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A NEW AND UNUSUALLY FLEXIBLE SCHEME FOR ANNULATION TO FORM FUSED CYCLOHEXENONE UNITS

E. J. Corey and Dale L. Boger

Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138, USA

We have recently described two different types of annulation methods leading to fused and spiro ring systems, one based on benzothiazoles as carbonyl equivalents[1] and the other on the use of pyridinium chlorochromate as a reagent for oxidative cation-olefin cyclization.[2] In continuation of our research on new annulation techniques we next turned to the exploitation of certain of the recently reported reactions of organometallic derivatives of N, N-dimethylhydrazones,[3,4] available by metallation (BuLi or lithium diisopropylamide) and subsequent reaction with cuprous iodide. Such Gilman reagents can be used effectively as enolate equivalents for conjugate addition to α,β-unsaturated esters.[5] Thus ethyl 1-cyclohexene-1-carboxylate (1) and the Gilman ate reagent from acetone N, N-dimethylhydrazone combine to afford after hydrazone cleavage the keto ester 2, a type of structure which provides opportunity for the development of a whole new set of annulation processes. The present paper demonstrates some of these possibilities, specifically for the synthesis of ring-fused cyclohexenone derivatives, and illustrates both the versatility and complementary nature of this approach as compared with the much used Robinson annulation technique.[6]

In order to conserve potentially valuable ligands, often a practical necessity in the effective use of Gilman ate reagents, we chose to utilize mixed cuprates having an inexpensive non-transferable group[7] in addition to the dimethylhydrazone-derived ligand. Mixed cuprates containing the phenylthio ligand[8] were found to be quite satisfactory since such reagents were formed smoothly and exhibited reactivity and selectively[9] closely comparable to the homo-cuprates derived from α-lithio N, N-dimethylhydrazones and cuprous iodide. Thus the unsaturated ester 1 and the mixed Gilman reagent from α-lithioacetone-N, N-dimethylhydrazone and cuprous thiophenoxide afford the keto ester 2 in about the same yield[10] as obtained with the homo-cuprate[3,4] (see procedure which follows).

The potential utility of the keto ester 2 and analogous intermediates, possessing two levels of carbonyl reactivity, for the preparation of annulated fused-ring cyclohexenones is noteworthy. In principle the difference in reactivity of the carbonyl groups can be utilized to direct annulation toward an enone structure possessing the carbonyl function either α or β to the ring-fusion. The application of the adduct 2 toward this end is illustrated in Scheme I. Two key intermediates, the enol-lactone 3 and the dione 4, can be prepared independently from keto ester 2, and these in turn allow the synthesis in good yield of the annulated fused-ring cyclohexenones 5, 6, 7 and 8 under the conditions outlined below. (The ring appendage in these illustrations was arbitrarily chosen as methyl.)

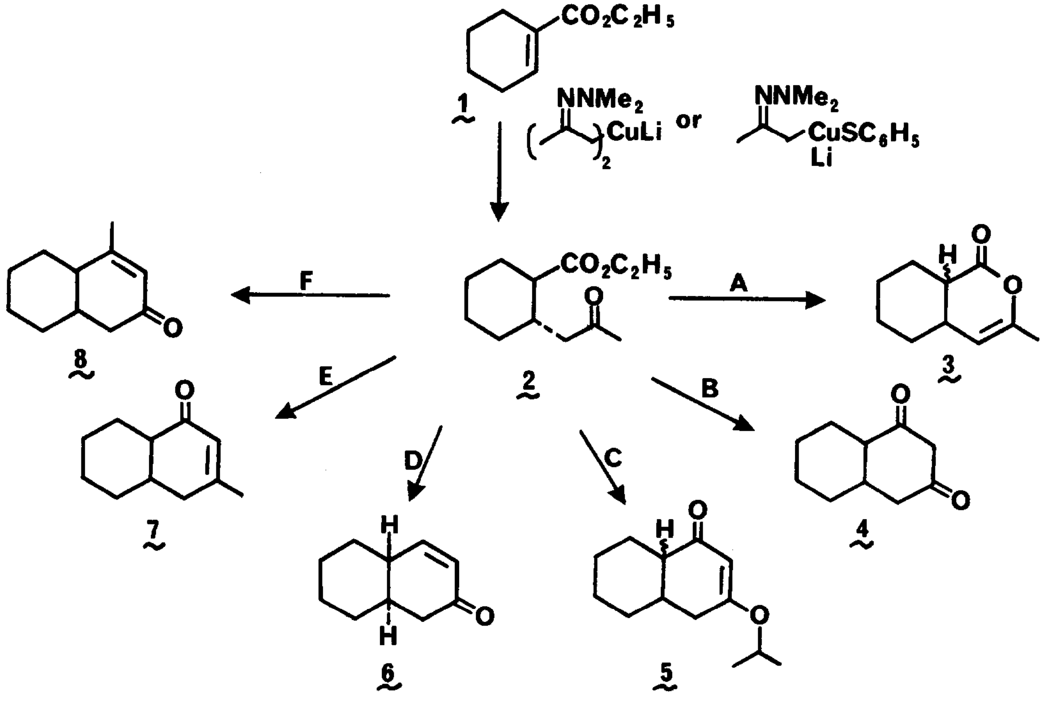
A: Hydrolysis of keto ester 2 to the corresponding keto acid[11] (9 ml tetrahydrofuran, 2 ml methanol, 1.25 ml 10% aqueous sodium hydroxide per mmol, 50°, 11 hr, 100%) and subsequent conversion of the keto acid to enol-lactone 3[12] (5.0 ml acetic anhydride, 50 mg anhyd. sodium acetate per mmol, 135-140°, 12 hr, argon atmosphere, 93-96% crude).[13,14]

B: Intramolecular acylation[15] of keto ester 2 (2-2.2 equiv sodium hydride, 10-12 ml benzene and 7μl methanol per mmol, 70°, 18-36 hr,[16] 80-86%) affords decalin-1,3-dione (4).[17]

C: Acid catalyzed enol ether formation of decalin-1,3-dione 4 (20 equiv isopropanol, 13 mg p-toluenesulfonic acid and 15 ml benzene per mmol, reflux for 2.5 hr followed by reflux for 16 hr with azeotropic removal of water using a Dean-Stark trap) affords cis/trans-3-isopropoxy-$\Delta^{2,3}$-1-octalone 5[18] (70%), R_f 0.63 and 0.59 (ether, SiO_2) accompanied by lesser amounts of the isomeric 1-isopropoxy-$\Delta^{1,2}$-3-octalone (20-24%), R_f 0.42 (ether, SiO_2); these were easily separated and purified by column chromatography (SiO_2, 30% ether-petroleum ether eluant).

D: Method (a): Reduction of 3 (1.1 equiv diisobutylaluminum hydride, 10 ml hexane per mmol, -78°, 1 hr) followed by acid-catalyzed aldolization of the crude reduction product (40 mg p-toluenesulfonic acid, 10 ml benzene per mmol, reflux, 3.5 hr, 68%, 63% overall from keto ester 2) affords trans-$\Delta^{1,2}$-3-octalone 6.[19]

Method (b): Reduction of 5 (1.0 molar equiv of lithium aluminum hydride, 10 ml ether per mmol, 25°, 1 hr) followed by acid-catalyzed hydrolysis and elimination of the crude reduction product (12 ml of 1 N HCl in 5/1 tetrahydrofuran-water per mmol, 25°, 5.5 hr, 76% overall from 5) affords trans-$\Delta^{1,2}$-3-octalone 6.[17,19]



E: Treatment of enol-lactone **3** with 1.1 equiv of α-lithiomethyl dimethylphosphonate[20] (10 ml of tetrahydrofuran per mmol, -78° for 2 hr, -78 to -10° for 2 hr, 25° for 2-2.5 hr, 48% overall from keto ester **2**) affords 3-methyl-$\Delta^{2,3}$-1-octalone **7**[2a] by way of an intramolecular Wadsworth-Horner-Emmons pathway.[14,21]

F: Addition of methyllithium to keto enol ether **5** (1.3 equiv methyllithium, inverse addition, 6-8 ml ether per mmol, -78° for 30 min, 0° for 30 min) followed by immediate acid treatment of the crude hydroxy enol ether (18 ml of 0.1*N* HCl in 5/1 tetrahydrofuran-water per mmol, 25°, 30 min, 96% overall from **5**) affords 1-methyl-$\Delta^{1,2}$-3-octalone **8**.[22]

To the extent that the unsaturated ester **1** serves as an appropriate model for similar and even more complex intermediates, the methodology disclosed herein is capable of broad application. Further the approach outlined here is unusually versatile as indicated by the synthesis of the five annulation products **4**-**8** from a common intermediate. Given these facts and the obvious utility of the annulation products themselves as objects for further elaboration, the consideration of these annulation methods is recommended.

A detailed experimental procedure for the synthesis of **2** via a mixed Gilman reagent follows.

*trans Ethyl 2-acetonyl-cyclohexane carboxylate **2**: acetone N, N-dimethylhydrazone phenylthio-mixed cuprate conjugate addition to **1**:* Soluble cuprous thiophenoxide was prepared as follows: distilled thiophenol (12.4 mmol, 1.38 g, 1.27 ml) in 5.0 ml of dry THF was cooled to 0° under argon and treated dropwise with 12.4 mmol of *n*-BuLi, and the resulting solution was further stirred at 0° for 10 min before addition to a suspension of purified[8] cuprous iodide (12.4 mmol, 2.36 g) in 24 ml of dry THF precooled to -78°. The resulting solution was allowed to stir at 0° until a clear pale yellow solution resulted, *ca.* 10 min.

Acetone N, N-dimethylhydrazone (12.0 mmol, 1.20 g, 1.58 ml) in 70 ml of dry THF was metallated as previously described[3,4] (12.0 mmol *n*-BuLi, -78°, 20 min). The resulting milky-white suspension at -78° was treated with the solution of cuprous thiophenoxide, 12.4 mmol, to give a clear yellow-pale orange solution which was further stirred at -78°[23] for 45 min. Ethyl 1-cyclohexene-1-carboxylate **1** (4.0 mmol, 616 mg) in 5-10 ml of THF was added and the reaction mixture was stirred at -78° for 2.5 hr, -45 to -50° for 2 hr, -23° for 2.5 hr, -23° to 0° for 2 hr before being quenched by the addition of 1.0 ml of methanol. The reaction mixture was partitioned between saturated aq. NH_4Cl (buffered to a pH of *ca.* 8 with conc. NH_4OH) and methylene chloride and vigorously stirred for 5 min. The insoluble cuprous thiophenoxide was filtered off and the organic phase was washed with one portion of saturated NH_4Cl/NH_4OH (pH *ca.* 8), dried (Na_2SO_4), and concentrated *in vacuo* affording the crude N, N-dimethylhydrazone derivative of **2** (*ca.* 80% pure), pmr ($CDCl_3$, ppm), 4.14 (2H, q, J=7Hz, $-OC\underline{H}_2CH_3$), 2.41 (6H, s, $-NMe_2$), 1.91 (3H, s, $-CH_3$), 1.27 (3H, t, J=7Hz, $-OCH_2C\underline{H}_3$).

The crude hydrazone was placed in 60 ml of THF, 12.5 ml pH 7 phosphate buffer and cupric chloride (2.0 equiv, 8.0 mmol, 1.08 g) in 20 ml of water was added and the resulting reaction solution was stirred at 25° for 5.5 hr. Extractive workup as described[24] (ether-saturated NH_4Cl/NH_4OH pH *ca.* 8) followed by chromatography of the crude product (45 g SiO_2, 45 x 1.5 cm, 25% ether-petroleum ether eluant) afforded 548 mg (848 theo, 65%, routinely 60-70%) of pure keto ester **2**,[4] pmr ($CDCl_3$, ppm), 4.10 (2H, q, J=7Hz,

-OC$\underline{H}_2$CH$_3$), 2.5 (3H, m), 2.12 (3H, s, -COCH$_3$), 2.0-1.2 (9H, m), 1.25 (3H, t, J=7Hz, -OCH$_2$C$\underline{H}_3$); ir (film) 1725 (broad strong CO) cm^{-1}; ms *m/e* at 212(M$^+$), 167, 166, 155 (base), 127, 109, 95, 81, 43.[25]

References and Notes

1. E. J. Corey and D. L. Boger, *Tetrahedron Lett.*, 5, 9, 13 (1978).
2. (a) E. J. Corey and D. L. Boger, *ibid.*, 2461 (1978); (b) E. J. Corey, H. E. Ensley and J. W. Suggs, *J. Org. Chem.*, **41**, 380 (1976).
3. E. J. Corey and D. Enders, *Tetrahedron Lett.*, 3, 11 (1976).
4. E. J. Corey and D. Enders, *Chem. Ber.*, **111**, 1337, 1362 (1978).
5. For a review on the conjugate addition of organo-cuprate reagents see, G. H. Posner, *Org. Reactions*, **19**, 1-113 (1972).
6. For a review see, M. E. Jung, *Tetrahedron*, **32**, 3 (1976).
7. See, for example, E. J. Corey and D. J. Beames, *J. Am. Chem. Soc.*, **94**, 7210 (1972).
8. For heteroatom mixed organo-cuprates such as phenylthio-mixed cuprates see, G. H. Posner, C. E. Whitten, and J. J. Sterling, *J. Am. Chem. Soc.*, **95**, 7788 (1973).
9. Studies in these laboratories have shown that the stereoselectivity (i.e., 1,4 vs 1,2 addition to α,β-unsaturated carbonyl compounds) of the N,N-dimethylhydrazone homo-cuprates and phenylthio-mixed cuprates are comparable while the phenylthio-mixed cuprates tend to be only slightly less reactive requiring only slightly longer reaction times and/or slightly higher reaction temperatures.
10. All yields reported herein refer to homogeneous samples isolated by column chromatography (SiO$_2$) unless otherwise noted; all compounds were fully characterized by pmr, ir, and mass spectral analysis.
11. Spectral data for 2-acetonyl-cyclohexane carboxylic acid; pmr (CDCl$_3$, ppm) peaks at 2.55 (3H, m), 2.14 (3H, s, -COCH$_3$), 2.0-1.1 (9H, m); ir (film) 3600-2400 (-CO$_2$H), 1715 (broad CO) cm^{-1}; ms *m/e* at 184(M$^+$), 81 (base); HRMS found 184.1098 (calcd 184.1099 for C$_{10}$H$_{16}$O$_3$).
12. Spectral data for **3**: pmr (CDCl$_3$, ppm) peaks at 5.0-4.75 (1H, m, olefinic), 1.86 (3H, broad s, methyl); ir (film) 1760, 1692, 1655 cm^{-1}; ms *m/e* at 166(M$^+$), 95 (base); HRMS found 166.0995 (calcd 166.0994 for C$_{10}$H$_{14}$O$_2$).
13. For a review on enol-lactone formation see, N. P. Shusherina and R. Y. Levina, *Russ. Chem. Rev.*, **37**, 198 (1968).
14. For a review on the use and reactions of enol-lactones see, J. W. Raynal, *Synthesis*, **1**, 49 (1969).
15. For a review on acylation of ketones see, (a) C. R. Hauser, F. W. Swamer and J. T. Adams, *Org. Reactions*, **8**, 59-196 (1954); for conditions similar to those described here see, (b) H. Conroy, *J. Am. Chem. Soc.*, **74**, 3046 (1952).
16. Occasionally the reaction slows markedly prior to completion; in such cases additional sodium hydride (0.5 equiv) and a catalytic amount of ethanol were added to effect completion.
17. H. Mühle and Ch. Tamm, *Helv. Chim. Acta*, **45**, 1475 (1962).
18. Spectral data for **5**: pmr (CDCl$_3$, ppm) peaks at 5.30 (1H, s, olefinic), 4.41 (1H, heptet, J=6Hz, -OC$\underline{H}$Me$_2$), 1.29 (6H, two d, J=6Hz, methyls); ir (film) 1640, 1600 cm^{-1}; ms *m/e* at 208(M$^+$), 94 (base).
19. The acid catalyzed equilibrium mixture of **6** consists of 96-97/3-4 *trans/cis* fused enone **6** containing *ca.* 5% of the non-conjugated Δ^{1,9}-3-octalone, see reference 1.
20. E. J. Corey and G. T. Kwiatkowski, *J. Am. Chem. Soc.*, **88**, 5654 (1966).
21. W. S. Wadsworth, Jr., *Org. Reactions*, **25**, 97-98 (1978).
22. Spectral data for **8**: pmr (CDCl$_3$, ppm) peaks at 5.81 (1H, s, olefinic), 1.88 (3H, broad s, methyl); ir (film) 3020, 2925, 2855, 2810, 1670 (CO), 1620 (C=C), 1440, 1415, 1375, 1330, 1290, 1275, 1250, 873, 855 cm^{-1}; ms *m/e* at 164(M$^+$), 69 (base); HRMS found 164.1201 (calcd 164.1201 for C$_{11}$H$_{16}$O); 2,4-DNP: ms *m/e* at 344(M$^+$); mp 150-152° [lit mp 154°, P. De Mayo and H. Takeshita, *Cand. J. Chem.*, **41**, 440 (1963)].
23. For the preparation of more hindered N,N-dimethylhydrazone phenylthio-mixed cuprates reaction temperatures of -23° are required; for instance α-lithio cyclohexanone N,N-dimethylhydrazone requires *ca.* 85 min at -23°.
24. E. J. Corey and S. Knapp, *Tetrahedron Lett.*, 3667 (1976).
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