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Acid-catalyzed rearrangements of some 1,6-diketones[†,‡]

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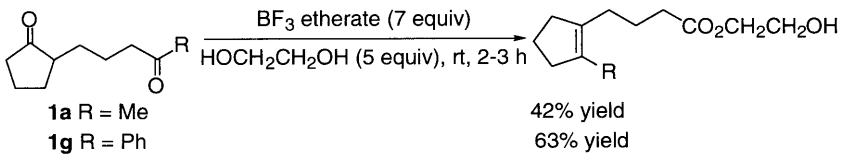
Abstract

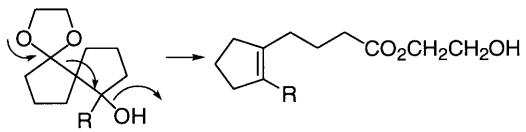
2-(4-Ketoalkyl)cyclopentanones, when subjected to the action of 1 M H_2SO_4 at reflux, undergo ring cleavage and formation reactions to give 4-(1-cyclopentenyl)butanoic acids. When the starting ring is six-membered instead, a bicyclic enone results. Mechanistic discussion and some experimental tests are put forth. © 2000 Elsevier Science Ltd. All rights reserved.

We report two deep-seated rearrangements of certain 1,6-diketones, prepared from carbonyl-protected δ-lithioketones,[1] when they are heated at reflux in 1 M H_2SO_4.[2] One rearrangement is that of cyclopentanones substituted at the α-position with a chain bearing a ketone group at the 4-position, e.g. **1** and results in the formation of a new five-membered ring and the cleavage of the original ring to a carboxylic acid (Table 1). When the substrate **1a** was labeled with ^{13}C at the chain carbonyl group (prepared[1] with the use of carbonyl-labeled acetyl chloride), the label in the product was located on the ring carbon atom attached to the methyl group.

Sakai and co-workers reported apparently related fragmentations/cyclizations, albeit in lower yields, under conditions used to prepare dioxolanes (Eq. (1)).[3] Unidentified products were also formed. Their mechanistic hypothesis involved an aldol reaction followed by acetalization and a Grob type fragmentation (Eq. (2)).[3]



(1)



(2)

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† Dedicated with affection to Professor Harry Wasserman on the occasion of his 80th birthday.

‡ Taken in part from the M.S. Thesis of Shirong Zhu, University of Pittsburgh, 1996.

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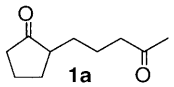
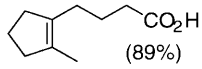
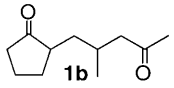
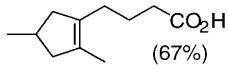
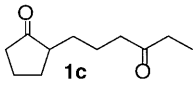
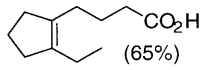
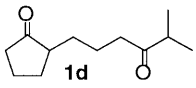
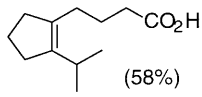
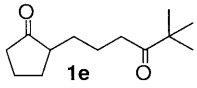
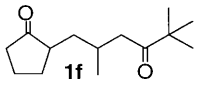
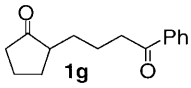
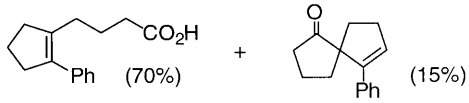
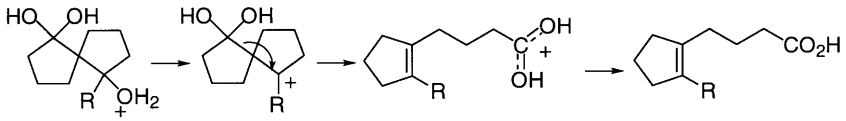
Table 1
Rearrangements of 2-(4-ketoalkyl)cyclopentanones in refluxing 1 M H_2SO_4

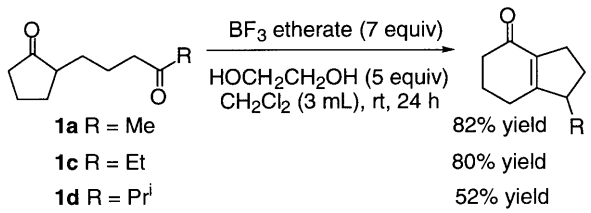
Ketone	Time	Products (yields)
 **1a**	69 hrs	 (89%)
 **1b**	24 hrs	 (67%)
 **1c**	24 hrs	 (65%)
 **1d**	48 hrs	 (58%)
 **1e**	14 days	no reaction
 **1f**	3 days	no reaction
 **1g**	3 days	 (70%) + (15%)

A mechanism analogous to that proposed by Sakai (Eq. (2)) for the fragmentation reactions in Eq. (1) would also rationalize our results if a ketone hydrate is substituted for the acetal (Scheme 1). However, one can not rule out the possibility that the unhydrated ketone is cleaved leading to an acylium ion intermediate. In the cases of **1e** and **1f**, steric hindrance presumably prevents the aldol formation.



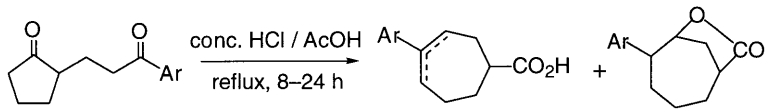
Scheme 1.

In a later paper, Sakai's group reported a different rearrangement for **1a**, **1c** and **1d** under similar conditions but in the presence of methylene chloride and for a longer time (Eq. (3)).[4]



(3)

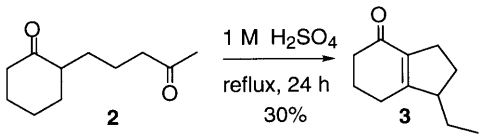
In fact, there is early precedent for this type of fragmentation under conditions in which acetals would not be involved. Buchanan and co-workers reported the ring expansions shown in Eq. (4).[5] A closely related reaction had been observed a few years earlier[6] but a key error in the assigned product structure was only corrected 22 years later.[7] These ring expansions were postulated to proceed by a normal intramolecular aldol condensation followed by protonation of the alkene and a fragmentation analogous to that in Scheme 1.



(4)

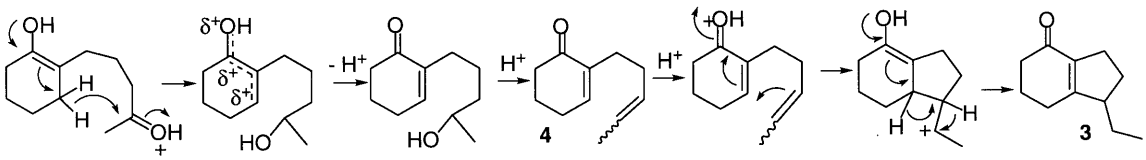
When the aryl group was replaced by an alkyl group bearing an α-proton, normal aldol products were observed but the ring expansions did occur under much harsher conditions, heating with tosic acid in ethylene glycol; in this case as well, there is a possibility that an acetal is an intermediate. When the substrate ring was larger than five-membered, normal aldol reactions rather than ring expansions were observed.

In contrast, when in our case, the cyclopentanone was replaced with a cyclohexanone, a different and even more deep-seated rearrangement occurred (Eq. (5)). The ^{1}H and ^{13}C NMR spectra of **3** compared very well with that reported by Sakai's group for the product of treatment of **1c** with BF_3 (Eq. (3)),[4] as well as those of the same compound produced by a more straightforward rearrangement.[8]



(5)

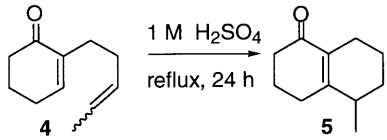
The process in Eq. (5) apparently involves redox processes. The hydride transfer in Scheme 2 would appear to fulfill this requirement. The cyclization followed by two 1,2-shifts shown in Scheme 2 is precedented, albeit for the case in which two methyl groups terminate the alkene system and another is at the β-position of the starting enone.[9]



Scheme 2.

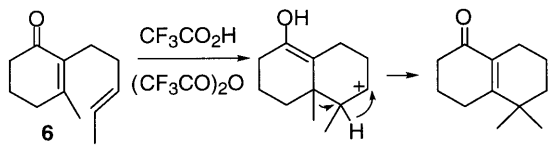
In order to provide one test of this mechanism, **4** was prepared by use of a Wittig reaction on the known[10] corresponding aldehyde. The ^{13}C NMR spectrum of **4** clearly indicated the presence of two, presumably geometric, isomers in very unequal amounts. Integration of the methyl doublets (with small further splitting) at δ 1.58 and 1.63 in the ^{1}H spectrum indicate a ratio, respectively, of about 70:30. The highest field ^{13}C peak at δ 12.76 is due to the methyl group of the major isomer as determined by a DEPT spectrum. The corresponding peak for the minor isomer is at δ 17.87. Thus, as expected[11] for a Wittig olefination with an unstabilized ylide, the alkene product is mainly *cis*.[12] This stereochemical elucidation becomes important in evaluating

the results of the mechanistic test (see below). When this mixture was treated under the conditions in Eq. (5), **3** could not be clearly identified in the reaction mixture. Instead, the enone **5** was detected in a yield somewhat under 20%.[13] Like its isomer **3**, **5** is UV active. The ^{1}H and ^{13}C NMR spectra of **5** compared well with that obtained by Sakai's group for the product of treatment of the chain homolog of **1a** with BF_3 (Eq. (3)).



(6)

The cyclization in Eq. (6) appears to be closely related to that suggested in Scheme 2 except that the cyclization, which is followed by the two hydride transfers, occurs in an *endo* rather than an *exo* fashion. In fact, at least for *trans* disubstituted alkenes, the *endo* mode is always observed.[9,14] A close analogy to the cyclization shown in Eq. (6) is the acid-induced ring closure of the β-methylated analogue **6** of *trans* **4**. Sutherland and co-workers have found the product to be that of *endo* ring closure, followed by a hydride and a methyl transfer (Eq. (7)).[9]



(7)

However, very little if anything is known about the regiochemistry of acid-induced ring closures of the *cis* isomers of compounds like **4**. If the *cis* isomer had been the minor isomer in our synthetic sample of **4**, and if such *cis* isomers were to give *exo* ring closures, it would be conceivable that the *exo* cyclization product, ethyl compound **3**, derived from the small quantity of *cis*-**4** present, would be a minor product in the mechanistic test but would be undetectable due to its low yield; note that the yield of **3** from rearrangement of **2** (Eq. (5)) was only 30%. Under such circumstances, the mechanistic test would have been inconclusive in ruling out the mechanism in Scheme 2 since it is possible that *cis*-**4** could have been the main isomer formed from the dehydration postulated in Scheme 2. However, since the *cis* isomer is actually the major component of the synthetic mixture of **4**, we are forced to conclude that the mechanism in Scheme 2 is not viable. We leave it to others to rationalize this unusual rearrangement.

Acknowledgements

We are grateful to the National Science Foundation for financial support, Dr Fu-Tyan Lin for help in NMR spectroscopy, Dr Kasi Somayajula for help with the mass spectra, MDL Information Systems and DuPont-Pharmaceutical for generous software and database support, and Professor Peter Wipf for useful suggestions.

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