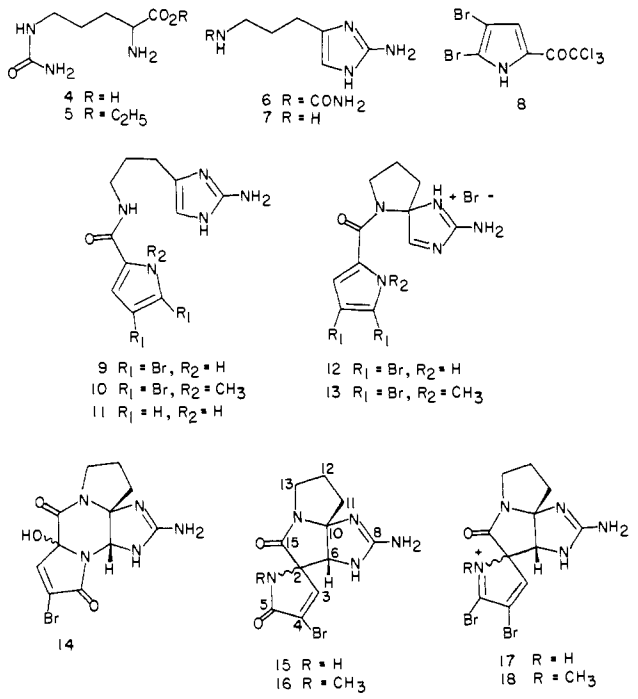
Chart I



obtained in ~50% yield after the free base had been chromatographed on silica gel with $CHCl_3$–CH_3OH–NH_4OH (80:20:3) as eluent.

Exposure of dihydrooroidin hydrochloride (**9**·HCl) to 1 equiv of bromine in acetic acid caused rapid precipitation of an insoluble, highly unstable salt which remains to be fully characterized. Its infrared spectrum (Nujol) lacks the amide II band at 1525 cm^{-1} present in the spectrum of dihydrooroidin (**9**). This salt combined rapidly with methanol to afford an equally unstable product, which according to field desorption mass spectrometry resulted from addition of methanol. Ultraviolet absorption at 279 nm pointed to the survival of the dibromopyrrolecarboxamido group, but quantitative evaluation is meaningless because tribromide ion [UV max (CH_3CN) 269 nm] may be present. An entirely analogous product was prepared by bromination of the *N*-methyl derivative **10**. These observations and others to be discussed in the sequel are in agreement with structures **12** and **13** but do not exclude others.

When treated with potassium *tert*-butoxide (1.5 equiv) in 2-butanol (20 °C, 20 min) **12** was quantitatively converted to racemic dibromophakellin (**1**). Comparison of IR, UV, and NMR spectral data of the hydrochloride of racemic **1**, mp 221–223 °C dec, racemic *N*-acetyldibromophakellin, mp 234–236 °C dec, and racemic hydroxylactam **14**, mp >300 °C dec, with literature[3] values of the corresponding derivatives prepared from natural dibromophakellin established identities. Bromination of the amide **11**[9] in acetic acid followed by treatment with base gave mostly dihydrooroidin (**9**) and very little dibromophakellin (**1**). This experiment demonstrated the following: (a) as shown previously,[10] pyrrole-2-carboxylates brominate at C-4 and C-5; (b) bromination of the pyrrole ring, under these conditions, is faster than oxidative cyclization; (c) the latter process is retarded and/or intermediate **12** is destroyed by excess hydrogen bromide.

A second mode of cyclization was observed when the hydrobromides of **12** and **13** were dissolved in dimethyl sulfoxide or dimethylformamide. Evaporation of the solvents under vacuum followed by crystallization of the residues from CH_3OH–$CHCl_3$ afforded the hydrobromides of the dilactams **15** and **16**. Compound **15** appears to be a single isomer: mp 239–241 °C dec (66% yield); IR (Nujol) 3500, 1720 (sh), 1710 (sh), 1690, 1600 cm^{-1}; UV (CH_3OH) 235 nm (ϵ 5300); NMR (Me_2SO-d_6) δ 9.50, 9.40, 8.58, 8.02 (2), all exchangeable with D_2O, 7.52 (s, 1), 4.63 (s, 1), 3.47 (m, 1), 3.2 (m, 1), 2.0–2.4 (m, 4); ^{13}C NMR δ 23.99 (C-12), 34.82 (C-11), 42.53 (C-13), 59.00 (C-6), 73.39 (C-2), 86.39 (C-10), 119.33 (C-4), 145.62 (C-3), 157.21 (C-8), 167.79, 168.57 (C-5 and C-15).

The *N*-methyl derivative **16** on the other hand is a mixture of diastereomers according to the ^1H NMR spectra. In the absence of added base, the pyrrole ring in **12** and **13** thus undergoes electrophilic substitution on carbon to afford the bromoimines **17** and **18**, which then hydrolyze to the pyrrolinones **15** and **16**. Under *basic* conditions the pyrrole is deprotonated, and the resulting highly nucleophilic anion cyclizes with formation of a new N–C rather than C–C bond.

Acknowledgment. This investigation was supported by the National Institutes of Health (GM 09868), a National Research Service Award (2 T32 CA 09112) from the National Cancer Institute, DHEW, and the Hoffmann-La Roche Foundation. High-resolution mass spectra were provided by the facility, supported by the National Institutes of Health (Grant RR 00317) (principal investigator, Professor K. Biemann), from the Biotechnology Resources Branch, Division of Research Resources. We thank Dr. C. Costello for help with mass spectra.

Registry No. (±)-**1**, 80875-81-6; (±)-**1** HCl, 80923-89-3; (±)-**1** N^2-Ac, 80875-82-7; L(+)-**4**, 372-75-8; L(+)-**5**, 80822-58-8; **6** PICRATE, 80822-60-2; **6** HCl, 80822-61-3; **7** 2HCl, 80822-62-4; **8**, 50371-52-3; **9**, 80822-63-5; **10**, 80822-64-6; **11**, 80822-65-7; (±)-**12** HBr, 80822-66-8; (±)-**13** HBr, 80822-67-9; **14**, 80923-90-6; **15**, 80822-68-0; **15** HBr, 80822-69-1; (±)-**16**, isomer I, 80822-70-4; (±)-**16**, isomer II, 80875-83-8; (±)-**16** HBr, isomer I, 80875-84-9; (±)-**16** HBr, isomer II, 80923-91-7; **17**·HBr, 80822-71-5; (±)-**18**·Br^-, isomer I, 80845-42-7; (±)-**18**·Br^-, isomer II, 80876-85-3.

(9) First prepared by P. Arrhenius.

(10) Hodge, P.; Rickards, R. W. *J. Chem. Soc.* **1965**, 459. Anderson, H. J.; Lee, S.-F. *Can. J. Chem.* **1965**, *43*, 409.

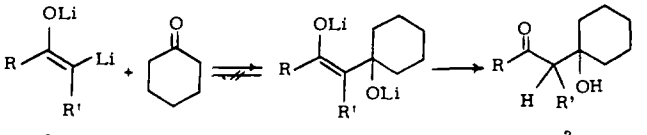
Additions of α-Keto Dianions to Sterically Congested Carbonyls[1]

Conrad J. Kowalski* and Kevin W. Fields

Department of Chemistry, University of Notre Dame
Notre Dame, Indiana 46556

Received October 13, 1981

Herein we report the reaction of α-keto dianions[2] (**1**) with



aldehydes and ketones to afford aldol-type products (**3**) or the corresponding dehydrated enones. This process differs from the simple aldol condensation in three important respects. The dianions **1** appear to be considerably more nucleophilic than simple enolates and thus react even with very hindered carbonyl compounds. The initial reaction of such dianions (**1** → **2**) appears to be irreversible, unlike the often readily reversible aldol condensation.[3] The regiospecific alkoxy enolate intermediate (**2**)

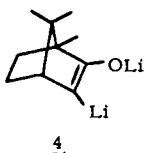
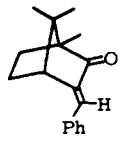
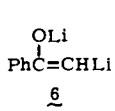
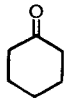
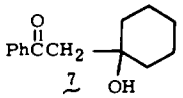
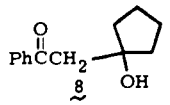
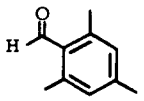
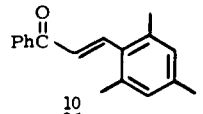
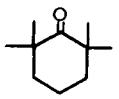
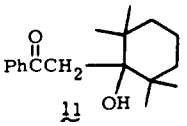
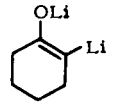
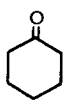
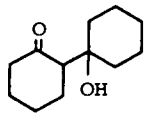
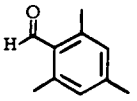
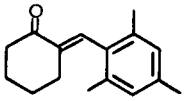
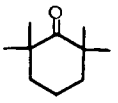
(1) Presented in part at the 181st National Meeting of the American Chemical Society, Atlanta, GA, March 1981; American Chemical Society: Washington, D.C., 1981; ORGN 84.

(2) Kowalski, C. J.; O'Dowd, M. L.; Burke, M. C. Fields, K. W. *J. Am. Chem. Soc.* **1980**, *102*, 5411.

(3) For a recent discussion of some readily reversible aldol condensations see: (a) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066. For several leading references to recent aldol chemistry see: (b) Heathcock, C. H.; Hagen, J. P.; Jarvi, E. T.; Pirrung, M. C.; Young, S. D. *J. Am. Chem. Soc.* **1981**, *103*, 4972. (c) Evans, D. A.; Nelson, J. V., Vogel, E.; Taber, T. R. *Ibid.* **1981**, *103*, 3099. (d) Evans, D. A.; McGee, L. R. *Ibid.* **1981**, *103*, 2876. (e) Meyers, A. I.; Yamamoto, Y. *Ibid.* **1981**, *103*, 4278. (f) Masamune, S.; Choy, W.; Kerdesky, F. A. J.; Imperiali, B. *Ibid.* **1981**, *103*, 1566.

0002-7863/82/1504-1777$01.25/0

Table I

Entry	Dianion	Carbonyl Compound	Product[14]	Yield[a]
1	 4	PhCHO	 5	77%
2	 6		 7	88%
3	6		 8	61%
4	6	$HCC(CH_3)_3$	$PhCCH_2CHC(CH_3)_3$ 9	84%
5	6		 10	67%
6	6		 11	62%
7	 12		 13	64%
8	12		 14	58%
9	12		see Scheme I	
10	6 or 12	acetone or 2-octanone	enolization	

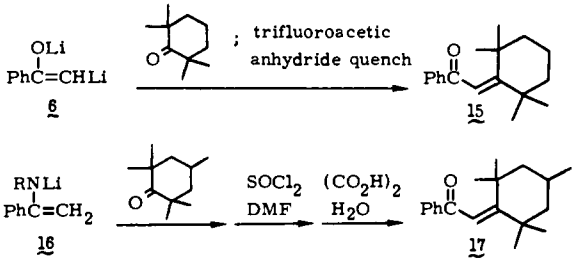
[a] Yield of isolated, pure material, based on bromo enol acetate precursor of dianion used.

formed in dianion condensations is rather unique[4] and can lead to products other than simple aldols (**3**).

Listed in Table I are reactions of several α-keto dianions[5] with a variety of aldehydes and ketones. It should be noted in general that those entries that involve dianions reacting with aromatic aldehydes (entries 1, 5, and 8) all produce enone products directly, not hydroxy ketones. At present it is still unclear whether enone formation occurs via decomposition of an intermediate such as **2** prior to quenching or via dehydration of the benzylic alcohol products during workup. In all other cases, however, β-hydroxy ketones can be isolated.

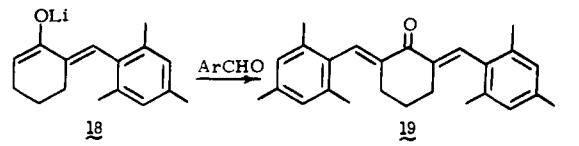
Reaction of dianion **6** with cyclopentanone (entry 3) is particularly interesting, since cyclopentanone is notorious for undergoing enolization in preference to 1,2 additions.[7] Attempts by us to add the simple lithium enolate monoanion of acetophenone to cyclopentanone under a variety of conditions never afforded more than 5% of aldol product **8**. By contrast, use of dianion **6** produces adduct **8** in 61% isolated yield.

Acetophenone enolate monoanion also fails to react with 2,2,6,6-tetramethylcyclohexanone, presumably due to extreme hindrance about the carbonyl group. However, dianion **6** adds to this ketone at 0 °C, producing hydroxy ketone **11** in 62% yield (entry 6). By simply changing the quench used in this reaction from dilute acid to trifluoroacetic anhydride, the related enone product **15** could be obtained in 72% yield. This change utilizes



the alkoxy enolate intermediate (similar to **2**) present in this reaction, to allow direct formation of enone **15** in a single step that does not involve hydroxy ketone **11**. This result is particularly interesting in contrast with the previously reported three-step preparation of the related enone **17**[8] (i.e., **16** → **17**) using more classical intermediates.[9]

Similar reactions are also observed for the secondary α-keto dianion (**12**) of cyclohexanone. While addition to cyclohexanone is uneventful (entry 7), reaction of **12** with cyclopentanone under the same conditions used for the primary dianion (entry 3) affords primarily enolization. This difference is not yet understood. Addition of dianion **12** to the hindered carbonyl group of mesitaldehyde (entry 8) affords monoadduct **14** in 58% yield. Attempts to react this same aldehyde with the simple lithium enolate of cyclohexanone give no reaction at low temperatures. At room temperature, the reaction produces mixtures that optimally contain only 20% of adduct **14**. The major product from these reactions, even with 1 equiv of aldehyde, is the diadduct **19**; no hydroxy



ketone is ever observed. Presumably, for this highly hindered aldehyde, the sluggish nature of the normal aldol condensation allows enolate-exchange reactions to become competitive, leading to multiple substitution (i.e., **14** → **18** → **19**); these are similar to polyalkylation problems encountered during sluggish alkylation reactions.[10] By contrast, only traces of the diadduct **19** are observed in the dianion process employing 1 equiv of aldehyde.

Although the simple enolate anion of cyclohexanone is unreactive toward 2,2,6,6-tetramethylcyclohexanone, cyclohexanone

(4) Interesting chemistry of alkoxy ester enolates analogous to **2** has been reported: Frater, G. *Helv. Chim. Acta* **1979**, *62*, 2825; **1980**, *63*, 1383.

(5) α-Keto dianions[2] are prepared in ether from the corresponding bromo enol acetates[2,6] by reaction with methyllithium (2.2 equiv, 0 °C) and then *tert*-butyllithium (2.2 equiv, −78 °C to room temperature, or −78–0 °C for dianion **6**, which is never warmed above 0 °C). Just over 1 equiv of the carbonyl compound is added at −78 °C, and the solutions are allowed to warm to room temperature (0 °C for dianion **6**). After cooling again, the solutions are quenched with dilute hydrochloric acid to afford the products shown. Exceptions to this procedure are entries 2 and 3, which were not warmed after adding ketone but quenched at −78 °C after 10 min.

(6) Kowalski, C.; Creary, X.; Rollin, A. J.; Burke, M. C. *J. Org. Chem.* **1978**, *43*, 2601.

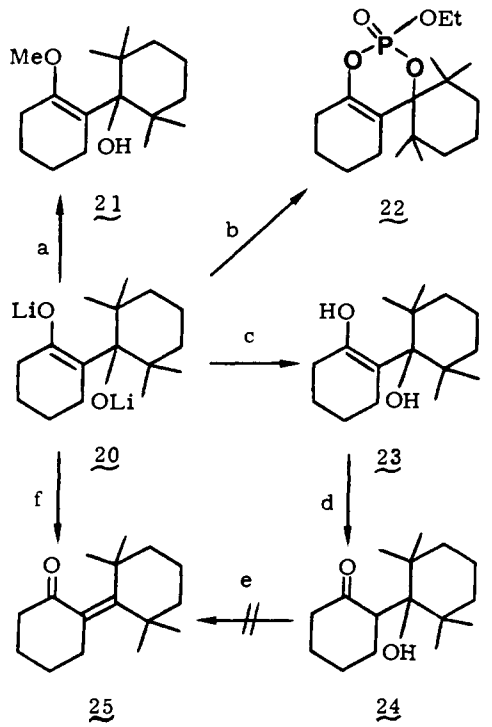
(7) Wadsworth, W. S.; *Org. React.* **1975**, *25*, 102 and references therein.

(8) Arnett, J. F.; Walborsky, H. M. *J. Org. Chem.* **1972**, *37*, 3678.

(9) Wittig, G.; Reiff, H. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 7.

(10) House, H. O. "Modern Synthetic Reactions", 2nd ed.; Benjamin: Menlo Park, CA, 1972; p 560.

Scheme I[a]



[a] Reaction key: (a) excess Me_2SO_4, HMPA, 60% (MeI fails to react); (b) Cl_2PO_2Et, 43%; (c) H_2O, NH_4Cl, 0 °C, 55%; (d) silica gel, 25%; (e) *p*-TsOH, toluene, Δ (retroaldol occurs); (f) $(CF_3CO)_2O$, 55%.

dianion **12** adds completely to this ketone to afford intermediate **20** (entry 9). Several reactions of this intermediate are outlined in Scheme I. Most noteworthy among these is the formation (on aqueous quenching of **20**, reaction c) of the solid hydroxy enol **23**,[11] in 55% yield after recrystallization. While isolation of this enol product was unexpected, stable enols have been observed in other hindered molecules[12] and in this case serve to emphasize the extreme crowding in the system. Enol **23** does rearrange on silica gel to the aldol product **24**, but a competing retroaldol reaction destroys most of the product. Attempted dehydration of **24** affords only retroaldol products. Dealing with the troublesome hydroxy ketone **24** can be avoided altogether, however, by quenching intermediate **20** with trifluoroacetic anhydride to obtain the very congested olefin **25** directly in a single step.

Although α-keto dianions add to a variety of ketones, it is important to note that simple methyl ketones (e.g., acetone or 2-octanone) undergo mainly enolization by both dianions **6** and **12** under the conditions described (entry 10). These results are difficult to understand in view of the successful addition of dianion **6** to highly enolizable cyclopentanone. Little effort has thus far been expanded on this aspect of the problem, however, as normal kinetic aldol condensations at unhindered ketones generally proceed quite well.[13] Further studies related to the enolization question, as well as applications of these dianion condensations to synthesis (e.g., tetra-*tert*-butylethylene) are currently under way.

Acknowledgment. Support of this investigation was provided by the National Cancer Institute, DHEW, under Grant No. 27157, by the National Science Foundation under Grant No. CHE-8111128, by the 3M Corp. under a 3M Corp. Young Faculty Grant, and by the Lubrizol Corp. via a fellowship to K.W.F. (1980–1981).

Registry No. 4, 74636-48-9; **6**, 74636-46-7; **8**, 80926-16-5; **9**, 80926-17-6; **11**, 80926-18-7; **12**, 74636-49-0; **14**, 80926-19-8; **15**, 80926-20-1; **19**, 80926-21-2; **21**, 80926-22-3; **22**, 80926-23-4; **23**, 80926-24-5; **24**, 80926-25-6; **25**, 80926-26-7; benzaldehyde, 100-52-7; cyclohexanone, 108-94-1; cyclopentanone, 120-92-3; 2,2-dimethylpropanal, 630-19-3; 2,4,6-trimethylbenzaldehyde, 487-68-3; 2,2,6,6-tetramethylcyclohexanone, 1195-93-3; acetone, 67-64-1; 2-octanone, 111-13-7.

Cyclohepta-1,2,4,6-tetraene

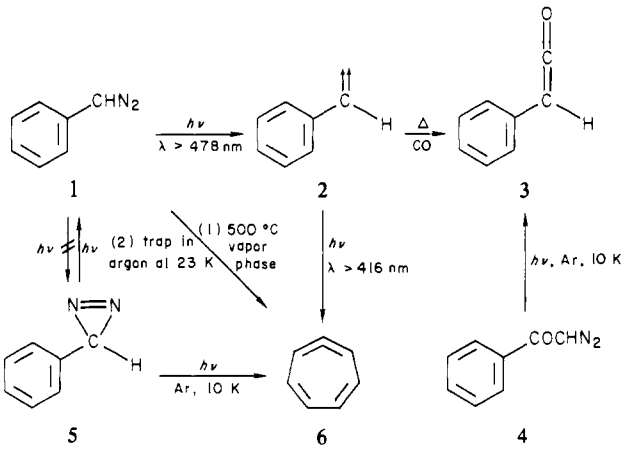
Paul R. West, Orville L. Chapman,* and Jean-Pierre LeRoux

Department of Chemistry, University of California Los Angeles, California 90024

Received April 17, 1981

Despite intense investigation during the past 20 years, spectroscopic observation of phenylmethylene is limited to the ESR spectrum of the triplet ground state,[1] and the structures of the first-formed products from photolysis and thermolysis are not known. We present the infrared and ultraviolet spectra of phenylmethylene and describe the thermal and photochemical ring expansion of phenylmethylene to cyclohepta-1,2,4,6-tetraene.

Irradiation (λ > 478 nm) of phenyldiazomethane (**1**) matrix-



isolated in argon at 10 K gave phenylmethylene (**2**). The matrix was deposited on cesium iodide for the infrared spectrum (Figure 1a) and on sapphire for the ultraviolet spectrum (Figure 2). The C–H deformations of the phenyl group are changed very little in going from **1** to **2** as is the C–H deformation mode of the methine hydrogen at 445 cm^{-1}. The ultraviolet spectrum of **2** is characterized by highly structured absorptions between 370 and 434 nm with a prominent maximum at 430 nm.[2] Extinction coefficients were not determined, but the fact that infrared observations could be made on the same matrix shows that the UV extinction coefficients are small. The identity of phenylmethylene was confirmed by an experiment in an argon matrix doped with 0.25% carbon monoxide. After generation of phenylmethylene (infrared monitoring), the matrix was warmed to the softening point, at which point phenylketene (**3**) was formed. Authentic phenylketene was generated by irradiation of diazoacetophenone in argon at 10 K. As a final precaution, phenyldiazirine (**5**) was

(11) **23**: mp 117.5–119 °C; IR ($CHCl_3$) 3250 (enol OH), 1645 (C=C) cm^{-1}; NMR ($CDCl_3$) δ 2.3–2.0 (m, 4 H, allylic), 1.8–1.5 (m, 10 H), 1.27 (s, 6 H, CH_3), 1.12 (s, 6 H, CH_3). Anal. Calcd for $C_{16}H_{28}O_2$: C, 76.14; H, 11.18. Found: C, 76.16; H, 10.87.

(12) Hart, H. *Chem. Rev.* **1979**, *79*, 515.

(13) Gaudemar-Bardone, F.; Gaudemar, M. *J. Organomet. Chem.* **1976**, *104*, 281. See also ref 3.

(14) All new compounds afforded proper combustion or exact mass spectral analysis, as well as suitable IR and NMR spectra. Products **5**,[15] **7**,[16] **10**,[17] and **13**[18] were previously reported compounds.

(15) Kossanyi, J.; Furth, B.; Morizeer, J. P. *Tetrahedron* **1970**, *26*, 395.

(16) Nozaki, H.; Oshima, K.; Takai, K.; Ozawa, S. *Chem. Lett.* **1979**, 379.

(17) Fuson, R. C.; Jackson, H. L. *J. Am. Chem. Soc.* **1950**, *72*, 1637.

(18) Hawkins, E. G. E.; Large, R. *J. Chem. Soc., Perkin Trans. 1* **1974**, 280.

(1) Trozzolo, A. M.; Murray, R. W.; Wasserman, E. *J. Am. Chem. Soc.* **1962**, *84*, 4990–4991.

(2) The ultraviolet spectrum is inconsistent with the emission spectrum tentatively ascribed to phenylmethylene.[3]

(3) Becker, R. S.; Bost, R. O.; Kolc, J.; Bertoniere, N. R.; Smith, R. L.; Griffin, G. W. *J. Am. Chem. Soc.* **1970**, *92*, 1302–1311.

0002-7863/82/1504-1779$01.25/0