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METHODS FOR THE SYNTHESIS OF BENZOFURAN DERIVATIVES (REVIEW)

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Data published in the last 15 years on methods for the construction of the benzofuran ring are reviewed. The mechanisms of the reactions and their use in the synthesis of biologically active substances are discussed.

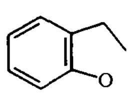
In their structural diversity and in the extent to which they occur in nature the derivatives of benzofuran are significantly inferior both to the isoelectronic analog indole and to chroman. The broad spectrum of pharmacological activity in individual benzofurans indicates that the search for new biologically active compounds in this series of compounds is of undoubted interest. From this standpoint synthetic methods may be of invaluable assistance in the production of specific structures characterized by given pharmacological qualities.

All the known methods for the synthesis of benzofurans can be arranged into two groups. The first group involves the formation of an annellated heterocyclic ring (in this case furan) by the intramolecular cyclization of benzene derivatives. Methods of the second group are encountered more rarely and involve the creation of an annellated carbocyclic ring.

In some cases benzofuran derivatives are obtained more conveniently from other bi- or tricyclic structures [1].

METHODS FOR THE SYNTHESIS OF BENZOFURAN DERIVATIVES BASED ON CONSTRUCTION OF THE HETEROCYCLE

Methods are known for the synthesis of benzofurans by the construction of the furan ring according to one of the following four possible types:



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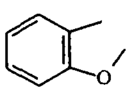

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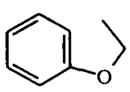

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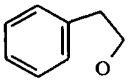

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Of these the first three have been used for a long time [2]. The fourth, involving the formation of a bond between the oxygen and the aryl carbon, was only proposed recently [3].

Syntheses of Type 1

All the condensation methods involve the formation of a C–O bond, i.e., are of the first type. The starting compounds are *ortho*-substituted phenols. Substituents at the *ortho* position must contain an electron-deficient β-carbon atom, which is the structural unit of some unsaturated fragment or is attached to an atom characterized by a sufficiently strong M effect. The sim-

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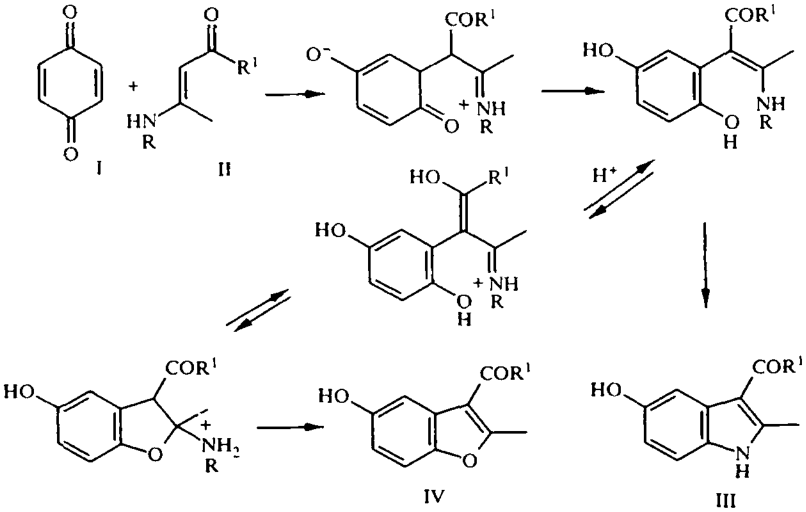
plest and most obvious example of such a reaction is the cyclodehydrogenation of 2-styrylphenol with the formation of 2-phenylbenzofuran [4].

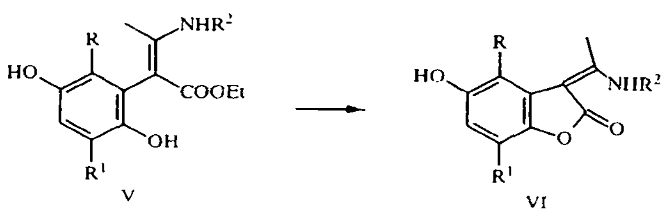
Among known methods of the first group attention is drawn to the Nenitzescu method, which involves Michael condensation of quinones with enamines followed by cyclization [5-9]. The ease of varying the structures of the initial enamines makes it possible to extend the range of target compounds considerably, and this is extremely useful in the synthesis of biologically active compounds [10-15]. In addition to substituted quinones it is also possible to use arenesulfonamides as starting compounds [16]. The reaction can take place in two or more alternative directions under the same conditions. Benzofuran and indole derivatives can be obtained depending on the structure of the enamine, and the proportion of the benzofuran derivative increases in the transition from N-alkyl- to N-aryleneamines [12].

The condensation of the quinone (I) and enamine (II) in nitromethane gives the indole derivative (III). In an acidic medium, however, the adduct is protonated at the nitrogen atom, as a result of which the only one nucleophile — oxygen — remains. Closure of a furan (IV) and not a pyrrole ring therefore occurs [17].



The effect of the nature of the solvent on the direction of the process is observed in the case of the reaction of 2-acetyl-1,4-benzoquinone with an enamine in acetic anhydride and in toluene [18]; in the first case 4-acetyl-5-hydroxy-2-methylbenzofuran is obtained, and in the second its 2,3-saturated analog is obtained.

If the initial enaminohydroquinone (V) contains bulky substituents in the benzene ring and at the nitrogen atom, in an acidic medium (acetic acid, sulfuric acid) a butyrolactone ring (VI), not a furan ring, is formed. This is explained by a decrease in the rate of acid hydrolysis of the enamines on account of the steric inhibition of enamine conjugation [19] in the presence of strong acids.

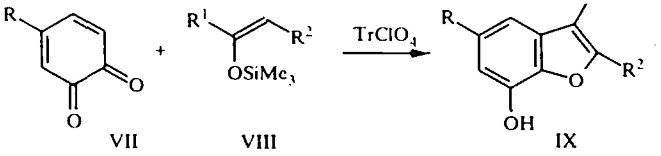


In the reaction of quinones with the morpholine enamine of benzyl methyl ketone the reaction takes place exclusively at the methyl group with the formation of 2-benzylbenzofuran [20].

The production of 3-benzofuryl phenyl ketone as a result of the introduction of 1-benzyl-2-dimethylamino-1-propene into the Nenitzescu reaction has been described [12, 21].

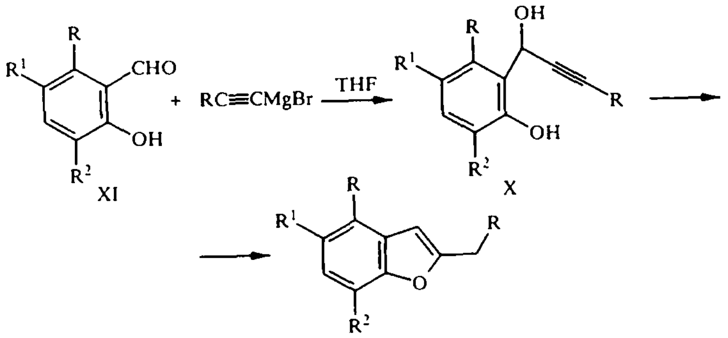
There are data indicating that 1,2-benzoquinone (VII) also enters into an addition reaction [8, 22] with derivatives of trimethylsilyloxyethylene (VIII) to form 7-hydroxybenzofuran (XI).

In order to avoid the formation of a mixture of five- and six-membered benzo heterocycles the initial 2-hydroxyaryl 2-methylpropenyl ketone was iodinated in the presence of silver acetate or mercuric oxide [23], leading to 3-hydroxy-2-(2-iodo-2-methylethyl)benzofurans. A similar mechanism with the concurrent formation of benzofuran and coumarin was also observed in the Wittig reaction [24, 25]. The condensation of salicylaldehyde with isocyanide [26] to produce 2-aminobenzofuran can also be included here.

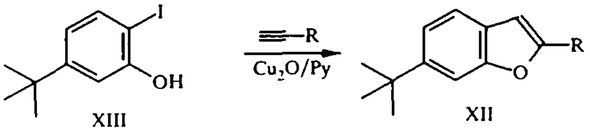


R^1 = Ph,CH_2Ph; R^2 = Me,Ph

Similarly, the ethynyl-substituted analogs and particularly 3-(2-hydroxyphenyl)-1-propyn-3-ol (X) [27], obtained by the reaction of salicylaldehyde (XI) with the Iotsich reagent, undergo cyclization to benzofuran derivatives.



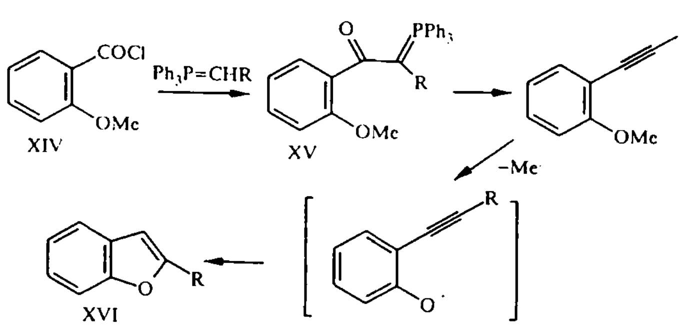
The synthesis of 2-substituted benzofurans (XII) [28-31] from 2-halogenophenols (XIII) and various acetylides, formed in the reaction mixture after the addition of copper(I) acetylide and oxide in nitrogen [32], has also found widespread use as a preparative method.



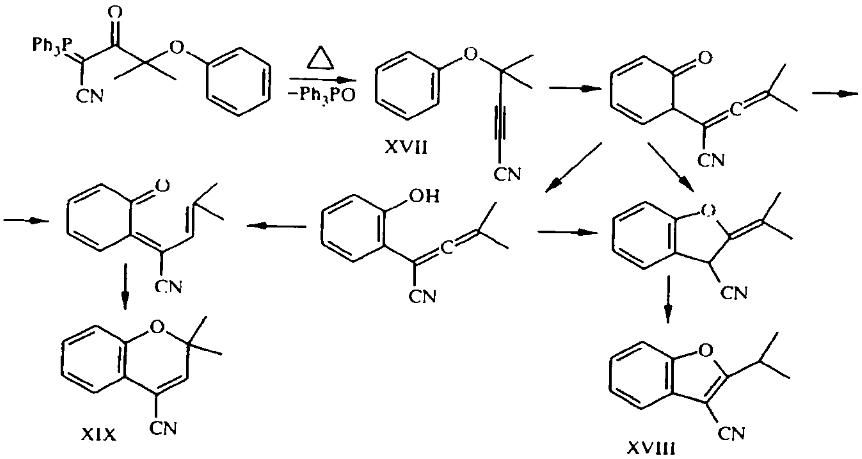
Here it is possible to use various palladium-containing catalysts [33-36], lithium chloride [37], and also a phase-transfer catalyst (tetrabutylammonium chloride) [33, 37]. Unfortunately the conditions of the method do not make it possible to obtain the 3-substituted derivatives. It should be noted that the course of the reaction is not affected by substituents at any other positions. The method has been used in the synthesis of egonol [38]. By using the corresponding derivatives of aniline it is possible by this method to obtain derivatives of indole or 3-phenylcinnoline [36], and from 2-ethynylmethylphenol it is possible to obtain derivatives of chroman, etc. [34].

The aminals of aromatic 2-hydroxyaldehydes react with acetylene derivatives when heated and form 2-vinylidene-3-aminobenzofurans [39]. The intramolecular cyclization of 2-methoxy-1-propargylbenzene in trimethylpyridine in the presence of lithium iodide takes place by a similar mechanism [40]. A similar reaction occurs during the photochemical decarboxylation of diarylcyclopropenone [31]. As a rule, however, a mixture of 2-phenylethynylphenol and the expected cyclization production (2-phenylbenzofuran) is formed.

In the synthesis described above the initial acetylene derivatives are often obtained by the Wittig reaction in the reaction of 2-methoxybenzoyl chloride (XIV) with methyltriphenylphosphorane [41] followed by vacuum pyrolysis of the intermediate β-ylide (XV), which is then converted into the benzofuran (XVI). The authors suggest that radical substitution occurs.

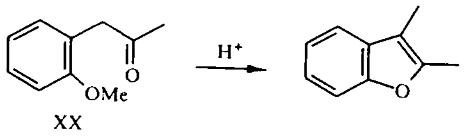


Aryl propargyl ethers (XVII) were used to obtain benzofurans by means of the Wittig reaction [24, 25, 42]. In this case both allylic carbons are identically electron-deficient, and the benzopyran (XIX) is therefore formed in addition to the benzofuran (XVIII).



7-Allyl-2-methylbenzofuran was obtained from phenyl 2-(2-propenylphenyl)isopropenethiolate by the Claisen rearrangement [43].

Apart from phenols containing unsaturated substituents, as indicated above, carbonyl and hydroxyl derivatives can also enter into reactions leading to the formation of a benzofuran ring [44]. For example, the cyclization of derivatives of 2-methoxyphenyl-2-propanone (XX) by the action of Lewis acids (boron tribromide in methylene chloride [45-47]), phenyl 2-R-hydroxybenzyl ketone in HCl [48], or phenoxypropiophenone in PPA [49] and the condensation of 2-hydroxyethylphenol with ethyl 4-hydroxybenzoate with boiling in an alcohol solution of HCl [44] also lead to benzofuran. Typical nucleophilic attack by the polarized carbon of the carbonyl group occurs, leading to the formation of a C–O bond.

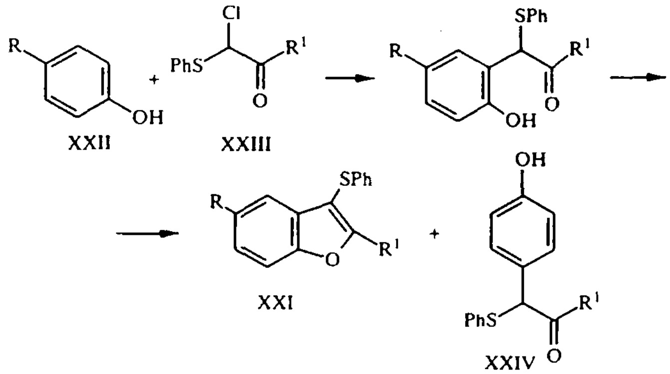


XX

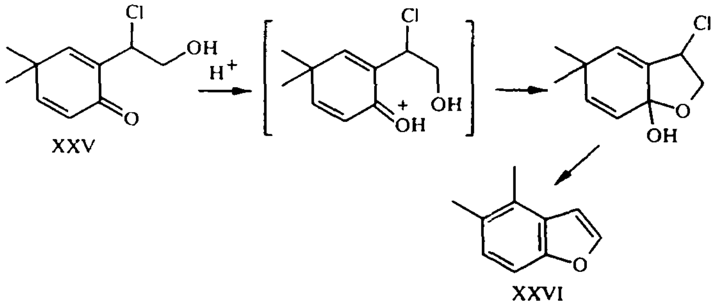
The rate of this reaction is increased if 2-acylbenzyl tetramethylphosphoramidate, for example, and not the methyl-substituted phenol is used [50]. The phosphorus-containing residue is clearly eliminated more readily than the methyl cation.

In the reaction of 4-methoxyphenol with 2-acetyl-2-chloroacetic acid [51] in the presence of sulfuric acid the carbonyl carbon combines with the aryl at the first stage, and the even less electron-deficient tertiary carbon then reacts with the oxygen to form 5-methoxyfuran-2-carboxylate. This type of reaction is convenient for the synthesis of biologically active compounds — derivatives of benzofuran-2-carboxylic acid from the corresponding keto acids [52] or diaryl-substituted analogs [53].

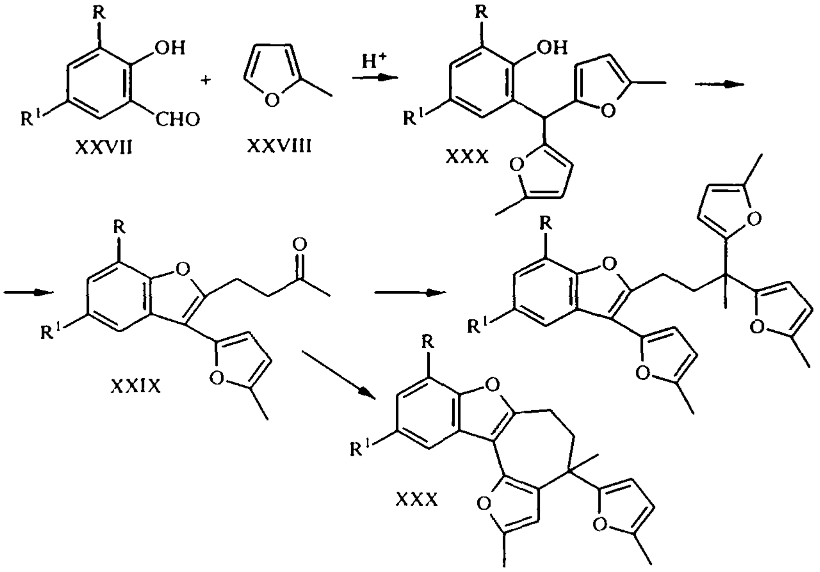
The initial 2-hydroxyacetophenones for the synthesis of the benzofurans (XXI) can be obtained as a result of the condensation of phenols (XXII) with substituted phenylthiochloro ketones (XXIII) in the presence of Lewís acids [54]. If R = H, a small amount of the *p* isomer (XXIV) is formed in addition to the main product. The thiophenol group is easily removed by the action of Raney nickel.



The internal cyclization of the cyclohexadienone derivative (XXV) in an acidic medium leads to closure of the benzofuran ring (XXVI) [55].



The pinacone reduction of salicylaldehyde results in the formation of *trans*-1,2-di(2-hydroxyphenyl)ethylene glycol [56]. The latter then undergoes a pinacoline rearrangement, leading to the production of benzofurylbenzofurans, 2-(2-hydroxyphenyl)-2,3-dihydrobenzofuran, and 2-(2-hydroxyphenyl)benzofuran in ratios depending on the temperature conditions.



Among the condensation methods it is also possible to include the unique reaction of salicylaldehydes (XXVII) with 2-methylfuran (XXVIII) in an acidic medium [57-59], which results in the formation of a series of products, including 3-furylbenzofuran (XXIX). It is possible to increase the yield of one or the other product to quantitative by changing the reaction conditions. It is noteworthy that this method is one of the few methods that make it possible to easily obtain 3-heteroaryl-substituted derivatives.

The methods for the production of hydroxyphenyldifurylmethanes (XXX) [60, 61] and their structural analogs [62] under conditions identical with those described above are quite laborious, and none of them can be regarded as a possible method for the synthesis of benzofurans [63].

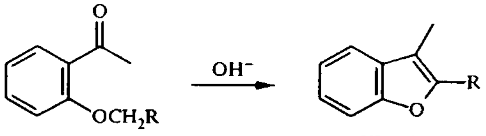
Alkaline condensation, the mechanism of which has been studied fairly well, is rarely used. 2-Phenylbenzofuran is obtained in the reaction, for example, of substituted salicylaldehyde with methyl 2-bromo-2-phenylacetate [64]. 3-Benzofuranone, which then changes into 2,3-disubstituted benzofuran, is formed from 2-hydroxyphenacyl chloride by boiling in alcohol with sodium acetate [65]. Cyclohexane-1,3-dione reacts similarly with ethyl 3-bromo-2-oxopropionate [66].

Diacetoxyiodobenzene substitutes the methylene proton in α-benzoyl-2-hydroxyacetophenone [67], thereby promoting the formation of 2-benzoyl-3-hydroxybenzofuran. The cyclization of 2-alkoxycinnamic acids leads to 2,3-dihydrobenzofuran-3-acetic acid [68].

Thus, the most important condition for the production of benzenes by intramolecular cyclization of *ortho*-substituted phenols is the presence of a substituent containing an electron-deficient β-carbon atom. This restricts the use of this type of synthesis for the production of 2(3)-substituted benzofurans on account of the possibility of deactivation of the attacking center.

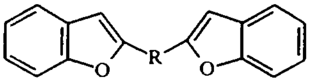
Syntheses of Type 2

Various types of intramolecular cyclization of 2-alkoxyacetophenones (XXXI), leading to 2-R-3-methylbenzofurans (XXXII), have been described. Sodium and potassium alcoholates [69, 70-73] or alkalis [74-76] in polar solvents [77, 78] have been used as condensing agents.



XXXI XXXII

Derivatives in which two benzofuran rings are linked to each other were obtained by this method [79-82].



R = bond, alkylene, carboxy, phenyl, naphthyl, heteroaryl, etc.

During the alkaline condensation of salicylaldehyde with 1,3-dichloroacetone in dioxane the di(2-formylphenoxy)acetone that forms is easily transformed into bisbenzofuryl ketone [83].

Cyclization is often preceded by Perkin condensation of the substituted benzaldehydes with methylene-active compounds [74, 84-87]. However, the use of this method in the synthesis of biologically active compounds is limited by the range of substituents that can be introduced into the furan ring [88].

The cyclization of 2-chloromethoxyphenylcarbonyl chloride or methyl 2-ethoxycarbonylphenoxyacetate [89] in the presence of triethylamine can be considered a modification of the method described above. It should be noted that a ketone is formed initially and then enters into characteristic [2 + 2]-cycloaddition, leading to the heterocycle [84, 90, 91].

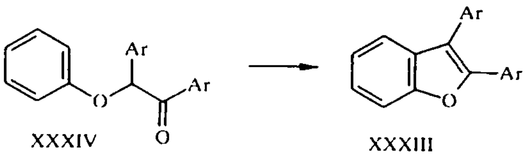
However, the reaction can lead to the formation of a whole series of products [92]. Thus, the cyclization of 2-(4-acetylphenoxy)acetic acid in dioxane gives 2,3-dihydrobenzofuran [73] and 2,3,4,5-tetrahydro-1-benzoxepin-3,5-dione in addition to the main compound. It was established that the yield of the latter was substantially increased when there were electron-donating substituents in the benzene ring, whereas accepting substituents favored the formation of the benzofuran. This reaction can also be realized under the conditions of acid catalysis [75, 85], as shown by the production of 3-methyl-2-phenylbenzofuran [93] by the cyclization of 2-acetylphenoxyphenyl ketone in the presence of titanium tetrachloride. The process can also take place by a radical mechanism, which is confirmed by the production of 3-aryl-2-vinylbenzofuran from the 1,5-biradicals generated during the irradiation of allyloxybenzylbenzene [94].

Carbonyl compounds [79, 81, 95, 96] and also the corresponding aryl cyanides [97], i.e., any compounds containing substituents with an electron-deficient α-carbon atom at the *ortho* position to the alkoxy group, can be used for the synthesis of benzofurans by this method.

By using this type of method it is possible to introduce any substituents into the benzene ring and at position 2 of the benzofuran ring.

Syntheses of Type 3

The intramolecular cyclization of 2-aryloxy-1,2-diarylethanol (XXXIV) [98] or other activated alkoxybenzenes [99] by heating in the presence of catalytic amounts of polyphosphoric acid can be used for the production of benzofurans with aromatic substituents at $C_{(2)}$ or $C_{(3)}$ (XXXIII).

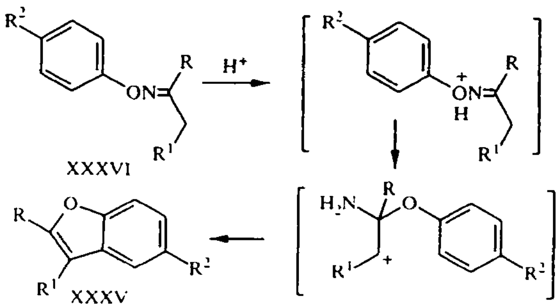


Two reaction mechanisms are possible, depending on the nature of the substituents: 1) direct electrophilic substitution; 2) cleavage of the initial compound with the formation of an acylcarbenium ion, which then attacks the carbon atom with closure of the furan ring.

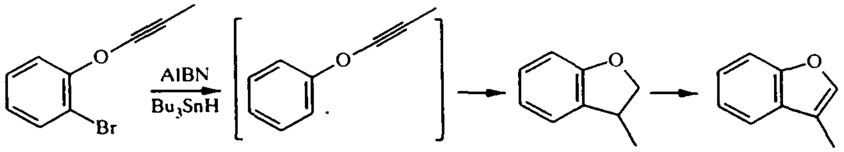
The method is convenient in that it is in practice possible to obtain benzofurans with any given substituents in the furan and, especially, in the benzene rings [100, 101]. In addition, it is one of the few methods that have been used successfully for the synthesis of biologically active heterocyclic derivatives of carboxylic acids. For instance, benzofuran-2-acetic acid [102], which is an inhibitor of the biosynthesis of leukotrienes, is obtained as a result of the cyclization of ethyl 3-oxo-2-phenoxybutyrate.

In the presence of thionyl chloride with the subsequent addition of aluminum chloride 2-(3,4-dichloro-5-methoxy)phenoxypentanoic acid rearranges to 4,5-dichloro-6-methoxy-3-oxo-2-propylbenzofuran [100].

The formation of the benzofurans (XXXV) by the cyclization of the O-aryloximes (XXXVI) by the mechanism of the Beckmann rearrangement is somewhat different. This process leads to the formation of a C–C bond with the participation of aliphatic and aromatic carbon atoms. Hydrochloric acid [103, 104] or sulfuric acid [105] in alcohol, DMSO, tetrahydrofuran [106], and others [107] have been used as acidic catalysts. As a result of the *anti* rearrangement the nitrogen atom adds a proton, and this leads to the formation of an electron-deficient center, thereby creating favorable conditions for ring closure.

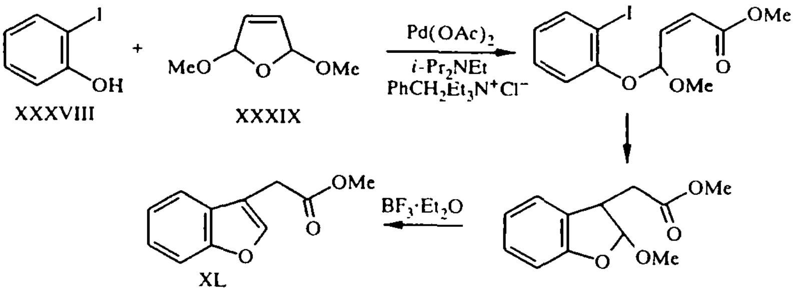


The bond between the alkyl and aryl carbon atoms is formed as a result of the intramolecular cyclization of 2-bromoethynyloxybenzene (XXXVII), 2-bromovinyloxybenzene [108], or benzoylmethylbenzenes [109] by a radical mechanism. Thus, during prolonged boiling in the presence of azoisobutyronitrile (AIBN) and tributylstannane the aryl radicals that form react with the ethynyl carbon atom.



XXXVII

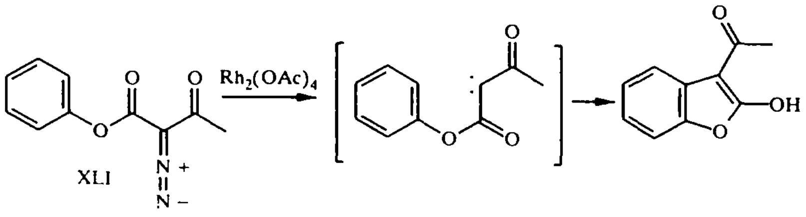
The product from the condensation of 2-iodophenol (XXXVIII) with 2,5-dimethoxy-2,5-dihydrofuran (XXXIX) also undergoes rearrangement to the corresponding benzofuran (XL) [110].



XXXVIII XXXIX XL

The intermediately formed carbenium ions [111] are often used for the synthesis of benzofuran derivatives, as illustrated for example by the production of 2,3-diphenylbenzofuran by the condensation of 4-methoxyphenyl 4-methoxyphenylchloromethyl ketone with 4-methoxyphenol [112]. The controlling stage of the process is the formation of the α-acylcarbenium ion as a result of the elimination of a chlorine atom. In the presence of potassium carbonate the conversion of the initial compounds remains low, and this is explained by neutralization of the hydrochloric acid released during condensation, which catalyzes the process. If resorcinol is used instead of phenol, furobenzofuran is formed. In another case the carbene is generated from the respective diazo compound (XLI) [111] in the presence of rhodium acetate, which unambiguously controls the direction of internal cyclization.

Modifications of the methods of synthesis corresponding to third type of reaction:



XLI

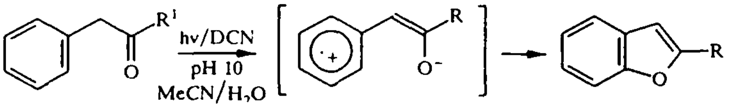
mostly take place by the S_E mechanism. As seen, there is a certain analogy with reactions of type 1, where the attacking particle is also an electron-deficient carbon.

Syntheses of type 3 have not found widespread use in laboratory practice on account of the use of relatively uncommon reagents.

Syntheses of Type 4

A distinctive feature of reactions of type 4 is the fact that the furan ring is formed through the formation of a bond between the oxygen and an aryl carbon.

During irradiation by a mercury lamp in the presence of 1,4-dicyanonaphthalene (DCN) [3] benzyl ketones (XLII) change into an intermediate radical, which is then transformed into the corresponding benzofuran (XLIII). Closure of the furan ring is preceded by intramolecular attack by the carbonyl oxygen. It should be noted that an attempt to use alkylbenzylcarbinols as starting compounds did not lead to the expected result.



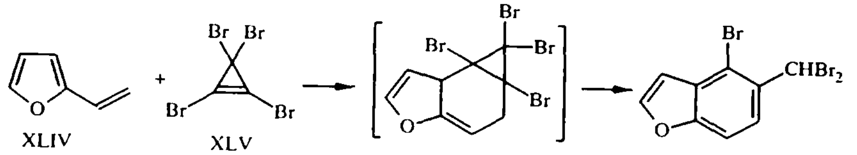
XLII XLIII

The 2-bromine-substituted analogs of the ketones (XLII) are also transformed into benzofuran through the formation of an organocopper compound [113]. It is clear that the synthons for this reaction can only be derivatives of benzyl ketone with sufficient electron deficiency at the *ortho* position of the aromatic ring, and this restricts the use of the method in laboratory practice.

METHODS FOR THE SYNTHESIS OF BENZOFURAN DERIVATIVES BASED ON CONSTRUCTION OF THE BENZENE RING

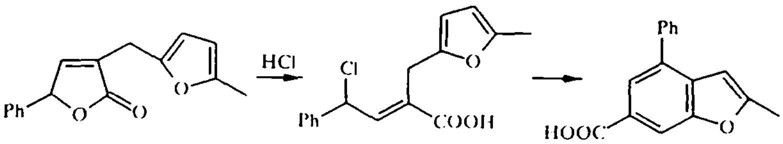
Methods for the synthesis of benzofurans based on furan derivatives are not marked by their diversity and amount to two types of reaction, i.e., Diels–Alder cycloaddition and S_E reactions.

The diene in the Diels–Alder cycloaddition [114, 115] was 2-vinylfuran (XLVI). The dienophiles can be both aliphatic (derivatives of ethylene or acrylic acid) [115] and alicyclic [in particular, derivatives of cyclopropene (XLV) [114].



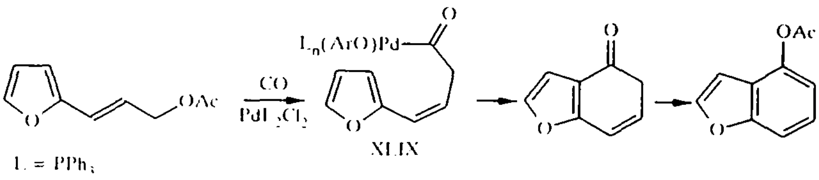
XLIV XLV

From α-substituted furans it is possible to obtain the corresponding benzofurans as a result of an intramolecular S_E reaction. An example is the cyclization of 2-(5-methyl-2-furylmethyl)-4-chloro-4-phenylcrotonic acid (XLVI), leading to 2-methyl-4-phenylbenzofuran-6-carboxylic acid (XLVII) [116]. The intermediate for the reaction is obtained from the corresponding lactone (XLVIII).



XLVIII XLVI XLVII

A method for the synthesis of benzofurans from 3(2)-(2-furyl)allyl acetates (XLIX) was described [117]. At the first stage the initial compound undergoes carbonylation, catalyzed by dichlorobis(triphenylphosphine)palladium, and at the second stage the carbonyl carbon attacks the β position of the heterocycle with subsequent cyclization. The position of the substituent in the furan ring does not affect the formation of the C–C bond.



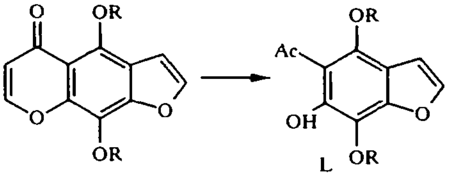
XLIX

It should be noted that furan derivatives are less readily available than aromatic compounds. In addition, there are more preparative methods for the construction of heterocycles than benzene compounds. As a result the methods for the production of benzofurans based on the construction of the aryl ring are significantly less widespread than the syntheses examined in the previous section.

METHODS FOR THE SYNTHESIS OF BENZOFURAN DERIVATIVES BASED ON THE TRANSFORMATIONS OF BI- OR TRICYCLIC OXYGEN-CONTAINING RINGS

Methods for the production of benzofurans from condensed systems were examined separately. On account of the relative shortage of the starting compounds and also the low yields of the desired products they are not of preparative significance.

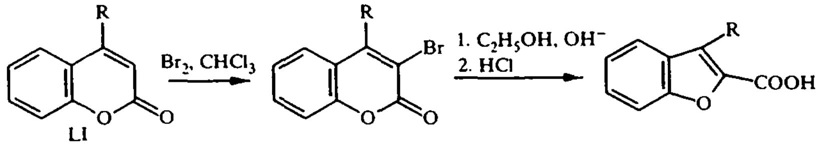
It is possible to obtain a benzofuran from the respective substituted furochromone by the action of alkali [118]. 5-Acyl-6-hydroxybenzofurans (L) can often be formed in such cases [119].



L

Psoralene is hydrolyzed to 3-(6-hydroxy-5-benzofuranyl)acrylic acid [120]. The unstable product 5-formyl-6-hydroxybenzofuran was isolated by the photolysis of furocoumarin [121]. The reaction of the respective aromatic aldehyde with kellinone in an alcohol solution of alkali resulted in the isolation of 3-aryl(pyridyl)benzofurans [122]. Unfortunately, however, the method cannot be used as a preparative method for the synthesis of 3-heteroaryl derivatives. The hydrazones of aromatic aldehydes also react with furobenzopyrans with the formation of 5-(N-heteroaryl)benzofuran [123].

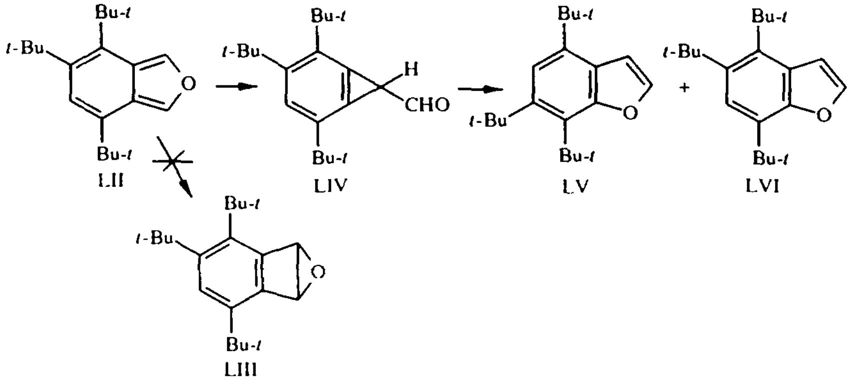
The coumarins (LI) or benzopyranones can be used as synthons for the production of benzofurans by the Fittig–Ebert–Perkin reaction [1, 124, 125] or by pyrolysis [126].



LI

3-Bromocoumarin behaves similarly to psoralene in an alkaline medium; cleavage of the C–O bond results in rearrangement to the corresponding acid, which is then transformed into the benzofuran [125]. In an acidic medium in the presence of an oxidant (hydrogen peroxide) a benzopyrylium salt undergoes recyclization to benzofuran [127].

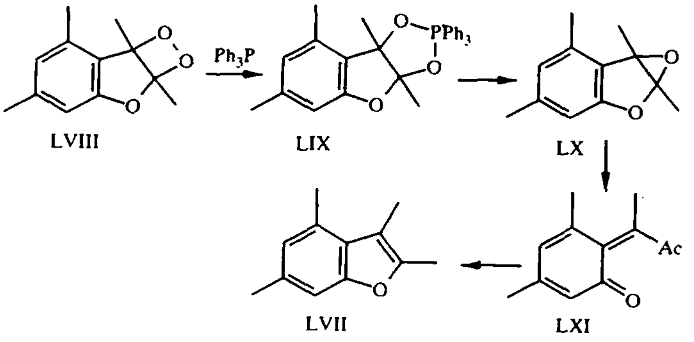
The synthon for the production of benzofuran may also be isobenzofuran (LII) [128], which contrary to expectations was converted as a result of irradiation by a high-pressure mercury lamp not into compound (LIII) but into (3,4,6-tri-*tert*-butylbenzo)cyclopropene-3-carbaldehyde (LIV). The latter in turn rearranged into a mixture of benzofurans (LV + LVI).



LII LIV LV LVI

LIII

The production of the benzofuran (LVII) from dioxetane through successive stages involving the intermediate phosphadioxolane (LIX), epoxide (LX), and quinonemethide (LXI), the structures of which were confirmed by an alternative synthesis with oxidation of the final product, is worth mentioning. The method could in principle be assigned to the type of reaction involving the formation of a furan ring as a result of the formation of a C–O bond.



In summarizing the data presented in the present review it is possible to reach the following conclusions: 1) preparative methods include methods for the synthesis of benzofuran derivatives based on construction of the heteroaryl ring; 2) the most convenient are the methods for the synthesis of benzofurans based on *ortho*-substituted phenols (2-iodophenol, ethers of 2-hydroxybenzyl ketone, alkoxyacetophenone, salicylaldehyde) and also by the Nenitzescu reaction; this approach is convenient due to the possibility of varying the substituents in the benzene ring; 3) the dehydrogenation of the 2,3-saturated analogs of benzofurans or the reduction of benzofuranone, which are often intermediate compounds in the synthesis of benzofurans from benzene compounds, lead to derivatives of benzofuran; 4) there are restrictions with the introduction of substituents into the furan ring, due to features of the cyclization mechanisms; the most favorable from this point of view is the method for the synthesis of benzofurans from derivatives of 2-aryloxyethanone; 5) the Nenitzescu reaction is suitable for the production of 5-hydroxybenzofuran derivatives, but the choice of target structures is limited by the dependence of the products on the nature of the solvent; 6) a promising method for the synthesis of benzofurans is the condensation of derivatives of salicylaldehyde and sylvane, the availability of which makes it possible to extend considerably the range of final products by the appropriate choice of starting compounds and by varying the reaction conditions.

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