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CYCLOPENTENONE SYNTHESIS FROM KETONES AND 1,1-DICHLOROALLYLLITHIUM

Tamejiro Hiyama*, Masaki Shinoda, and Hitosi Nozaki
Department of Industrial Chemistry, Kyoto University, Yoshida, Kyoto 606, Japan

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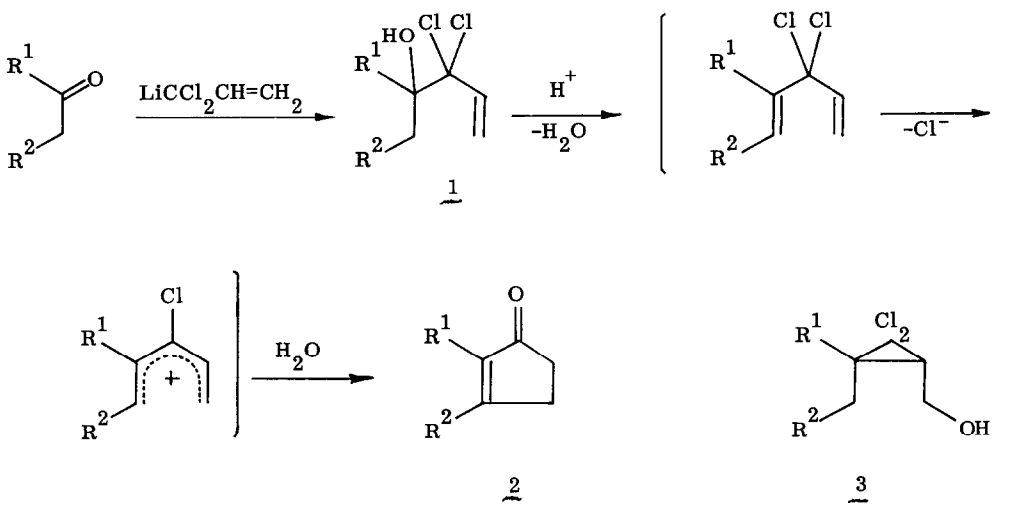
We wish to report a new, general, efficient method for cyclopentenone synthesis, principally based on the thermal conrotatory ring-closure of a chloropentadienyl cation followed by hydrolysis as shown in the following scheme. A dichlorohomoallyl alcohol 1, derived from a ketone and 1,1-dichloroallyllithium, is dehydrated by the action of acid to give a dichlorodiene which is further solvolyzed to the chloropentadienyl cation. The whole process, though unprecedented, may be rationalized by our previous observation[1] that dichlorocyclopropyl carbinol of type 3 is transformed to cyclopentenone 2 through such assumed intermediates upon acid-treatment.[2]

The dichlorohomoallyl alcohol 1 was prepared according to the recently established procedure.[3,4] Thus, lithium diisopropylamide was added dropwise in 1.5 to 2 hr to a mixture of a ketone and 3,3-dichloropropene in tetrahydrofuran (THF) at -78°C to give the corresponding adduct 1 in good yields.



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a, $R^1,R^2 = -(CH_2)_4-$; b, $R^1,R^2 = -(CH_2)_5-$; c, $R^1,R^2 = -(CH_2)_6-$;
d, $R^1,R^2 = -(CH_2)_{10}-$; e, $R^1 = CH_3$, $R^2 = n\text{-}C_5H_{11}$

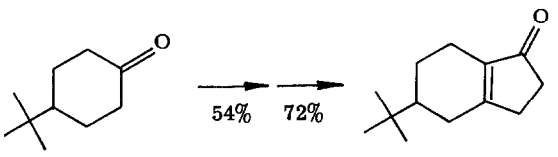
Table Cyclopentenone annulation

ketone	1,[a,b] % yield	2,[a,c] % yield
cyclohexanone	1a,[d] 56	2a, 71
cycloheptanone	1b, 63	2b, 87
cyclooctanone	1c, 68	2c, 80
cyclododecanone	1d, (66)[e]	2d, 90
2-octanone	1e, 73	2e, 87

[a]The products are characterized spectrometrically and analytically.
[b]The adducts listed here are the sole products in the reaction of 1,1-dichloroallyllithium and the corresponding ketones.
[c]Transformation of 1 to 2 is carried out in TFA at room temperature for a couple of hours.
[d]This compound has been synthesized by Seyferth et al. See ref 4.
[e]The yield is taken from the literature (ref 3).

The adduct was successively exposed to acidic conditions. First we have studied the conversion of 1d to 2d and soon found that various kinds of acids are effective, i.e., reagent, reaction temperature, % yield: hydrobromic acid-acetic acid, reflux, 3 hr, 55; titanium tetrachloride-dichloromethane, room temp., 3 hr, 81; trifluoroacetic acid (TFA), reflux, 1.5 hr, 89; TFA, room temp., 1.5 hr, 90. Thus, treatment of a variety of 1 with TFA under the last conditions gave results summarized in the above Table.

Apparently the present procedure is applicable to both cyclic and acyclic ketones[5] and particularly efficient for cyclopentenone annulation. Although cationic species are involved in the reaction sequence, transannular by-path is negligible[6] in the cyclization of 1c and the cyclopentenone 2c was obtained in 54% overall yield.[7] The cyclopentenones thus obtained are versatile intermediates for the synthesis of metacyclophanes[8] and also of large ring compounds[9] through ring-enlargement. The two-step process makes 5-substituted tetrahydroindanone derivatives much readily accessible as illustrated for the synthesis of 4.



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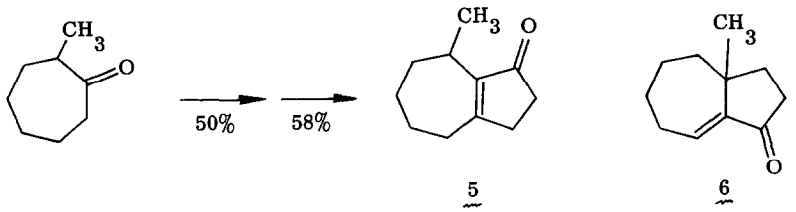
Regioselectivity of the cyclopentenone formation deserves to be mentioned. 2-Octanone was transformed exclusively to 2-methyl-3-pentyl-2-cyclopentenone (2e). The selectivity is explained in terms of the favored formation of more substituted olefin at the dehydration step.[10] On the other hand, when 2-methylcycloheptanone was treated with dichloroallyllithium and the adduct with TFA, the cyclopentenone 5[11] was produced exclusively without any trace of its isomer 6.[12,13] The product 5 has per se the skeleton as well as methyl substituent of guaiazulenoids. Investigation toward the synthesis of such natural products is currently in progress in our laboratory.[14]



5 6

A typical experimental procedure is illustrated for the synthesis of a hydroazulenone 2b. To a mixture of cycloheptanone (677 mg, 6.0 mmol) and 3,3-dichloropropene (800 mg, 7.2 mmol) in THF (15 ml) was added a THF (10 ml) solution of lithium diisopropylamide (9.0 mmol) dropwise at -78°C under a nitrogen atmosphere during the period of 1.5 hr. After the addition was completed, the reaction mixture was stirred at -78°C for another hour and then treated with methanol (2 ml). Usual work-up, followed by purification of the crude product on column chromatography (silica gel, hexane-ether 50:1), gave 1b (850 mg, 63% yield). NMR (CCl_4): δ 1.2-2.2 (m, 13H), 5.2-6.3 (ABC pattern, 3H); IR (neat): 3564, 3514, 1648, 980, 930 cm^{-1}.

The homoallyl alcohol 1b (447 mg, 2 mmol) was dissolved in TFA (3 ml) at room temperature under vigorous agitation, and the solution was stirred for 1.5 hr and neutralized with aqueous saturated sodium hydrogencarbonate solution. Extractive work-up and subsequent purification on preparative TLC (Merck Kieselgel 60 PF_{254}, dichloromethane-ether 10:1, R_f 0.4-0.5) afforded the desired cyclopentenone 2b (260 mg, 87% yield). Bp 128-132°C (bath temp)/4 Torr; NMR (CCl_4): δ 1.2-2.0 (m, 6H), 2.0-2.6 (m, 8H); IR (neat): 1690, 1641 cm^{-1}; MS: m/e 150 (M^+).

References and footnotes

1. T. Hiyama, M. Tsukanaka, and H. Nozaki, J. Am. Chem. Soc., 96, 3713 (1974). Three-carbon annulation: see M. E. Jung and J. P. Hudspeth, ibid., 99, 5508 (1977) and references cited therein.

2. Attempts to utilize the cyclization of chloropentadienyl cation are recorded by others. Y. Gaoni, Tetrahedron Lett., 2167 (1976); 371 (1977).

3. H. Taguchi, H. Yamamoto, and H. Nozaki, Bull. Chem. Soc. Jpn., 50, 1588 (1977).

4. D. Seyferth, G. S. Murphy, and R. A. Woodruff, J. Am. Chem. Soc., 96, 5011 (1974); J. Organomet. Chem., 66, C29 (1974).

5. The reaction with cyclopentanone gave, after column chromatography, a low yield of the adduct whose structure is tentatively assigned as 1-propenoylcyclopentene.

6. A. C. Cope, M. M. Martin, and M. A. McKervey, Quart. Rev. (London), 20, 119 (1966).

7. The yield is much improved as compared with the conventional one (28%) through the Stobbe condensation and polyphosphoric acid treatment (ref 8).

8. S. Hirano, H. Hara, S. Fujita, T. Hiyama, and H. Nozaki, Tetrahedron, 31, 2219 (1975).

9. a. D. Felix, J. Schreiber, G. Ohloff, and A. Eschenmoser, Helv. Chim. Acta, 54, 2896 (1971). b. M. Karpf and A. S. Dreiding, ibid., 59, 1226 (1976). c. W. Hoffmann and N. Muller, Tetrahedron Lett., 3585 (1976).

10. Similar selectivity is observed in the dehydration of 3. See ref 1.

11. Bp 122-128°C (bath temp)/3 Torr; NMR (CCl_4): δ 0.96 (d, J = 7 Hz, 3H), 1.1-2.1 (m, 6H), 2.1-3.2 (m, 7H); IR (neat): 1689, 1638 cm^{-1}; MS: m/e 164 (M^+).

12. Regioselectivity of the addition of 1,1-dichloroallyllithium to ketones is discussed by Seyferth (ref 4), and electronic factor is found crucial. However, steric factor also seems important in the reaction with 2-methylcyclohexanone, where the unsubstituted 3-carbon of the dichloroallyllithium solely attacks the carbonyl carbon (28% yield), NMR (CCl_4): δ 0.75 (d, J = 7 Hz, 3H), 0.9-2.7 (m, 10H), 4.12 (d, J = 7 Hz, 2H), 6.15 (t, J = 7 Hz, 1H); IR (neat): 3480, 1642, 1151, 988, 850, 785 cm^{-1}; MS: m/e 226 (M^+ + 4, 3%), 224 (M^+ + 2, 12%), 222 (M^+, 19%) in contrast to the reaction with cyclohexanone (see Table). Similarly the reaction of 3-octanone affords the C-3 adduct only (48% yield), whereas 2-octanone the C-1 adduct (Table).

13. Interestingly the compound 6 (IR (neat): 1716, 1643 cm^{-1}; NMR (CCl_4): δ 1.11 (s, 3H), 0.8-2.8 (m, 12H), 6.57 (dd, J = 5, 7 Hz, 1H); MS: m/e 164 (M^+)) was the major product in the acid-catalyzed dehydration of the 2-methylcycloheptanone-propargyl alcohol adduct (cf. ref 9b and 9c). Regioselectivity of this reaction will be published in due course.

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