SYNTHETIC APPROACHES TO THE 4H-PYRAN RING

C. Seoane and J. L. Soto*
Departamento de Química Orgánica. Facultad de Química.
Universidad Complutense. Madrid-3. SPAIN.

M. Quinteiro
Departamento de Química Orgánica. Universidad de Alcalá.
Alcalá de Henares (Madrid). SPAIN.

Abstract.- This article presents a systematization of the available synthetic procedures for the preparation of 4H-pyrans.

CONTENTS

1.- INTRODUCTION

The chemistry of pyran derivatives, many of which are present in a variety of natural products, has been widely studied and is covered even in general treatises of Organic Chemistry[1]. Reviews on simple aromatic pyran derivatives, such as pyrones[2,3] and pyrylium salts[4] have been published.

However, the situation is different[5] with the 4H-pyrans (or γ-pyrans), due primarily to the instability to be expected of such dienolic ethers lacking aromatic properties.

I

Thus, the synthesis of the unsubstituted 4H-pyran (I), the instability of which was predicted on the basis of O.M. calculations[6], was unsuccesfully attempted[7,8] and was not finally achieved until 1962, independently by Brandsma et al.[9] and Masamune and Castellucci[10]. It was, in fact, found to be an extremely unstable compound.

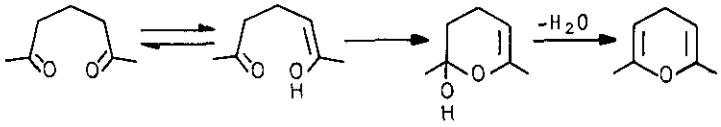
However, a high degree of stabilization of the pyran nucleus is achieved with the presence of substituents such as the phenyl group and other unsaturated groups and this fact has allowed the development of reasonably general synthetic procedures for substituted 4H-pyrans.

These syntheses of 4H-pyrans will be classified in this article in two main groups: syntheses by heterocyclization of open chain compounds and syntheses from compounds in which a six-membered oxigen ring is already present.

2.- SYNTHESIS OF 4H-PYRANS BY CYCLIZATION REACTIONS

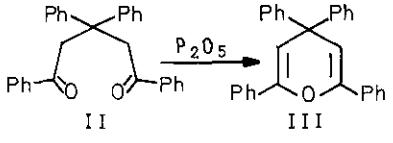
2.1.- Cyclization of δ-dicarbonyl compounds

Due to the wide applicability of the Paal-Knorr synthesis of furans[5,11,12] from γ-dicarbonyl compounds, the ring closure of δ-diketones was the basis for the first attempts to prepare 4H-pyrans, according to the scheme below.

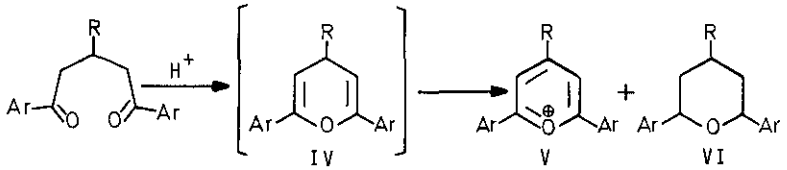


However, the ease with which aliphatic δ-diketones cyclize to cyclohexenones through an intramolecular aldol condensation[13,14] prevents this synthesis in most cases. The formation of 4H-pyrans has only been achieved with dicarbonyl compounds in which adequate structural features prohibit the cyclization to cyclohexenone derivatives.

Thus, the lack of appropriate enolizable hydrogens in diphenacyldiphenylmethane (II) permits its cyclization to 2,4,4,6-tetraphenyl-4H-pyran (III) in high yield upon treatment with phosphorus pentoxide, as reported by Peres de Carvalho[15,16]. However, such a reaction is non of general application to the synthesis of 4H-pyrans. If the two phenyl groups are not present in the 4-position, the resulting pyrans (IV) are too unstable to be isolated and, in the reaction conditions, disproportio



II III



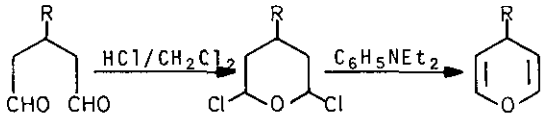
IV V VI

R= H, Me, Ph

nates to pyrylium salt (V) and tetrahydropyran (VI)[17].

Also, in the preparation of pyrylium salts starting from diketones, the existence of an intermediate 4H-pyran has been postulated. This species dehydrogenates in the reaction medium and leads finally to the pyrylium salt[18,19].

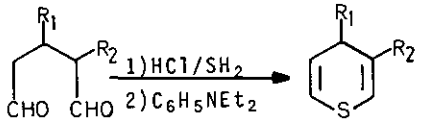
The cyclization of δ-dialdehydes to 4H-pyrans is also possible in a two step reaction which is based on the procedure described by Brandsma and Arents[20] for the preparation of divinyl ethers, which involves treatment with hydrogen chloride followed by dehydrohalogenation of the resulting dihalogenated ether. Thus, the unsubstituted 4H-pyran (I) can be obtained by application of this method to glutaraldehyde[9]. Similarly, glutaraldehyde derivatives lead to some otherwise inaccesible monoalkyl substituted 4H-pyrans (VII)[21].



VII

R= H or Alkyl

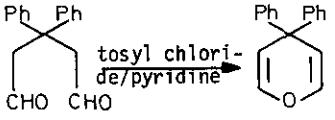
The preparation of thiopyrans (VIII) can be achieved by a modification of this procedure involving the use of hydrogen sulfide in the first step[9,21].



VIII

R_1, R_2= H or Alkyl

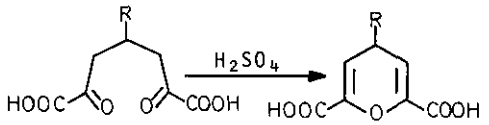
In some instances the direct, one step cyclization of dialdehydes, such as 3,3-diphenylglutaraldehyde, to 4H-pyrans (IX) can be carried out in good yield upon treatment with tosyl chloride[22].



IX

The preparation of 2,6-difunctionalized 4H-pyrans is achieved by using, as the starting dicarbonyl compound, α,α'-diketopimelic acid, which upon treatment with sulfuric acid, cyclizes to 4H-pyran-2,6-dicarboxylic acid (X)[8], a compound of some biological interest[23,24]. This synthesis was later optimized[25,26] and has been made extensive to 4-substituted derivatives and derivatives in the carboxyl group[26-28].

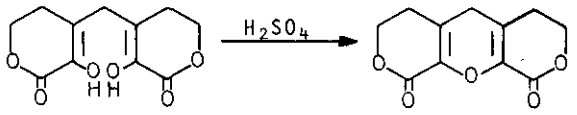
However, all attempts to prepare the unsubstituted 4H-pyran by decarboxylation of X have resulted in decomposition of X[8].



X

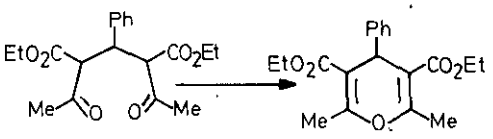
R= H, Me, Et, n-Hexyl

The cyclization with sulfuric acid of the so-called methylenebis-α-tetronic acid (XI) to pyran XII is an extension of these reactions[29].



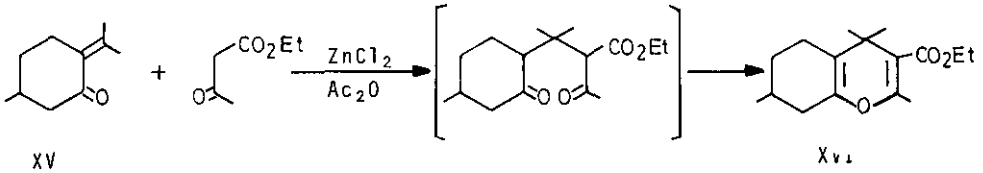
XI XII

A 3,5-difunctionalized 4H-pyran (XIV) is obtained as a by-product in the preparation of benzylidenebis-(acetoacetic ester) (XIII) resulting from the cyclization of the later[30,31].



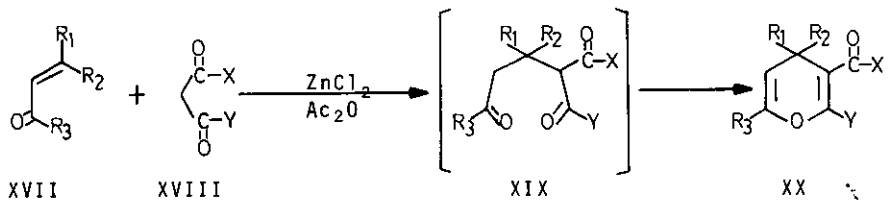
XIII XIV

A rather general method of cyclization of δ-dicarbonyl compounds to 4H-pyrans was developed by Wolinsky and Hauer. They found that the diketone resulting from the zinc chloride catalyzed condensation of pulegone (XV) with ethyl acetoacetate cyclized to 4H-pyran XVI[32]. The use of acetic anhydride as the solvent prevents the formation of the cyclohexenone.



XV XVI

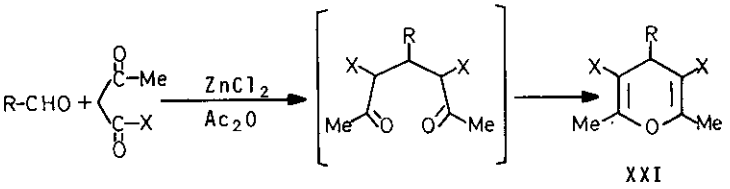
This reaction can be applied to a variety of α,β-unsaturated ketones (XVII) and β-dicarbonyl compounds (XVIII). The δ-diketone (XIX) obtained from this in situ condensation always cyclizes to the 4H-pyran (XX)[33]. Although the yields are not high, the ready availability of the starting materials and the lack of an alternate route to these compounds makes this an attractive synthetic procedure. However, if α,β-unsaturated aldehydes (XVII, R_3=H) are used, the corresponding less substituted pyrans are too unstable to be easily handled and purified.



XVII XVIII XIX XX

a: X=OEt; Y=Me
b: X=Y=Me
c: X=OEt; Y=Ph

A further extension of this synthesis involves the generation of δ-diketones through the condensation of β-dicarbonyl compounds with aldehydes[33,34]. The 4H-pyrans obtained (XXI), which have only a substituent in the 4-position, are rather unstable compounds.



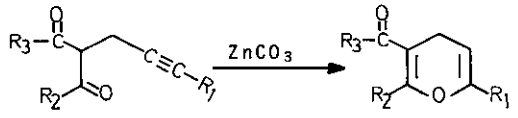
XXI

X= Me, OEt

2.2.- Cyclization of acetylenic carbonyl compounds

The second reaction type leading to 4H-pyrans is the cyclization by the attack of a carbonyl oxigen to a carbon-carbon triple bond.

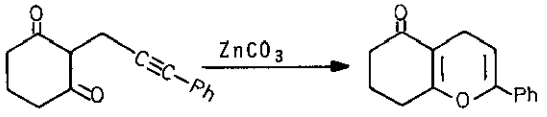
Treatment of δ-acetylenic ketones (XXII) with zinc carbonate brings about the formation of pyrans (XXIII)[35]. If a terminal alkyne is used (R_1=H), the formation of the pyran does not occur and furans are obtained instead.



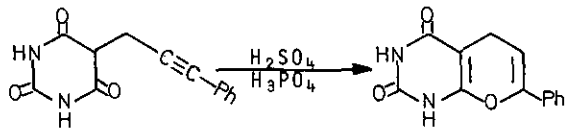
XXII XXIII

R_1= Alkyl or Aryl; R_2,R_3= Alkyl

This reaction can also be applied to 2-(3-phenylpropargyl)cyclohexane-1,3-dione (XXIV)[36] and 5-phenylpropargil barbituric acid (XXV)[37] and the corresponding bicyclic 4H-pyrans XXVI and XXVII are obtained. In both cases, the presence of the phenyl group is neccessary.

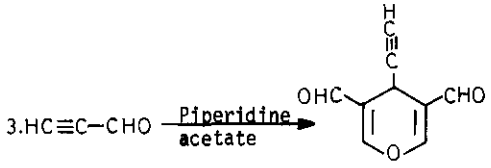


XXIV XXVI



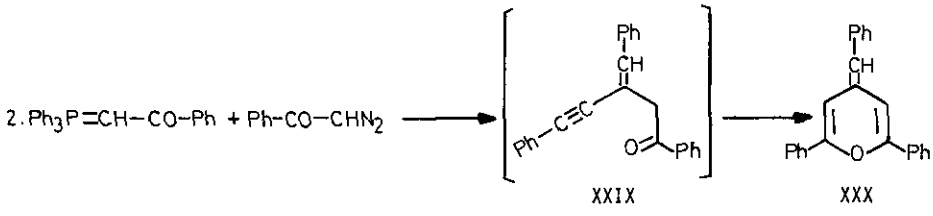
XXV XXVII

A particular example of this synthesis of 4H-pyrans is the trimerization of propargyl aldehyde to XXVIII[38] for which a wrong structure of 2H-pyran was formerly proposed[39].



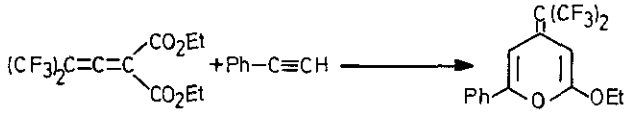
XXVIII

The synthesis of methylene-4H-pyrans of type XXX from the reaction of acylmethylenephosphoranes with benzoyldiazomethane appears also to occur through the cyclization of an intermediate acetylenic ketone (XXIX)[40-43]. Acid chlorides, acid anhydrides and β-keto esters[44] and substituted malonic esters[45] react also with the phosphoranes to give pyrans.



XXIX XXX

A similar synthesis involving the reaction of allenes XXXI with phenylacetylene to give XXXII has also been described[46].

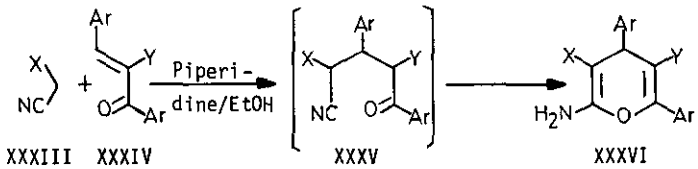


XXXI XXXII

2.3.- Cyclization of δ-cyanoketones.

The nucleophilic attack of a carbonyl oxygen to a cyano group is a third way of cyclization leading to the 4H-pyran ring.

In this manner, the Michael addition of malononitrile (XXXIII, X=CN) or ethyl cyanoacetate (XXXIII), X=CO_2Et) to α-aroylcinnamonitriles (XXXIV, Y=CN) affords a δ-cyanoketone (XXXV), the spontaneous cyclization of which in the reaction medium, followed by an imino-enamino tautomerization, yields pyrans XXXVI[47-49].

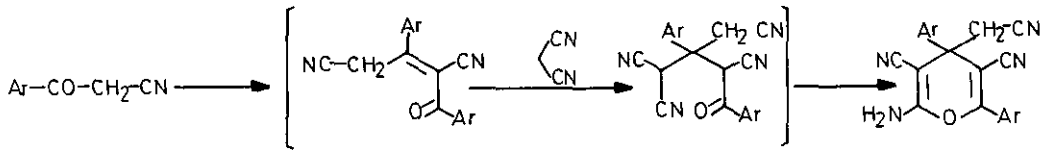


XXXIII XXXIV XXXV XXXVI

X= CN or CO_2Et; Y= CN, CO_2Et or COMe

Since the starting compounds are easily accessible through a Knoevenagel condensation of aromatic aldehydes and benzoylacetonitriles, and the pyrans XXXVI are obtained in high yield, this reaction is a useful synthetic procedure for the preparation of 2-aminopyrans. It can be made extensive to ethyl α-benzoylcinnamates (XXXIV, Y=CO_2Et)[50] and *α-ylidene-β-diketones* (XXXIV, Y=COR)[51].

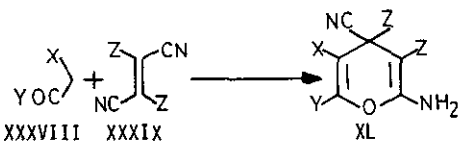
2-Aminopyrans result also[52] from the reaction of benzoylacetonitriles with malononitrile in a one step reaction through a self condensation of the benzoylacetonitrile followed by a Michael addition of malononitrile and cyclization to XXXVII.



XXXVII

The limitation of these reactions lies in the fact that they can only be applied in those cases in which the starting compound has an electron withdrawing group Y, since the presence of such a group stabilizes the enolic form of the carbonyl group in the intermediate δ-cyanoketone. Thus, the reaction of malononitrile with benzylideneacetophenones (XXXIV, Y=H) affords only the δ-cyanoketone (XXXV, Y=H) which cannot be cyclized to the 4H-pyran[53].

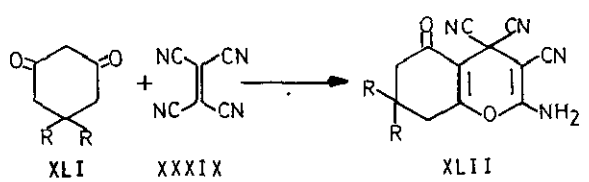
4,4-Disubstituted 2-aminopyrans (XL) can be prepared by cyclization of the δ-cyanoketones resulting from the reaction of other activated olefins, such as XXXIX, with active methylene compounds containing appropriate functional groups (XXXVIII)[54,55].



XXXVIII XXXIX XL

Z= CN or CO_2Et; X= C_6H_5-CO; Y= Me or C_6H_5

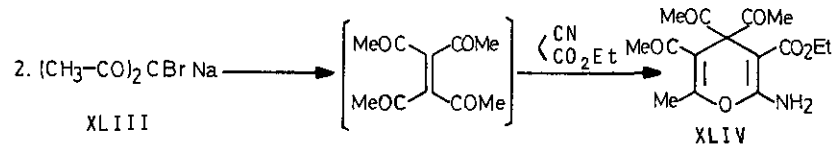
If cyclic diketones (XLI), such as *dimedone, are used as active methylene* compounds, bicyclic 2-aminopyrans (XLII) result[54,56].



XLI XXXIX XLII

R= H, Me

In a similar manner, barbituric acids give rise to pirimidopyrans[57]. Finally,the reaction of ethylcyanoacetate with the sodium salt of 3-bromo-2,4-pentanedione (XLIII), which dimerizes in situ to an activated olefin, is another example of a cyclization of a δ-cyanoketone to 2-aminopyran (XLIV)[58].

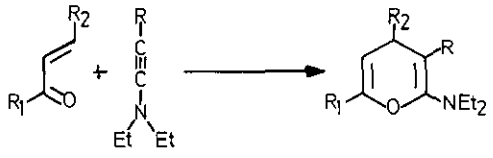


XLIII XLIV

2.4.- Cycloaddition of triple bonds to α,β-unsaturated carbonyl compounds

Besides the cyclizations described, [4+2] cycloaddition reactions of carbon-carbon triple bonds to α,β-unsaturated carbonyl compounds have also been employed for the synthesis of 4H-pyrans. The most appropriate dienophiles seem to be the ynamines (acetylenic tertiary amines).

Thus, the reaction of ynamines XLVI with α,β-unsaturated ketones XLV is a good procedure for the obtention of N,N-dialkylaminopyrans in moderate yield[59,60] through an ionic, highly regioselective cycloaddition.

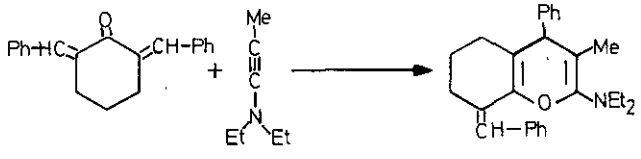


R,R1,R2=Me or Ph

XLV XLVI XLVII

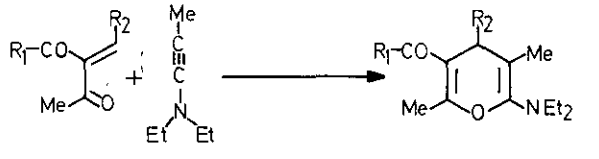
Silylated ynamines (XLVI, R=Me_3Si) give rise to the corresponding pyrans (XLVII, R=Me_3Si)[61].

Cyclic α,β-unsaturated ketones (XLVIII) afford bicyclic pyrans (XLIX) by reaction with ynamines XLVI[62].



XLVIII XLVI XLIX

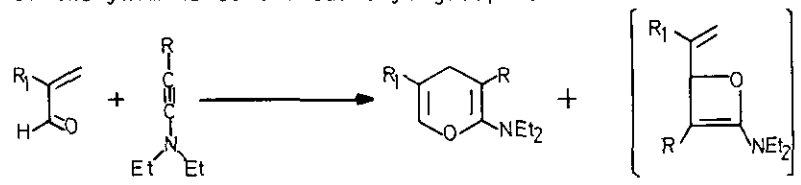
Pyrans LI resulting from the reaction of ynamines with unsaturated diketones L have shown antihypertensive and coronary dilating activity[51].



L XLVI LI

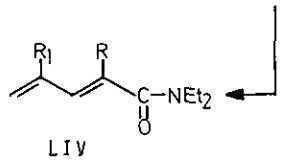
R_1 =Alkyl
R_2 =Alkyl or Aryl

These cycloaddition reactions can also be applied to α,β-unsaturated aldehydes (LII), but the yields are lower because, besides the corresponding pyran (LIII), the reaction affords also a biethylenic amide of type LIV, resulting from the [2+2] cycloaddition of the ynamine to the carbonyl group[63].



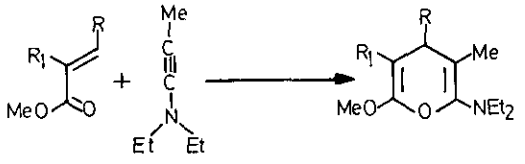
LII XLVI LIII

R_1=H, Ph
R= H, Me, Ph



LIV

The β-ketoesters (LV) react also with ynamines yielding 6-amino-2-alcoxypyrans (LVI)[64].

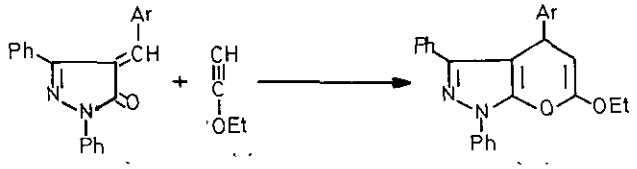


LV XLVI LVI

R,R_1= H,Me

In the case of unsubstituted esters (LV, R=R'=H), the formation of a cyclobutane derivative, through a [2+2] cycloaddition to the ethylenic bond of the ester, competes with that of the pyran.

Besides the ynamines, the only other type of dienophile used for 4H-pyran synthesis has been ethoxyethyne, which yields bicyclic pyran LVIII, by reaction with LVII[65].



LVII LVIII

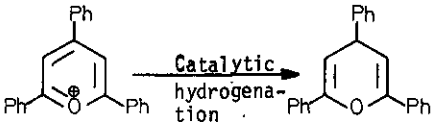
3.- SYNTHESIS OF 4H-PYRANS FROM COMPOUNDS WITH PREFORMED OXIGEN RING

3.1.- From pyrylium salts

The ready availability of pyrylium salts[4] makes them suitable starting materials for the preparation of 4H-pyrans and several reactions leading to these pyrans have been studied.

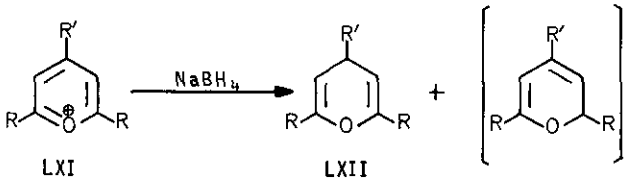
3.1.1.- Reduction of pyrylium salts

The catalytic reduction of 2,4,6-triphenylpyrylium salts (LIX) was reported to yield pyran LX[66], but there was no subsequent confirmation of this reaction.

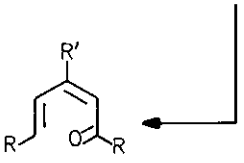


LIX LX

The reduction of substituted pyrylium salts LXI to pyrans LXII with sodium borohydryde is also possible[67,68], but, together with the 4H-pyran, 2,4-dien-1-ones (LXIII) are formed by way of 2H-pyrans resulting from the hydryde attack at the 2-position[68,69] and, in some instances, 1,5-diones are also formed through ring opening of the 2H-pyran[70].



LXI LXII



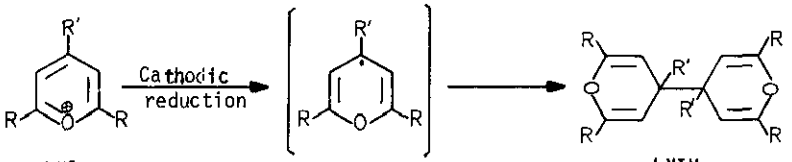
LXIII

R= Ph, alkyl
R'=H, Ph, alkyl

The relative amounts of products depend on the substituents R and R'[71]. The higher yield in 4H-pyran is obtained when the substituent in the 4-position is hydrogen (LXI, R'=H), due in part to steric effects. However, an increase in size for the 2-substituents causes an increase in the amount of 2-attack, lowering the yield in 4H-pyran. This fact has been rationalised on the basis of the Hard and Soft Acids and Bases Theory, taking into account the effect of the substituents on the coefficients of the 2 and 4 positions of the pyrylium ring.

Several other agents, such as formate ion, are also able to reduce pyrylium salts to the corresponding 4H-pyrans in low yields[72,73].

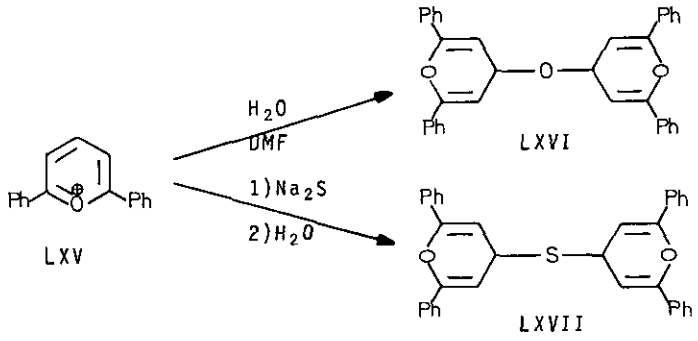
A particular case occurs in the cathodic reduction of pyrylium salts bringing about their reductive dimerization, through a pyranyl radical, to bipyrans LXIV[76,77]. The same result is achieved using zinc[78] or the potassium salt of cyclooctatetraene[79] as the reducing agent.



LXI LXIV

R= Me, Ph, t-But; R'= H, Me

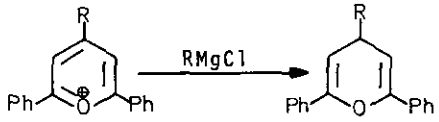
Dipyranyl ether LXVI and dipyranyl thioether LXVII are obtained in low yield by treatment of 2,6-diphenylpyrylium perchlorate (LXV) with water in DMF/piperidine and sodium sulfide respectively[80,81].



3.1.2.- Alkylation of pyrylium salts

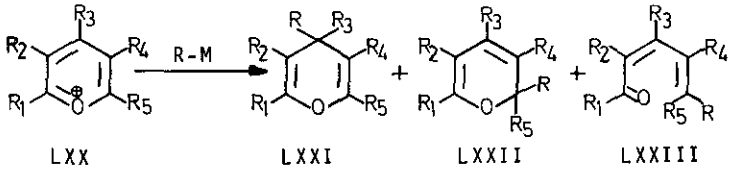
A convenient method leading to 4H-pyrans consists in the nucleophilic addition of R anions to 2,6-disubstituted pyrylium salts, in which the γ-attack is preferred due to steric factors and to the higher reactivity of the γ-position in respect to the α-ones[4].

Thus, 2,6-diphenylpyrylium perchlorate (LXVIII) reacts with Grignard reagents yielding 4H-pyrans LXIX[82-84]. Similar reactions are known in the flavylium derivatives[85,86]. Lithium phenyl acetylide reacts in the same manner as Grignard reagents [87].



R= Alkyl or Aryl

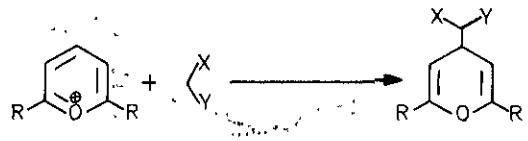
Pyrylium salts bearing substituents in the 4-position (LXX) are also able to react with Grignard and other organometallic reagents[88-91] but, together with the 4H-pyran (LXXI), a certain amount of 2H-pyran LXXII resulting from α-attack of the nucleophile is also obtained. In some instances, the pyran undergoes ring opening to the corresponding dienone (LXXIII)[92]. The relative amount of products depends on



R_1-R_5= H, Me, Ph; R= Me, n-But, i-prop, t-But,

the nature of the substituents and the organic group of the organometallic reagent, as well as the nature of the metal (Mg, Na, Li) and the solvent used as the reaction medium. An attempt has been made to rationalise these results on the basis of the Hard and Soft Acids and Bases Theory[92-94].

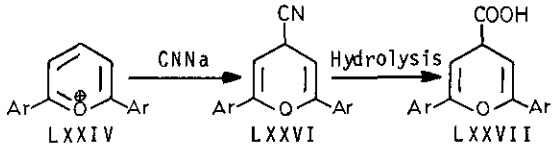
Pyrylium salts LXIV react also with the anions of active methylene compounds such as 1,3-diketones, malononitrile, ethyl cyanoacetate and benzoylacetonitrile yielding 4H-pyrans LXXV[82,95-97].



LXXIV LXXV

X,Y= COR, CN, CO_2Et

In the same manner behave other carbon nucleophiles such as the anions of nitromethane[82,83] acetone[73] cyanide ion[81,98], which, by reaction of 2,6-disubstituted pyrylium salts affords 4-cyanopyrans (LXXVI) which can be hydrolised to the corresponding 4-pyrancarboxylic acids (LXXVII).



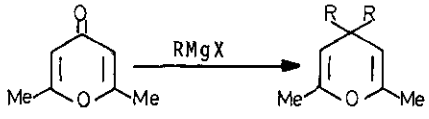
LXXIV LXXVI LXXVII

Finally, some nitrogenated nucleophiles such as potassium phtalimide[81] or phosphorus nucleophiles[99] also transform pyrylium salts into 4-substituted 4H-pyrans.

3.2.- From other pyran compounds

Other pyran-type compounds can also be used as starting materials for the preparation of 4H-pyrans.

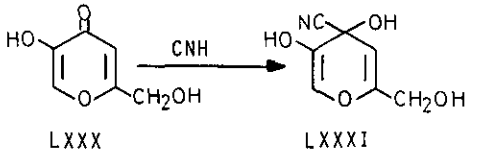
Gompper and Christmann[100-102] have reported the reaction of γ-pyrones LXXVIII with Grignard reagents to yield 4,4-disubstituted 4H-pyrans (LXXIX), but this reaction was later contested[33].



LXXVIII LXXIX

R= Alkyl or Aryl

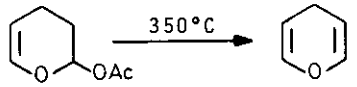
The reaction of cyanide ion with Kojic acid (LXXX) is another of the few examples of transformation of pyrones into 4H-pyrans (LXXXI)[103].



LXXX LXXXI

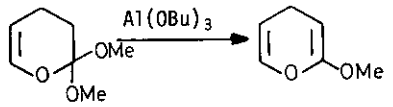
Elimination reactions of dihydropyrans lead also to 4H-pyrans. Thus, the pyrolysis of 2-acetoxy-2,3-dihydropyran (LXXXII) allows the preparation of unsubstituted

4H-pyran (I) as an unstable compound isolable only by gas chromatography[10].



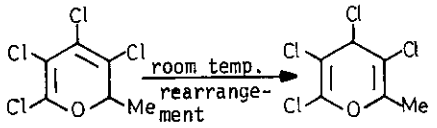
LXXXII I

Similarly, 2,2-dimethoxy-2,3-dihydropyran (LXXXIII) yields 2-methoxy-4H-pyran (LXXXIV) upon treatment with aluminium tert-butoxide[104].



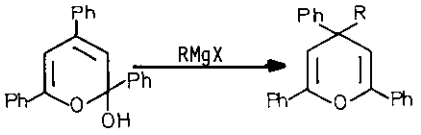
LXXXIII LXXXIV

The rearrangement of some 2H-pyrans, such as LXXXV, can also form 4H-pyrans (LXXXVI)[105,106].



LXXXV LXXXVI

2-Hydroxy-2,4,6-triphenyl-2H-pyran (LXXXVII), resulting from the hydrolysis of 2,4,6-triphenylpyrylium perchlorate, has been reported to afford 4H-pyrans LXXXVIII in low yield by reaction with Grignard reagents[107].



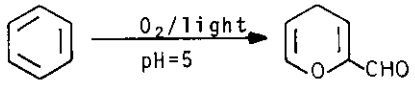
LXXXVII LXXXVIII

R= Aryl or benzyl

4.- MISCELLLANEOUS SYNTHESES

Other special reactions leading to 4H-pyrans will be finally mentioned.

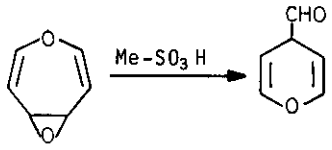
The photo-oxidation of benzene in aqueous acidic solution under UV irradiation



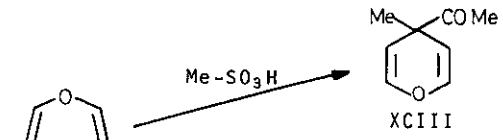
LXXXIX

affords a low yield of 2-formyl-4H-pyran (LXXXIX)[108,109].

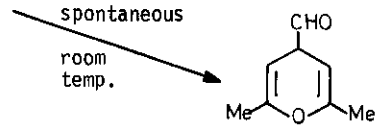
4-Formyl-4H-pyran (XC) can be prepared in quantitative yield, within seconds, through an interesting acid-catalyzed rearrangement of sym-oxepin oxide (XCI)[110]. Similarly, 4,5-dimethyl-sym-oxepin oxide (XCII) rearranges to 4-methyl-4-acetyl-4H-pyran (XCIII) or 2,6-dimethyl-4-formyl-4H-pyran (XCIV) depending upon the reaction conditions used for the in situ generation of the oxepin oxide[111].



XC XCI

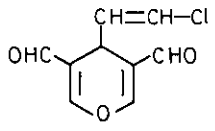


XCII XCIII

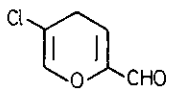


XCIV

Finally, 4-(2-chlorovinyl)-3,5-diformyl-4H-pyran (XCV) has been prepared by alkaline hydrolysis of 2-chloroacrolein[112,113] and 5-chloro-2-formyl-4H-pyran (XCVI), by heating of 2-chloroacrolein dimer[114].



XCV



XCVI

From this survey it can be concluded that the best procedures for the preparation of 4H-pyrans are those which involve cyclization or cycloaddition reactions. The obtention of these heterocycles from other pyran derivatives, such as pyrylium salts, usually affords a mixture of 4H-pyran and a variable amount of 2H-pyran or the products derived from its ring opening.

In any case, none of the known synthetic methods of 4H-pyrans is of general applicability and the election of one or other of them must be determined by the nature of the substituents present in the ring.

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