ADVANCES IN CYCLOPENTENONE SYNTHESIS FROM FURANS

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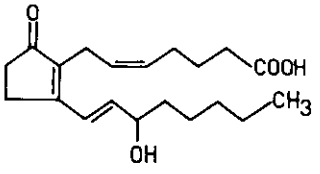
Abstract -- Both 2-furylcarbinols and their 5-methyl derivatives are turned into the isomeric cyclopentenones through a molecular rearrangement catalyzed by acids or zinc chloride. The reaction was completely stereospecific and its mechanism was explained in terms of a thermal electrocyclic reaction 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 develope efficient routes to these molecules[4]



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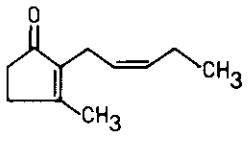

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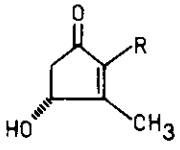

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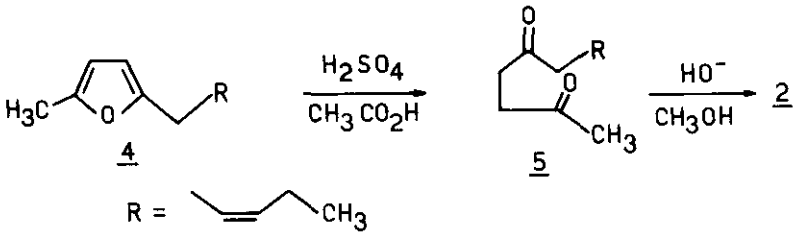
From an examination of the literature, it was possible to see that a great many syntheses of these products were available, generally based on the same approach: the prior preparation of 1,4-diketones, which are subsequently cyclized in base to cyclopentenones[4]. Other reported routes, for example based 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 utility[4].

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-diketones[4]. 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:

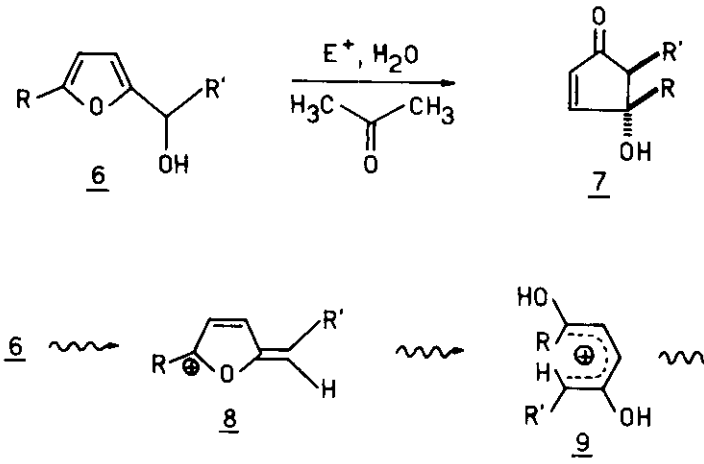
1) Molecular rearrangement of 2-furylcarbinols

2) Cyclization of trans-ene-dicarbonyl compounds

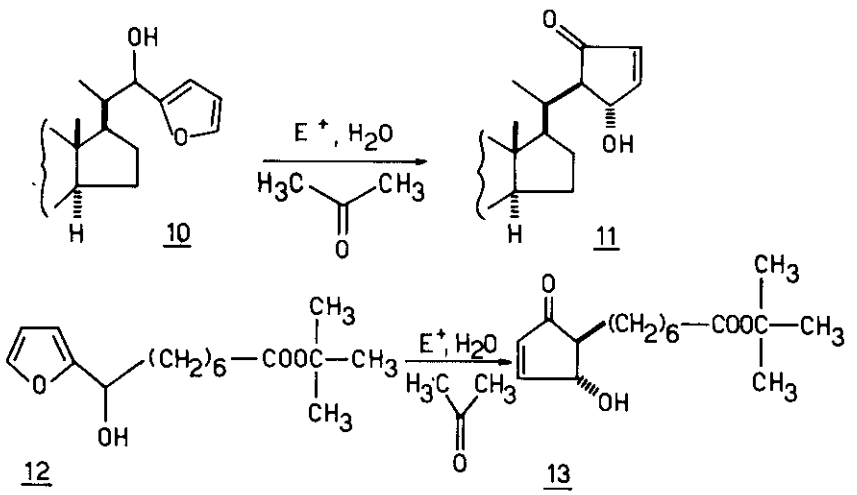
3) One-pot cyclization of 2-(5-methyl-2-furyl)-1,3-dicarbonyl compounds.

1) Molecular rearrangement of 2-furylcarbinols

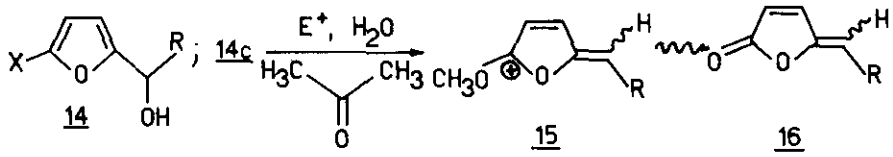
2-furylcarbinols 6, easily obtained by usual procedure of a Grignard reaction, could be turned into the corresponding cyclopentenones 7, through a molecular rearrangement catalyzed by acid or zinc chloride[6,7]. The reaction was completely stereospecific and the mechanism was explained in terms of a thermal electrocyclic reaction of a 4 π-electrons system[8]; 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 steroid[12] and prostaglandin field[13].
It made easily accessible a large variety of cyclopentenone derivatives, most of those unknown.

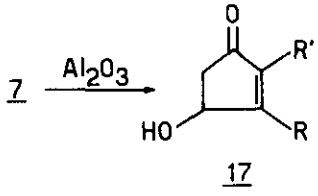


In order to investigate the role of the key intermediate 8 in the rearrangement, several furan derivatives 14 (a, b, c) were prepared[14].



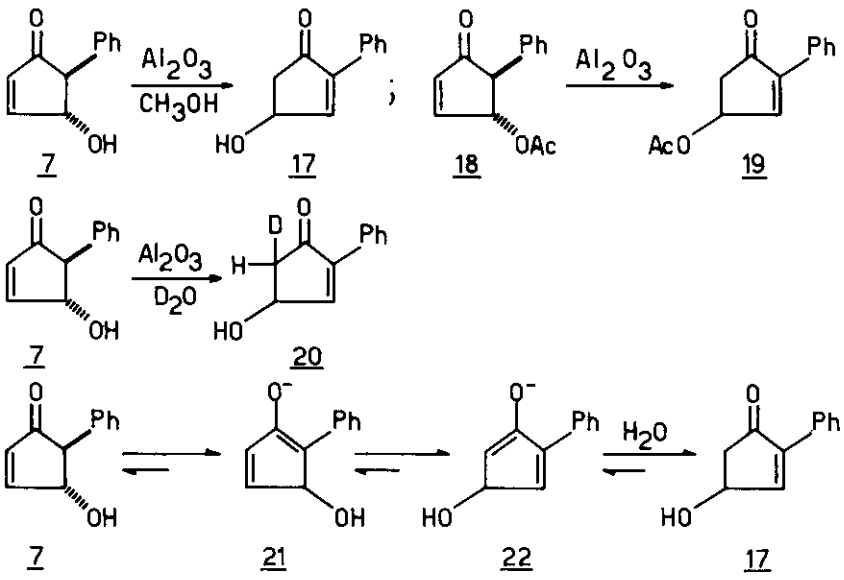
a = -Br
b = -NO_2
c = -OCH_3

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 yield[14]. 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 ring[14].
The compounds 7, isomerized into 3-oxo-5-hydroxy-cyclopentene derivatives 17, are interesting intermediates for prostaglandin and rethrolone syntheses[15].



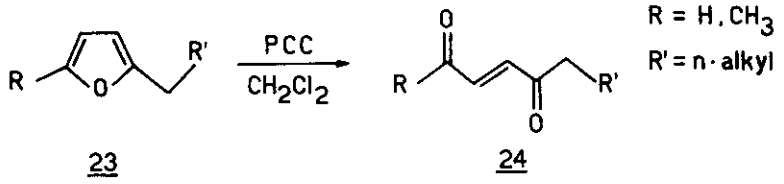
This isomerization was achieved in convenient manner, by an intramolecular migration of the alcoholic function[16,17]. The conversion is shown to occur through an alumina-catalyzed process of intramolecular hydration.
The experimental results, reported in the scheme 2, were in agreement with a mechanism 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

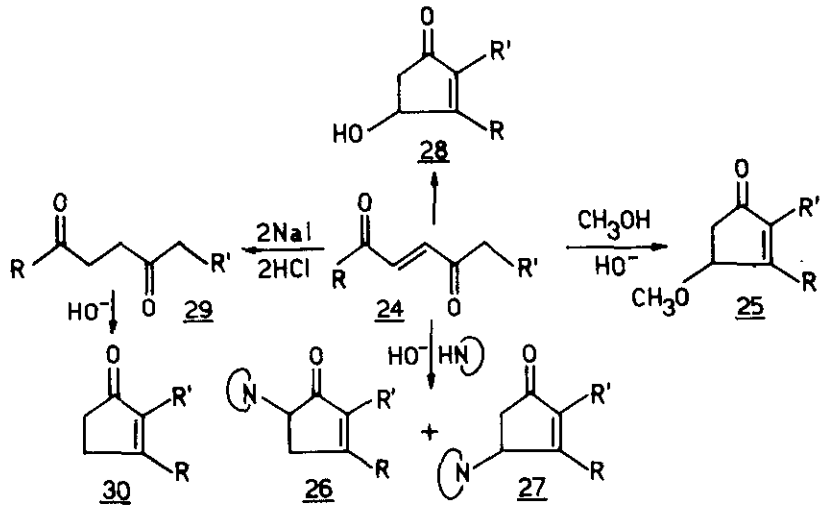
During the studies on the reactivity of pyridinium chlorochromate (PCC), the synthesis of trans-ene dicarbonyl compounds 24 was carried out[18], through an oxidative ring fission of furan derivatives 23 with PCC.



These compounds were rarely considered useful for cyclopentenone synthesis[19]; 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

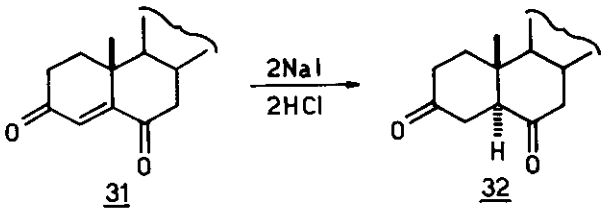
has been demonstrated (Scheme 3).

Scheme 3



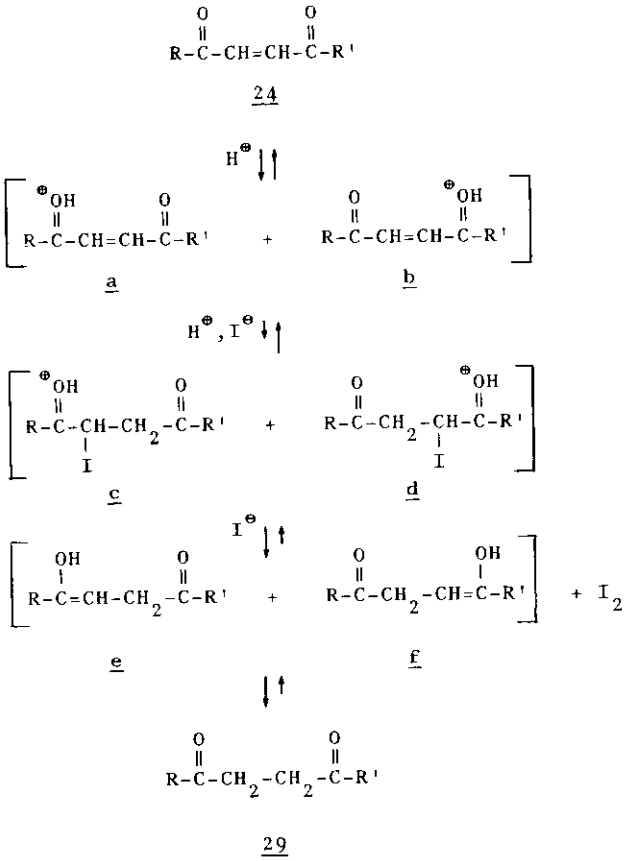
In fact, base-catalyzed cyclization afforded only 5-methoxycyclopentenone 25 (thermodynamically controlled product)[18]; the same reaction with cyclic secondary amines gave 4-amino- and 5-aminocyclopentenones 26 and 27, never prepared before (kinetically controlled products)[22]. One-pot procedure allowed 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, enedicarbonyl 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 yields[24].

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 mechanism[24] (Scheme 4).



31 32

Scheme 4

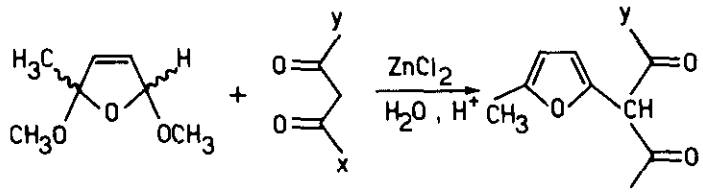


24 a b c d e f 29

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.

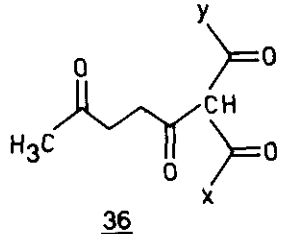
3) One-pot cyclization of 2-(5-methyl-2-furyl)-1,3-dicarbonyl compounds.

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 34[25].



33 34 35

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.



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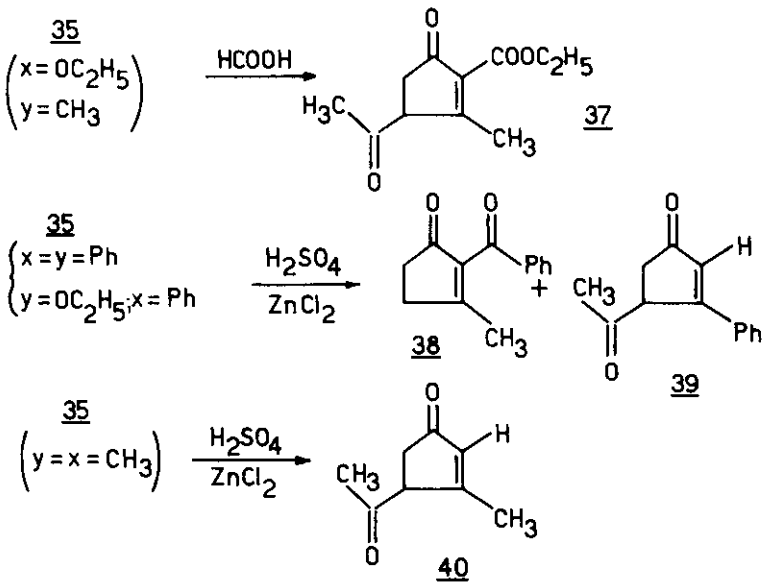
35, treated in acidic medium, underwent opening of the furan ring and subsequent cyclization to give cyclopentenones (scheme 5)[26]. The substituent pattern of the final products depended upon whether the ring-opened intermediate 36 cyclized directly or underwent first an acidic-catalyzed β-diketone fission.

This procedure provided a flexible sequence for the preparation of various synthetically interesting cyclopentenones, most of those never prepared before[26].

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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