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A NOVEL METHOD FOR CYCLOPENTANONE ANNULATION. THE USE OF 1-(2-KETOALKYL) CYCLOPROPANOLS TO OBTAIN CYCLOPENTANONES.

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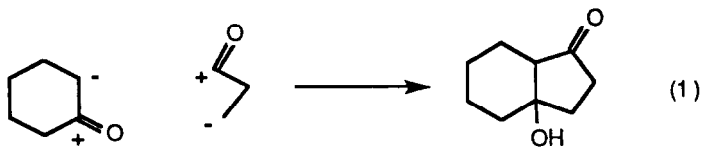
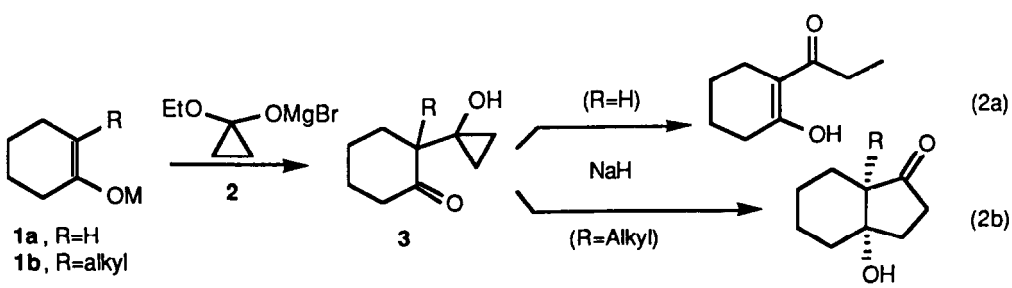
Abstract: The condensation of alkyl-substituted thermodynamic enolates with ethyl bromomagnesium cyclopropanone hemiacetal (a cyclopropanone equivalent) provides 1-(2-ketoalkyl) cyclopropanols which in turn are converted into 3-hydroxycyclopentanones by treatment with base.

The annulation of a cyclopentanone onto a pre-existing organic framework has received considerable attention in the literature.[1] The use of a formal [3+2] protocol is an attractive approach in general to five-membered rings (Eq. 1).[2] Herein, we describe studies in this area which involve the reaction of a cyclopropanone equivalent with a suitable enolate to give a 1-(2-ketoalkyl) cyclopropanol. Once in place, the cyclopropanol behaves as a homo-enolate[3] and is subsequently converted into a cyclopentanone.



(1)

Our initial efforts in this area were concerned with the cyclopropanol **3a** derived from cyclohexanone enolate **1a** and the bromomagnesium derivative **2** of cyclopropanone ethyl hemiketal.[4,5] The reaction product obtained upon treatment of **3a** with sodium hydride is that of an apparent quenched β-enolate (Eq. 2a).[5] If an alkyl group is present in place of the offending acidic proton α to the carbonyl group, then the conversion of a pendant cyclopropanol to the corresponding fused hydroxycyclopentanone occurs (Eq. 2b). An example of this rearrangement was recently reported by Narasimhan and Patil in a similar context.[6]

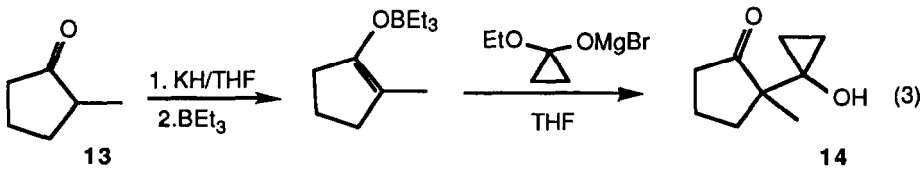


1a, R=H
1b, R=alkyl

(2a)

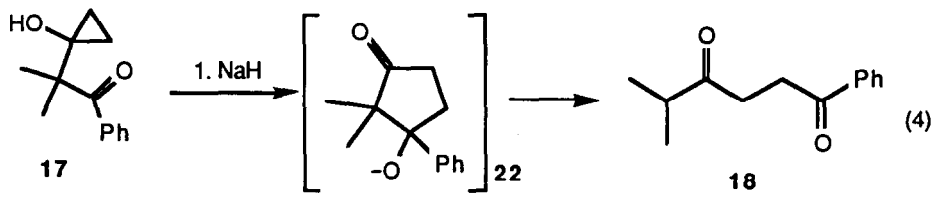
(2b)

The procedure developed by Holton[7] was used for the formation of thermodynamic enolates. This method involves the reaction of 2-alkyl ketones with bromomagnesium diisopropylamide (except for entry E of Table 1). These enolates undergo condensation with **2** resulting in the cyclopropanols listed in Table 1. For entry E, we made use of a procedure developed by Negishi[8] for the selective generation of thermodynamic boron enolates of cyclopentanones (Eq. 3). The use of the magnesium enolate of 2-methylcyclopentanone gave only self-aldol products and recovered starting ketone **13.**



13 **14**

The standard conditions employed to transform a cyclopropanol into a cyclopentanone were the addition of the alcohol to sodium hydride at 0 °C in an ether/ hexane (1:1) mixture followed by warming to 25 °C and quenching with methanol after 2 hours.[9] It is interesting to note that for entry F, the desired monocyclic product was not obtained under the standard conditions. Instead, the initially obtained cyclopentanone **22** undergoes a retro-aldol ring-scission to give dione **18** as the only product (Eq. 4).



17 **18**

There is clearly a need for improvement of the yields of the initially formed cyclopropanols. Efforts currently underway in our laboratories include these optimization studies and the application of this new method of cyclopentannulation to the synthesis of natural products.

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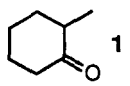
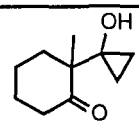
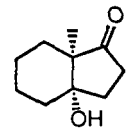
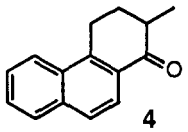
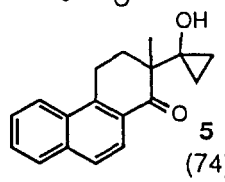
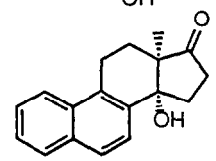
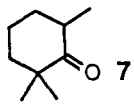
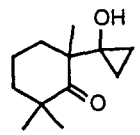
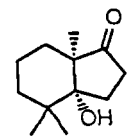
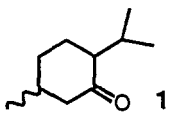
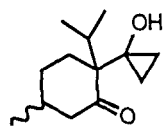
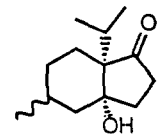
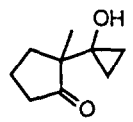
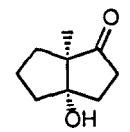
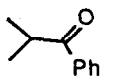
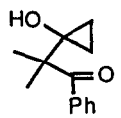
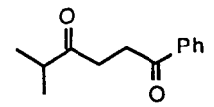
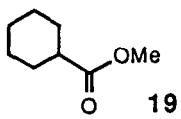
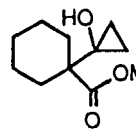
Table 1

Entry	Ketone	Cyclopropanol (%yield)[a]	Product (%yield)[a]
A	 **1**	 **2** (23)[b]	 **3** (71)[c]
B	 **4**	 **5** (74)[b]	 **6** (78)
C	 **7**	 **8** (52)[b]	 **9** (75)[c]
D	 **10**	 **11** (24)[b]	 **12** (67)
E	 **13**	 **14** (32)[d]	 **15** (68)
F	 **16**	 **17** (25)[b]	 **18** (93)
G	 **19**	 **20** (27)[e]	----[f]

[a]Yields reported are for chromatographically homogeneous isolated compounds. All new compounds were fully characterized by 300-MHz ^{1}H NMR and 75-MHz ^{13}C NMR and gave correct elemental analytical data. [b]ref.7. [c]ref.9. [d]ref.8. [e]ref.10. [f]We have been unable to effect the rearrangement of **20** using the standard conditions.

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9. Small amounts of 1,3-diketones obtained by quenching of apparent β-enolates were isolated for entries A (2-methyl-2-propionylcyclohexanone, 8%) and C (2-propionyl-2,6,6-trimethylcyclohexanone, 6%).

10. The procedure followed for this reaction was from ref. 5, footnote 12.

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