FURYL(ARYL)METHANES AND THEIR ANALOGS. (REVIEW)

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The literature data on furyl(aryl)methanes are systematized and analyzed for the first time. Results obtained by the authors on the synthesis, reactions, and application of these compounds are reviewed.

INTRODUCTION

Furyl(aryl)methanes are understood to incorporate at least two aromatic rings on one sp^3-hybridized carbon atom with one of the rings being furan. For some time furyl(aryl)methanes have been overshadowed by their aromatic analogs. This is probably due to the lower stability of the furan rings compared with the aromatic ones. On the other hand, the lability of the furan ring enables it to be used as a building block in organic synthesis. Recent research has demonstrated that furyl(aryl)methanes can act as convenient synthones for preparing a wide range of compounds of various classes. Furthermore, practical applications in various branches of industry, agriculture, and medicine have been found.

The synthesis and chemical reactions of furyl(aryl)methanes are discussed in the present review. We have used several early references because these data have not previously been systematized.

1. SYNTHESES OF FURYL(ARYL)METHANES

1.1. Syntheses from Organometallic Compounds and *via* Reduction of Alcohols and Ketones

Synthesis from organometallic compounds is one of the routes for preparation of furyl(aryl)alkanes. Thus, furylthienylmethane is obtained in ~50% yield by metallation of thiophene with butyllithium and reaction of the resulting 2-thienyllithium with 2-chloromethylfuran [1].

Gillman and Wright [2] synthesized the difurylmethane I by the reaction of 2-chloromercuriofuran with furfuryl chloride in ether. The yield was 9.5%. Compound I is also produced in even lower yield by the reaction of furylmagnesium bromide with furfuryl chloride [3] and in 14% yield from furyllithium cuprate and bromochloromethane [4].


I
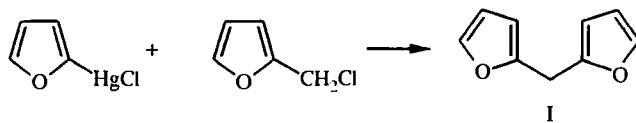
A convenient method for synthesis of difurylmethane is the reaction of furyllithium with furfurol and subsequent reduction of the intermediate carbinol with $NaBH_4$–CF_3COOH [4]. It was noted that this is the optimal method for synthesis of difurylmethane because the product yield is 64% and the undesirable side products are

held to a minimum. This system was used [5] to prepare diheteroarylmethanes *via* reduction of the corresponding alcohols in 32-76% yields. The reduction of heteroaryl(aryl)carbinols by other reagents has also been reported [6, 7].

The preparation of difuryl- and furylheteroarylmethanes *via* reduction of ketones has been studied [3, 8-11]. Difurylmethane was synthesized from di-2-furylketone *via* reduction by sodium in ethanol [3]. The reaction of pyrrolylfurylketone with LiAlH₄ produces the corresponding 2-pyrrolyl(2-furyl)methane in 40% yield [8]. The optimization of this method that was proposed by Clezy and Piepa [9] enabled the yield of pyrrolylfurylmethane to be increased significantly to 75%.

X = O. NH
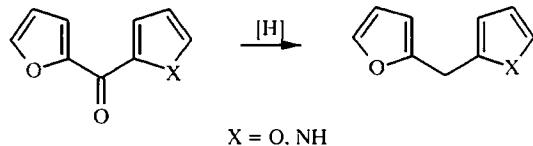
The principal drawbacks of these methods are the labor-intensiveness, low product yields for the reaction of organometallic compounds with furan derivatives, and the difficulty of furyl(heteroaryl)carbinols and furyl(heteroaryl)ketones synthesis. These reasons prompted a search for new methods and conditions for preparation of furylalkanes.

## 1.2. Alkylation of Furan Compounds by Alcohols and Other Compounds

The alkylation of furan by furylcarbinols has been reported [12, 13]. The reaction, which is catalyzed by 20% HCl, produces the corresponding difurylalkanes in yields less than 22%.

R. R¹ = H. Me
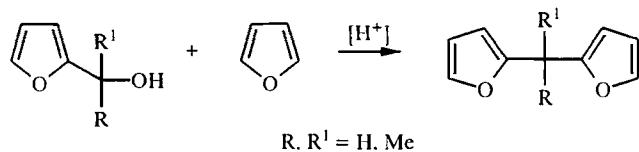
2,2-Difurylpropanes were synthesized by reaction of tertiary alcohols, e.g. 2-(2-furyl)-propan-2-ol or 2-(2,5-dimethylfur-3-yl)-propan-2-ol, with 2-methylfuran in the presence of BF₃·Et₂O or HClO₄. The yields after purification were ~30% [14].

An original method for synthesis of asymmetric difurylmethane derivatives by condensation of furylphosphorylcarbinols IIa,b with furan has been proposed [15]. The direction of the reaction depends on the temperature. If the condensation is performed in CH₃CN saturated with gaseous HCl at 25°C, phosphonate IIIa is

R = PO(OEt)₂   IIa R¹ = Me   IIb R¹ = H


IVa

IIIa
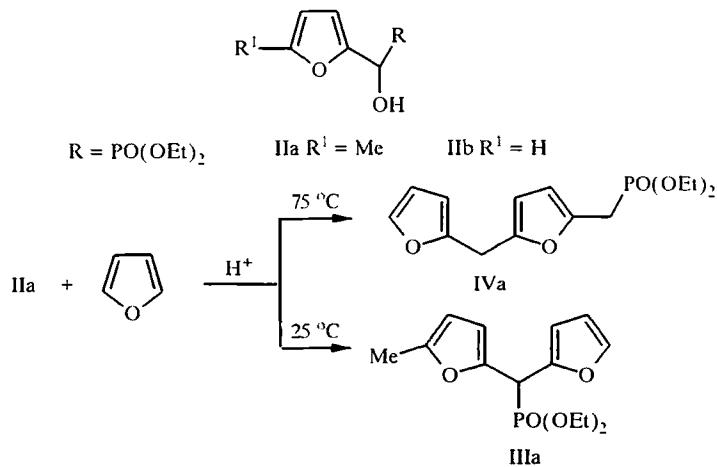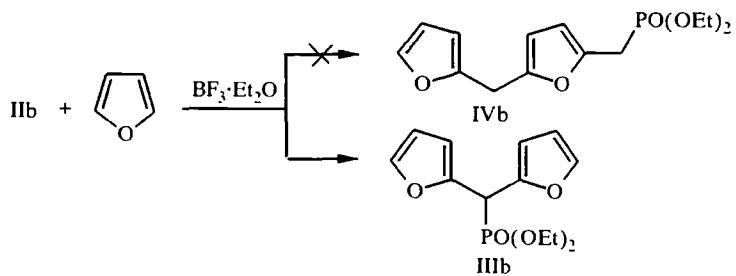
isolated in 77% yield. Increasing the temperature to 75°C produces phosphonate IV (83% yield). Attempts to alkylate furan with furylphosphorylcarbinol IIb under analogous conditions were unsuccessful. Compound IIIb could be synthesized in 81% yield by boiling furan with IIb in CH_3CN in the presence of $BF_3 \cdot Et_2O$.

A synthesis of difurylalkyne derivatives was devised by Denisov et al. [16] during a search for methods of synthesis and functionalization of new alkyl-substituted synthones. The condensation of a furylalkynylcarbinol complex V with 2-methylfuran in the presence of $BF_3 \cdot Et_2O$ gave VI in 60% yield.
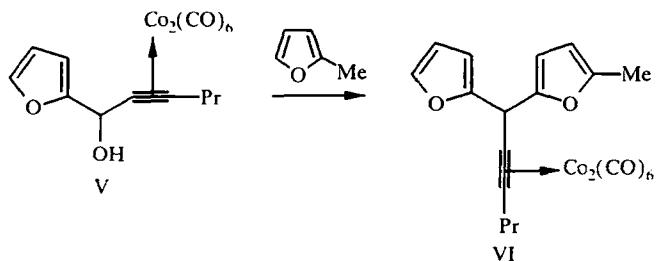
The alkylation of furan by alcohols was used [17] to synthesize furyldiarylmethanes. It was found that substituted furans in benzene in the presence of catalytic amounts of $HClO_4$ react with benzhydrol derivatives to produce the corresponding furyldiarylmethanes in 72-96% yield.
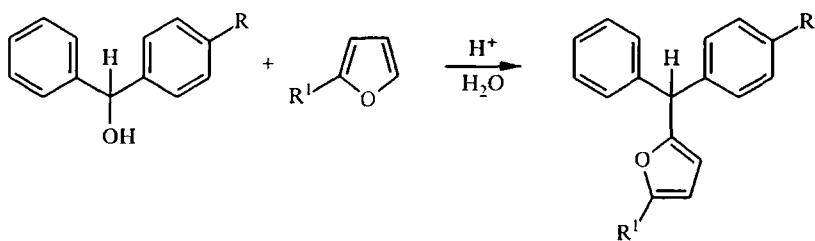
Using $BF_3 \cdot Et_2O$ to catalyze the reaction of furan with furfuryl alcohol gives difurylmethane in 16-28% yield if the reaction is performed in CH_2Cl_2 or without solvent [18].

The condensation of furfuryl alcohol with furan in the presence of the strong-acid sulfonated cation exchanger Amberlyst 15 has been studied [19, 20]. The yield of difurylmethane was 65%. The use of the ion-exchange resin in the H^+-form as the acid catalyst rather than the usual catalysts in processes involving acidophobic heterocyclic compounds is proposed to decrease tar formation and to increase the yield of the desired product.

Difurylalkanes can be synthesized in high yields under acid-catalysis conditions by alkylation of 2-methylfuran with 2-methyl-5-vinylfuran or 2-isopropenyl-5-methylfuran [21]. Polymeric products incorporating alkenylfurans were not observed.

Reaction of 2-methylfuran with methylacrylate in the presence of $Pd(OAc)_2$ gives the usual substitution product and 1,1'-bis(5-methylfur-2-yl)ethane (22%) and methyl 3,3'-bis(5-methylfur-2-yl)propionate (10%) [22].
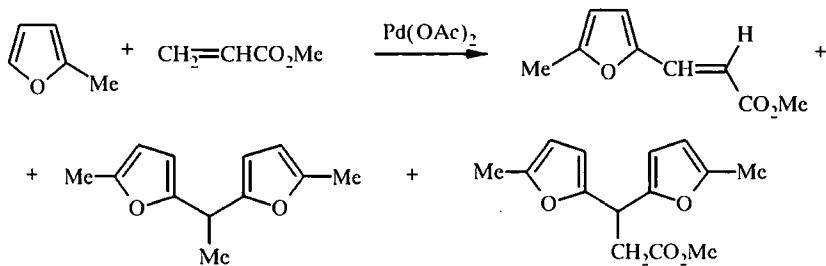
Minor products from the cycloaddition reaction of 2-substituted furans with ethyl propiolate promoted by AlCl$_3$ [23] are 3,3-di(5-R-fur-2-yl)propionates (R = Me, 0.7%; R = Ph, 7%).
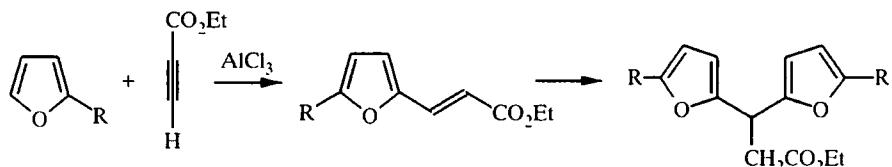
Alkylation of 2-methylfuran and furan by vinyl ethers in the presence of acid catalysts produces 1,1-di(5-methylfur-2-yl)ethane and 1,1-difurylethane [24, 25]. The alkylation was studied using the reaction of 2-methylfuran or furan with vinylbutyl or vinylphenyl ethers in the presence of H$_2$SO$_4$, HCl, AlCl$_3$, BF$_3$·Et$_2$O, or a butanol solution of iron chloride as examples. It was found that the yields of the corresponding difurylmethane varied in the range 12-58% depending on the catalyst used for the reaction of 2-methylfuran with vinylbutyl ether.
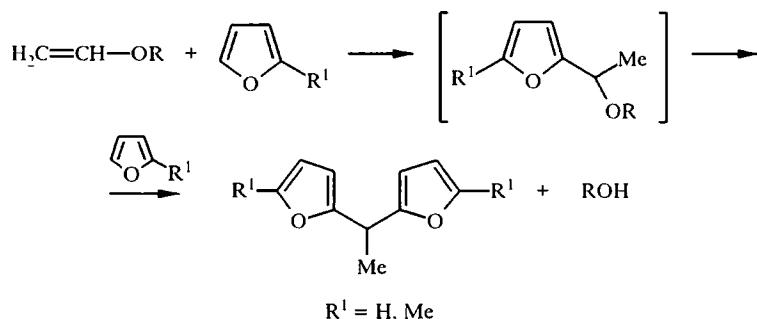
The reaction of 2-methylfuran with dihydropyran without a solvent and with SO$_3$ passing through the mixture gives 1,1-bis(5-methylfur-2-yl)-5-(tetrahydropyranyl-2-oxy)pentane in 67% yield [26]:
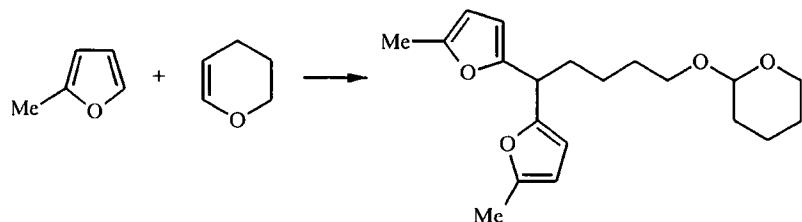
The main product obtained from the reaction of 2-propoxytetrahydrofuran with 2-methylfuran in absolute ether in the presence of AlCl$_3$ is 4,4-bis(5-methylfur-2-yl)butan-1-ol [27].
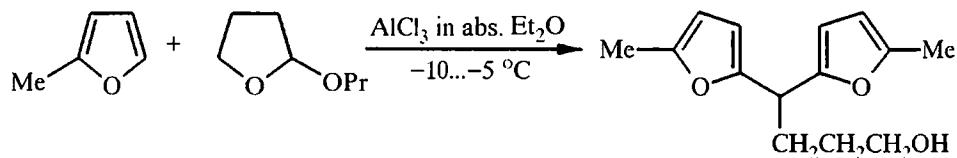
One of the products from the reaction of 1-ethoxyisochroman with furan that is catalyzed by $BF_3 \cdot Et_2O$ is 2-[di(fur-2-yl)methyl]phenethyl alcohol (15% yield) [28].
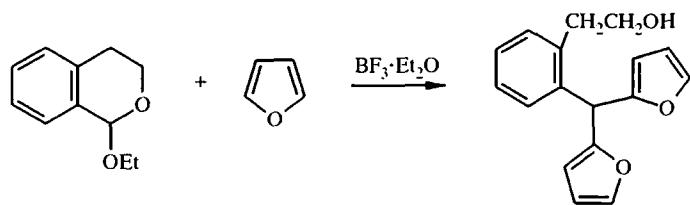
4,4-Bis(5-methylfur-2-yl)but-2-enoic acid was isolated in 20% yield from the products of the reaction of 4-hydroxybut-2-eneolide and 2-methylfuran in ether in the presence of $Mg(ClO_4)_2$ [29].
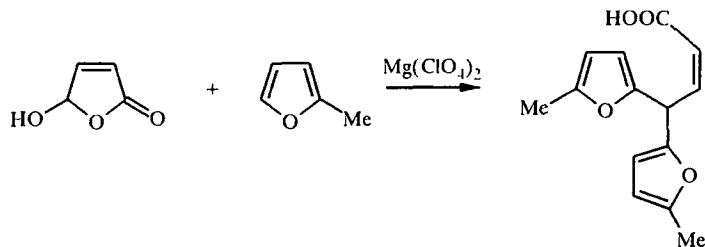
Mndzhoyan et al. [30] used the alkylation of methyl 2-furoate by the methyl ester of 5-chloromethylfuran-2-carboxylic acid in the presence of $AlCl_3$ to prepare the difurylmethane derivative. The yield was 51%.
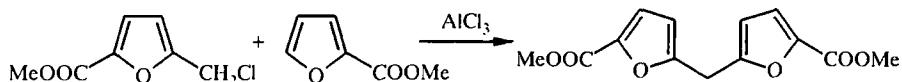
According to the literature [31], the alkylation of methyl furoate by CCl_4 in the presence of $AlCl_3$ produced tri(5-methoxycarbonylfur-2-yl)chloromethane·$AlCl_3$ complex, hydrolysis of which gave the substituted trifurylcarbinol in 25% yield:
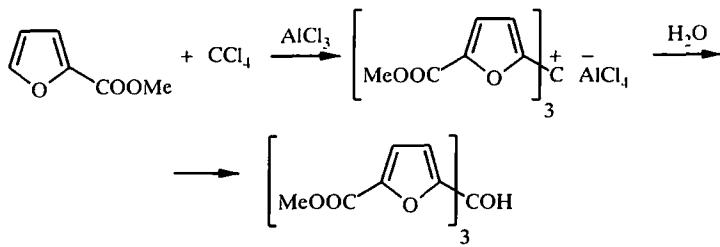
The alkylation in benzene of 3,5-dialkylfurans by $CHCl_3$ that is catalyzed by $HClO_4$ (57-60%) gave the corresponding trifurylmethanes in yields of 75-85% [32, 33].

Friedel–Crafts alkylation of 2-methylfuran by methyl (chloro)methoxyacetate in the presence of $ZnCl_2$ [34] produces in 46% yield the difurylacetic acid derivative VII. The probable mechanism of the conversion was proposed. It was found that the reaction occurs in two steps. The second is facilitated by HCl that is formed in the first step in the reaction of methyl (chloro)methoxyacetate with 2-methylfuran. The use of bis(trimethylsilylacetamide) to bind the released HCl enabled the intermediate VIII to be isolated in 25% yield.

ZnCl$_2$

Cl$^-$—ZnCl$_2$

Me ⌐O MeO CO$_2$Me

Me ⌐O$^{(+)}$ H CO$_2$Me OMe

$\xrightarrow{-HCl}$

Me ⌐O CO$_2$Me OMe

VIII

Me ⌐O CO$_2$Me $^+$OMe H Cl$^-$

Me ⌐O CO$_2$Me

Me O

Me ⌐O CH$_2$ CO$_2$Me +

Me ⌐O CO$_2$Me O Me

VII
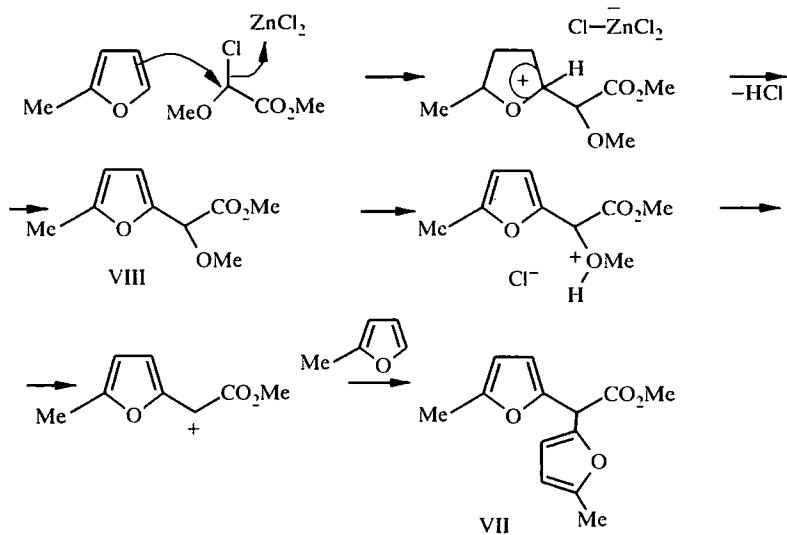
Alkylation of furan derivatives containing a carboxylic or ester group by α-chlorinated ethers in the presence of Zn made it possible [35] to synthesize the corresponding difurylalkanes in 30-60% yield.

Katritzky et al. [36] developed a new route for synthesis of symmetric and asymmetric 1,1-bis(heteroaryl)alkanes. They proposed the use of N-(α-benzotriazol-1-ylalkyl)carbamates because it was known that the benzotriazolyl anion can act as a good leaving group. The reaction of these compounds with a two-fold molar excess of a heterocyclic compound in the presence of ZnCl$_2$ in methylene chloride gave a series of symmetric diheteroarylalkanes IX in excellent yields. Using a molar equivalent of the heterocycle produces a mixture of compounds X and XI in a total yield up to 80% and a small quantity of compound IX. Reaction of the resulting mixture (without isolation) with another heterocycle produced the asymmetric diheteroarylalkanes in yields from 56 to 95%.

ZnCl$_2$
CH$_2$Cl$_2$
$\xrightarrow{20\ ^\circ C}$

+ X Me

R NHCO$_2$Me

R Me X +

X

+ Me X NHCO$_2$Me R

XI

+ Me X X Me R

IX

R = H, i-Pr, Ph; X = O, S
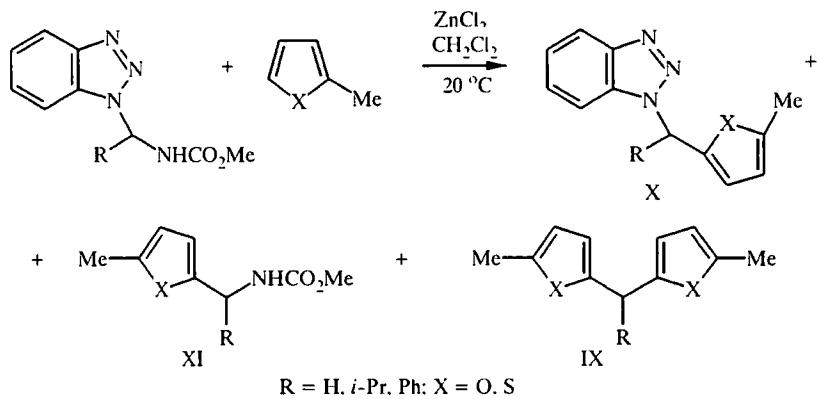
In another study Katrizky et al. [37] proposed a slightly different route for preparation of asymetric diheteroarylalkanes. Thus, condensation of 2-(α-benzotriazol-1-ylmethyl)furans XII with various heterocyclic compounds gave the corresponding furylheteroarylmethanes. The subsequent conversions of the lithium derivatives of XII shown above produces the furylheteroarylalkanes XIII.

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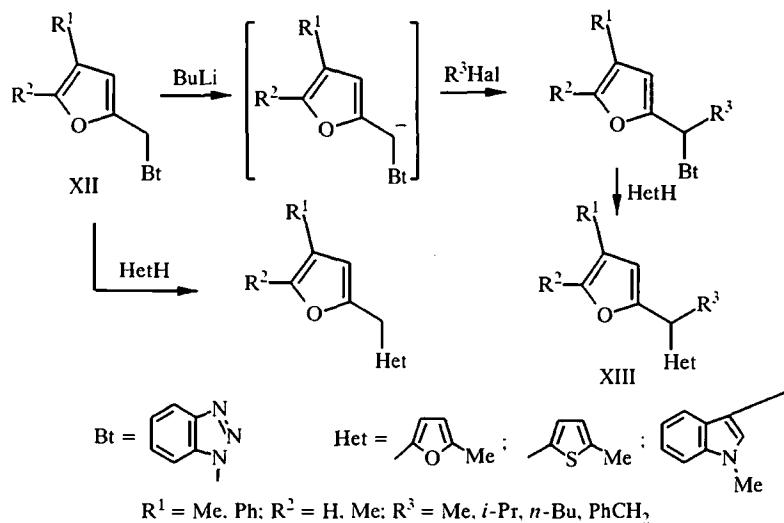
1.3. Condensation of Furan Derivatives with Carbonyl Compounds

The synthesis of polyfurylalkanes *via* condensation of aldehydes and ketones with furans under acid catalysis conditions is the most general and most common method for preparing compounds of this class.
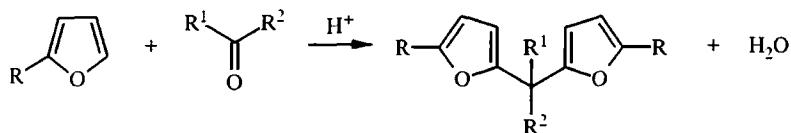
The principal barriers on the route for synthesis of polyfurylalkanes using acid catalysts is the high acidophobicity of furan and its homologs. This explains the use in early research of furan derivatives containing only electron-withdrawing substituents that increase the stability of the furan ring toward the action of acids.

Dinelli and Marini [38, 39] synthesized difurylalkane derivatives in ~30% yield *via* condensation of ethyl furoate with formic and acetic aldehydes using conc. H_2SO_4 as the catalyst and solvent. However, a product could not be isolated under these conditions from the reaction of the ethyl ester of furan-2-carboxylic acid and benzaldehyde. This product was identified only qualitatively.

Under analogous conditions the reaction of ethyl 2-furoate and chloral [40] produced the furan analog of DDT, 1,1-bis(5-carbomethoxyfur-2-yl)-2,2,2-trichloroethane (68% yield).

Pennenan and Nyman [41] developed a synthesis of bis(5-carbomethoxyfur-2-yl)methanes *via* condensation of methyl furoate with aldehydes in conc. H_2SO_4.

R = H. Me. Et. Ph. Me(CH$_2$)$_2$, CCl$_3$. o,m,p-O$_2$NC$_6$H$_4$
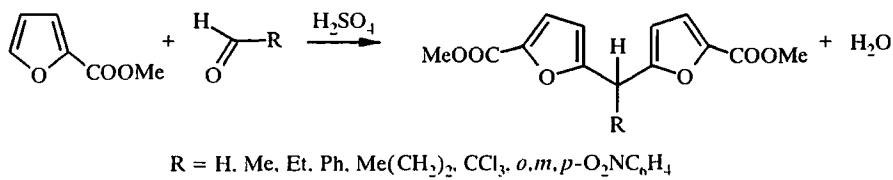
According to the literature [41], the nature of the R group has slight effect on the yields of the condensation products, which lie in the range 60-84%, if aliphatic aldehydes are used. However, the yields depend directly on the nature of the substituent for the aromatic derivatives. Thus, the yield of difurylarylmethane was only 6% for the reaction with benzaldehyde. Introducing electron-wihdrawing substituents (NO$_2$) into the benzene ring increased the yields to 20-67% (depending on the position of the substituent). It was noted that the condensation does not occur if benzaldehydes with electron-donating substituents are used.

It was stated in later studies [42-44] that carrying out the synthesis without solvent and with conc. H_2SO_4 added to a mixture of 2-methylfuran and a carbonyl compound produces the polyfurylalkanes in rather high yields from 40 to 77%.

Glukhovtsev et al. [45-47] devised syntheses of symmetric and asymmetric hydroxy derivatives of difurylmethane *via* condensation of furans with aliphatic aldehydes and ketones without solvent and with catalytic amounts of 50% H_2SO_4. The yields of the symmetric difurylalkanes were 25-60%; of asymmetric, 16-20%.

Brown et al. [13, 48] prepared difurylalkanes in 17-20% yield by reacting furan and acetone or pentan-3-one in ethanol in the presence of 37% HCl. They found that the polycondensation occurs simultaneously to give trimers and cyclic tetramers, tetraoxaquaterenes.

R = Me, Et
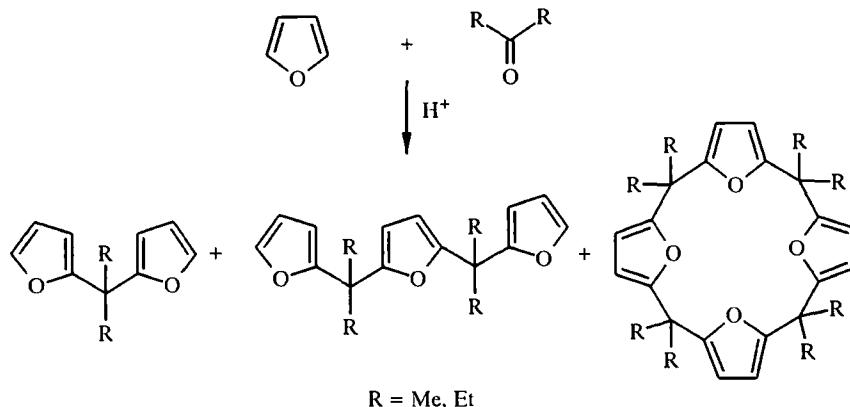
The HCl-catalyzed condensations of furan and 2-methylfuran with aldehydes, chloro-containing aldehydes, ketones, and keto acids have been described in detail [12]. It was found that the products from the reaction of furan compounds with aldehydes and ketones are difurylalkanes, which are produced in yields from 11 to 63% (the exception is the condensation of furan with formaldehyde, where the yield was only 1.7%), whereas difuryl-substituted acids result from the reactions with keto acids. It was noted that furan and 2-methylfuran do not react with benzaldehyde and furfurol under these conditions.

According to the literature [49], bis(fur-2-yl)methane was prepared in 14% yield from the reaction of furan with formalin in the presence of 48% HF.

An original method for synthesis of difurylmethane diamines that is widely used in the production of plastics has been examined [50, 51]. The condensation of furfurylamine and aldehydes is recommended to be performed in HCl, which in this instance acts as the solvent and catalyst and also deactivates the amino group, thereby avoiding the occurrence of undesirable side reactions on the amino group. The yields of the difurylmethane derivatives depended on the acid concentration and were 20-30% for formaldehyde and 45-70% for acetaldehyde [50]. Condensation of furfurylamine with aldehydes and ketones (including benzaldehyde) in conc. HCl [51] enabled the yields to be increased to 85-95%. A drawback of the method is the lack of a solvent, which prohibits crystalline substances from being used.

Replacement of H_2SO_4 by 85% H_3PO_4 enabled α-chloro-β,β-difurylalkanes to be prepared in 50-68% yield *via* condensation of alkyl- and chlorofurans with α-chloro-substituted aldehydes and ketones and their derivatives [52].
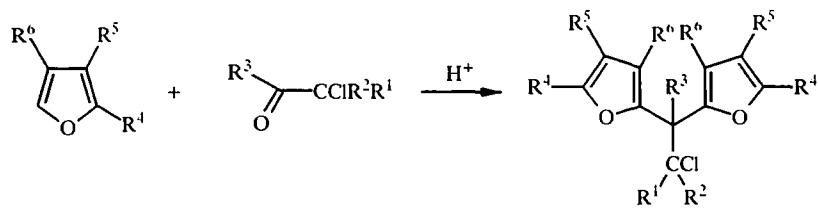
R^1 = H, Cl; R^2 = H, Cl, Me, Et, CHClMe; R^3 = H, Me, CH_2Cl;
R^4 = H, Cl, Me, Et; R^5 = R^6 = H, Cl

Bis(5-formamidomethylfur-2-yl)alkanes are interesting as intermediates in the synthesis of oligomers for the production of polyurethanes, which are produced in ~40% yield by reaction of N-furfurylformamide with aldehydes in aqueous H_3PO_4 [53, 54].

The use of $HClO_4$ as a catalyst is highly promising for the synthesis of polyfurylalkanes and their derivatives. Performing the reaction in benzene with catalytic amounts of $HClO_4$ enables any reagents to react, regardless of their aggregate state and substituents. In particular, the reaction of substituted benzaldehydes with furan derivatives in benzene in the presence of catalytic amounts of 58% $HClO_4$ gives in high yields the difurylmethane derivatives [55, 56]. Esters of oxocarboxylic acids give the corresponding derivatives of difurylmethane [57, 58]. The condensation of furan aldehydes with alkylfurans under these conditions gives trifurylmethanes.

Trifurylalkanes can be prepared in 60-92% yield by reaction of alkylfurans with anhydrides and chloroanhydrides of aliphatic acids in benzene in the presence of a catalytic amount of 58% $HClO_4$ [59-61].

It was also reported that $Mg(ClO_4)_2$ can be used as a catalyst for the condensation of substituted benzaldehydes and 2-methylfuran [62].

Difurylalkyne derivatives XIV were observed among the products from the reaction of substituted propargylaldehydes with furan [63, 64].
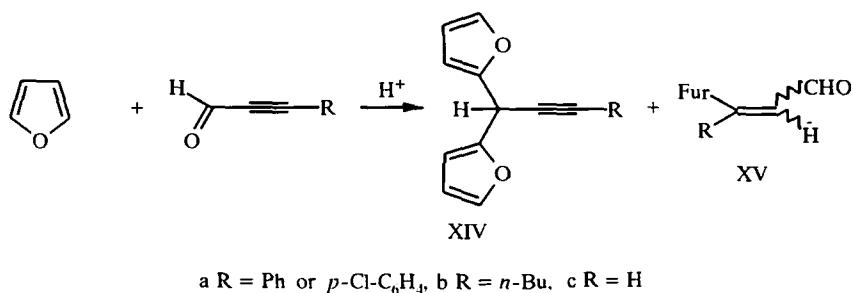

a R = Ph or p-Cl-C$_6$H$_4$, b R = n-Bu, c R = H

It was found that the substituent has a large effect on the direction of the condensation of α-acetylene-aldehydes with furan in CH_2Cl_2/HCOOH. Thus, electrophilic substitution involving the carbonyl group predominates for R = Ph or p-ClC$_6$H$_4$. The principal product is XIV. For an alkyl substituent, a mixture of XIV and XV is formed. For R = H, the predominant product is the so-called Michael pseudoadduct XV.

Reactions of furan derivatives with carbonyl compounds that are catalyzed by Lewis acids should be mentioned. In particular, the reaction of furan and 2-methylfuran with carbonyl compounds in the presence of equimolar amounts of $AlCl_3$ was studied [65]. This method can be used for synthesis of asymmetric difurylalkanes. The condensation products are difurylalkanes (60-93% yields). The reaction occurs with functionally substituted ketones (5-chloropentan-2-one, bromo acetone, acetoacetic ester). This enables substituted bisfurylalkanes to be prepared and used as intermediates for further transformations.

Using strong-acid ion-exchange resins instead of mineral and Lewis acids reduces tar formation and increases the yield of product. Thus, French researchers proposed a method for synthesis of difurylmethane derivatives in quantitative yields *via* condensation of 2-pentenylfuran [66] and 2-methylfuran [67] with aliphatic and aromatic aldehydes in the presence of the ion-exchange resins Lewatit SP 120 and Lewatit SPC 108. Similar results were obtained for the reaction of 2-methylfuran with formaldehyde that is catalyzed by the ion-exchange resin Amberlyst 15 [19].

The following mechanism is proposed for the condensation of furan derivatives with carbonyl compounds [41, 49, 61]:
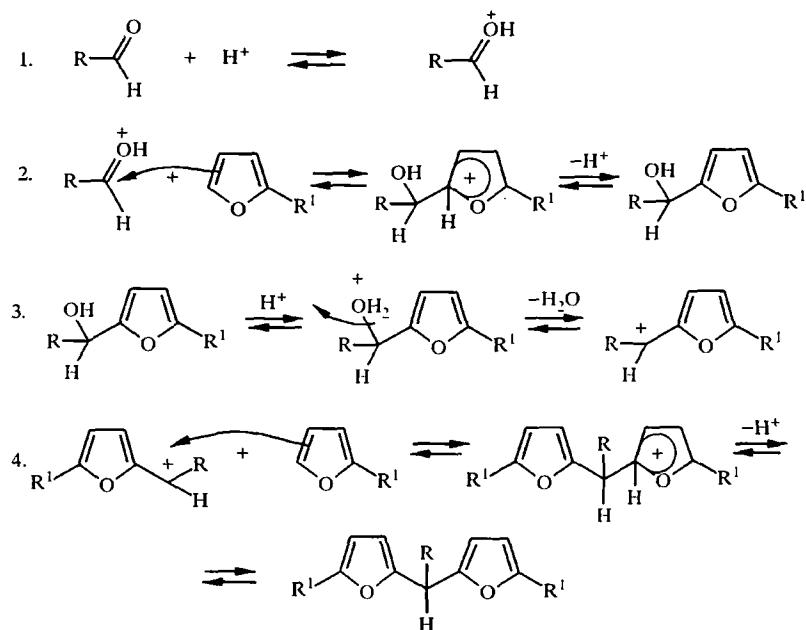
The intermediate alcohol cannot be isolated in the majority of instances, with the exception of the reaction with paraformaldehyde, where derivatives of furfuryl alcohol were obtained [19, 41].

The reaction of furans with carbonyl compounds containing fluorine or chlorine atoms in the α-position relative to the carbonyl group represents a special case [68, 69]. The $HClO_4$-catalyzed reaction of 2-R-furans with hexafluoroacetone produced in high yield the corresponding carbinols [68]. In this case the difurylmethanes were not observed. The presence of two trifluoromethyl groups, which have strongly negative inductive effects, activates the C=O group of the carbonyl compound so much that it reacts with furan even without an acid catalyst [70] or in the presence of a weak acid like KU-2 [71]. However, electron-withdrawing substituents in the resulting carbinol decrease the basicity of the hydroxyl oxygen, making further reaction with furan impossible.

R = H. Me. Ph. CH₂OMe
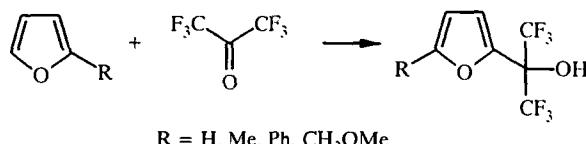
Nevertheless, the condensation of 2-methylfuran with trifluoroacetone produces an alcohol and the difurylpropane derivative in 10 and 45% yields, respectively.
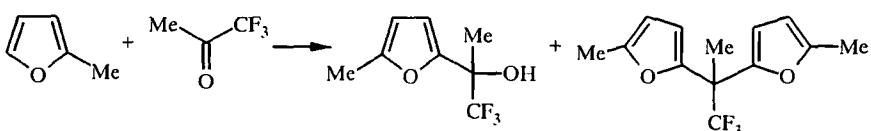

Analogous results have been obtained in other studies [41, 72]. It was found [41] that the intermediate carbinol can be isolated in 7% yield and the difurylmethane derivative in 83% yield from the reaction of chloral with methyl 2-furoate in conc. HCl at 0°C.
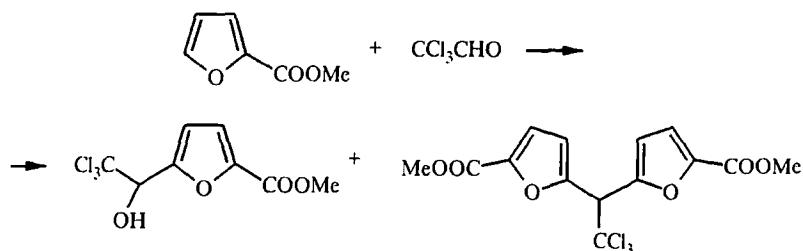
The preparation of 1-(fur-2-yl)-2,2,2-trichloroethanol in 45% yield from the reaction of furan with chloral in glacial acetic acid in the presence of ZnCl₂ was previously reported [40]. It was noted that the condensation product of methyl 2-furoate with chloral under more forcing conditions (conc. H₂SO₄ by the Dinelli method) is the corresponding difurylethane (68% yield).

1.4. Acid-catalyzed Selfcondensation of Furan Derivatives

Alkylfurans exhibit acidophobicity in transformations of furan compounds in the presence of both protonic and aprotic acids. This leads to complex product mixtures that include difurylmethane derivatives. For example, the "resinous" products from transformations of furan in the presence of HCl [73, 74] and of 2-methylfuran in the presence of H₃PO₄ [75] contained tetramers with the difurylmethane moiety.

$$R\text{—furan} \xrightarrow{[H^+]} \text{tris-furyl-CH}_2\text{—CH—CH}_2\text{OH}$$

R = H, Me
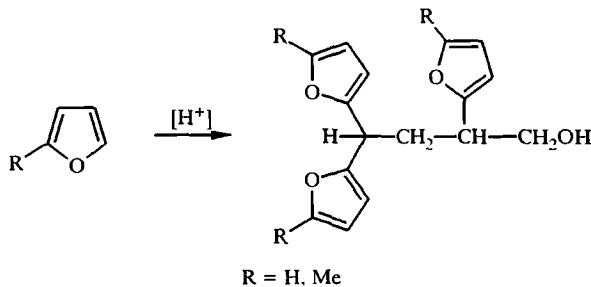
Under conditions where the furan ring is opened hydrolytically (aqueous H₂SO₄), the self-condensation product of 2-methylfuran with the structure shown below was obtained in 66% yield [76]:

$$\left[\text{Me—furan—CHCH}_2\text{CH}_2\text{COMe} \right]_2$$
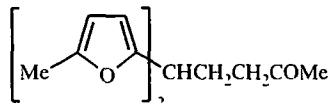
A hypothesis was made based on experimental results [77] that the acid-catalyzed polymerization of furfurol is accompanied by the formation of species containing trifurylmethane structures.

Self-condensation of furfuryl alcohols is an especially interesting method for preparation of symmetric difurylalkanes. Difurylmethane was isolated in low yields [79-83] from a mixture of furfuryl alcohol oligomerization products under acidic conditions. Difurylmethane derivatives were observed as side products from the liquid-phase catalytic hydration [84] and decarbonylation of furfurol in the presence of 5% Pd/C [85] and from the electrochemical reduction of 5-methylfurfurol [86]. The self-condensation of 5-hydroxymethylfurfuryl amine in 5.1 M HCl produces the difurylmethane diamine (<10% yield) [50]. Hydrothermolysis of alkylfurylcarbinols at 300°C and pH 7 [87] produces the corresponding difurylalkanes in ~15% yield. The preparation of the difurylalkane derivatives in all these studies is a side reaction that is of little preparative significance owing to the

$$\text{furan-carbinol} \xrightarrow[-RCHO]{[H^+]} \text{difurylalkane}$$

R = H, Me; R¹ = H, Alk; R² = H, Alk
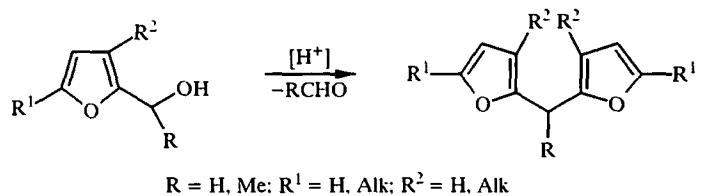
low yields. However, preparative syntheses of 3,5-dialkyl-substituted 2-furylcarbinols in 60-80% yield in the presence of polyphosphoric acid [88], Ag⁺ ions or Cl₃CCOOH [89] were proposed. Thus, a mechanism including the formation of a carbcation owing to the dehydration of a protonated alcohol with subsequent electrophilic substitution in the 2-position of the furan ring was proposed [86, 88, 89]. Obviously this mechanism predominates

R = H. Me: R^1 = H. Alk: R^2 = H. Alk
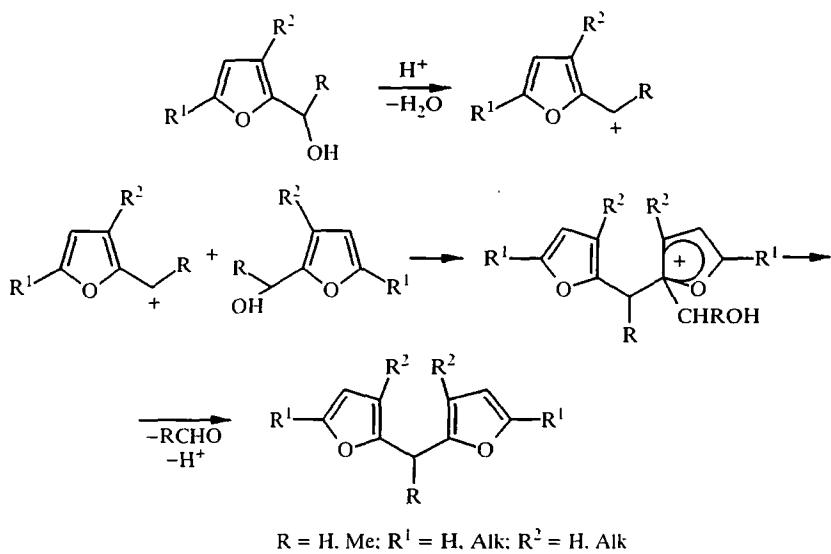
in aqueous solutions at moderate temperatures. Nelson and Hallen [87] proposed that a pyrolytic process is also possible because difurylmethane is observed as a volatile component of coffee [90] and in condensed cigarette smoke [91]. They favored an alternate formation mechanism for difurylmethanes that includes a triene intermediate:
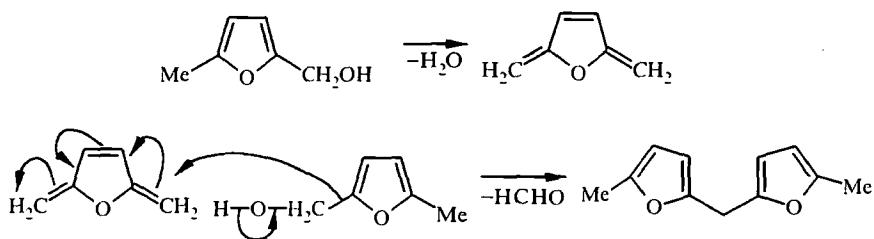
The proposed mechanisms suggest that the difurylmethane derivatives produced during the self-condensation of the furfuryl alcohols are formed through cleavage of the C–Fur bond.

An example of the self-condensation of furan compounds that is accompanied by cleavage of a C–Fur bond is the transformation under acidic conditions of 2-(5-methylfur-2-yl)-1,3-dioxolane XVI into the trifurylmethane XVII [92]. The influence of acid catalysts on the selectivity and path of the reaction of 5-methylfurfurol with ethyleneglycol was studied. It was found that the less acidic catalyst, the more preferred was the formation of dioxolane XVI (its yield using KU-2 is 70-80%). Conversely, more acidic catalysts enhance the formation of trifurylmethane XVII. The most versatile catalyst is Amberlyst 15. Either XVI or XVII can be prepared by varying the amount of it.

768
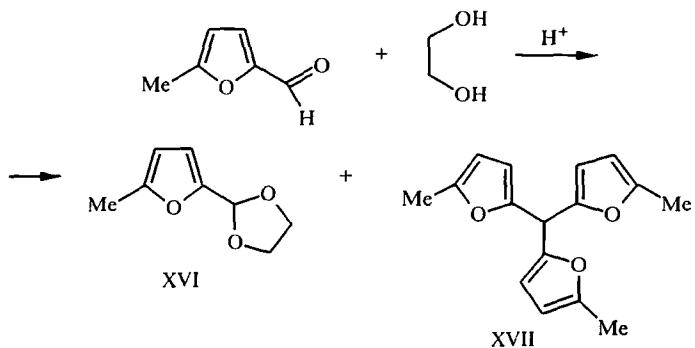
A similar transformation was observed during an unsuccessful attempt to prepare the ethylene glycol acetal of pyrrolaldehyde in the presence of TsOH [93]. The principal product under these conditions was tripyrrolylmethane.

An analogous phenomenon apparently occurred during an attempt to synthesize the furan analog of 2-aryl-1,3-dioxolanium perchlorate by the literature method [94]. Instead of the expected 2-(5-methylfur-2-yl)-1,3-dioxolanium perchlorate, tris(5-methylfur-2-yl)carbenium perchlorate was obtained in 90% yield [92, 95]. In this instance trityl perchlorate acted as the hydride ion acceptor and the acid catalyst.
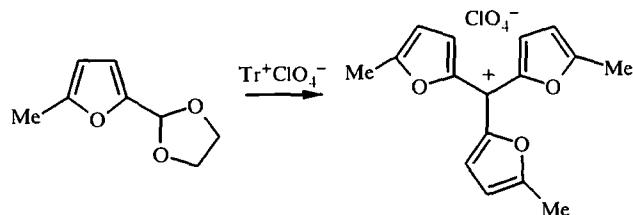
1.5. Other Methods for Preparation of Furyl(aryl)methanes

3,4-Dihydroxy-2,4-dimethylcyclobutene-1-carboxylic acid is a decomposition product of the photodimer 2,6-dimethyl-4-pyrone. Under acidic conditions it transforms into 5,5-bis(3,5-dimethylfur-2-yl)-4-methylpentan-2-one [96]:
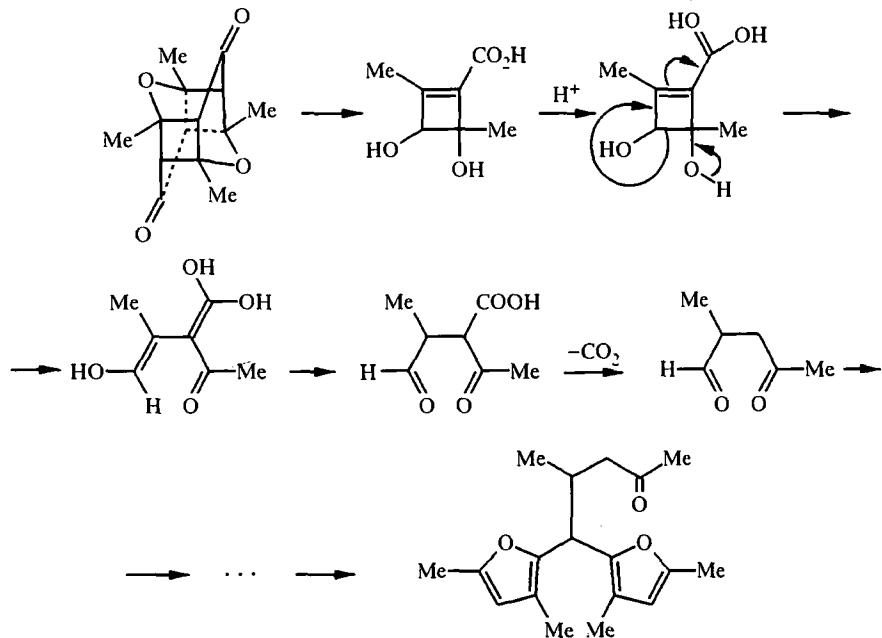
Compound XIX is obtained *via* the pinacol rearrangement of the ditertiary α-glycols XVIII in the presence of boric acid [97].

XVIII   XIX

R = Me, Et, Pr
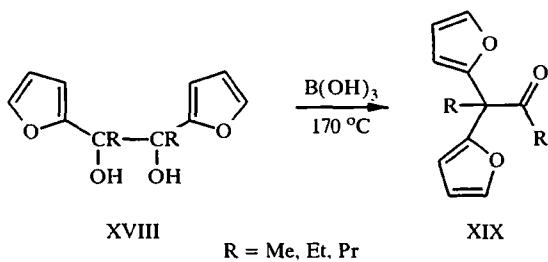
An unusual arylation of the side chain of dimethylfuran has been reported [98]. 5-Methylfur-2-ylphenylmethane was isolated from the reaction products of N-nitrosoacetanilide with 2,5-dimethylfuran:

Me—furan—Me $\xrightarrow{\text{PhN(NO)Ac}}$ Me—furan—CH$_2$—Ph
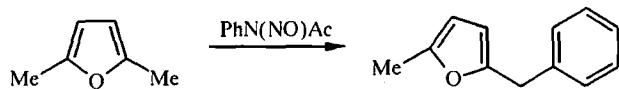
2. PROPERTIES OF FURYL(ARYL)METHANES

2.1. Reactions of Substituents

The promise of using difurylalkanes in the production and modification of polymers defined one of the areas in which chemical transformations of these compounds were investigated. This is the functionalization with reactive groups in the 5-position of the furan ring.

Methods for synthesis of dihydrazides, diacylchlorides, and diacylazides based on difurylalkanedicarboxylic acids and their esters were proposed [99, 100].

HOOC—furan—CR—furan—COOH

$\downarrow$ SOCl$_2$, C$_n$H$_6$, C$_5$H$_5$N

MeOOC—furan—CR—furan—COOMe   ClOC—furan—CR—furan—COCl

$\downarrow$ N$_2$H$_4$·H$_2$O, EtOH $\downarrow$ NaN$_3$, H$_2$O, Me$_2$CO

H$_2$NHNOC—furan—CR—furan—CONHNH$_2$ $\xrightarrow[\text{H}_2\text{O}]{\text{NaNO}_2, \text{HCl}}$ N$_3$OC—furan—CR—furan—CON$_3$

R = H, Me, p-O$_2$N-C$_6$H$_4$, CCl$_3$
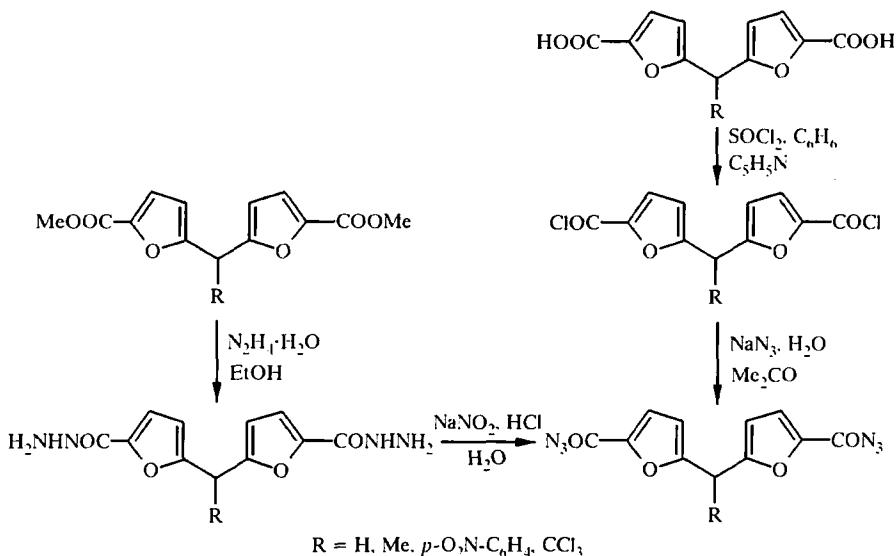
The attempted preparation of diisocyanates containing the NCO group in the 5-position of both furan rings from diacylazides via the Curtius rearrangement was unsuccessful owing to the extreme instability of furylisocyanates, especially in the presence of water traces [101].

Analogous results have been reported [54]. Diisocyanates based on di(aminomethyl)difurylalkanes have been synthesized. These compounds are more stable and are used to produce polyurethanes:

H$_2$NCH$_2$—furan—CR—furan—CH$_2$NH$_2$ $\xrightarrow[\text{2. COCl}_2]{\text{1. HCl}}$

$\longrightarrow$ OCNCH$_2$—furan—CR—furan—CH$_2$NCO

R = H, Me
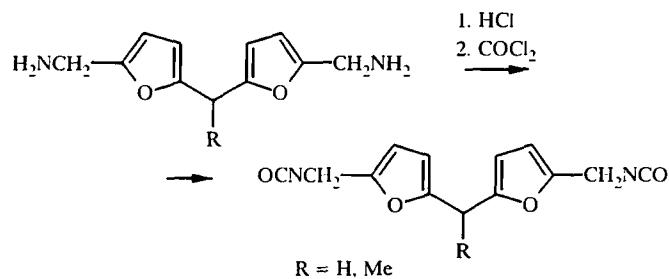
2.2. Electrophilic Substitution and Cycloaddition

Furyl(aryl)methanes containing the furan moiety can be involved in reactions characteristic as for aromatic compounds and dienes.

The properties of furylalkanes that are reminiscent of aromatic compounds include electrophilic substitution on the furan ring. Glukhovtsev et al. [102] studied reactions of difurylalkanes with trifluoroacetic anhydride in order to introduce the trifluoroacetyl radical in the α-position and prepare new compounds with promise as biologically active substances. The yields were 54-75%.

$$RR^1C \left[\underset{O}{\bigcirc} \right]_2 + \ (CF_3CO)_2O \ \longrightarrow \ RR^1C \left[\underset{O}{\bigcirc} \underset{\underset{O}{\parallel}}{C}CF_3 \right]_2$$

$$R = H, R^1 = Me; \ R = H, R^1 = C_2H_5;$$
$$R = R^1 = Me; \ \ \ R = H, R^1 = C_3H_7$$
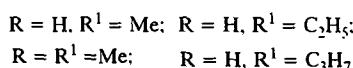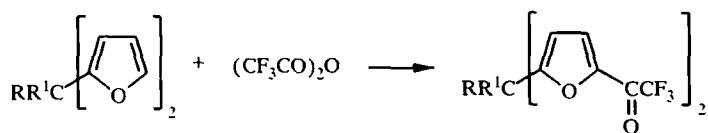
Nucleophilic addition of furans to the double bond of α,β-unsaturated carbonyl compounds (18-58% yields) was used to prepare oxoderivatives of difurylalkanes [45, 46].
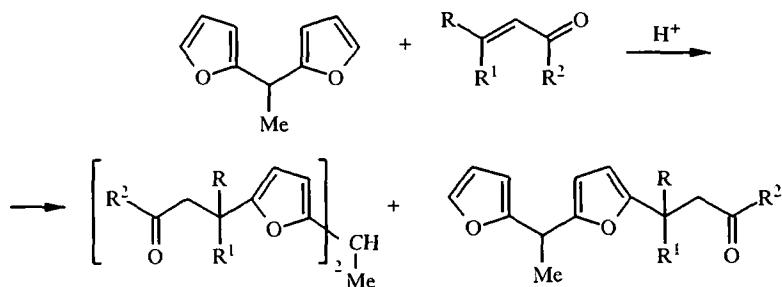
Vilsmeier formylation of difurylmethane gave the corresponding diformyldifurylmethane in ~45% yield [103].
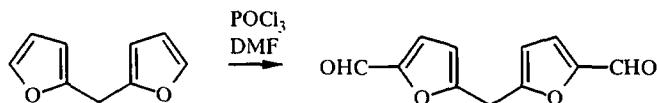
Formyl derivatives of difurylmethane are used to prepare Schiff-base macrocycles [104, 105] and to synthesize furan analogs of biladienes [103].
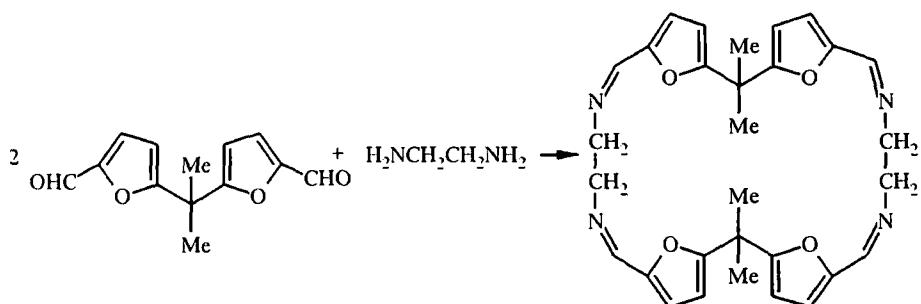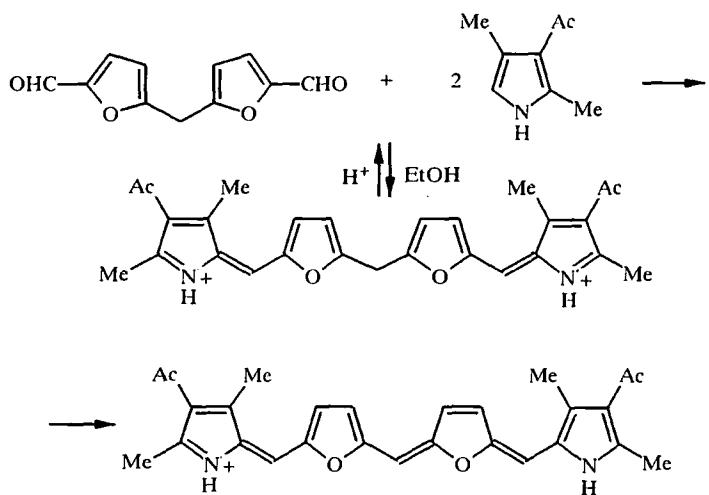
Other macrocycles, quaterenes, are formed *via* electrophilic substitution between carbonyl compounds and difurylalkanes in the presence of such acid catalysts as HCl, gaseous HCl, and BF₃·Et₂O [4, 13, 18, 48, 106, 107]. The nitration of *gem*-difurylalkanes in the 5-position of both heterocycles has been reported [106]. At the same time, the presence of a furan ring in furyl(aryl)alkanes determines that cycloaddition to these compounds also takes place. The reaction of furylthienylmethane with maleic anhydride to give the corresponding adduct has been described [1].

The reaction of difuryl-R-methanes with N-(3,5-dichlorophenyl)maleimide has been studied [108].

R = H. Me. Ph. 5-Me-2-furyl. 4-Br(Cl)C₆H₄, 4-Me(2-MeO)C₆H₄
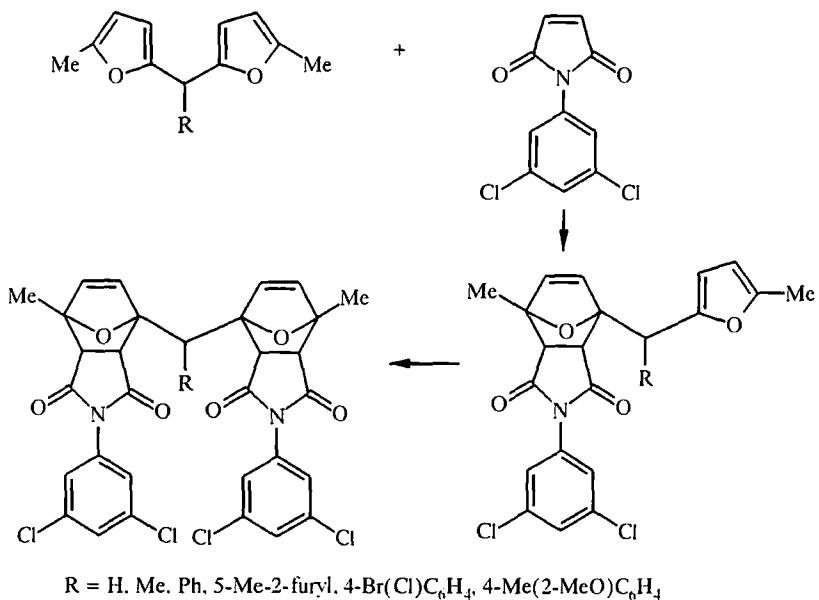
Tetrasubstituted methanes were found to be unreactive. Difurylmethane, 1,1-difurylethane, and trifurylmethane produce the mono- and diadducts whereas difurylarylmethanes give only the monoadducts.

2.3. Hydrogenation and Hydrogenolysis

Hydrogenation of 2,2-difurylpropane on Pd/C (Ru/C) in isopropanol or methanol produces in 100% yield 2,2-bis(tetrahydrofur-2-yl)propane [109]. Macrocycles containing tetrahydrofuran moieties are obtained on Rainey nickel [110] and Ru/C or Ru-Rh/C [111]. Compared with the starting calixfurans, these macrocycles possess certain advantages where used as carriers of alkali metal cations.

n = 1–3

R, R^1 = H. Me. CH$_2$CH$_2$CO$_2$Et
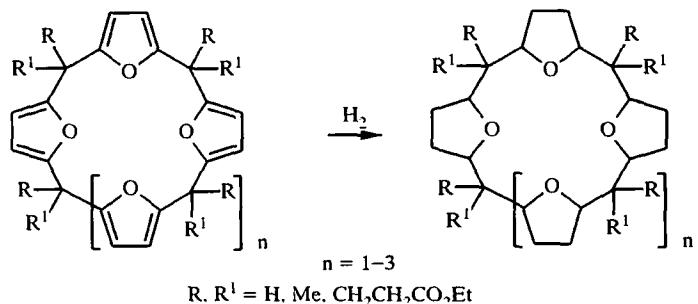
Hydrogenation of furylalkanes is often accompanied by hydrogenolysis. Hydrogenation of 1,1-difuryl-ethane in absolute ethanol on Ru or Pt catalysts (70-100°C, 100-130 atm) [112] proceeds smoothly to give diastereomers of 1,1-bis(tetrahydrofur-2-yl)ethane XX. However, a mixture of the hydrogenation and hydrogenolysis products 5-(tetrahydrofur-2-yl)-1-hexanol XXI and 11-methyl-1,6-dioxaspiro[4,6]undecane XXII is formed on upon hydrogenation on a Pd catalyst.

XX   XXI   XXII
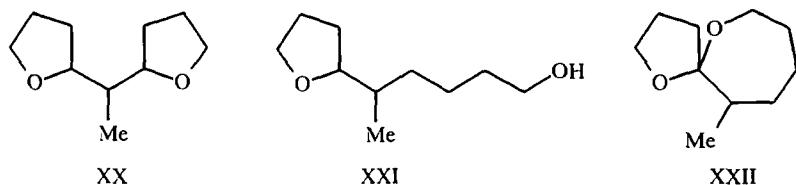
Vapor-phase hydrogenolysis of difurylmethane and 1,1-difurylethane in a flow system over 10% Pt/C at 180-280°C produces selectively at the C–O bonds removed from the substituent to form in each case only one diketone [113].

R = H. Me
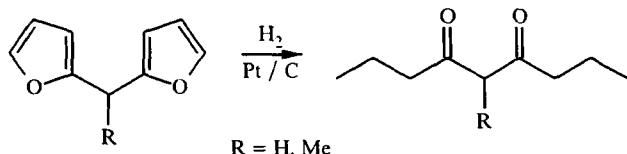
Such selectivity is not observed for the hydrogenolysis of bis(5-methylfur-2-yl)methane.

2.4. Oxidation

The fact that furyl(aryl)alkanes have two reactive centers that are susceptible to oxidation should be considered in reviewing their reactions. These centers are the furan ring itself and the methyne or methylene carbon, whichever occurs.

Oxidation of polyfuryl(aryl)alkanes under forcing conditions results in the decomposition of the furan ring. Oxidation of (5-methylthien-2-yl)furylmethane by such reagents as K$_3$[Fe(CN)$_6$] or KMnO$_4$ produces thiophene-2,5-dicarboxylic acid [1, 114]:
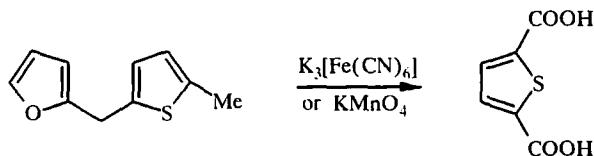
Electrochemical oxidation of difurylmethane under mild conditions in methanol in the presence of ammonium bromide as electrolyte gave bis(2,5-dimethoxy-2,5-dihydrofur-2-yl)methane XXIII [115].

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XXIII
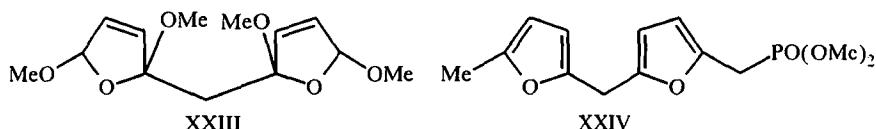
XXIV

Attempted selective oxidative opening of one of the furan rings in XXIV was unsuccessful and produced complicated mixtures [116].

Oxidation of calixarene XXV by bromine in methanol gave bis(*trans*-endione) XXVI in 10% yield [117]. Replacement of methanol by aqueous acetic acid enabled the yield to be increased to 65-74%. It should be noted that using a four-fold excess of bromine did not open more than two of the furan rings. However, oxidation of calixarene XXV by *m*-chloroperbenzoic acid (MCPBA) produces the octaketone XXVII.

XXV
Br$_2$
HOAc, H$_2$O
XXVI
MCPBA
XXVII
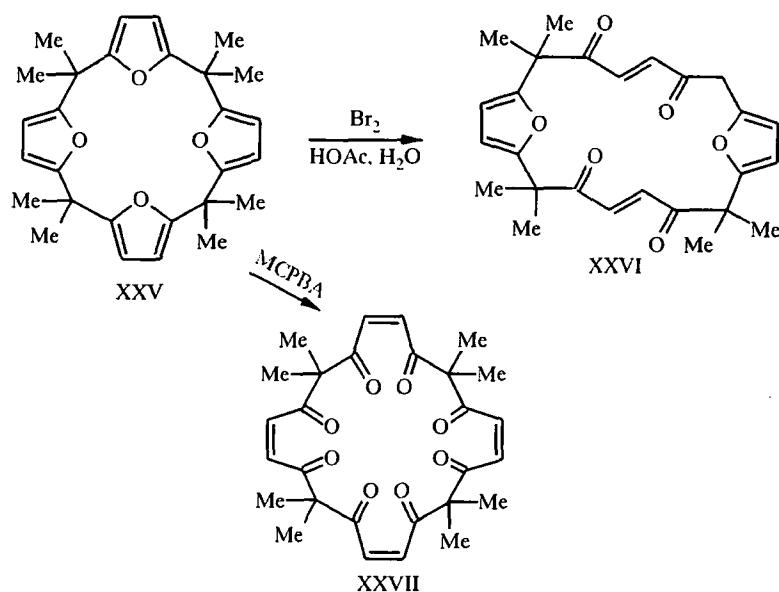
Oxidation of bis(5-methoxycarbonylfur-2-yl)methane by chromic anhydride in boiling acetic acid produced the corresponding difurylketone in 62% yield [31].

MeOOC — O — CH$_2$ — O — COOMe → MeOOC — O — CO — O — COOMe
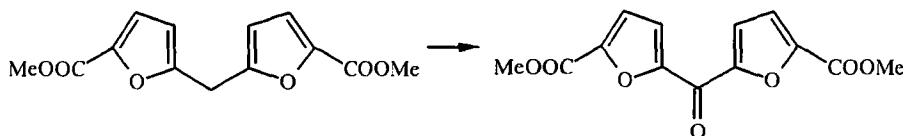
Treatment of trifurylmethane with various oxidative-dehydrogenation reagents (trityl perchlorate, *o*-chloranil, SbCl$_5$, and bromine in the presence of acid) gave a trifurylcarbenium salt [118].

Me — O — CH — O — Me
[O]
Me — O — C$^+$ — O — Me X$^-$

X$^-$ = ClO$_4$$^-$, SbCl$_6$$^-$
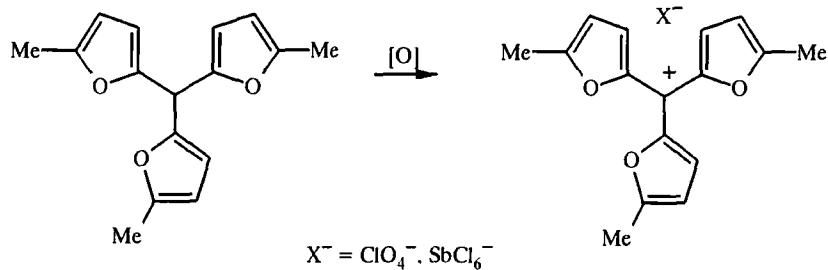
The corresponding salts are also produced by the reaction of arylfurylmethanes with trityl perchlorate [118].

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Oxidation of calixfurans XXVIII by HNO_3 and ceric ammonium nitrate [119, 120] or dichlorodicyanoquinone [121] with subsequent treatment with $HClO_4$ produces the corresponding dications XXIX:

XXVIII   XXIX

R = H. Et
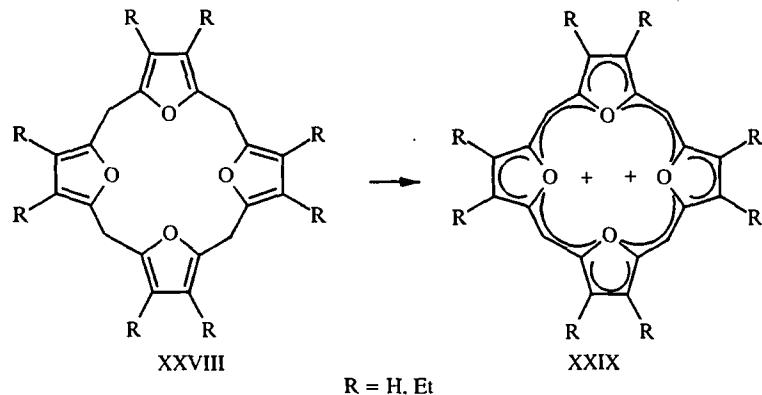
The one-electron oxidation of 1,1-bis(5-trifluoroacetylfur-2-yl)alkanes by Cu(II) salts has been described [122]. The reaction occurs after preliminary protolytic dissociation in dipolar aprotic solvents or in alcohols in the presence of bases:

R = Me. Et, Pr
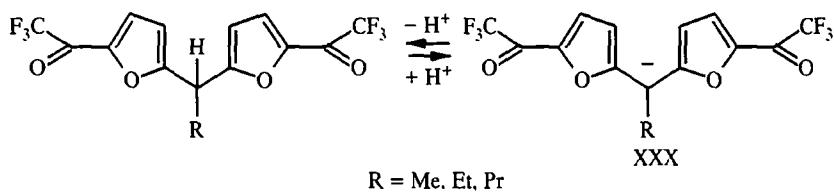
The nature of the ligand affects the reaction path of the free radicals formed. Thus, reaction of 1,1-bis(trifluoroacetylfur-2-yl)ethane with $Cu(ClO_4)_2$ in methanol gives mainly 2,2,3,3-tetra(5-trifluoroacetylfur-2-yl)butane, which is the recombination product.
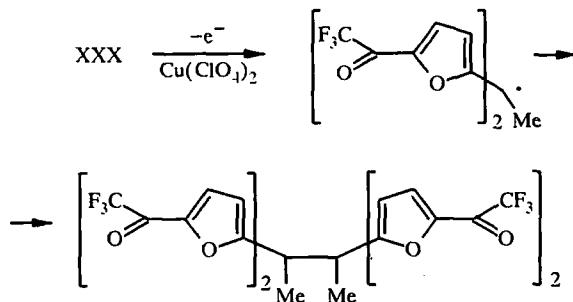
If $CuCl_2$ is used as the oxidant under the same conditions in methanol, the methoxy derivative of the difurylalkane is obtained.
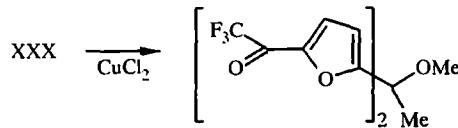
This last compound may be formed by the oxidation of the radical to the carbonium ion with subsequent solvolysis.

2.5. Opening and Recyclization of the Furan Ring

Opening of the furan ring plays a fundamental role in the chemistry of furan. This reaction is rather widely used in organic synthesis to prepare various classes of compounds. In particular, the preparation of 1,4-dicarbonyl compounds from furans is an important route for synthesis of naturally occurring cyclopentenones.

Italian researchers [116] have studied the capability of using selective opening of one of the two furan rings in difurylalkanes and their stepwise transformation into γ-dicarbonyl compounds and/or carboxylic derivatives.

Boiling the difurylmethane XXIV in aqueous acetic acid in the presence of H_2SO_4 leads to selective hydrolysis of the methyl-substituted furan ring to form 1,4-dicarbonyl compound XXXI in 75% yield. The furan ring with the dimethoxyphosphorylmethyl sustituent is not affected by the acid-catalysis conditions.
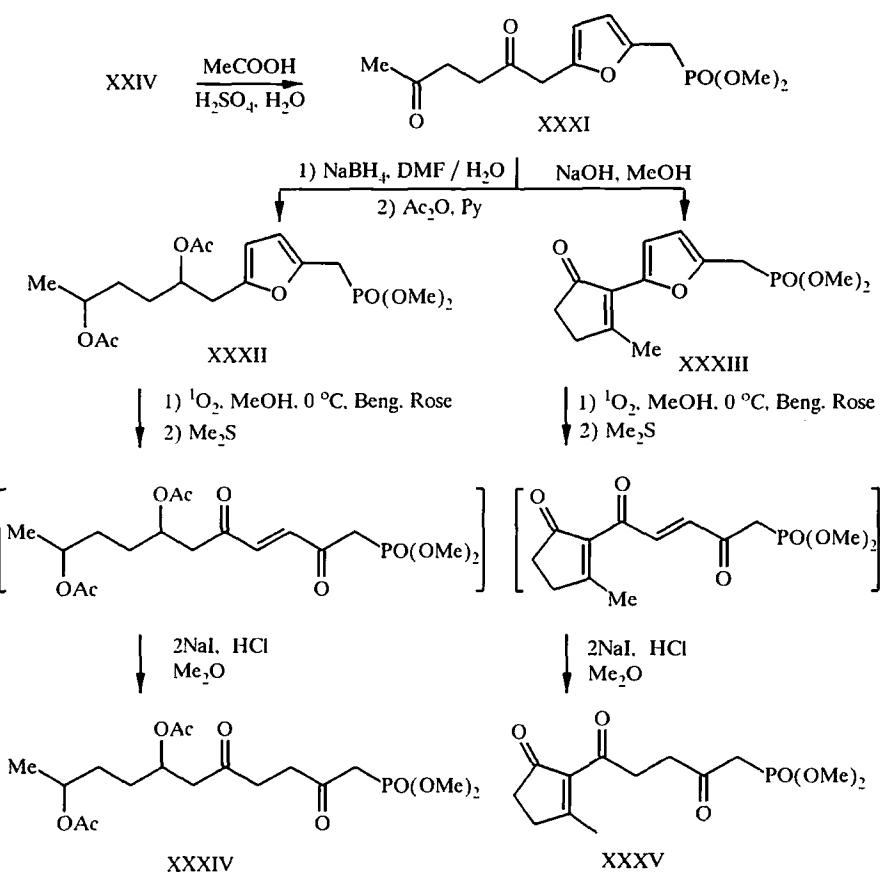
It should be noted that photo-oxidation of compounds XXXII and XXXIII in the presence of bengal rose, oxygen bubbling, subsequent treatment of the reaction mixture with dimethylsulfide, and reduction by sodium iodide produce the corresponding 1,4-diketones XXXIV and XXXV in quantitative yields.

According to Gubina et al. [123], difurylalkyl(aryl)methanes react with H_2S under acidic conditions to give furylthienylalkyl(aryl)- or dithienylalkyl(aryl)methanes. If the reaction is carried out in ethanol saturated with HCl, only one furan ring recyclizes to form 1-(5-methylfur-2-yl)-1-R-1-(5-methylthien-2-yl)methanes.

$R = Me, Et, Ph, p\text{-}MeOC_6H_4, p\text{-}BrC_6H_4$
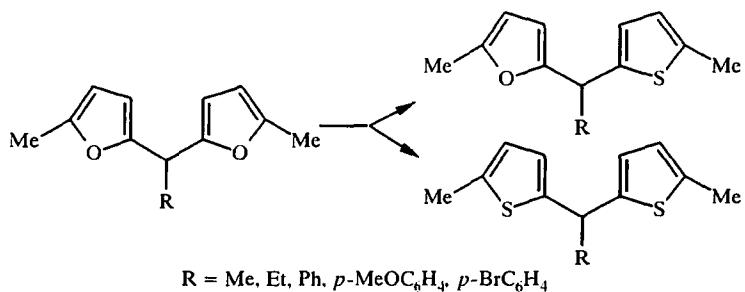
Recyclization of difurylarylmethanes in isopropanol gives only dithienylarylmethanes.

A probable mechanism of the transformations was proposed. Thus, the recyclization in the presence of acid occurs through two independent paths. These involve the intermediate formation of dicarbonyl compounds and the direct transformation of the furans into thiophenes.

Under analogous conditions 2-hydroxyaryldifurylmethanes XXXVI transform into benzofuran derivatives [124, 125]. The reaction of salicylaldehydes with 2-methylfuran in benzene in the presence of $HClO_4$ does not stop with the formation of the aryldifurylmethanes XXXVI but produces a mixture of products:

R = H, Br, Na; R^1 = H, Me, Br, NO$_2$
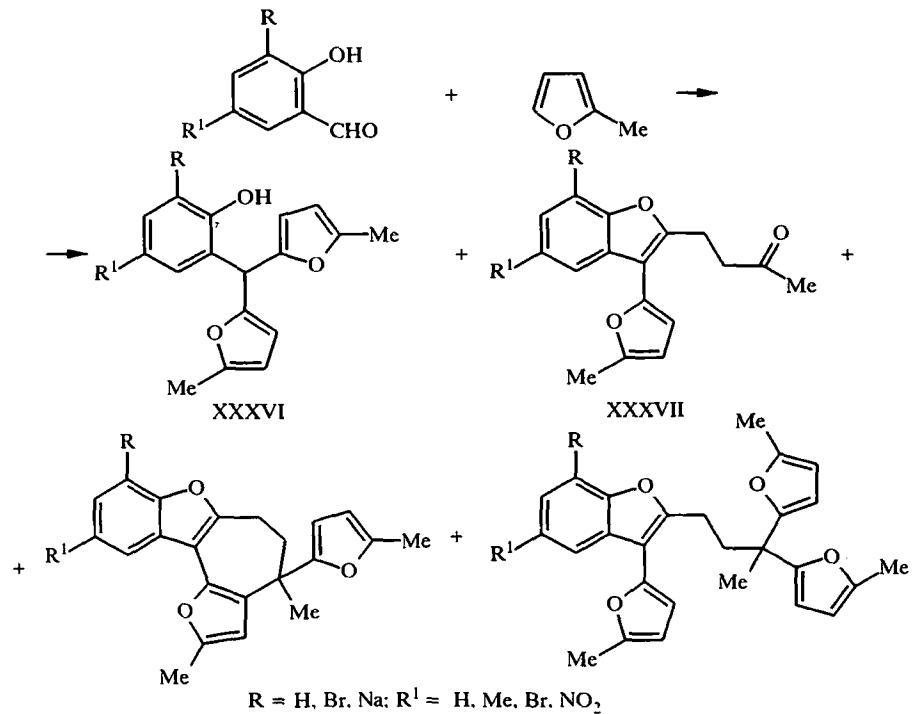
The selective conversion of aryldifurylmethanes XXXVI into ketones XXXVII if the reaction is performed in ethanol saturated with gaseous HCl was reported later [126]. The mechanism of this reaction is similar to that proposed earlier [127] for the transformation of furans into thiophenes and selenophenes. The difference is that the opening of the furan ring occurs intramolecularly for the preparation of the benzofuran ketones.

R = H, Br, NO$_2$, R^1 = H, Br, Me, NO$_2$
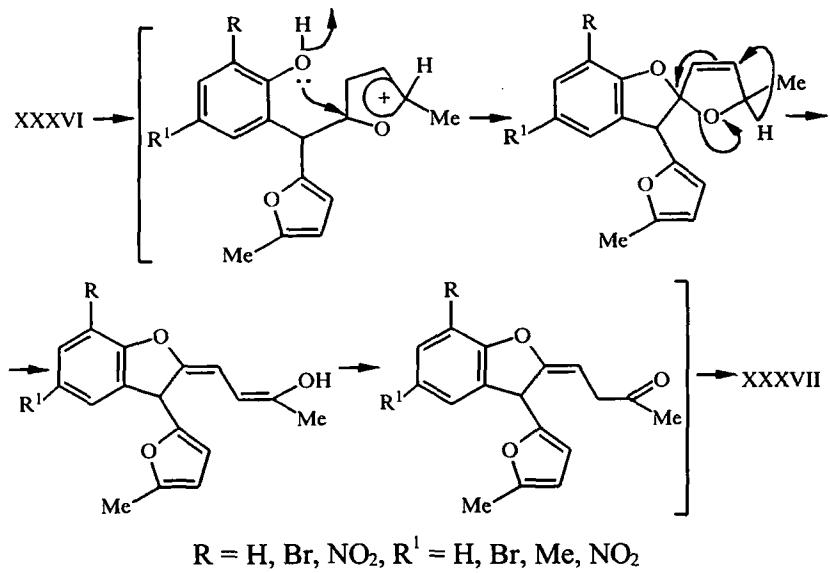
Another example of the use of furyl(aryl)methanes to synthesize heterocycles is the transformation of 2-nitroaryldifurylmethanes into carbazole derivatives *via* deoxygenation in the presence of triethylphosphite [128, 129]. It was proposed that the reaction occurs through cycloaddition of the nitrene formed by the deoxygenation to one of the furan rings with subsequent opening of this ring.

R = Me. Et. *i*-Pr. *t*-Bu
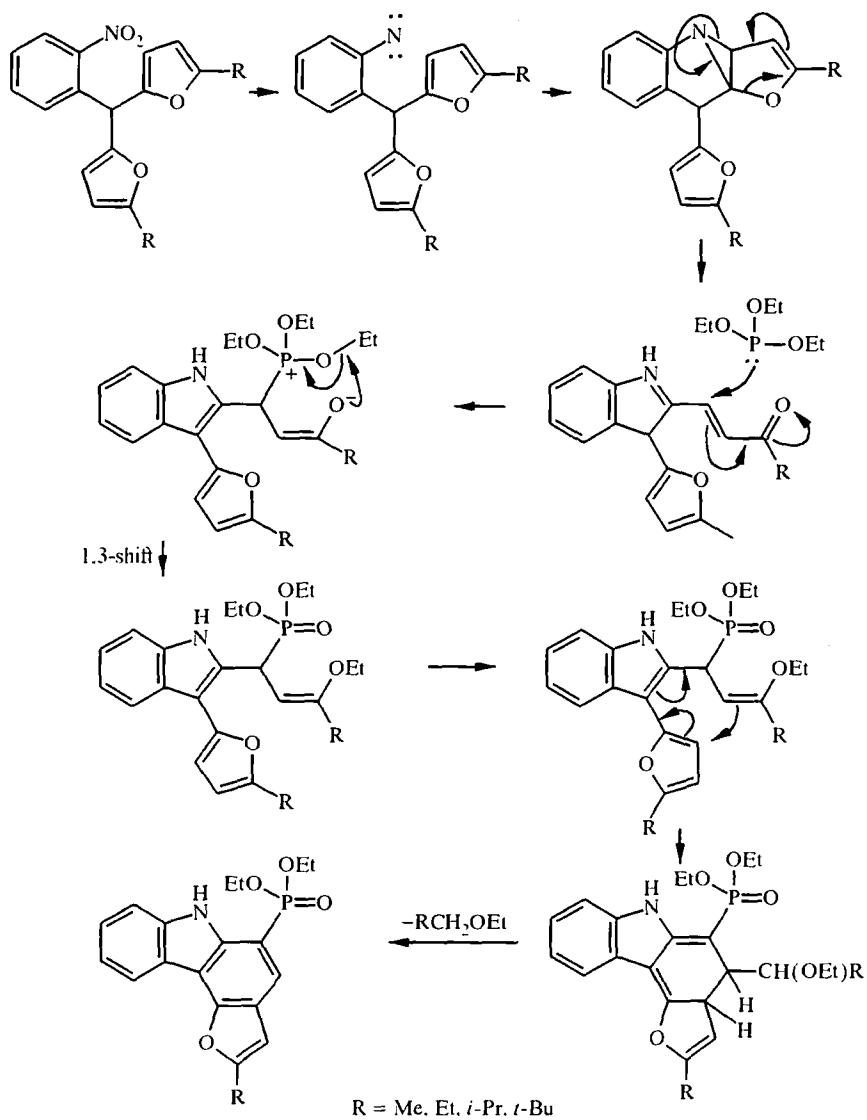
It was noted that deoxygenation of *o*-nitrophenyldi(pyrrolyl)methane apparently proceeds through a different mechanism and produces a pyrroloquinoline:
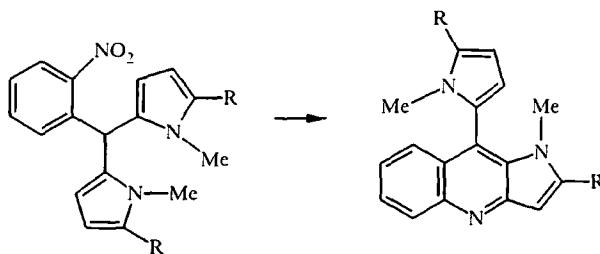
The transformation of 2-nitrophenyldi(furyl)methane XXXVIII upon reduction by $SnCl_2 \cdot 2H_2O$ in methanol in the presence of HCl or Me_3SiCl into the 3-(fur-2-yl)indole has been reported [130]. The hypothesis initially offered [130] that this transformation occurs through the intermediate hydroxylamine XXXIX with subsequent attack of the electrophilic nitrogen atom into the 2-position of the furan ring was refuted. Experimental data [131, 132]

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suggested that the most probable intermediate of this reaction is the nitroso compound XL. The proposed mechanism includes an intramolecular Diels–Alder reaction between the furan ring and the nitroso group of the intermediate XL with subsequent cleavage of the bridging ether bond in the strained adduct and formation of the indolooxazine XLI, the reduction of which produces the corresponding ketone XLII.
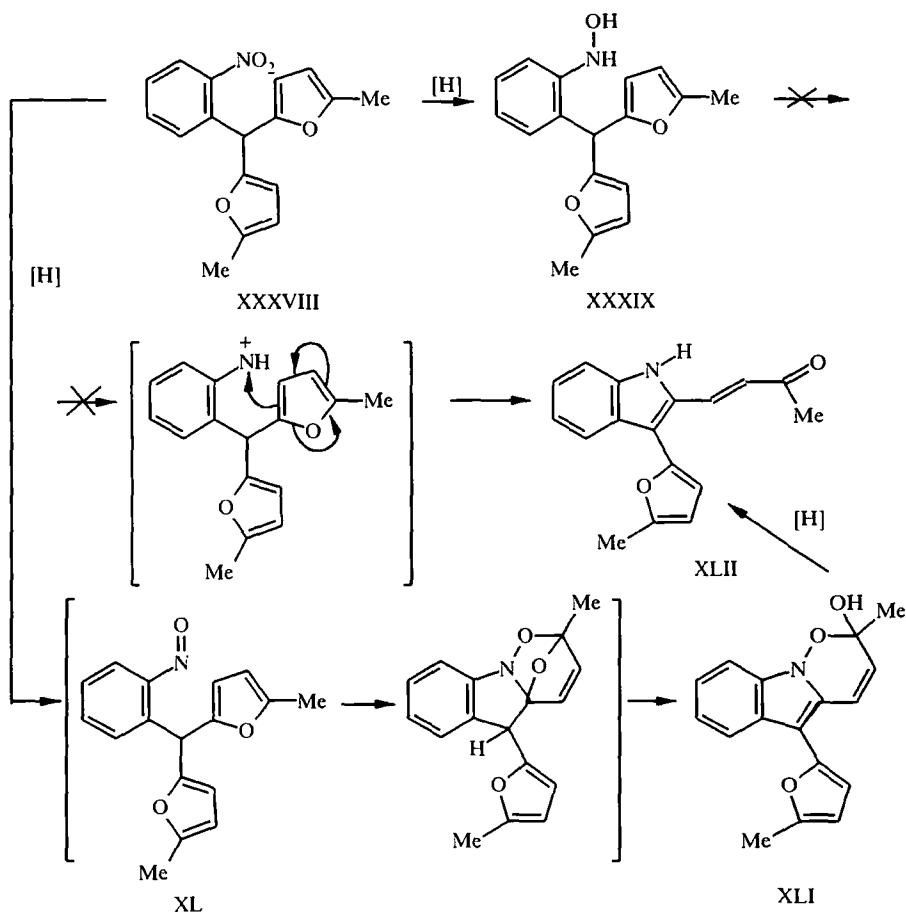
According to the literature [129], all attempts to prepare diazocompounds of 2-aminophenyldifurylmethanes using sodium nitrite in order to prepare new heterocyclic systems have been unsuccessful owing to extensive polymerization of the reaction mixture. However, the use of organic nitrites in this reaction enabled cinnoline derivatives to be prepared in rather high yields [131, 133]:

R = H, OMe

779
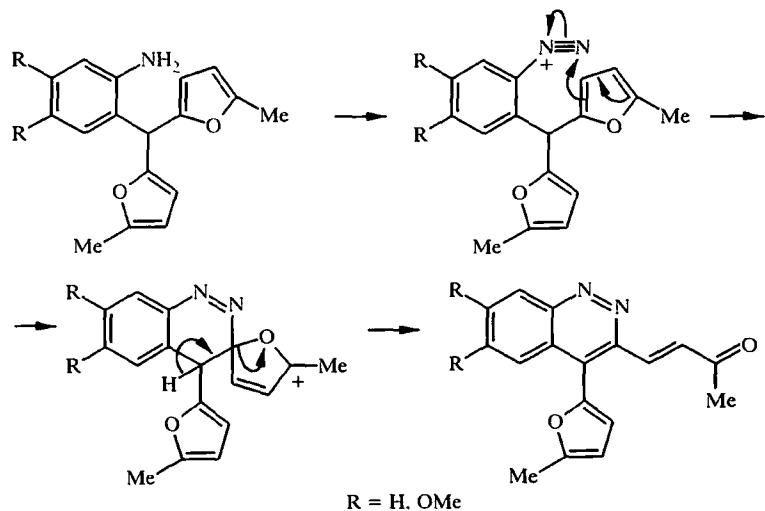
Treatment of difuryl-R-methanes with trityl perchlorate produces the corresponding perchlorates [118]. However, the reaction of 2-hydroxyaryldifurylmethanes with $Tr^+ClO_4^-$ produces oxazulenium derivatives in one step and in high yields [134, 135]. Azazulenium derivatives are obtained from 2-acylaminoaryldifurylmethanes under analogous conditions [132]:

X = O, NAc
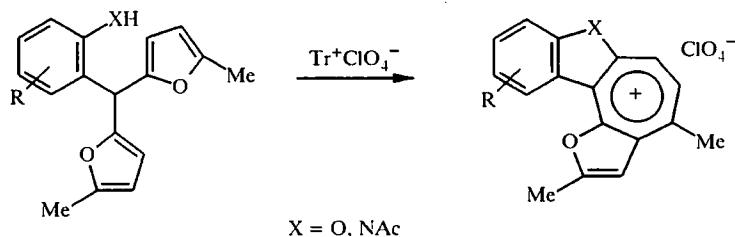
It was demonstrated in a subsequent study [136] that oxazulenium perchlorates can be prepared directly from salicylaldehyde derivatives and 2-methylfuran by boiling in dioxane with a small excess of $HClO_4$. The 2-hydroxyaryldifurylmethanes do not need to be isolated.

2.6. Cleavage of the C–Fur Bond in Polyfurylarylmethanes

Still another interesting property of polyfurylarylmethanes should be mentioned. A strong bathochromic shift of the absorption maximum in the electronic spectra is observed on dissolution of these compounds in conc. H_2SO_4 [43, 137]. The maximum λ_{max} of furylalkanes in ethanol occurs at 220-240 nm whereas that for polyfurylalkanes in conc. H_2SO_4 is observed at ~500 nm. The appearance of color in the solutions was explained by the presence of pentacoordinate carbon atom [137]. An analogous phenomenon was observed earlier for a series of polyarylmethanes [138]. However, the appearance of color was attributed to the formation of cations through cleavage of C–Ar bonds and loss of the most basic ring. It was subsequently demonstrated that color development in the presence of acid in a series of furyl(aryl)methanes is due to loss of one of the furan rings [139]. It was also found that this process in several instances is accompanied by secondary hydride-shift reactions.

Reactions involving cleavage of a C–Fur bond were also performed on a preparative scale. It was reported [140] that condensation of 2,4-dimethoxybenzaldehyde with 2-methylfuran in benzene in the presence of catalytic amounts of $HClO_4$ produces the dimethyl ether of resorcinol and trifurylmethane in addition to aryldifurylmethane. It was hypothesized that the appearance of the last compound in the reaction mixture results from the reaction of the difurylmethyl cation that is formed after the loss of the aromatic moiety in the aryldifurylmethane with an excess of 2-methylfuran. However, subjecting XLIII to the reaction conditions gave the same products [92]. In this case, this is only possible if both the C–Ar and C–Fur bonds break.

XLIII

tar
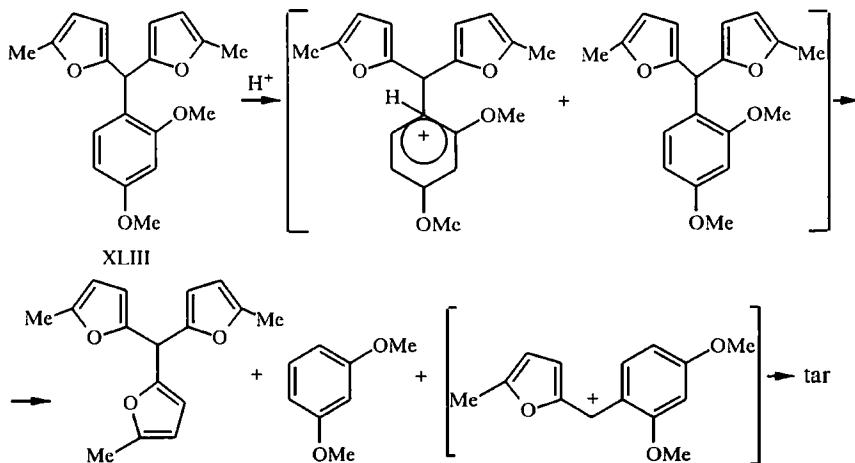
It was found [131, 141] that transformation of isothiocyanates XLIV into the corresponding thiazines XLV under acidic conditions is accompanied by rearrangement with a shift of the furan ring.

R = H. OMe
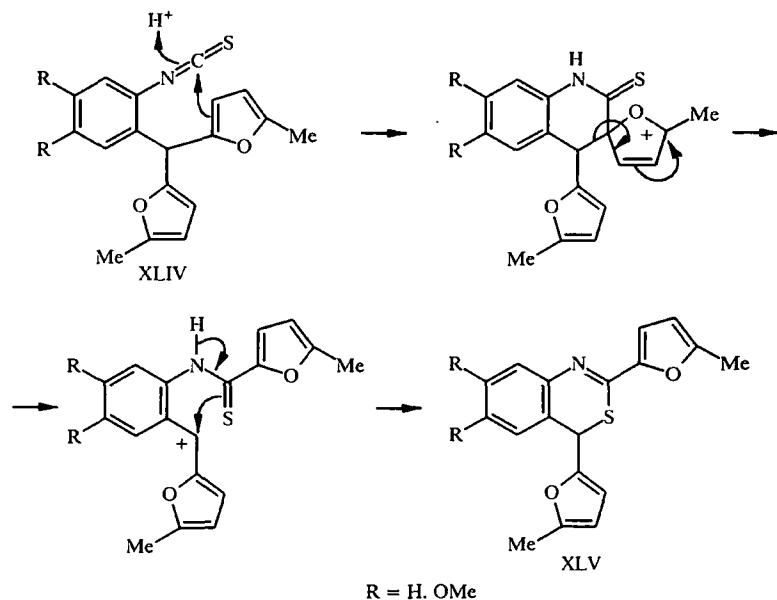
Another example illustrating the lability of the C–Fur bond in furyl(aryl)alkanes is the formation of salt XLVII from *gem*-trifurylethane XLVI during the treatment of the latter with trityl perchlorate [92]. The high stability of the cation XLVII is the key to this transformation.
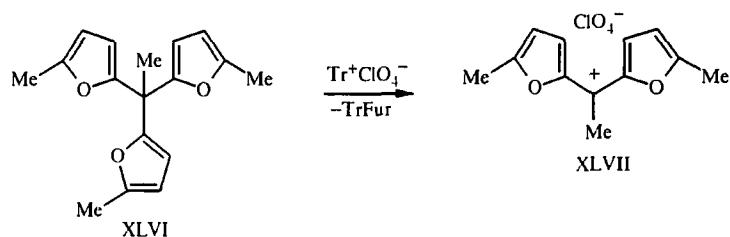
2.7. Other Reactions Of Furyl(Aryl)Methanes

It was found that storage in light or under UV irradiation of 2-nitroaryldifurylmethanes XLVIIIa,b in THF solution transforms them into the 4,9-dihydrofuro[3,2-*b*]quinoline derivatives XLIXa,b [142, 143].

a R = H. b R = OMe

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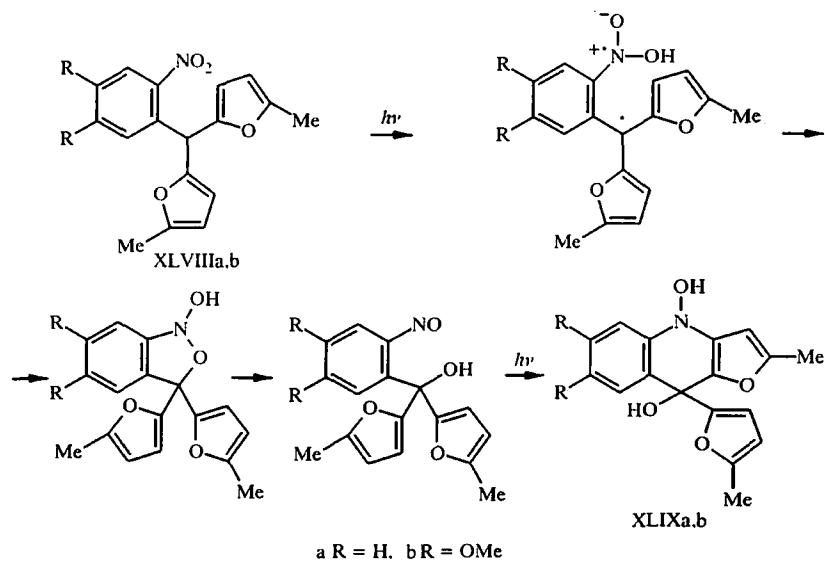
A method for synthesis of 3-(fur-2-yl)indoles (30-40% yield) *via* cyclization of 2-(2-nitrophenylethenyl)-furans in the presence of triethylphosphite was proposed [144].

R = R = H; R = R = OCH₂O; AIBN – azobisisobutyronitrile
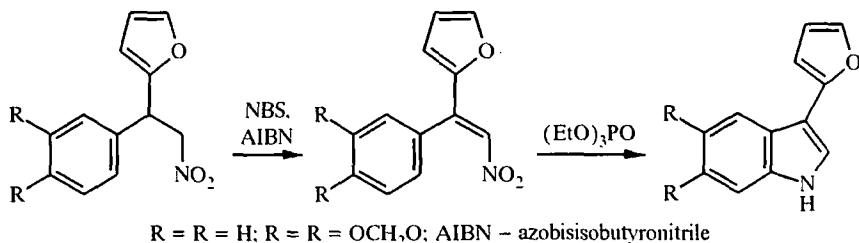
A search for the optimal synthetic conditions of XLVIIIb [145] revealed that condensation of 6-nitroveratraldehyde and 2-methylfuran in benzene in the presence of Me₃SiCl produces a complicated mixture. Separation of the mixture by preparative liquid chromatography gives the desired product, the starting aldehyde, and compound L. It was proposed that this transformation proceeds through a tautomeric form of one of the furan rings.
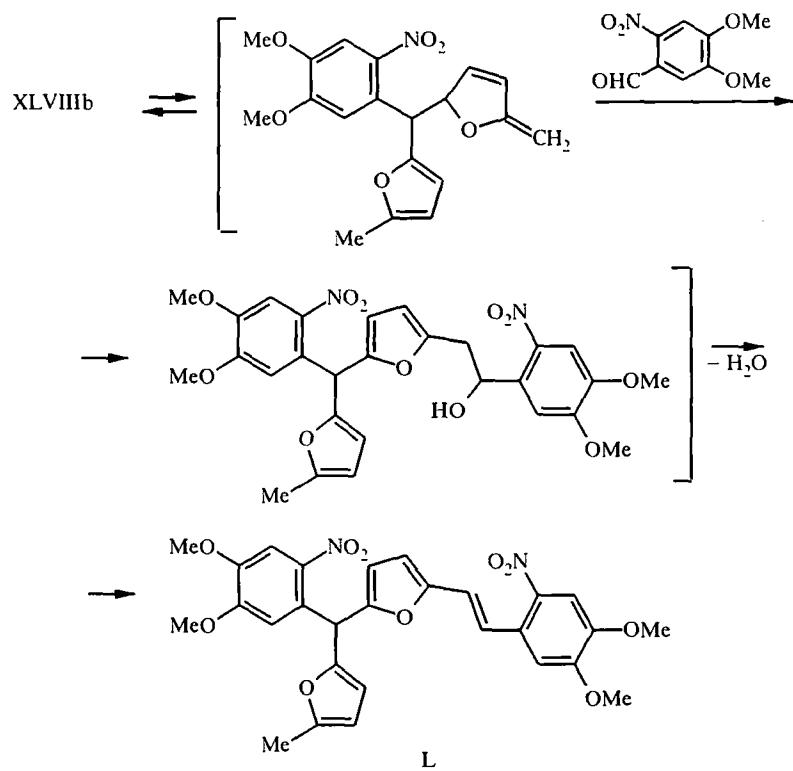
It was noted that lithiation of difurylalkanes is variable. Thus, treatment of 2,2-difurylpropane with butyllithium lithiates the furan rings in the 5-position [146] whereas lithiation of the central carbon atom occurs for difurylmethane under analogous conditions [4].

3. PRACTICAL APPLICATION OF FURYL(ARYL)METHANES

The use of furyl(aryl)methanes in the production and modification of polymeric materials is very important. These compounds are used as monomers to synthesize polyurethanes [147-152] and polyacylsemicarbazides [153, 154], as plastifiers of polyvinyl chloride [155, 156], as binders for the production of block-polymers [157], and as linkers for polyamide and epoxide resins [158]. Such interest in these compounds is in turn related to the ability to synthesize them from furfuryl alcohol, a product obtained from an annually renewable

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resource (agricultural wastes) and not from petroleum. This makes polymers based on difurylalkanes insensitive to fluctuations in the price of oil and reduces their cost. However, it should be noted that the physicochemical properties of the polymers are not degraded by replacing the traditional oligomers and monomers by the furan analogs despite the cheaper production [159-161]. The furyl(aryl)methanes are also interesting in the chemistry of synthetic dyes [162] and in copying technology [163].

The practically useful properties of compounds containing the difurylalkane moiety are not constrained by the technology. It has been reported [90] that difurylmethanes occur in the volatile components of roasted coffee. This was confirmed using model reactions [164]. Furthermore, difurylalkanes are found among the numerous components contributing to the flavor and aroma of caramel [165, 166], rum [167], and licorice [168]. Difurylmethane derivatives have been detected in condensed cigarette smoke [91] and among the volatile products formed during preparation of certain foods [169]. This makes them interesting to the food industry.

Certain difurylmethane derivatives possess insecticidal [170-172] and acaricidal [172] properties and exhibit antimutagenic [173] and tuberculostatic [174] activity.

CONCLUSION

The present review documents the importance of and prospects for the chemistry of furyl(aryl)methanes and enables further study of these compounds to be predicted. The structural peculiarities determine the different reaction transformations of furylalkanes. One of the most interesting routes is the opening of the furan ring that occurs *via* various mechanisms and is very interesting for synthesis of new carbo- and heterocyclic systems based on polyfuryl(aryl)alkanes.

Thus, furyl(aryl)methanes will be the subject of future research that will eventually enable a more complete understanding of this interesting class of compounds to be formulated and will make it possible to devise simple methods for preparation of previously inaccessible compounds based on them.

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