

ADVANCES IN CYCLOPENTENONE SYNTHESIS FROM FURANS

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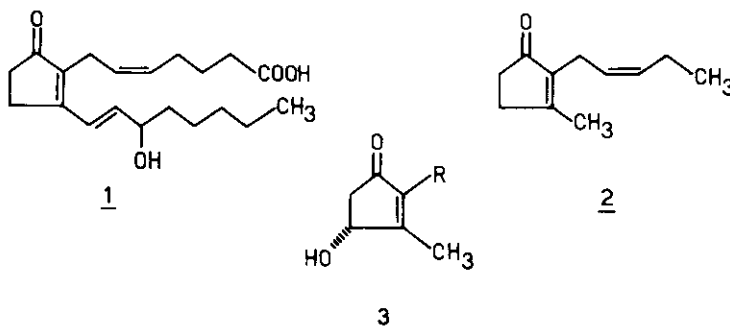
Abstract -- Both 2-furylcarbinols and their 5-methyl derivatives are turned into the isomeric cyclopentenones through a molecular rearrangement catalyzed by acids or zinc chloride. The reaction was completely stereospecific and its mechanism was explained in terms of a thermal electrocyclic reaction of a 4π -electrons system; it showed a wide applicability and made easily available a large variety of cyclopentenones.

The oxidative ring fission of 2,5-dialkylfurans by pyridinium chlorochromate gave trans-ene dicarbonyl compounds; these were efficient building blocks for the cyclopentenone synthesis and several applications are described.

2-(5-methyl-2-furyl)-1,3-dicarbonyl compounds, a new class of furan derivatives, afforded readily manipulable functionalized cyclopentenones, by a simple one-pot procedure, consisting first of the acid-catalyzed furan ring opening and, then, the intramolecular cyclization of the γ -diketone intermediates, directly to cyclopentenones in the same medium.

The cyclopentenone molecule and its 4-hydroxy derivatives are present in several biologically active natural products as major structural features. These include prostaglandins 1, a family of mammalian hormones 1, cis-jasmone 2, a perfume 2, and rethrolones 3, the ester components of the insecticidal pyrethrins 3.

These have given rise to considerable interest and efforts to develop efficient routes to these molecules 4

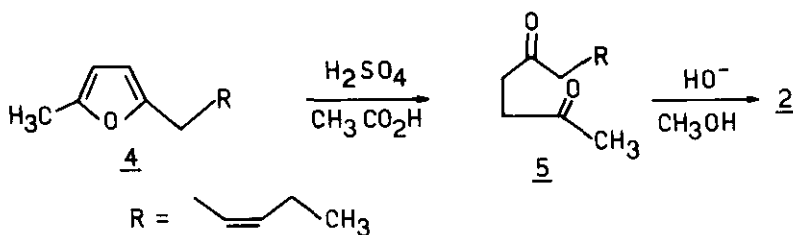


From an examination of the literature, it was possible to see that a great many syntheses of these products were available, generally based on the same approach: the prior preparation of 1,4-diketones, which are subsequently cyclized in base to cyclopentenones⁴. Other reported routes, for example based on modification of dioxocyclopentanes or involving some form of molecular rearrangement, showed some limitations (complex multi-step syntheses, or employment of expensive intermediates, or sophisticated experimental conditions), which have restricted their utility⁴.

Our group began to work in this field about 1975; the purpose was to perform new syntheses of these compounds with the following features: inexpensive starting materials, easy to find or to prepare, simple, mild, effective experimental conditions and high yields.

We thought to utilize furans because they are easily available; then, they could be considered "depot compounds" of 1,4-diketones. In fact, in past years, furans received attentions only as precursor of the γ -diketones⁴. The well-known Büchi synthesis of 2 follows this methodology: the key intermediate 5 was obtained by acid-catalyzed ring opening of the dialkylfuran 4 (scheme 1)⁵

Scheme 1

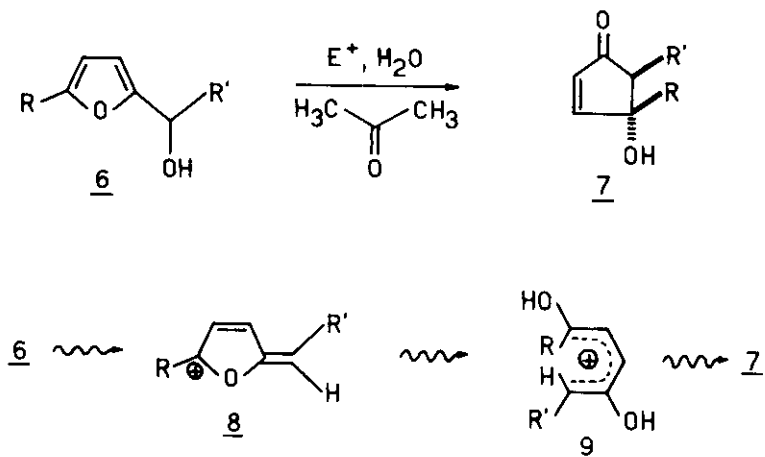


Our approaches are based on the following routes:

- 1) Molecular rearrangement of 2-furylcarbinols
- 2) Cyclization of trans-ene-dicarbonyl compounds
- 3) One-pot cyclization of 2-(5-methyl-2-furyl)-1,3-dicarbonyl compounds.

- 1) Molecular rearrangement of 2-furylcarbinols

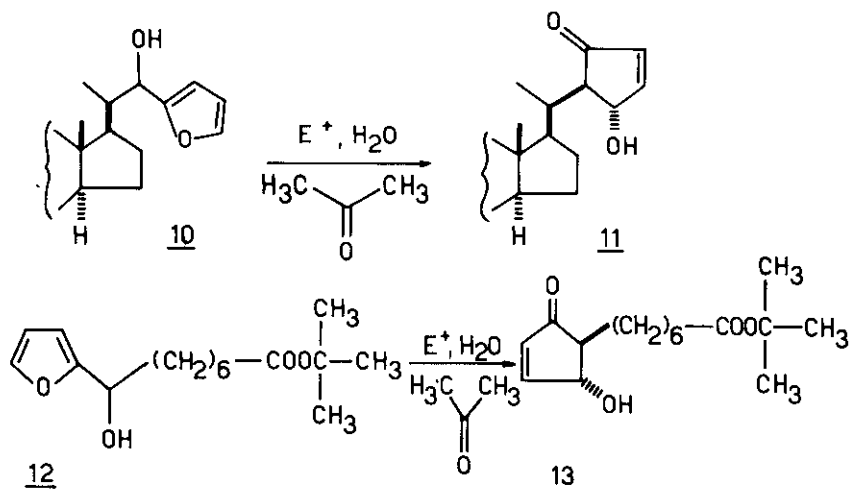
2-furylcarbinols 6, easily obtained by usual procedure of a Grignard reaction, could be turned into the corresponding cyclopentenones 7, through a molecular rearrangement catalyzed by acid or zinc chloride^{6,7}. The reaction was completely stereospecific and the mechanism was explained in terms of a thermal electrocyclic reaction of a 4 π -electrons system⁸; the key-step in the conversion was the formation of the carbonium ion 8, which first led to the pentadienyl cation 9, and then to the final products 7



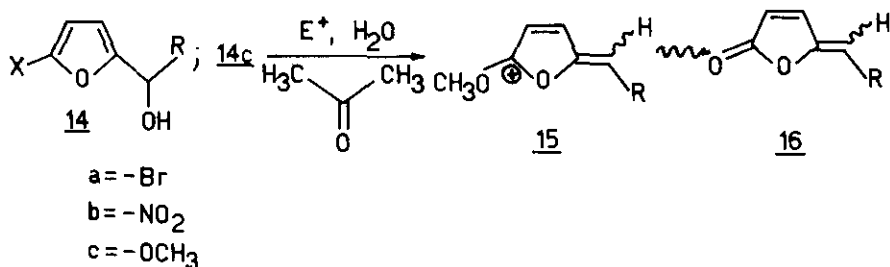
The above result pointed out the interesting capability of 2-furylcarbinols to be precursors of the cation **9**, that undergoes conrotatory electrocyclic ring closure to **7** (Nazarov reaction)⁹; this type of cyclopentenone synthesis was often limited by the available methods to construct the precursors of the cation **9**^{10,11}.

This reaction was completely original and showed a large applicability, also in steroid¹² and prostaglandin field¹³.

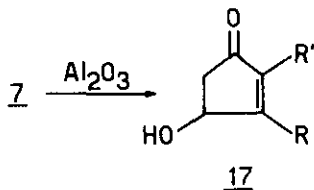
It made easily accessible a large variety of cyclopentenone derivatives, most of those unknown.



In order to investigate the role of the key intermediate **8** in the rearrangement, several furan derivatives **14** (a, b, c) were prepared¹⁴.



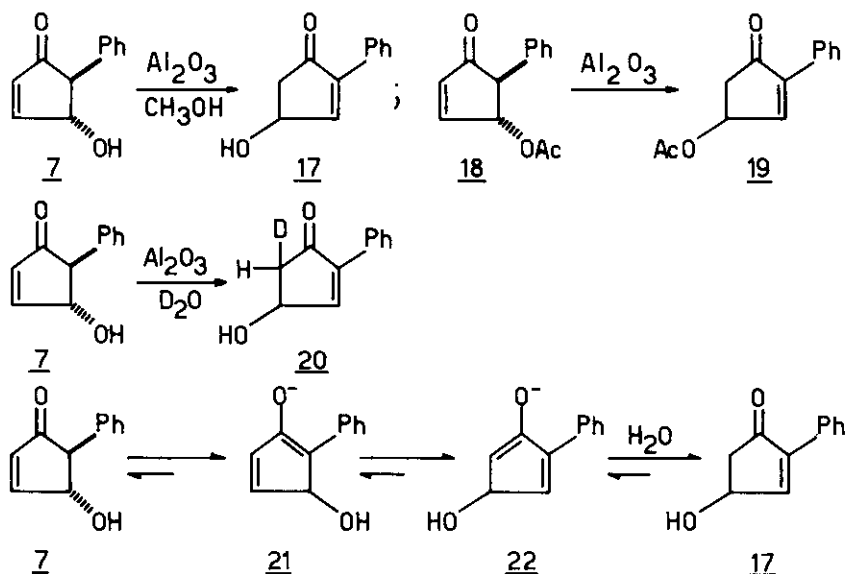
As to be expected, 14a and 14b were stable, also under drastic experimental conditions. On the contrary, 14c was a very reactive intermediate; the strong electron donor effect of the methoxy group favored the formation of the cation 15, increasing both reaction rate and yield¹⁴. 4-Ylidene butenolides 16 were obtained, but their formation was in agreement with the presence of a common intermediate, the reactivity of which was governed by the methoxyl group on furan ring¹⁴. The compounds 7, isomerized into 3-oxo-5-hydroxy-cyclopentene derivatives 17, are interesting intermediates for prostaglandin and rethrolone syntheses¹⁵.



This isomerization was achieved in convenient manner, by an intramolecular migration of the alcoholic function^{16,17}. The conversion is shown to occur through an alumina-catalyzed process of intramolecular hydration.

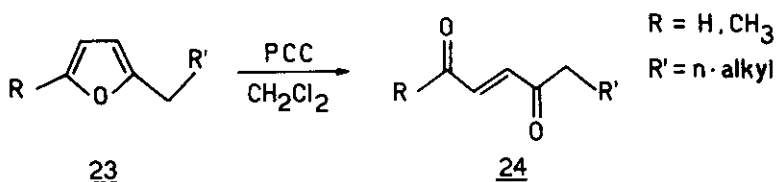
The experimental results, reported in the scheme 2, were in agreement with a mechanism via the enolate ion 21, which rearranged into the more stable one 22 (scheme 2)¹⁷

Scheme 2



2) Cyclization of trans-ene dicarbonyl compounds

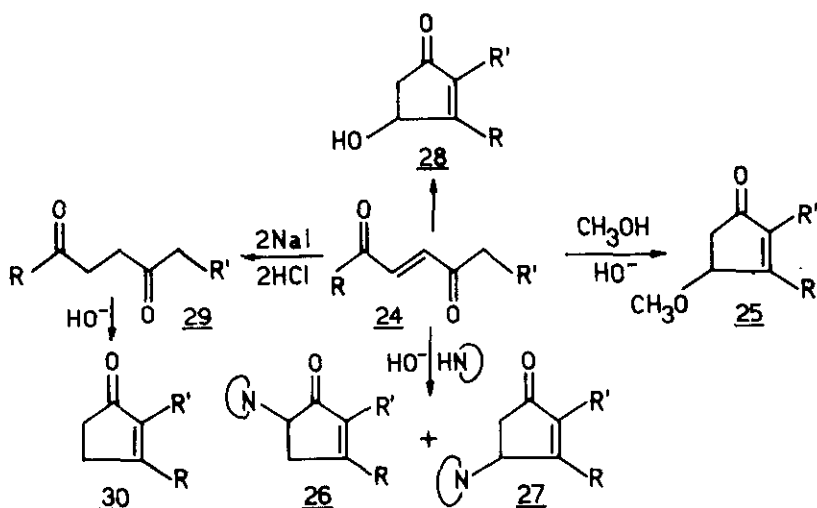
During the studies on the reactivity of pyridinium chlorochromate (PCC), the synthesis of trans-ene dicarbonyl compounds 24 was carried out¹⁸, through an oxidative ring fission of furan derivatives 23 with PCC.



These compounds were rarely considered useful for cyclopentenone synthesis¹⁹; only the cis-isomers were utilized to build up cyclopentenones by an intramolecular condensation^{20,21}. On the contrary their great versatility in this field

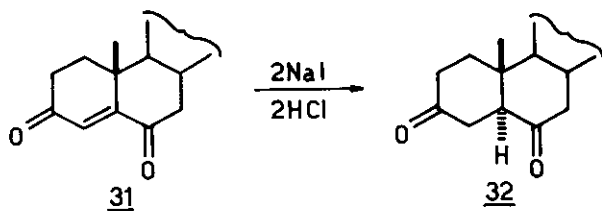
has been demonstrated (Scheme 3).

Scheme 3

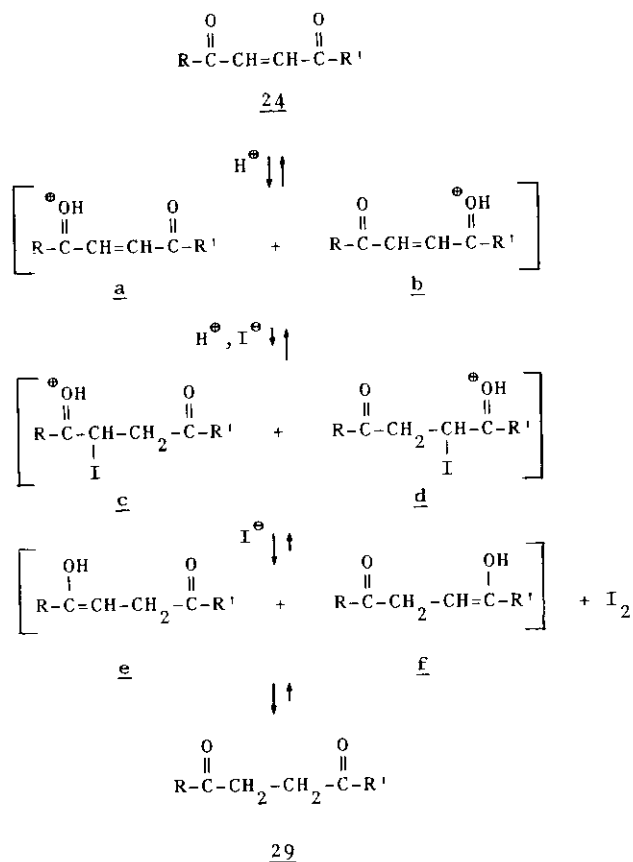


In fact, base-catalyzed cyclization afforded only 5-methoxycyclopentenone **25** (thermodynamically controlled product)¹⁸; the same reaction with cyclic secondary amines gave 4-amino- and 5-aminocyclopentenones **26** and **27**, never prepared before (kinetically controlled products)²². One-pot procedure allowed to convert directly **24** into 4-hydroxy derivatives, first by the trans-cis photoisomerization of **24** and then by the condensation in base to cyclopentenones **28**²³. At last, enediacarbonyl compounds, treated with sodium iodide and hydrochloric acid in acetone, were rapidly and quantitatively reduced to their saturated analogues **29**²⁴. This reaction was also available in the steroid field and was completely stereospecific. The known available methods for this reduction either require expensive reagents or afford only low yields²⁴.

This mild, new reduction failed with butenedioic acids and esters, or with α , β -unsaturated monocarbonyl compounds. This different behaviour was fully in agreement with the proposed mechanism²⁴ (Scheme 4).



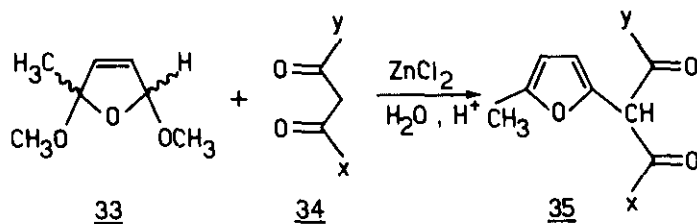
Scheme 4



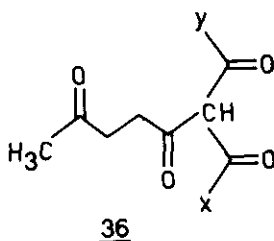
This mechanism explains why the procedure fails in the above-mentioned cases: the elimination of iodide ion requires the presence of a strongly electron-withdrawing substituent at the C-atom α to the C-atom bearing the iodine to ensure the necessary delocalization of the resultant negative charge.

3) One-pot cyclization of 2-(5-methyl-2-furyl)-1,3-dicarbonyl compounds.

Recently, the synthesis of a new class of furans, 2-(5-methyl-2-furyl)-1,3-dicarbonyl compounds 35, has been reported by an intermolecular condensation of 2-methyl-2,5-dihydro-2,5-dimethoxyfuran 33, with an appropriate active methylene compound 34²⁵.

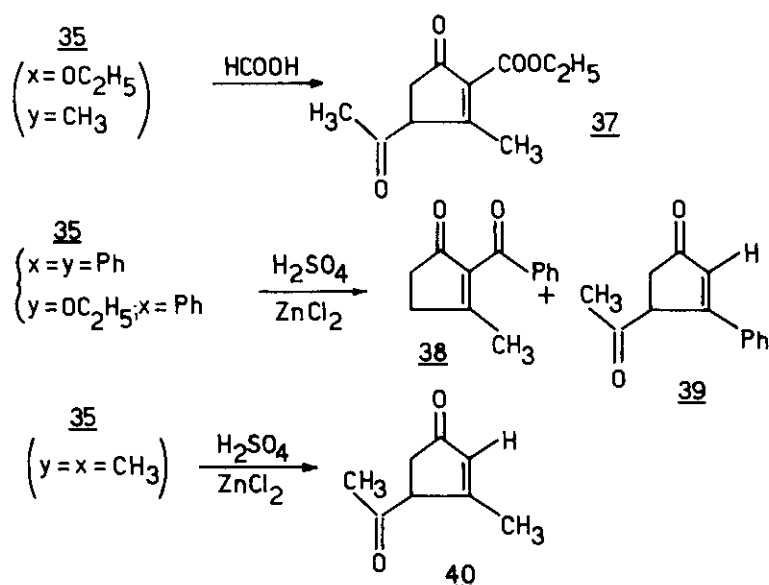


Compounds 35 can be considered precursors of 1,4-diketones of type 36 (with an adjacent active group), capable of undergoing cyclization in the same acidic medium in which the opening of furan ring occurred.



35, treated in acidic medium, underwent opening of the furan ring and subsequent cyclization to give cyclopentenones (scheme 5)²⁶. The substituent pattern of the final products depended upon whether the ring-opened intermediate 36 cyclized directly or underwent first an acidic-catalyzed β -diketone fission. This procedure provided a flexible sequence for the preparation of various synthetically interesting cyclopentenones, most of those never prepared before²⁶.

Scheme 5



Conclusion

It can be seen from the above discussion that furans are highly versatile building blocks for organo-chemical synthesis of cyclopentenones; further studies on the reactivity of these intermediates should find out new their original applications, particularly in the field of naturally occurring substances.

ACKNOWLEDGEMENT

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