).

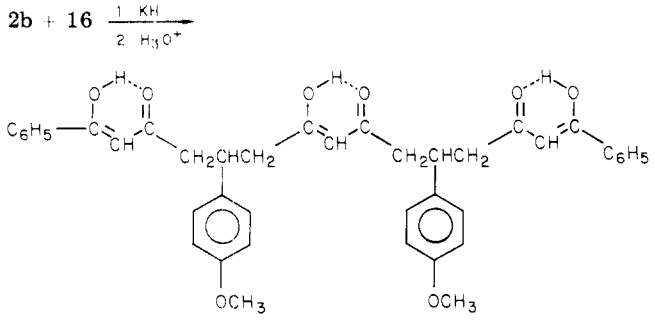
(7) H. O. House, "Modern Synthetic Reactions", 2nd ed., W. A. Benjamin, New York, 1972, p 600 ff.

(8) C. R. Hauser, P. J. Hamrick, Jr., and A. T. Stewart, *J. Org. Chem.*, **21**, 260 (1956).

than unsaturated β-diketones such as **2a**, are produced in the reactions of **1a** and **1b** with this ketone.

One might reasonably question why the aldol dianion **15a** reacts with aldehyde to yield **16**. Apparently, the slow generation of the dianion of **1a** and its low concentration (either in solution or on the surface of the KH) do not permit rapid conversion of **1a** into **15a**. The high concentration of aldehyde relative to **15a** allows it to react as shown in Scheme III. This reaction must proceed more rapidly than formation of the dianion of **1a**. Evidence for this sequence of events was obtained from the reaction of **1a** (1 equiv) and *p*-anisaldehyde (2 equiv), which afforded only unsaturated β-diketone **2b**. Thus, the controlling factor in terms of competitive reactions must be the concentration of the dianion of **1a**.

The Michael acceptor ability of monoanion **16** (Ar = *p*-$CH_3OC_6H_4$) was further demonstrated by reaction of 2 equiv of this intermediate (prepared from **2b**) with 1 equiv of acetylacetone (**1b**) in the presence of excess KH to produce the novel hexaketone **18**. The ^1H NMR spectrum



18

of the crude product revealed two distinguishable enolic absorptions (ratio 2:1) and two vinyl absorptions (ratio 2:1). There was no absorption characteristic of alkene **2b** or diketone **1b**. The presence of diastereomers and several possible enol forms of **18** made isolation of a single crystalline product difficult.

Although **16** (Ar = *p*-$CH_3OC_6H_4$) reacted readily with the dianions of **1a** and **1b**, less nucleophilic addends such as the potassium enolates of pinacolone and acetophenone failed to yield identifiable Michael products.

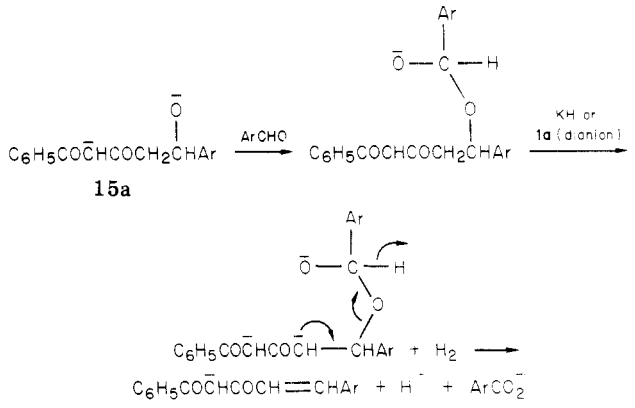
Isolation of bis unsaturated product **10** rather than the expected tetraketone from reaction of acetylacetone (**1b**) with *p*-anisaldehyde presumably results from the fact that the intermediate alkene monoanion undergoes ionization of a terminal methyl proton more rapidly than **1b** is converted to its dianion.

Experimental Section

Melting points and boiling points are uncorrected. H_2 volumes were measured in a gas buret over water and are corrected to standard temperature and pressure. Analyses are by Galbraith Laboratories, Knoxville, TN. ^1H NMR spectra were obtained on a Jeolco PS-100 spectrometer. Chemical shifts are in parts per million relative to internal Me_4Si and splittings are in hertz. All reagents were purified by distillation or recrystallization. KH (22–24% dispersion in mineral oil) was used as received (Apache or Alfa). THF was distilled from $LiAlH_4$ and stored with 4A or 5A molecular sieves under a nitrogen atmosphere.

Apparatus and General Methods. All KH reactions were carried out in a 125-mL three-necked flask containing a magnetic stirring bar and fitted with a pressure-equalized addition funnel, rubber sleeve stoppers, and a gas outlet connected through a moisture trap to a 1-L gas buret. The mineral oil dispersion of KH was magnetically stirred in the plastic bottle received from the manufacturer. A wide bore (2–3-mm opening) pipet was used for transfer of KH to the reaction vessel. Dry, oxygen-free N_2 was swept through the reaction vessel prior to transfer of KH and

Scheme III



15a

16

during the hexane washings. Hexane (50 mL) was added to the KH dispersion and magnetically stirred until homogeneous. After the solution settled for a few minutes, the hexane was carefully pipetted off. This operation was repeated three times. Forty milliliters of THF was added from a syringe. The N_2 flow was stopped, the gas buret was attached, and the diketone in THF solution was added, with temperature control of the reaction vessel maintained by a water bath at 20–30 °C. Standard gas law calculations were used to obtain H_2 volumes.

For some of the reactions, the hexane washings were omitted and the N_2 atmosphere was not used. We could detect no detrimental effects using this procedure, although it was necessary to wash the products with hexane to remove mineral oil. In certain cases, the mineral oil separated from the solid products and could be removed by pipet followed by a hexane wash.

Tetraketones 5a and 5b. Into the apparatus described above was transferred 4.44 g (26.0 mmol) of the mineral oil–KH dispersion. (Note: The same results were obtained with 40 mmol of KH.) After the described washing and addition of 40 mL of THF, the gas buret was attached and 10 mmol of benzoylacetone (**1a**) in 20 mL of THF was added slowly with magnetic stirring. H_2 evolution was rapid and 248 mL (corrected) of H_2 (11 mmol) was liberated during a 10-min period. No more H_2 was evolved during an additional hour. The solution was grayish white with just a tinge of yellow. A solution of 10 mmol of freshly distilled aldehyde (washed free of acid before distillation) in 20 mL of THF was placed in the additional funnel. Slow addition (3–10 min) of this solution was accompanied by rapid H_2 evolution and the solution became bright yellow. An additional 209 mL (9.3 mmol) of H_2 was liberated during addition of the aldehyde, with very little H_2 evolution after 10 min further reaction time. If addition of aldehyde was stopped, the solution became yellow-brown. When addition was resumed, the bright yellow color returned. After an additional hour, the brown mixture was treated with 5 mL of 6 M HCl in water. This resulted in 125 mL (5.6 mmol) of additional H_2 (total H_2 = 26.0 mmol).

The light-yellow THF solution was decanted from the salts and aqueous phase. The THF was removed by rotary evaporation under reduced pressure to leave a yellow pasty solid. If the mineral oil had not previously been removed (see Apparatus and General Methods), the yellow solid mixture was washed three times with hexane and the hexane washes were slowly evaporated to obtain a small amount of product.

The yellow solids were dissolved in ether and this solution was extracted with excess aqueous $NaHCO_3$. The $NaHCO_3$ extracts were heated to expel ether and then acidified with 6 M HCl. Cooling and filtering yielded pure aromatic acids.

The ethereal solution containing the tetraketone was dried ($MgSO_4$), distilled to remove most of the ether, and then taken up in 95% ethanol to crystallize the products.

By this procedure the following were obtained.

A. From *p*-Anisaldehyde and Benzoylacetone (1a). *p*-Anisic acid: 0.58 g (38% based on anisaldehyde, 76% based on Scheme II); mp 180–182 °C, not depressed on admixture with an authentic sample. 1,9-Diphenyl-5-(*p*-methoxyphenyl)-1,3,7,9-nonanetetrone (**5a**): 1.77 g (80%), white needles, mp 92–95 °C

(from ethanol). An analytical sample, mp 94–96 °C, was obtained by two further recrystallizations from ethanol. Anal. Calcd for $C_{28}H_{26}O_5$: C, 76.00; H, 5.92. Found: C, 76.14; H, 6.08.

B. From *p*-Tolualdehyde and 1a. *p*-Toluic acid: 0.51 g (75% based on Scheme II), mp 179–181.5 °C, not depressed on admixture with an authentic sample. 1,9-Diphenyl-5-(*p*-tolyl)-1,3,7,9-nonanetetraone (**5b**): 1.31 g (62%) of white needles, mp 100–103 °C (from ethanol). An analytical sample prepared by two additional recrystallizations from ethanol melted at 104–105.5 °C. Anal. Calcd for $C_{28}H_{26}O_4$: C, 78.85; H, 6.15. Found: C, 79.07; H, 6.39.

Compounds **5a** and **5b** both gave pale yellow solutions in ether, ethanol, and chloroform. Both compounds exist 90% in the enol form in chloroform solution at 25 °C (see Table I for ^{1}H NMR spectral assignments).

Cyclohexenones 6a and 6b. A benzene solution of 200 mg of **5a** was heated with 2.22 g of Silica Gel 60 (VWR Scientific) for 1 h with stirring. This mixture was transferred to the top of a 20 × 2.5 cm column of the same type of silica gel packed as a slurry in benzene. The third 100-mL benzene eluate contained 90 mg of **5a**. Further elution with ether–benzene (4:96) yielded 52 mg (26%) of **6a**, mp 145–149 °C (white feathery crystals from ethanol). An analytical sample prepared by another crystallization from ethanol had mp 155–156 °C. Anal. Calcd for $C_{28}H_{24}O_4$: C, 79.22; H, 5.70. Found: C, 79.11; H, 5.60.

When 600 mg of **5b** was treated by the same procedure, 155 mg (26%) of **6b** was obtained as white feathery crystals, mp 177.5–178.5 °C (from CH_3OH). Starting material was isolated but not weighed. Anal. Calcd for $C_{28}H_{24}O_3$: C, 82.33; H, 5.92. Found: C, 82.28; H, 5.97. Principal ^{1}H NMR chemical shifts for **6a** and **6b** appear in Table I.

Dipyrazole 7 from 5a. To a solution of **5a** (0.50 g, 1.13 mmol) in 20 mL of ethanol at reflux was added 25 drops of 85% hydrazine hydrate. After 2 h at reflux, the yellow solution had become colorless. The cooled solution was poured into 100 mL of water with precipitation of a white, gummy solid. Ether extraction, followed by addition of hexane, allowed crystallization of a white solid, mp 161–164 °C. Recrystallization from ether with a little added methanol yielded an analytical sample as white crystals, mp 165–166.5 °C (yield not determined). Anal. Calcd for $C_{28}H_{26}N_4O$: C, 77.39; H, 6.03; N, 12.89. Found: C, 77.34; H, 6.01; N, 12.77.

5-Hydroxy-1,5,5-triphenyl-1,3-pentanedione (3). The general procedure for reactions in KH was used. Treatment of 10 mmol of **1a** with 40 mmol of KH in THF at 25 °C resulted in immediate evolution of 11 mmol of H_2. Refluxing the reaction mixture for 2.5 h liberated an additional 4.5 mmol of H_2. The resulting suspension was cooled to 25 °C and 10 mmol of solid benzophenone was added. After 2 h a total of 20 mmol of H_2 had evolved. Normal workup followed by chromatography on silica gel (elution with hexane–benzene 80:20) yielded 1.86 g (54%) of **3**: mp 113–114 °C (lit.[4] mp 115–116 °C); ^{1}H NMR ($CDCl_3$) δ 15.9 (br s, 0.9, enol), 7.2–8.04 (m, 15), 6.26 (s, 0.9, vinyl), 5.33 (s, 1 OH), 4.11 (s, 0.2, CH_2), 3.67 (s, 0.2, CH_2-keto), 3.52 (s, 1.8, CH_2-enol).

In a similar reaction, without reflux, chromatographic separation was not required. Crystallization of the crude reaction product from 95% ethanol afforded 2.27 g (66%) of **3**, mp 115–116 °C.

6-Hydroxy-6,6-diphenyl-2,4-hexanedione (9). In a reaction similar to that used for the preparation of **3**, 10 mmol of **1b** was allowed to react with 10 mmol of benzophenone in the presence of 40 mmol of KH at 25 °C for 1 h to afford 2.28 g (81%) of **9**: mp 131–132 °C (lit.[4] mp 133–135 °C); ^{1}H NMR ($CDCl_3$) δ 14.98 (s, 0.8), 7.66–7.40 (m, 10), 5.55 (s, 0.8), 5.29 (s, 1), 3.57 (s, 0.4), 3.32 (s, 2), 2.16 (s, 0.6), 2.05 (s, 2.4).

Benzylation of Acetylacetone (1b) To Form 8. To a stirred slurry of 40 mmol of KH (hexane washed) in 140 mL of THF was added 1.05 g (10 mmol) of acetylacetone (**1b**) in 20 mL of THF. H_2 (11.5 mmol) evolved rapidly. The mixture was heated at reflux for 4 h with evolution of an additional 4 mmol of H_2. After the mixture was cooled to 25 °C, benzyl chloride (1.26 g, 10 mmol) was added through a rubber septum with a syringe. After a reaction period of 20 min, aqueous HCl was added. The THF layer was concentrated and GC analysis (6.3% Carbowax 20 M on Gas Chrom Z at 150 °C) showed the presence of 6-phenyl-2,4-hexanedione (**9**) (peak enhancement with an authentic sample prepared by the method of Huckin and Weiler).[9] The yield was calculated to be 19% based on peak area in the GC.

5-Hydroxy-1-phenyl-5-(*p*-methoxyphenyl)-1,3-pentanedione (4). This compound was prepared by the method of Light and Hauser;[4] mp 101.5–103 °C (lit.[4] mp 103–105 °C); ^{1}H NMR ($CDCl_3$) δ 2.84 (m, 2), 3.74 (s, 3), 4.08 (s, 0.2), 5.10 (dd, 1), 6.07 (s, 1), 6.79 (d, 2), 7.20 (d, 2), 7.35 (m, 3), 7.76 (m, 2), no discernible OH or enol H, but a broad absorption from δ 13 to 16.

Reaction of 4 with KH. Synthesis of 5a. To 40 mmol of hexane-washed KH in 80 mL of THF was added a solution of **4** (5 mmol) in 20 mL of THF. H_2 evolution proceeded rapidly (10 mmol) and the solution turned yellow-green, then yellow-brown. After 10 h, the mixture was hydrolyzed with cold 6 M HCl (much H_2). TLC of the reaction mixture showed a small spot for benzoylacetone (**1a**) and *p*-anisic acid and a large spot for **5a**. This reaction was not processed for isolation of products.

Reaction of 4 with KH and Anisaldehyde. To 7.27 g (40 mmol) of hexane-washed KH in 100 mL of THF was added 1.49 g (5 mmol) of alcohol **4**. H_2 evolved rapidly (10 mmol) and the solution took on a yellow coloration. Addition of 1.36 g (10 mmol) of *p*-anisaldehyde in 20 mL of THF caused liberation of H_2 (7.0 mmol). Acidification and the usual workup yielded 0.9 g (58%—or 116% based on Scheme II) of *p*-anisic acid, mp 182–184 °C. TLC of the crude reaction mixture (before removal of *p*-anisic acid) showed a faint spot for **5a** and large spots for **2b** and *p*-anisic acid. Alkene **2b** was isolated as bright yellow crystals, mp 121–123 °C (a mixture of **2b** and its cis isomer). Further crystallization raised the melting point to 125–127 °C. A yield of **2b** was not determined.

***trans*-1-Phenyl-5-(*p*-methoxyphenyl)-4-pentene-1,3-dione (2b).** In the apparatus described above, 4.08 g (22.9 mmol based on H_2 evolution in this experiment) of KH–oil dispersion and 40 mL of THF were stirred while a solution of 1.62 g (10 mmol) of benzoylacetone (**1a**) and 2.72 g (20 mmol) of *p*-anisaldehyde in 15 mL of THF was added slowly. H_2 evolution was rapid and the solution became yellow (512 mL of H_2 = 22.9 mmol). After the solution was stirred for 30 min, 8 mL of 3 M HCl was added (no H_2 evolved). The THF was decanted from the aqueous phase and evaporated to yield a yellow solid. Hexanes (3 × 50 mL) were used to remove the mineral oil. The yellow solid was taken up in ether and washed with aqueous $NaHCO_3$ solution. The ether was evaporated without drying and the residue was taken up in 100 mL of hot 95% ethanol. Cooling and concentration of the mother liquor yielded three crops of bright yellow crystals, 1.85 g (66%), of **2b**, mp 123.5–27 °C (mostly 126.5–127 °C). **2b** prepared in this experiment was identical with that prepared in two steps by the method of Light and Hauser;[4] ^{1}H NMR ($CDCl_3$) δ 3.74 (s, 3), 6.18 (s, 1), 6.40 (d, J = 15, 1), 6.76 (d, J = 8, 2), 7.35 (m, 5), 7.52 (d, J = 15, 1), 7.82 (m, 2), 16.0 (br s, 1).

Acidification of the $NaHCO_3$ extracts yielded 0.93 g (61% based on Scheme II) of *p*-anisic acid, mp 183–185 °C.

Attempted Reaction of Monoanion of 1b with Benzophenone in the Presence of NaH. To a slurry of 1.67 g (10 mmol) of KH in 130 mL of THF was added dropwise 1.05 g (10.5 mmol) of acetylacetone (**1b**) in 20 mL of THF. Addition was accompanied by the evolution of 10 mmol of H_2. After a reaction period of 2 h no additional H_2 was evolved. Then 1.44 g (30 mmol of a 50% mineral oil dispersion) of NaH was quickly added to the reaction mixture. A slight effervescence was observed on the addition of the NaH. The resulting slurry was stirred for an additional 1 h after which time 1.82 g (10 mmol) of benzophenone was added to the reaction mixture. After 3 h, 1.1-mmol additional hydrogen had evolved. The solution was processed in the usual manner, and TLC analysis (hexane–benzene, 1:1) indicated only starting materials; **9** had not formed.

Michael Addition of 1a to 2b. Addition of 1.62 g (10 mmol) of **1a** in 20 mL of THF to a slurry of 7.27 g (40 mmol) of hexane-washed KH in 140 mL of THF resulted in liberation of 10.3 mmol of H_2. When 1.40 g (5.0 mmol) of **2b** in 20 mL of THF was added, 6.8 mmol of H_2 was liberated. After the solution was stirred for 3 h, the mixture was hydrolyzed with dilute HCl. The THF was removed and the residue was dissolved in ether, dried ($MgSO_4$), and concentrated. Cooling resulted in deposition of

(9) S. N. Huckin and L. Weiler, *J. Am. Chem. Soc.*, **96**, 1082 (1974).

1.70 g (77%) of **5a**, mp 92–96 °C. Admixture with **5a** prepared above, mp 92–96 °C.

Attempted Michael Reaction with the Mo⁻ anions of 1a and 2b. A solution of the monoanion of **1a** (from 1.62 g, 10 mmol of **1a** with 1.76 g (9.7 mmol) of KH–oil dispersion, 8.8 mmol of H_2 evolution) in 15 mL of THF was added slowly to a solution of the monoanion of **2b** (from 2.80 g, 10 mmol, of **2b** and 1.76 g, 9.7 mmol, of KH–oil dispersion, 9.1 mmol of H_2 evolution) in 15 mL of THF. No H_2 was evolved during the addition of the monoanion of **1a** to the monoanion of **2b**. After stirring for 14 h, cold dilute HCl was added and the THF was removed. The residue was dissolved in ether and TLC showed the presence of **1a** and **2b** only.

1,15-Diphenyl-5,11-bis(*p*-methoxyphenyl)pentadecane-1,3,7,9,13,15-hexone (18). To the anion of **2b**, prepared from 1.40 g (5.0 mmol) of **2b** and 3.56 g (19.7 mmol) of KH in 40 mL of THF, was added 0.25 g (2.5 mmol) of **1b** in 5 mL of THF. H_2 evolution was rapid during the addition of **2b** and **1b**. The yellow solution turned reddish-orange during the 4-h reaction period. The mixture was poured into 200 mL of ice water. H_2 evolution occurred. After washing the clear yellow aqueous solution with two 25-mL portions of hexane, 6 M HCl was added to yield an emulsion from which an oil separated. Ether extraction, drying ($MgSO_4$), and evaporation of the solvent left a yellow oil (1.6 g). Upon standing for 2 days at room temperature, the oil partially solidified. It was recrystallized from CCl_4, followed by a rapid ether wash to yield 0.40 g of white crystals, mp 112–115 °C. Anal. Calcd for $C_{41}H_{40}O_8$: C, 74.52; H, 6.10. Found: C, 74.28; H, 5.97. Principal ^1H NMR shifts appear in Table I. The spectrum of the crude reaction mixture was identical with that of the crystallized material. When a portion of the noncrystallized material was refluxed with water, then cooled, an amorphous solid, melting from 35 to 50 °C, was obtained. Upon standing, it slowly became a viscous oil.

1,7-Bis(*p*-tolyl)-1,6-heptadiene-3,5-dione (10). Addition of 10 mmol of **1b** to 40 mmol of KH in THF yielded 11 mmol of H_2. Treatment of this mixture with 10 mmol of *p*-tolualdehyde gave vigorous H_2 evolution. After 3 h, acidification and subsequent extractions yielded *p*-toluic acid and a yellow-orange oil. Crystallization attempts were unsuccessful. Distillation yielded one fraction, bp 180–200 °C (0.4 mm), which solidified. Recrystallization from methanol yielded 0.88 g (41%) of a yellow solid: mp 203–207 °C; ^1H NMR ($CDCl_3$) δ 2.4 (s, 6), 5.78 (s, 1), 6.42 (s, 1), 6.59 (s, 1), 7.0–7.62 (m, 10), 15.5 (br s, 1).

Registry No. **1a**, 93-91-4; **1b**, 123-54-6; *trans*-**2b**, 72610-53-8; *cis*-**2b**, 72610-54-9; **3**, 72610-55-0; **4**, 72610-56-1; **5a**, 72610-57-2; **5b**, 72610-58-3; **6a**, 72610-59-4; **6b**, 72610-60-7; **7**, 72610-61-8; **8**, 52393-50-7; **9**, 72610-62-9; **10**, 72610-63-0; **18**, 72610-64-1; *p*-anisaldehyde, 123-11-5; *p*-tolualdehyde, 104-87-0; *p*-anisic acid, 100-09-4; *p*-toluic acid, 99-94-5; benzophenone, 119-61-9; benzyl chloride, 100-44-7.

Homologation of Carbonyl Compounds to Aldehydes with Lithium Bis(ethylenedioxyboryl)methide

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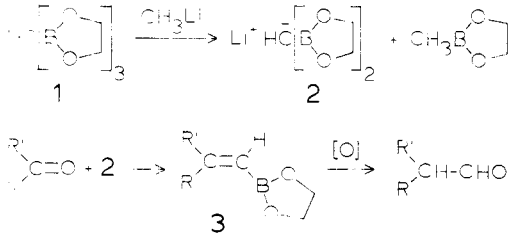
Received August 30, 1979

Tris(ethylenedioxyboryl)methane reacts with methyllithium at −78 °C in THF to form lithium bis(ethylenedioxyboryl)methide, which reacts with aldehydes and ketones to form 1-alkene-1-boronic esters. These need not be isolated for efficient oxidation by sodium perborate to the homologated aldehydes, which are easily purified. Systematic investigation of the reaction conditions to optimize yields at each step was undertaken. Possibly hazardous 2:1 aldehyde–hydrogen peroxide adducts were found to form under neutral conditions with dilute (5%) hydrogen peroxide. Hydrogen peroxide was also found to cause some carbon–carbon bond cleavage during oxidation of alkeneboronic acids. Both problems were avoided by the use of sodium perborate instead. Reaction of lithium bis(ethylenedioxyboryl)methide with benzoyl chloride or methyl benzoate followed by hydrolysis was found to yield acetophenone. A significant error in one previous description of the synthesis of the key starting material, tris(dimethoxyboryl)methane, is noted.

Introduction

The reaction of tris(ethylenedioxyboryl)methane (**1**) with alkyllithium to form lithium bis(ethylenedioxyboryl)methide (**2**) and condensation of aldehydes or ketones with **2** to form 1-alkene-1-boronic esters (**3**)[1] suggest the possibility of an efficient aldehyde homologation process based on this chemistry.[2]



The traditional method for accomplishing such homologations is the Darzens glycidic ester condensation, which often suffers from low yields.[3] An important exception is the efficient Darzens homologation of β-ionone, used as a step in the synthesis of vitamin A.[4] More recently developed homoloating agents include Wittig reagents bearing alkoxy[5] or phenylthio[6] substituents, though these, too, have limitations with respect to yields and convenience. After our preliminary communication appeared, a very promising aldehyde homologation based on chloro(trimethylsilyl)methyllithium was reported by Magnus and co-workers.[7]

Results

The preparation of the key starting material, tris(dimethoxyboryl)methane, in 60–80-g batches has been de-

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