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Annelation of furan rings to arenes

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Benzo[*b*]furans have been used in various fields of chemistry and technology due to their unique physical, chemical and biological properties. It is primarily a wide range of biological activities of natural and synthetic benzo[*b*]furan derivatives and their polyfused analogues (naphthofurans, anthrafurans, *etc*.) that attracts a significant scientific interest in the context of using these heterocycles as privileged scaffolds in drug design. This survey covers those methods for the annelation of a furan ring to arenes that have been developed mostly during the last decade. We also analyze trends in synthetic methods of benzo[*b*]furans. Some synthetic schemes are highly efficient in the synthesis of polyfunctionalized furan derivatives.
The bibliography includes 110 references.

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I. Introduction

Development and improvement of synthetic methods for the preparation of heteroaromatic systems is one of the most rapidly progressing areas of today's organic chemistry.[1] Approaches based on highly selective and economical catalytic heterocyclization reactions now acquire the greatest value.[2]

Benzo[*b*]furan and its fused analogues, such as naphtho[*b*]furan and anthra[*b*]furan, have long been the subjects of research for heterocyclic chemists. Furan-containing aromatic systems have been demanded in various fields of chemistry and technology due to their diversified reactivities, unique photo- and physicochemical properties and high biological activities.[3]

Recent years have seen a splash of interest in fused furan derivatives, which are widely used primarily in medicinal chemistry for drug design.[4–9] The high interest in these compounds is, to a great deal, due to a wide range of biological activities of natural and synthetic benzo[*b*]furans and their analogues, including anti-inflammatory, fungicidal, anti-arrhythmic, antitumour and other activities.[4–8] Plants have been found to contain great amounts of neolignans containing benzofuran moieties, some of them serving as a biologically active base of drugs used in conventional medicine. For example, cicerfuran (**1**), which was derived from the roots of leguminous (*Cicer bijugum*) plants, has fungicidal activity.[10] Extracts of *Zanthoxylum ailanthoides* tree plants contain ailanthoidol (**2**), which has anticancer, antioxidant and anti-inflammatory properties.[11] Moracines M (**3**) and C (**4**), which also have an anti-inflammatory effect and high antibacterial activity, were isolated from the bark and roots of some mulberry (*Morus alba*) species.[12] Caleprunin A (**5**) and similar 2-acetylbenzo[*b*]furans, which exhibit psychoactive and antipyretic effects, were derived from *Calea prunifolia* flowering plants.[13]

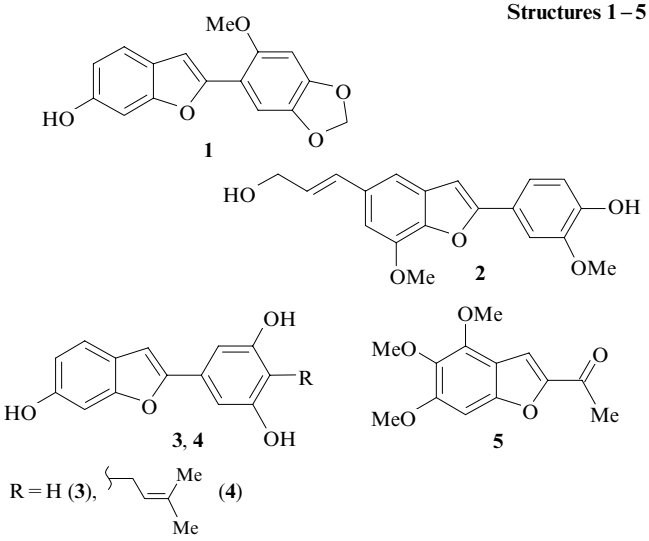
Some pharmaceuticals based on synthetic benzo[*b*]furan derivatives were recommended for use in clinical practices. Among the drugs, we can mention amiodarone (**6**) and

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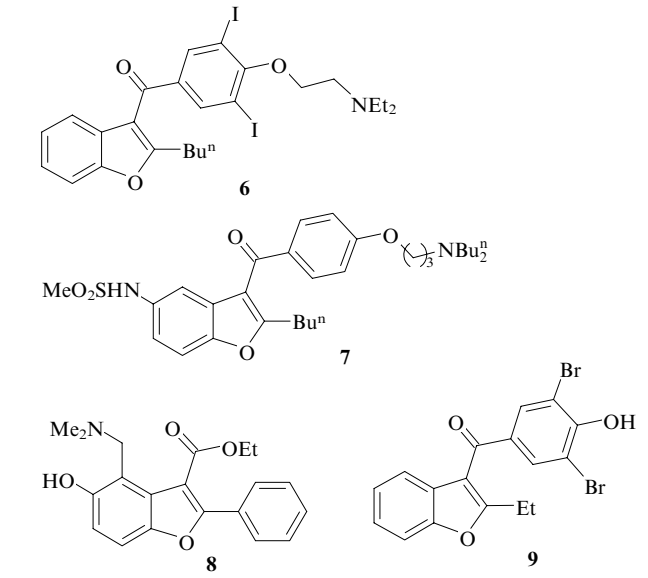
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Structures 1–5



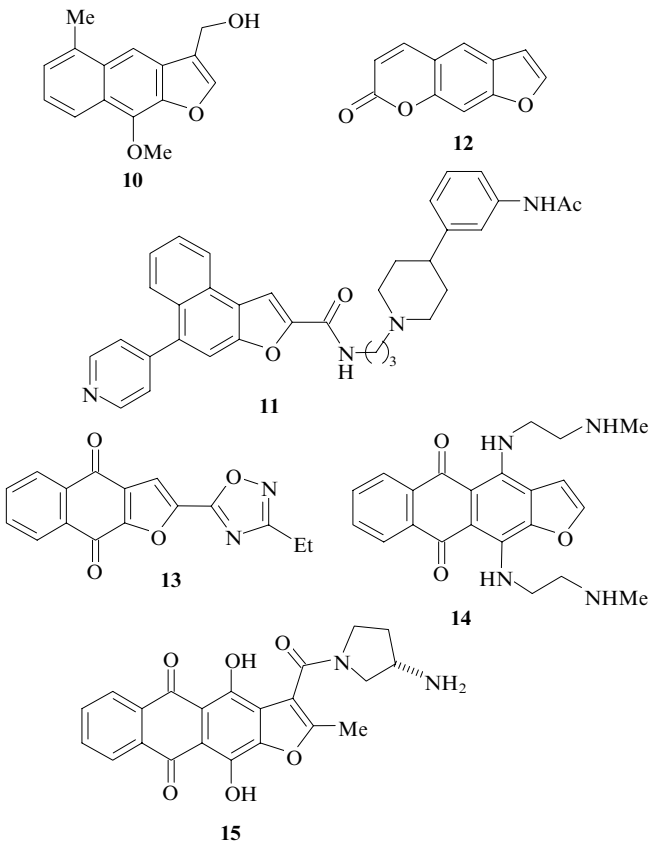
dronedarone (**7**), which are antiarrhythmic agents;[14] phanicaberan (**8**), which is an antispasmodic;[15] and benzbromaron (**9**), a hyperuricemic agent for treating gout.[16]

Structures 6–9



Fused benzo[*b*]furans also have a high pharmacological potential. Furanoeremophilane analogues (exemplified by compound **10**), for example, show antioxidant and antibacterial activities.[17] Functionalized naphtho[2,1-*b*]furan-2-carboxamide **11** is an effective antagonist for a melanin-concentrating hormone receptor [with half-inhibitory concentration (IC_{50}) of 10 nmol litre^{-1}] and can serve to develop agents against obesity, anxiety and depression.[18] Fused furanocoumarins, *e.g.*, psoralen (**12**), have photodynamic activities and are used in the treatment of skin diseases (vitiligo and psoriasis).[19,20] Naphtho[2,3-*b*]furan-4,9-dione derivative **13** suppresses keratinocyte hyperproliferation due to the generation of superoxide radicals and the subsequent destruction of the mitochondria.[21] In the series of 4,11-diaminoanthra[2,3-*b*]furan-5,10-dione **14** analogues, there are highly active inhibitors of topoisomerases 1 and 2 (Ref. 22) and inhibitors of SIRT1 and tNOX enzymes, which have high cytotoxicity, specifically against resistant tumour cell lines.[23,24] Of special interest are anthra[2,3-*b*]furan-5,10-dione-3-carboxamide derivatives with their antitumour activities.[25] Compound (**15**), the leader of this series, succeeded in advanced preclinical trials to be qualified for phase 1 clinical trials.

Structures 10–15



Thus, benzo[*b*]furan derivatives and their (poly)fused analogues are extensively studied as a chemical class promising for drug design. An overview and systematization of the available documents on furan ring annelation methods are in great demand for the development of new synthetic schemes, and they stipulate progress in a targeted search for biologically active furan-containing fused systems.

The relevant documents published during the last three or four decades have in part been overviewed.[26,27] These review articles comprise the description of methods for preparing and modifying furan, benzo[*b*]furan and benzo[*c*]-furan derivatives, and selected synthetic schemes for naphtho[*b*]furan derivatives.[28] However, review by Kwiecie *et al.*[26] is the only one concerned with the preparation of benzo[*b*]furan derivatives and, although published rather recently, mostly focuses on documents published before 2005. An inspection of publications issued during the last 5–7 years shows that the potential of synthetic routes to benzo[b]furan derivatives and their fused analogues have been enhanced significantly just in recent years. Further, the mentioned review[26] lacks information on some important heterocyclization reactions.

The focus of our review is on the documents concerning the annelation of furan ring to aromatic rings that appeared during the last decade. The heterocyclization reactions producing a furan moiety are classified here according to

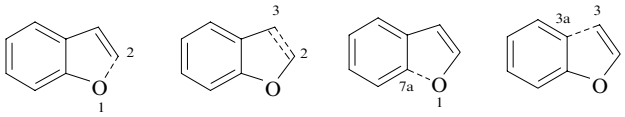


Figure 1. Types of benzo[*b*]furan bonds formed upon heterocyclization (shown by dashed lines).

the type of newly formed bond: O – C(2), C(2) – C(3), C(7a) – O and C(3) – C(3a) (Fig. 1).

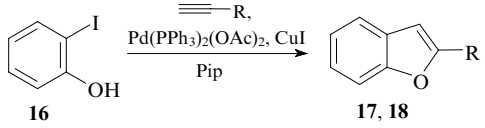
II. Heterocyclization to generate O – C(2) bond of benzo[*b*]furans

The intramolecular addition of an oxygen atom to the double or triple carbon – carbon bond is the underlying idea of most efficient preparative schemes for preparing benzo[*b*]furans. Synthetic approaches to the generation of O – C(2) bond of the furan ring are rather extensive. For example, *o*-alkynylphenols and their analogues are cycloisomerized to benzo[*b*]furans with high yields under transition-metal catalysis. There are examples of using *o*-halophenols as precursors. In this case, a palladium-catalyzed cross-coupling reaction involving terminal alkynes is carried out, followed by the heterocyclization of the thus-prepared adduct. Phenols that bear an allyl moiety in the *ortho*-position can also be used for preparing benzo[*b*]furans under metal-complex catalysis conditions. Other significant schemes to annelate a furan ring to an aromatic ring involve the cyclization of salicylaldehyde or its analogues and unsubstituted phenol or its derivatives.

II.1. Annelation of furan ring involving *o*-halophenols

The most convenient route to annelate a furan ring to a benzene ring is Sonogashira reaction of 2-halophenols with terminal alkynes followed by heterocyclization. Arcadi's team was the first to describe such a method for preparing 2-substituted benzo[*b*]furans in 1986.[29] 2-Iodophenol (**16**) undergoes cross-coupling with alkynes in piperidine (Pip) under bimetallic catalysis by Pd^{II} complexes and Cu^{I} salts. The process is accompanied by the addition of a hydroxide group to the ternary bond of the intermediate to yield 2-substituted benzofurans **17** and **18** (Scheme 1).

Scheme 1

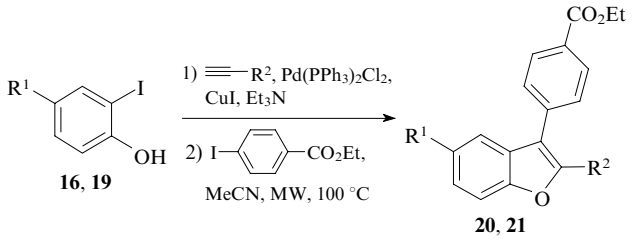


16 **17**, **18**

R = Ph (**17**, 80% yield), $CH(OH)C_5H_{11}$-n (**18**, 84%)

In 2013, Larock *et al.*[30] extended the possibilities of this method by proposing a high-yield one-pot synthesis of a series of 3-substituted benzo[*b*]furans. The first step, which is similar to the above-described reaction and is a reaction of 2-iodophenols **16** and **19** with alkynes catalyzed by the Pd^{II} – Cu^{I} bimetallic system, yields 2-substituted benzofurans. The thus-prepared compounds are further modified in position 3 of the heterocycle *in situ* by microwave (MW)-assisted treatment with aryl iodides to yield benzo[*b*]furans **20** and **21** in high yields (Scheme 2). Commercially available 2-chlorophenol can also be used in this reaction catalyzed by $Pd(MeCN)_2Cl_2$ in the presence of a phosphine ligand and lithium *tert*-butoxide as the base.[31]

Scheme 2

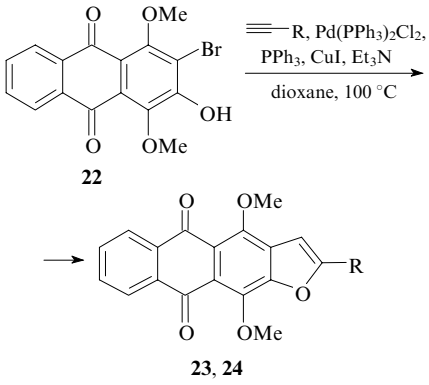


16, **19** **20**, **21**

R^1 = H (**16**, **20**), CO_2Me (**19**, **21**); R^2 = 4-$MeOC_6H_4$ (**20**, 94% yield), Ph (**21**, 92%)

A similar method involving benzo[*b*]furans was used to prepare anthra[2,3-*b*]furan-5,10-dione derivatives. 3-Bromo-2-hydroxy-1,4-dimethoxyanthraquinone (**22**) undergoes palladium-catalyzed cross-coupling with terminal alkynes. The substitution of the alkyne moiety for the halogen atom and subsequent cyclization to form a furan ring produces 2-substituted 4,11-dimethoxyanthra[2,3-*b*]furan-5,10-diones, for instance, derivatives **23** and **24** (Scheme 3).[32]

Scheme 3

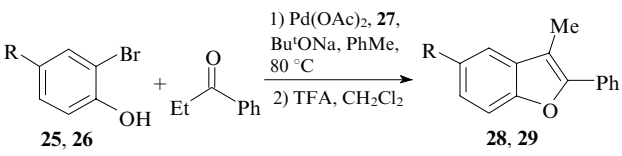


22 **23**, **24**

R = Ph (**23**, 65% yield), CH_2OH (**24**, 43%)

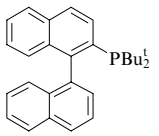
Cross-coupling of *o*-halophenols with ketones in enol form is described. Eidamshaus and Burch[33] developed a two-step scheme for preparing benzofurans, where 2-bromophenols **25** and **26** react with propiophenone under palladium acetate catalysis in the presence of phosphine ligand **27**. The cross-coupling adduct undergoes intramolecular cyclization, when treated with trifluoroacetic acid (TFA), to yield 3-methyl-2-phenylbenzofurans **28** and **29** (Scheme 4).

Scheme 4



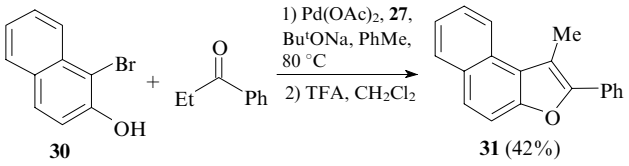
25, **26** **28**, **29**

R = H (**25**; **28**, 76% yield), F (**26**; **29**, 84%); **27** =



The above-described method also applies to prepare angular naphthofurans. 1-Bromo-2-naphthol (**30**) reacts with propiophenone under similar conditions and converts to 3-methyl-2-phenylnaphtho[2,1-*b*]furan (**31**) in a moderate yield (Scheme 5).[33]

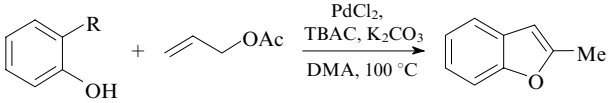
Scheme 5



30 **31** (42%)

One more route to annelate the furan ring is the palladium-catalyzed coupling of *o*-halophenols with allyl acetate (Heck reaction) followed by intramolecular cyclization. 2-Iodophenol (**16**) and 2-bromophenol (**25**) enter $PdCl_2$-catalyzed reaction with allyl acetate in the presence of tetra-n-butylammonium chloride (TBAC) and potassium carbonate, and the subsequent attachment of the hydroxy group at the double bond of the intermediate and the β-elimination of the acetoxy group yield 2-methylbenzo[*b*]-furan (**32**) (Scheme 6).[34]

Scheme 6



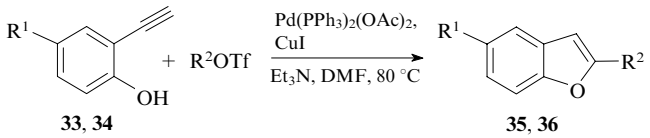
16, **25** **32** (52%–71%)

R = I (**16**), Br (**25**); DMA is *N*,*N*-dimethylacetamide

II.2. Heterocyclization of *o*-alkynylphenols

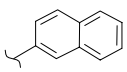
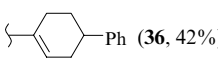
Studying the synthetic potential of cross-coupling reactions as a way to annelate the furan ring to an aromatic ring, Arcadi *et al.*[35] prepared a series of 2-substituted benzo[*b*]-furans from 2-ethynylphenols. When catalyzed by the bimetallic system consisting of a Pd^0 complex and CuI, compounds **33** and **34** react with aryl and vinyl halides in the presence of a base to yield heterocyclization products **35** and **36** (Scheme 7). The process mechanism involves the tandem of the Sonogashira cross-coupling of 2-ethynylphenols with halogenated derivatives or trifluoromethylsulfonates (triflates, OTf) and the intramolecular cyclization of the intermediate product. Noteworthy, the initial *o*-ethynylphenols are less reactive than the intermediates.

Scheme 7



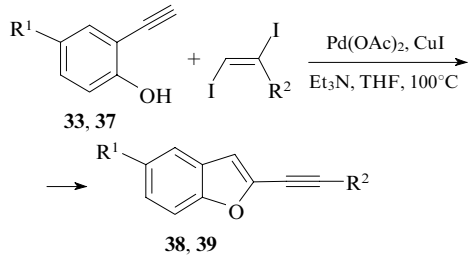
33, **34** **35**, **36**

R^1 = H (**33**, **35**), CN (**34**, **36**);

R^2 =  (**35**, 87% yield),  (**36**, 42%)

The replacement of aryl and vinyl halides by 1,2-diiodoethylene derivatives in the reaction with *o*-ethynylphenols gives rise to a reaction cascade that involves Sonogashira cross-coupling, heterocyclization and the elimination of an HI molecule. Benzofurans having an acetylene moiety in position 2 can be produced in this way. So, 2-ethynylphenols **33** and **37** yield desired 2-alkynyl derivatives **38** and **39** upon long-term heating (for 18–30 h) with 1,2-diiodoethylenes (Scheme 8).[36]

Scheme 8

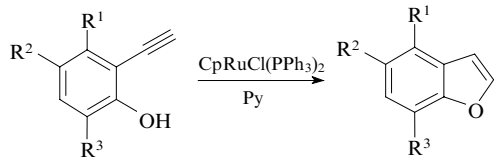


33, **37** **38**, **39**

R^1 = H (**33**, **38**), NO_2 (**37**, **39**); R^2 = CO_2Et (**38**, 33% yield), Ph (**39**, 91%)

A preparative route to convert *o*-ethynylphenols to 2,3-unsubstituted benzofurans was developed later. For example, the cycloisomerization of 2-ethynylphenols **40** and **41** in the presence of ruthenium complex $CpRuCl(PPh_3)_2$ (Cp is cyclopentadienyl) in pyridine (Py) yields benzofurans **42** and **43** (Scheme 9).[37]

Scheme 9

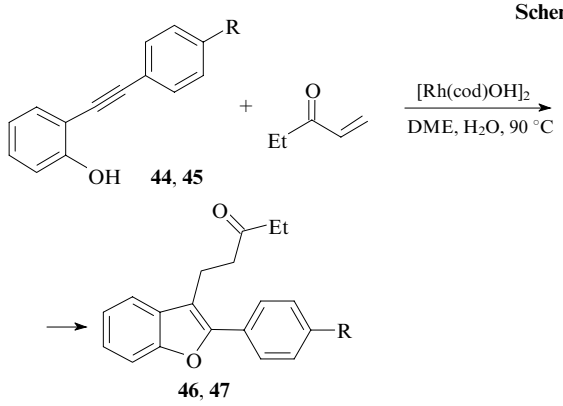


40, **41** **42**, **43**

Compounds	R^1	R^2	R^3	Yield (%)
40, **42**	CH_2OH	H	OMe	82
41, **43**	H	Ph	H	84

Rhodium(I) complexes are also efficient catalysts for the cycloisomerization of *o*-alkynylphenol. These catalysts make it possible to cyclize the furan ring modified at position 3 by means of an electrophilic Michael acceptor. For example, the cross-coupling of compounds **44** and **45** with vinyl ethyl ketone in dimethoxyethane (DME) catalyzed by the $[Rh(cod)OH]_2$ (cod is cycloocta-1,5-diene)

Scheme 10



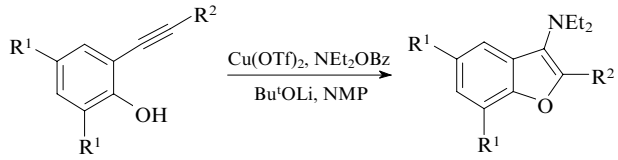
44, **45** **46**, **47**

R = H (**44**; **46**, 94% yield), OMe (**45**; **47**, 91%)

dimeric complex was used to produce benzo[*b*]furans **46** and **47** in high yields (Scheme 10).[38]

Hirano *et al.*[39] developed an efficient synthesis of 3-aminobenzofurans from *o*-alkynylphenols. Compounds **44** and **48** undergo intramolecular cyclization under the action of copper(II) triflate in *N*-methyl-2-pyrrolidone (NMP) in the presence of lithium *tert*-butoxide, and the subsequent amination by *O*-benzoylhydroxylamine yields 3-aminobenzofuran derivatives **49** and **50** (Scheme 11).

Scheme 11



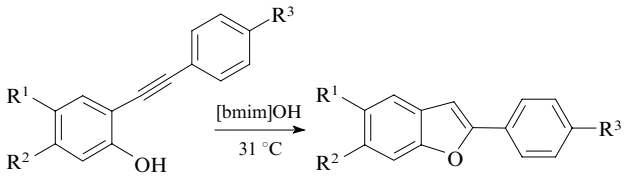
44, **48** **49**, **50**

R^1 = H, R^2 = Ph (**44**; **49**, 61% yield); R^1 = Cl, R^2 = Bu^n (**48**; **50**, 77%)

Ionic liquids are efficient for the heterocyclization of *o*-alkynylphenols.

Siddiqui *et al.*[40] heated compounds **44**, **51** and **52** in 3-n-butyl-1-methylimidazolium hydroxide ([bmim]OH) to prepare 2-substituted benzofurans **17**, **53** and **54** (Scheme 12). In this case, the ionic liquid performed as the base and solvent. This method is convenient and environmentally friendly, as ionic liquids, unlike many organic solvents and bases, are not toxic to humans and the environment, are easy to recycle and satisfy the green chemistry principles.

Scheme 12

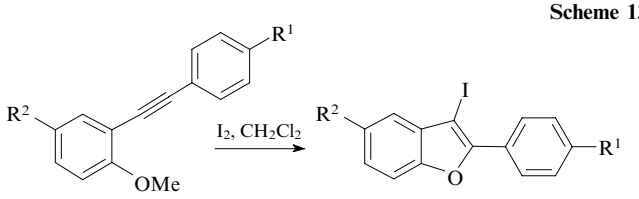


44, **51**, **52** **17**, **53**, **54**

Compounds	R^1	R^2	R^3	Yield (%)
44, **17**	H	H	H	97
51, **53**	OMe	OMe	H	80
52, **54**	NO_2	H	F	84

Larock and co-workers[41] developed a method for the cyclization of *o*-alkynylanisols by electrophiles at room temperature. Compounds **55**–**57**, which were prepared by Sonogashira cross-coupling of 2-iodoanisols with terminal alkynes, were converted by iodine in methylene chloride to 2-substituted 3-iodobenzofurans **58**–**60** in high yields (Scheme 13).

Scheme 13



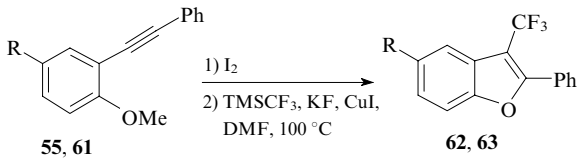
55–**57** **58**–**60**

R^2 = H: R^1 = H (**55**; **58**, 87% yield), OMe (**56**; **59**, 99%);
R^1 = H, R^2 = OMe (**57**; **60**, 74%)

In 2014, Wang *et al.*[42] modified the above-described method in order to prepare benzofurans that contain a trifluoromethyl group in position 3. Their scheme comprises two stages without separation and purification of the intermediate (one-pot synthesis).

The first stage is an analogue of the reaction in Scheme 13: (2-methoxyphenyl)alkynes **55** and **61**, when treated with iodine *in situ*, form 3-iodobenzofurans, which at the second stage are trifluoromethylated by trimethyl(trifluoromethyl)silane ($TMSCF_3$) in the presence of potassium fluoride and copper(I) iodide in dimethylformamide to yield 3-(trifluoromethyl)benzofurans **62** and **63** in 89% and 62% yields (Scheme 14).

Scheme 14

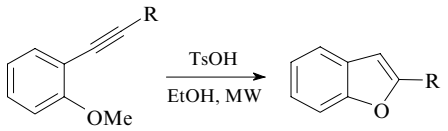


55, **61** **62**, **63**

R = H (**55**, **62**), CO_2Me (**61**, **63**)

p-Toluenesulfonic acid (TsOH) appears to be an efficient reagent for the microwave-assisted cyclization of *o*-alkynylanisols. Diarylacetylene **56** and enyne **64**, each containing a benzene ring with a methoxy group in the *ortho*-position to the triple bond, were cyclized in the presence of TsOH to produce 2-substituted benzofurans **65** and **66** in good yields (Scheme 15).[43]

Scheme 15

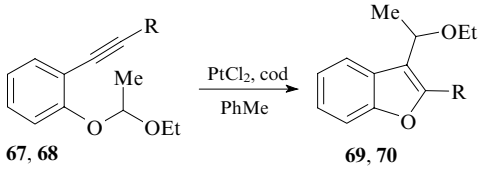


56, **64** **65**, **66**

R = 4-$MeOC_6H_4$ (**56**; **65**, 76% yield), $Me_2C{=}CH$ (**64**; **66**, 72%)

o-Alkynylphenol acetals undergo intramolecular cyclization followed by the migration of the acetal moiety to position 3 of the furan ring. Compounds **67** and **68** can easily be converted to benzo[*b*]furans **69** and **70** in toluene under catalysis with platinum(II) chloride in the presence of cycloocta-1,5-diene (Scheme 16).[44] The presence of cyclooctadiene was critical for the preparation of compound **69**, as the yield of desired product increased from 20% to 92% in the presence of this ligand. Another specific feature of the method is a considerable reduction in the yield of benzo[*b*]furans upon the introduction of an electron-withdrawing group into the substituent R.

Scheme 16

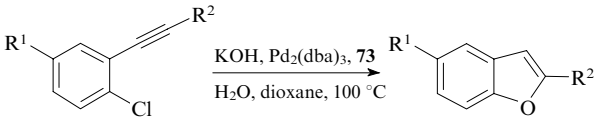


67, **68** **69**, **70**

R = $Cl(CH_2)_4$ (**67**; **69**, 92% yield), 4-$F_3CC_6H_4$ (**68**; **70**, 61%)

Buchwald and co-workers[45] developed an efficient route to annelate the furan ring, which consists in the palladium-catalyzed reaction of substitution of a hydroxy group for the halogen atom in (*o*-haloaryl)alkynes, followed by intramolecular cyclization. (2-Chlorophenyl)alkynes **71** and **72** in the presence of ligand **73** are converted by potassium hydroxide to 2-substituted benzofurans **74** and **75** in high yields; the process is catalyzed by palladium complex $Pd_2(dba)_3$ (dba is dibenzylydeneacetone) (Scheme 17).

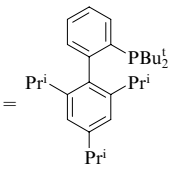
Scheme 17



71, **72** **74**, **75**

R^1 = H, R^2 = n-C_8H_{17} (**71**; **74**, 83% yield);
R^1 = CF_3, R^2 = 3-Th (**72**; **75**, 87%);
Th is thienyl

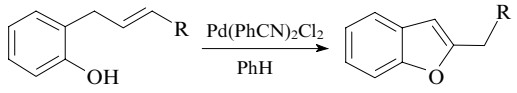
73 =



II.3. Annelation of the furan ring *via* 2-allyl- and 2-vinylphenols

Phenols that contain an allyl or a vinyl moiety in the *ortho*-position, like their acetylene analogues, can efficiently be subjected to metal-catalyzed intramolecular cyclization. Hosokawa *et al.*[46] were the first to describe the synthesis of benzo[*b*]furans from 2-allylphenols using palladium compounds as catalysts, and then studied the potential of this reaction for use. Phenols **76**–**78** are cyclized to 2-substituted benzofurans **32**, **79** and **80** in moderate yields in the presence of dichlorobis(benzonitrile)palladium in benzene (Scheme 18).[47]

Scheme 18

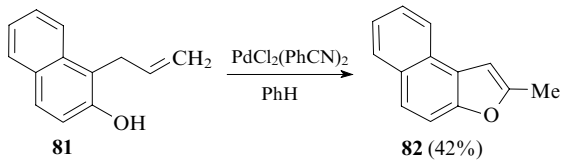


76–**78** **32**, **79**, **80**

R = H (**76**; **32**, 31% yield), Me (**77**; **79**, 26%), Ph (**78**; **80**, 53%)

That method appeared to be suitable for preparing naphtho[*b*]furans, too. Under similar conditions, 1-allyl-2-naphthol (**81**) yields naphthofuran **82** (Scheme 19).[47]

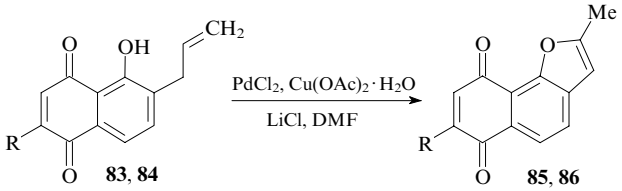
Scheme 19



81 **82** (42%)

In 2014, this reaction was employed to annelate the furan ring in the synthesis of naphtho[1,2-*b*]furan-6,9-diones, potential antitumour agents. 6-Allyl-5-hydroxynaphthoquinones **83** and **84** yield heterocyclization products **85** and **86** under mild conditions in the presence of palladium(II), copper(II) and lithium salts in DMF (Scheme 20).[48]

Scheme 20

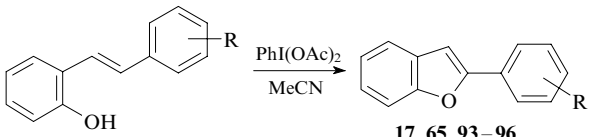


83, **84** **85**, **86**

R = H (**83**; **85**, 25% yield), Me (**84**; **86**, 31%)

The intramolecular cyclization of *o*-hydroxystilbenes by hypervalent iodine compounds in acetonitrile in the absence of transition-metal complexes is a more efficient way to prepare benzo[*b*]furans. Under these conditions, 2-hydroxystilbenes **87**–**92** are readily converted to 2-arylbenzofurans **17**, **65** and **93**–**96** (Scheme 21).[49]

Scheme 21

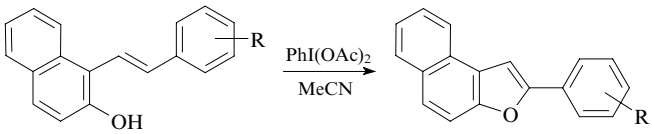


87–**92** **17**, **65**, **93**–**96**

R = H (**87**; **17**, yield 77%), 4-OMe (**88**; **65**, 87%), 4-Cl (**89**; **93**, 79%), 3-F (**90**; **94**, 68%), 3-NO_2 (**91**; **95**, 69%), 2-Me (**92**; **96**, 86%)

This method was also used to prepare angular naphtho[*b*]furans. In the presence of iodosobenzene diacetate, naphthols **97**—**99** are cyclized into naphtho[*b*]furans **100**—**102** in high yields (Scheme 22).[49]

Scheme 22

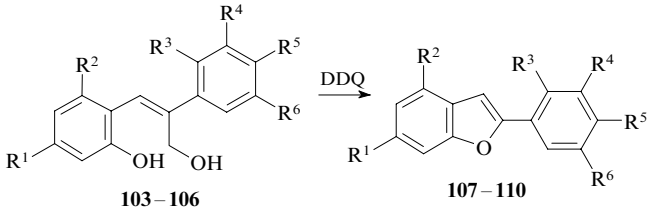


97–**99** **100**–**102**

R = H (**97**; **100**, 88% yield), 4-Cl (**98**; **101**, 91%), 3-OMe (**99**; **102**, 95%)

Analogues of *o*-hydroxystilbene were also used in the synthesis of native biologically active benzo[*b*]furan derivatives, analogues of native moracine A. Compounds **103**–**106**, which were prepared by the reduction of 3-phenylcoumarins, are oxidized by 2,3-dichloro-5,6-dicyanoben-

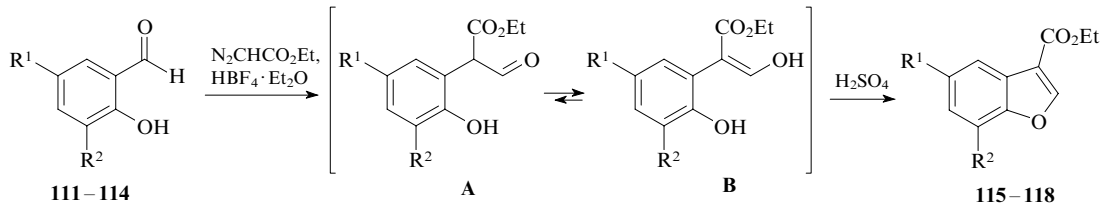
Scheme 23



103–**106** **107**–**110**

R^1 = R^2 = OMe, R^3 = R^5 = H, R^4 = R^6 = OBn (**103**; **107**, 36% yield);
R^1 = R^3 = R^5 = OBn, R^2 = R^4 = R^6 = H (**104**; **108**, 60%);
R^1 = R^3 = OMe, R^2 = R^4 = R^6 = H, R^5 = OBn (**105**; **109**, 65%);
R^1 = R^4 = OBn, R^2 = R^6 = H, R^3 = R^5 = OMe (**106**; **110**, 52%)

Scheme 24



111 – 114 **115 – 118**

$R^1 = R^2 = H$ (**111**; **115**, 91% yield), Cl (**114**; **118**, 99%); $R^1 = Cl$, $R^2 = H$ (**112**; **116**, 95%); $R^1 = H$, $R^2 = OMe$ (**113**; **117**, 97%)

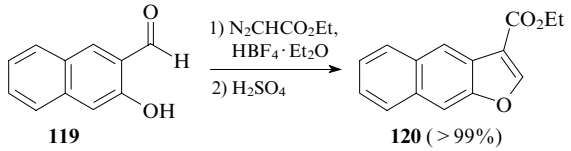
zoquinone (DDQ) to *o*-quinone methide, which involves the reduction of DDQ to DDQ-H_2. The subsequent intramolecular cyclization of *o*-quinone methide, the DDQ-H_2-catalyzed isomerization of the adduct and the elimination of formaldehyde produce 2-phenylbenzofurans **107 – 110** in moderate overall yields (see Scheme 23, where the yields are given on the basis of two stages).[50]

II.4. Cyclizations of 2-acylphenols and their derivatives

Salicylaldehyde and its analogues are widely used as semiproducts for preparing benzo[*b*]furans. The HBF_4-catalyzed reaction of salicylaldehyde (**111**) or its derivatives **112 – 114** with ethyl diazoacetate and subsequent dehydration by sulfuric acid produced benzofuran-3-carboxylic acid esters **115 – 118** in high yields (Scheme 24).[51] The suggested scenario of the process involves the catalyzed alkylation of the carbonyl carbon atom by ethyl diazoacetate followed by rearrangement to yield intermediate 2-(*o*-hydroxyphenyl)-2-ethoxycarbonylacetaldehydes **A**. The enol tautomeric forms **B** of these intermediates are subjected to intramolecular cyclodehydration to yield esters of 2-unsubstituted benzofuran-3-carboxylic acids **115 – 118**.

The last-described method is also efficient for preparing naphtho[*b*]furans. Under similar conditions, 3-hydroxynaphthalene-2-carbaldehyde (**119**) forms ethyl naphtho[2,3-*b*]-furan-3-carboxylate (**120**) in a quantitative yield (Scheme 25).[51]

Scheme 25

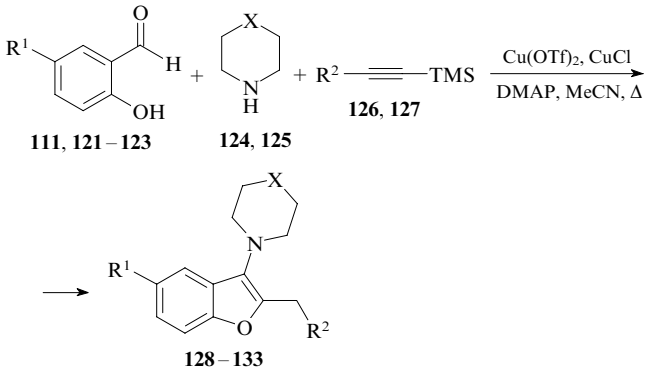


119 **120** (> 99%)

Sakai *et al.*[52] developed a method for annelating the furan ring to a benzene moiety through the multicomponent conversion of salicylaldehyde or its derivatives. A series of 3-aminobenzo[*b*]furan derivatives **128 – 133** were prepared by reacting aldehydes **111** and **121** through **123** (where $R^1 = H$, Me, NO_2, and Br, respectively) with piperidine (**124**) or morpholine (**125**) and alkynylsilanes **126** ($R^2 = Ph$), **127** ($R^2 = n\text{-}C_7H_{15}$) under catalysis by copper salts in the presence of 4-dimethylaminopyridine (DMAP) (Scheme 26).

An original route to benzo[*b*]-furans was proposed through reacting *o*-hydroxyaceto(benzo)phenones with 1,1-dichloroethylene under alkaline conditions. *o*-Hydroxyaceto(benzo)phenones **134 – 136** are condensed with 1,1-dichloroethylene under the action of potassium *tert*-butoxide. The resulting intermediates **C** are low-stable and are readily rearranged and dehydrated under the action of acids to form benzofuran-2-carbaldehydes **137 – 139** (Scheme 27).[53]

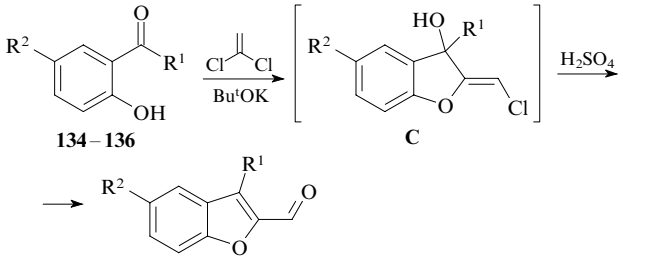
Scheme 26



111, 121 – 123 **124, 125** **126, 127** **128 – 133**

Product	R^1	R^2	X	Yield (%)
128	H	Ph	CH_2	91
129	Me	Ph	CH_2	90
130	NO_2	Ph	CH_2	50
131	Br	Ph	CH_2	65
132	H	Ph	O	99
133	H	n-C_7H_{15}	CH_2	65

Scheme 27



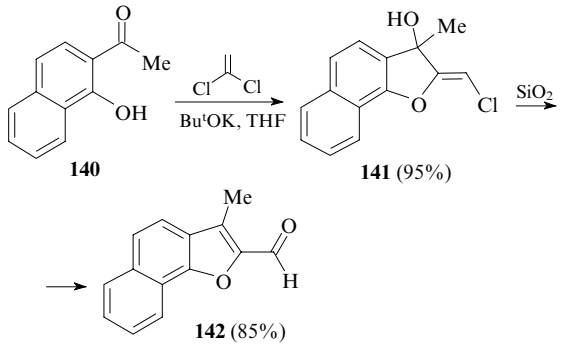
134 – 136 **C** **137 – 139**

R^1 = Me: $R^2 = H$ (**134**; **137**, 97% yield), Br (**135**; **138**, 93%);
R^1 = Ph, $R^2 = H$ (**136**; **139**, 94%)

This method applies to prepare angular naphtho[*b*]furans. The condensation of 1-hydroxy-2-naphthyl methyl ketone (**140**) with 1,1-dichloroethylene occurs in a similar manner (see Scheme 27), except for the stage of conversion of compound **141**. The desired product, which is naphthofuran-2-carbaldehyde **142**, was obtained by the column chromatography purification of compound **141** (Scheme 28).[53]

Pei *et al.*[54] developed a regioselective method for preparing 2- and 3-substituted benzofurans using 2-hydroxy-α-chloroacetophenone. The reaction of 2-(chloromethylcarbonyl)phenol with n-butylmagnesium chloride at temperatures in the range from −78 to −30 °C produces chlorohydrin **143**, which can be further regioselectively modified in two directions. Re-treatment with Grignard

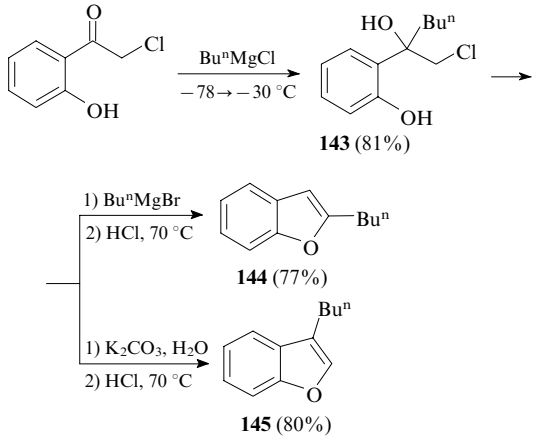
Scheme 28



140 **141** (95%) **142** (85%)

reagent initiates the [1,2]-migration of the aryl and the elimination of the chloride ion, followed by the dehydration of compound **143** to yield 2-n-butylbenzofuran (**144**). In the presence of potassium carbonate, intermediate alcohol **143** experiences direct cyclization, followed by dehydration to form 3-n-butylbenzofuran (**145**) (Scheme 29).

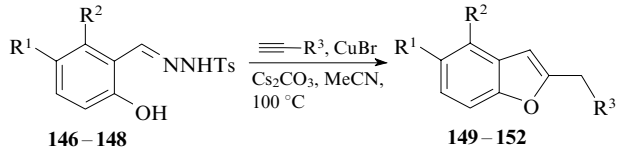
Scheme 29



143 (81%) **144** (77%) **145** (80%)

Salicylaldehyde *N*-tosylhydrazone is also suitable for annelating the furan ring in reaction with terminal alkynes. Hydrazones **146**–**148**, prepared from the proper salicylaldehyde derivatives, enter the copper-catalyzed coupling–cyclization reactions to yield 2-substituted benzofurans **149**–**151** and naphthofuran **152** (Scheme 30).[55]

Scheme 30



146–**148** **149**–**152**

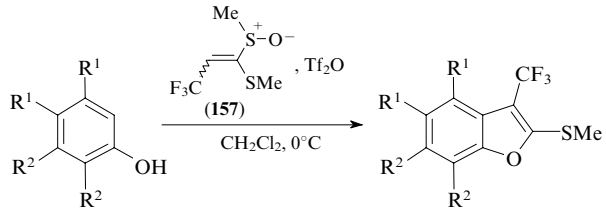
$R^1 = R^2 = H$ (**146**): $R^3 = 4\text{-MeOC}_6H_4$ (**149**, 85% yield), $4\text{-F}_3\text{CC}_6H_4$ (**150**, 86%); R^1 = Br, R^2 = H (**147**): R^3 = Ph (**151**, 79%); $R^1 - R^2$ is benzo (**148**): R^3 = H (**152**, 53%)

II.5. Annelation of the furan ring involving unsubstituted phenol and its analogues

Heterocyclization involving phenols with vacant *ortho*-positions is a rather promising strategy to synthesize benzo[*b*]furans due to the availability of the precursor compounds and the facility of process implementation.

The underlying reaction of an efficient and versatile method for preparing heteroaromatic systems containing a 3-trifluoromethylbenzo[*b*]furan moiety is the Pummerer reaction of *ortho*-unsubstituted phenols [phenol (**153**), α- and β-naphthols (**154**, **155**) and 9-hydroxyphenanthrene (**156**)] with 3-(2,2,2-trifluoroethylidene)-2,4-dithiapentane 2-oxide (**157**). This reaction yields heterocyclization products **158**–**161** in good yields (Scheme 31).[56, 57] The reaction scheme includes the nucleophilic attack of the phenol at the sulfur cation activated by trifluoromethane sulfonic acid anhydride; then, the thus-prepared adduct is subjected to [3,3]-sigmatropic rearrangement, followed by cyclization and elimination of MeSH. We should mention that the methylsulfanyl group in position 2 is suitable for subsequent modifications, for example, for substitution by an aryl group *via* palladium-catalyzed cross-coupling with aryl metal complexes.[56, 57]

Scheme 31

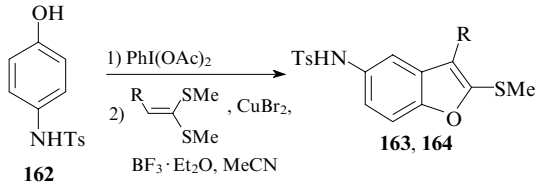


153–**156** **158**–**161**

$R^1 = R^2 = H$ (**153**; **158**, 85% yield); R^1 = H, $R^2 - R^2$ is benzo (**154**; **159**, 52%); $R^1 - R^1$ is benzo, R^2 = H (**155**; **160**, 74%); $R^1 - R^1 = R^2 - R^2$ is benzo (**156**; **161**, 74%)

A furan ring is also formed in the reaction of *p*-(*N*-tosylamino)phenol (**162**) with ketene thioacetals in the presence of a hypervalent iodine compound, catalyzed by a two-component system of boron trifluoride etherate and copper(II) bromide (Scheme 32).[58] Although the conditions of this reaction are similar to those of the preceding method, the authors suggest another reaction scenario. Compound **162** is oxidized by a hypervalent iodine compound *in situ* to form mono-(*N*-tosyl)imine quinone, and then boron trifluoride activates the imine group and initiates the copper(II) bromide-activated regioselective Michael addition of the ketene thioacetal. Subsequent intramolecular cyclization affords 5-(*N*-tosyl)aminobenzo[*b*]furans **163** and **164** in moderate yields.

Scheme 32

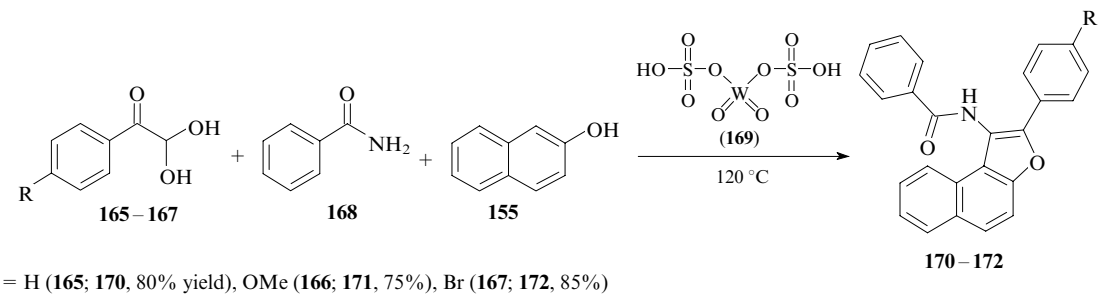


162 **163**, **164**

R = NO_2 (**163**, 61% yield), CN (**164**, 63%)

For β-naphthol, a method is described where angular 3-amido-2-arylnaphthofurans are prepared by the three-component reaction of β-naphthol, benzamide and arylglyoxal hydrates. Arylglyoxal hydrates **165**–**167** are fused with benzamide **168** when catalyzed by tungstate sulfuric acid **169**, then β-naphthol (**155**) is added and the subsequent intramolecular cyclization affords just 3-amido-2-arylnaphthofurans **170**–**172** (Scheme 33).[59] This method meets the

Scheme 33

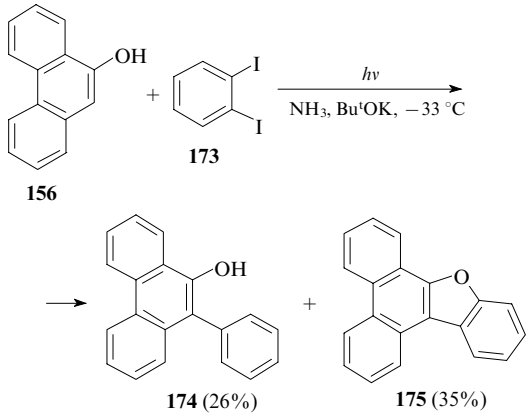


R = H (**165**; **170**, 80% yield), OMe (**166**; **171**, 75%), Br (**167**; **172**, 85%)

set of green chemistry principles, as organic solvents are absent in the reaction and catalyst **169** is relatively environmentally safe and can be recycled.

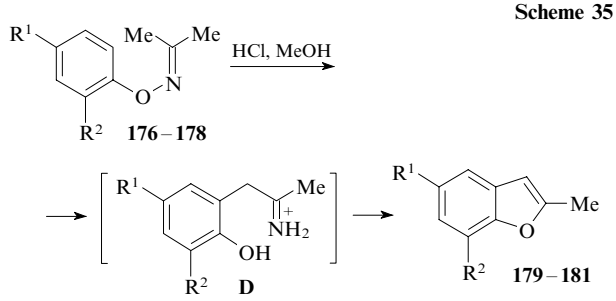
For annelating furan rings to phenanthrenes, Tempesti *et al.*[60] proposed a method involving a photochemical reaction of 9-hydroxyphenanthrene (**156**) with *o*-dihalobenzenes. Under light irradiation, electron transfer occurs from the 9-hydroxyphenanthrene anion generated by potassium *tert*-butoxide to 1,2-diiodobenzene (**173**). The thus-produced radicals initiate a chain reaction to yield two products: 9-hydroxy-10-phenylphenanthrene (**174**) and phenanthro[9,10-*b*]benzofuran (**175**) (Scheme 34). Noteworthy, both products are forming concurrently, and their ratio does not vary over time.

Scheme 34



The rearrangement of *O*-aryloximes under acidic conditions is a well-studied method for preparing benzo[*b*]furan derivatives. Mooradian[61] was the first to perform such a reaction in 1967; later, Mooradian and Dupont[62] described the mechanism of [3,3]-sigmatropic rearrangement, which resembles the Fischer reaction mechanism. The treatment of

Scheme 35



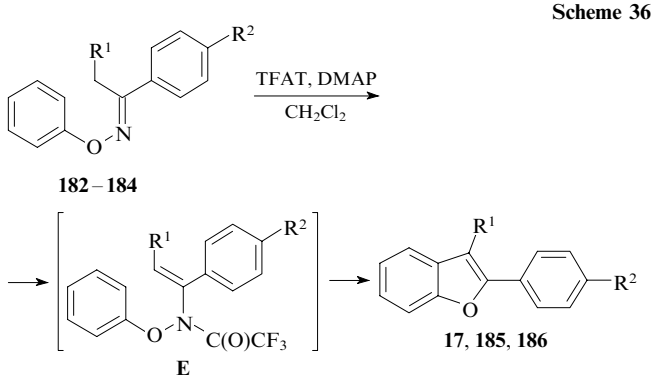
R^1 = NO_2, R^2 = H (**176**; **179**, 90% yield); R^1 = R^2 = NO_2 (**177**; **180**, 20%); R^1 = H, R^2 = NO_2 (**178**; **181**, 50%)

O-aryloximes **176**–**178** by hydrochloric acid in ethanol yields heterocyclization products **179**–**181** through the stage of producing salts **D** (Scheme 35).[62] Shevelev and coworkers[63, 64] used this scheme to prepare an extended series of nitrobenzo[*b*]furans that contained substituents in positions 2 and 3 of the heterocyclic ring.

Takeda *et al.*[65] developed a method to prepare benzo[*b*]furans using an analogous rearrangement of *N*-trifluoroacetyl derivatives of enehydroxylamine. Phenone *O*-phenyloximes **182**–**184** are acylated by trifluoroacetyl triflate (TFAT) in the presence of 4-dimethylaminopyridine to form *N*-(trifluoroacetyl)enehydroxylamines **E**. The latter experience *in situ* [3,3]-sigmatropic rearrangement (cyclization) followed by the elimination of the trifluoroacetamide group to yield benzo[*b*]furans **17**, **185** and **186** in high yields (Scheme 36).

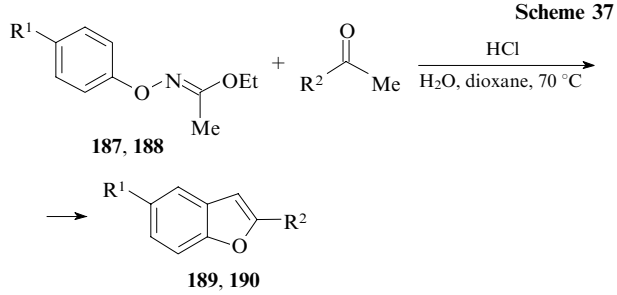
A similar conversion of *O*-arylhydroxylamines to 2-substituted benzo[*b*]furans is also possible. The treatment of *O*-ethylacetohydroxamate tautomers **187** and **188** by ketones in aqueous medium in the presence of hydrochloric

Scheme 36



R^1 = H: R^2 = H (**182**; **17**, 99% yield), Br (**184**; **186**, 96%); R^1 = Me, R^2 = OH (**183**; **185**, 86%)

Scheme 37



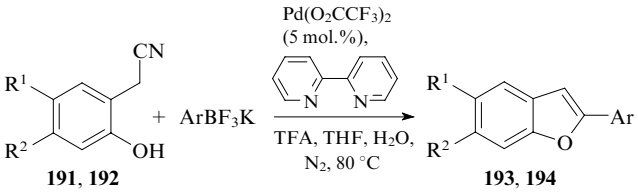
R^1 = Bu^t (**187**, **189**), Cl (**188**, **190**); R^2 = Ph (**189**, 86% yield), Ad (**190**, 83%); Ad is 1-adamantyl

acid in dioxane affords 2-substituted benzofurans **189** and **190** (Scheme 37).[66]

II.6. Other ways to generate O–C(2) bond of benzo[*b*]furan

Recently, a research team[67] from Wenzhou University (China) published a method of palladium-catalyzed addition of aryl trifluoroborates to aliphatic nitriles, which was adapted to an efficient production of benzofuran derivatives. 2-(2-Hydroxyphenyl)acetonitriles **191** and **192** are subjected to one-pot arylation by potassium aryl trifluoroborate under mild catalytic conditions and then converted by intramolecular heterocyclization to 2-arylbenzofurans **193** and **194** in high yields (Scheme 38). The suggested reaction scheme comprises the addition of $ArPd(CF_3CO_2)L$ (L = 2,2′-bipyridine) to the nitrile nitrogen atom, followed by the transfer of the aryl group to the nitrile carbon atom, the hydrolysis of the intermediate ketimine and heterocyclization.

Scheme 38

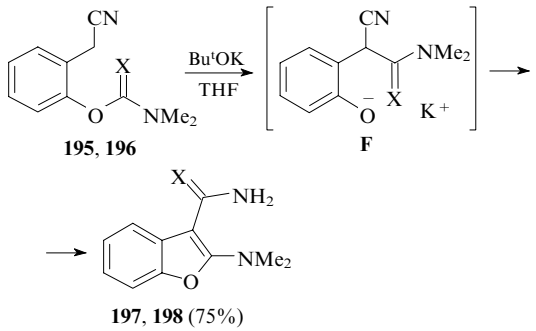


191, **192** **193**, **194**

R^1 = Me, R^2 = H (**191**, **193**); R^1 = H, R^2 = OMe (**192**, **194**);
Ar = Ph (**193**, 91% yield), 4-$Bu^tC_6H_4$ (**194**, 90%)

Kim *et al.*[68] described the intramolecular cyclization of 2-(cyanomethyl)phenylcarbonyl compounds and their sulfur-containing analogues. The reaction of 2-(cyanomethyl)-phenylcarbamate (**195**) and its thio analogue **196** in the presence of potassium *tert*-butoxide involves rearrangement into intermediates **F**. Subsequent cyclization, involving the hydrolysis of cyano group, affords 2-aminobenzofuran-3-carboxylic acid amides **197** and their thio analogues **198** in 75% yield (Scheme 39). This method was modified as follows: the acid catalysis of intramolecular ring closure in intermediates **F** was followed by microwave irradiation, but this had no significant influence on cyclization efficiency.[68]

Scheme 39



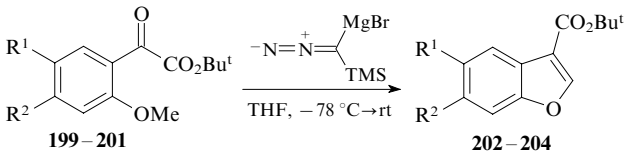
195, **196**

197, **198** (75%)

X = O (**195**, **197**), S (**196**, **198**)

Hari *et al.*[69] prepared *tert*-butyl esters of benzofuran-3-carboxylic acids with free position 2 from (2-methoxyphenyl)-2-oxoacetates **199**–**201**. The latter are converted by diazotrimethylsilylmethylmagnesium bromide [TMSC(MgBr)N_2] to alkylidenecarbenes, which further undergo intramolecular cyclization with the elimination of the carbene and the formation of *tert*-butyl benzofuran-3-carboxylates **202**–**204** in moderate yields (Scheme 40).[69]

Scheme 40

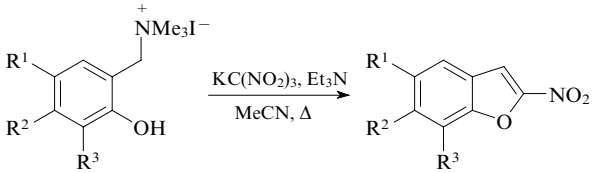


199–**201** **202**–**204**

R^1 = H: R^2 = H (**199**; **202**, 55% yield), OMe (**200**; **203**, 62%);
R^1 = Cl, R^2 = H (**201**; **204**, 40%)

Klimochkin's research team[70] developed a scheme to produce 2-nitrobenzo[*b*]furans from *o*-quinone methide derivatives. *o*-Quinone methides were shown to react with potassium trinitromethanide at the carbon atom as a soft nucleophilic centre. Reactions of *o*-quinone methides, generated from quaternized Mannich bases **205**–**207**, with potassium trinitromethanide in the presence of triethylamine in boiling acetonitrile yield 2-nitrobenzofuran derivatives **208**–**210** (Scheme 41).

Scheme 41

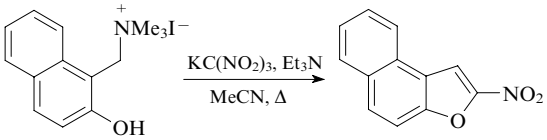


205–**207** **208**–**210**

R^1 = R^2 = Me, R^3 = H (**205**; **208**, 79% yield); R^1 = R^3 = H,
R^2 = CO_2Me (**206**; **209**, 51%); R^1 = CO_2Me, R^2 = H,
R^3 = OMe (**207**; **210**, 60%)

The last-described approach can also serve to produce naphtho[*b*]furans. Under similar conditions, β-naphthol derivative **211** yields 2-nitronaphtho[2,1-*b*]furan (**212**) in a moderate yield (Scheme 42).[70]

Scheme 42

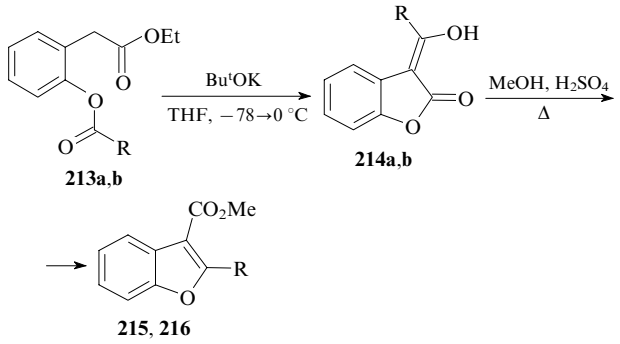


211 **212** (56%)

Kang *et al.*[71] adapted the Madelung indole synthesis to prepare 2,3-substituted benzo[*b*]furans by means of the two-stage cyclization of 2-(2-acyloxyphenyl)acetic acid esters. At temperatures in the range from 78 to 0 °C in the presence of potassium *tert*-butoxide, ethyl 2-acyloxyphenylacetates **213a**,**b** are converted to benzo[*b*]furan-2(3*H*)-ones **214a**,**b** in high yields. Boiling of compounds **214a**,**b** in methanol in the presence of H_2SO_4 affords 2-substituted benzo[*b*]furan-3-carboxylic acid methyl esters **215** and **216** (Scheme 43). The merits of this method are high yields and the facility of purification of desired compounds.[71]

In 2015, Xu *et al.*[72] described the synthesis of a benzofuran system from *cis*-2-(2-bromophenyl)-3-phenylacrylic acids **217**–**219**. The bromine atom in phenylacrylic acids **217**–**219** is replaced by a hydroxy group under microwave

Scheme 43



213a,b **214a,b** **215, 216**

R = Ph (**213a**; **214a**, 87% yield; **215**, 90%);
4-BrC_6H_4 (**213b**; **214b**, 85%; **216**, 91%)

exposure in the presence of catalytic amounts of copper(II) acetate and 1,10-phenanthroline (1,10-Phen) as the ligand. The subsequent oxidative cyclization of intermediates **G** in a one-pot variant affords 2-arylbenzo[*b*]-furan-3-carboxylic acids **220**–**222** in high yields (Scheme 44). An optimized scheme, which was approved in the preparation of a set of 28 benzo[*b*]furan-3-carboxylic acids, laid the basis to the preparative scheme for neolignan moracine M (**3**) in 64% total yield.

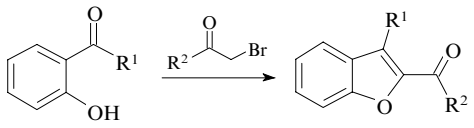
One more unique method for preparing native biologically active benzo[*b*]furan **3** was developed by Celaje *et al.*[73] The underlying idea of the method is the photochemical oxidation of resveratrol (**223**) by oxygen. The addition of singlet oxygen to the C=C double bond of compound **223** by the [4+2]-cycloaddition scheme yields a cyclic peroxide, which is then converted to tautomer **224**. The synthesis was performed on the microscale with CD_3CN used as a solvent for monitoring the reaction by ^{1}H NMR spectroscopy. Peroxide **224** is stable at room temperature, but experiences rearrangement and dehydration under heating to yield benzo[*b*]furan **3** (Scheme 45).

III. Heterocyclization to generate C(2)–C(3) bonds of benzo[*b*]furans

III.1. Annelation of the furan ring using 2-acylphenols

An efficient method to prepare 2-substituted benzo[*b*]-furans is the Rap–Stoermer reaction between salicylaldehyde or its analogues and α-haloketones or α-haloacetates. In the presence of a base, salicylaldehyde (**111**) or 2-hydroxyacetophenone (**134**) is reacted with α-bromoketones and ethyl α-bromoacetate, and the alkylation intermediate undergoes intramolecular cyclodehydration to yield 2-substituted benzofurans **225**–**230** (Scheme 46).[74, 75] The preferred bases are alkali metal carbonates or tertiary amines, and the preferred solvent is acetonitrile or water.[74, 75]

Scheme 46

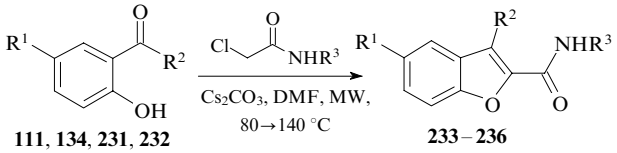


111, 134 **225–230**

R^1 = H (**111**): R^2 = Ph (**225**, 96% yield), OEt (**226**, 95%), 4-MeOC_6H_4 (**227**, 90%); R^1 = Me (**134**): R^2 = Ph (**228**, 72%), 4-MeC_6H_4 (**229**, 81%), 4-BrC_6H_4 (**230**, 60%)

In a similar manner, Xie *et al.*[76] prepared a series of benzo[*b*]furan-2-carboxamides from salicylaldehyde (**111**) and its derivatives. Compounds **111**, **134**, **231** and **232** react with α-chloroacetic acid amides in the presence of Cs_2CO_3 under microwave exposure to undergo heterocyclization yielding benzofuran-2-carboxamides **233**–**236**, which have prominent anti-inflammatory, analgesic and antipyretic activities (Scheme 47).

Scheme 47

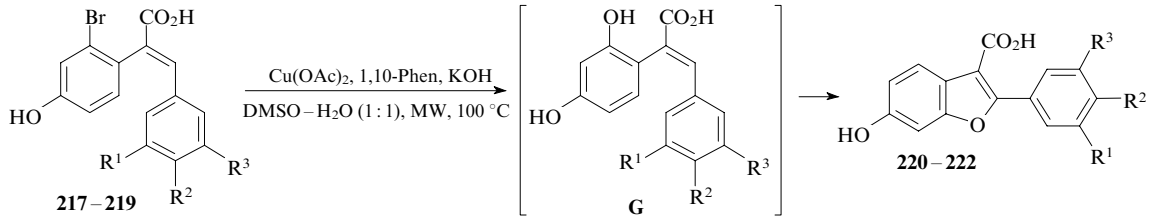


111, 134, 231, 232 **233–236**

Substrate	R^1	R^2	Product	R^3	Yield (%)
111	H	H	**233**	H	43
134	H	Me	**234**	Ph	55
231	H	Et	**235**	H	76
232	Cl	Ph	**236**	H	70

Noteworthy is the failure to perform a similar one-pot heterocyclization for preparing anthra[2,3-*b*]furan-5,10-

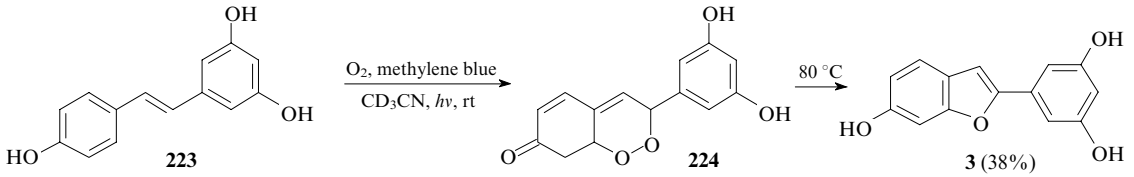
Scheme 44



217–219 **G** **220–222**

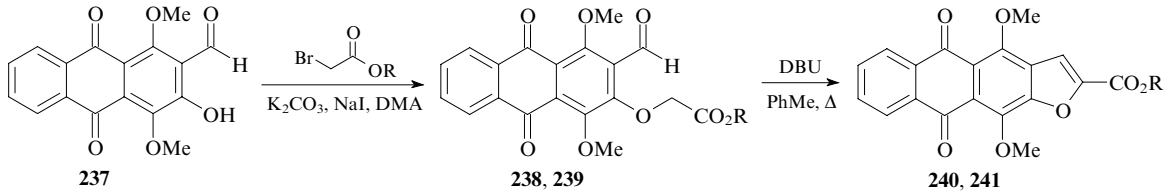
R^1 = R^3 = OMe, R^2 = H (**217**; **220**, 90% yield); R^1 = H, R^2 = OMe, R^3 = OH (**218**; **221**, 88%); R^1 = R^3 = H, R^2 = Cl (**219**; **222**, 87%)

Scheme 45



223 **224** **3** (38%)

Scheme 48



237 **238**, **239** **240**, **241**

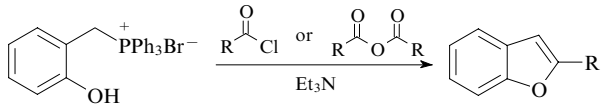
R = Et (**238**, 86% yield; **240**, 34%); Bu^t (**239**, 89%; **241**, 37%)

dione derivatives by reacting salicylaldehyde analogue **237** with α-bromoacetic acid esters. A two-stage method was used to prepare anthra[2,3-*b*]furan-2-carboxylic acid derivatives with the isolation and purification of reaction intermediates. The first stage comprised O-alkylation of aldehyde **237** by bromoacetic acid esters under heating in *N*,*N*-dimethylacetamide in the presence of potassium carbonate to provide 3-formylanthraquinon-2-yloxyacetic acid esters **238** and **239**. Cyclodehydration of these esters to anthra[2,3-*b*]furan-2-carboxylic acid esters **240** and **241** is induced by diazobicyclo[5.4.0]undec-7-ene (DBU) under boiling in toluene (Scheme 48).[77]

III.2. Annelation of the furan ring using triphenyl(2-hydroxybenzyl)phosphonium salts

Some preparative methods for the production of benzo[*b*]-furans are based on the intramolecular Wittig reaction involving esters of (2-hydroxybenzyl)triphenylphosphonium salts. This type of heterocyclization to the furan ring was first described by Hercouet and Le Corre[78] in 1979. The acylation of (2-hydroxybenzyl)triphenylphosphonium bromide (**242**) by carboxylic acid chlorides or anhydrides in triethylamine, followed by intramolecular cyclization, yields 2-substituted benzo[*b*]furans **79**, **243** and **244** in good yields (Scheme 49).

Scheme 49



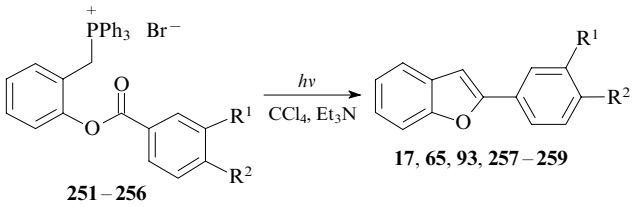
242 **79**, **243**, **244**

R = Et (**79**, 77% yield), Pr^n (**243**, 79%), 2,3-dihydrofuran-2-yl (**244**, 93%)

This method is suitable for preparing optically active 2-substituted benzo[*b*]furans. For example, phosphonium salt **242** (3 equiv.) reacts under basic conditions with amino acids **245**–**247** activated by 2,4,6-trichloro-1,3,5-triazine to form *S*-isomers of 2-substituted benzofurans **248**–**250** (Scheme 50).[79]

The intramolecular ester Wittig reaction is efficient under photochemical activation. The light irradiation of (2-acyloxybenzyl)triphenylphosphonium bromides **251**–**256** in carbon tetrachloride in the presence of triethylamine considerably accelerates intramolecular cyclization to benzofurans **17**, **65**, **93** and **257**–**259** (Scheme 51).[80] The advantage of this method consists in high reaction rates and, frequently, high yields of desired compounds.

Scheme 51



251–**256** **17**, **65**, **93**, **257**–**259**

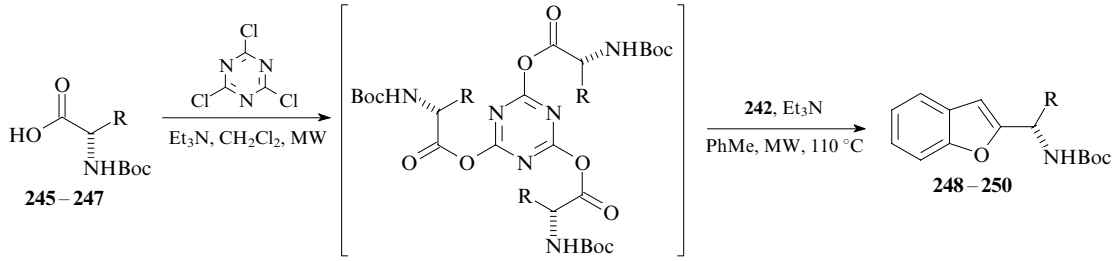
R^1 = H: R^2 = H (**251**; **17**, 52% yield), OMe (**252**; **65**, 72%), Cl (**253**; **93**, 61%), NO_2 (**256**; **259**, 81%); R^1 = OMe: R^2 = H (**254**; **257**, 87%), OMe (**255**; **258**, 83%)

III.3. Metathesis cyclization of O-vinyl derivatives of 2-vinylphenols to benzofurans

During last decades, catalytic alkene metathesis reactions have come into wide use in organic synthesis, and intramolecular metathesis appeared efficient for preparing five-membered heterocycles.[81] This strategy to synthesize benzo[*b*]furans was pioneered by Grubbs and co-workers[82] in 1994. 2-Vinylphenol vinyl esters **260** and **261** in the presence of Schrock catalyst **262** are cycloisomerized to 2-substituted benzo[*b*]furans **80** and **243** in high yields (Scheme 52).

Later, van Otterlo *et al.*[83] performed a similar ring closure metathesis reaction using a second-generation ruthenium Grubbs catalyst. The precursor compounds were 2-vinylphenol vinyl ethers **263**–**268**, which readily converted, when catalyzed by complex **269**, to functionalized benzofurans **270**–**275** (Scheme 53).

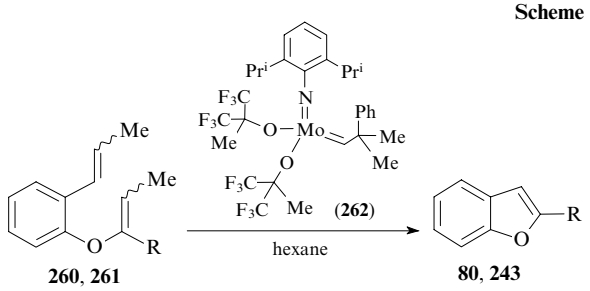
Scheme 50



245–**247** **248**–**250**

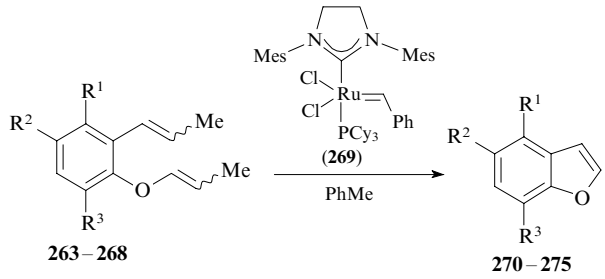
R = Bu^i (**245**; **248**, 63% yield), Bn (**246**; **249**, 58%), Me (**247**; **250**, 66%); Boc is *tert*-butoxycarbonyl

Scheme 52



R = Bn (**260**; **80**, 87% yield), Pr^n (**261**; **243**, 87%)

Scheme 53



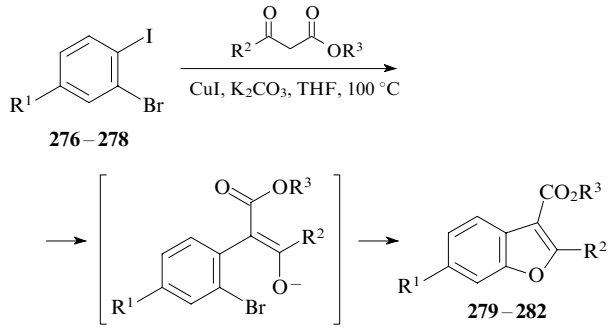
R^1 = R^3 = OMe, R^2 = H (**263**; **270**, 100% yield); R^1 = H, R^2 = R^3 = OMe (**264**; **271**, 96%); R^1 = R^2 = H: R^3 = Ph (**265**; **272**, 63%), CHO (**266**; **273**, 70%), NO$_2$ (**267**; **274**, 82%); R^1 = R^3 = H, R^2 = NO$_2$ (**268**; **275**, 92%); Cy = cyclo-C$_6$H$_{11}$, Mes = 2,4,6-Me$_3$C$_6$H$_2$

IV. Annelation of the furan ring to arenes *via* generation of C(7a) – O bond

IV.1. Cyclization using *o*-dihaloarenes and their analogues

An efficient method was recently developed for preparing benzofuran-3-carboxylic acids through reacting *ortho*-substituted dihalobenzenes with dicarbonyl compounds. 1-Bromo-2-iodobenzene (**276**) and its derivatives **277** and **278** undergo heterocyclization with β-ketoesters catalyzed by copper(I) salts in the presence of potassium carbonate to yield 2,3-substituted benzofurans **279** – **282** (Scheme 54).[84]

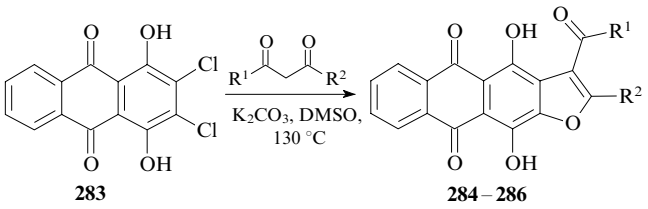
Scheme 54



Substrate	R^1	Product	R^2	R^3	Yield (%)
276	H	**279**	Me	Et	83
276	H	**280**	Me	Bn	71
277	Me	**281**	Me	Et	88
278	Cl	**282**	$(CH_2)_2$Ph	Et	78

Gorelik and Mishina [85] were the first to use this method of annelating furan ring to prepare furanoquinizarin (4,11-dihydroxy-anthra[2,3-*b*]furan-5,10-dione) derivatives in 1983. The condensation of 2,3-dichloroquinizarin (**283**) with 1,3-diketones or β-ketocarboxylic acid esters in the presence of bases produces anthra[2,3-*b*]furan-5,10-diones **284** – **286** (Scheme 55), which have been patented as dispersed yellow dyes for polyester fibre.[86]

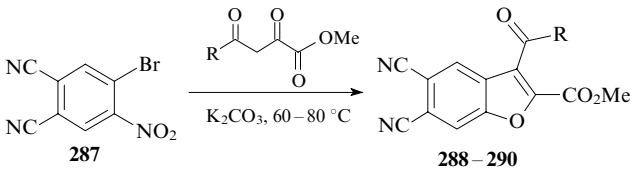
Scheme 55



R^1 = OEt, R^2 = Me (**284**, 58% yield); R^1 = R^2 = Me (**285**, 91%), Ph (**286**, 80%)

A similar method has recently been described for preparing 3-substituted benzo[*b*]furan-2-carboxylic acid esters from *o*-nitrohaloarenes. A reaction of 4-bromo-5-nitrophthalic acid dinitrile (**287**) with 2,4-dioxobutanoic acid derivatives in the presence of potassium carbonate affords heterocyclization products **288** – **290** in moderate yields (Scheme 56).[87] This method also succeeded in preparing benzo[*b*]furan derivatives by condensing picryl chloride with various β-dicarbonyl compounds.[88]

Scheme 56

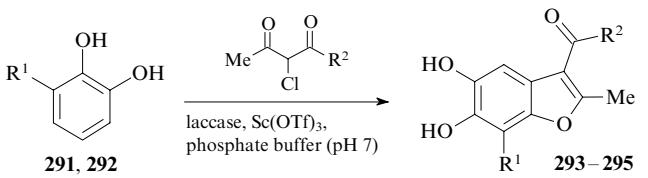


R = 4-MeC$_6$H$_4$ (**288**, 48% yield), 4-MeOC$_6$H$_4$ (**289**, 45%), 2-Th (**290**, 52%)

IV.2. Annelating the furan ring using pyrocatechol derivatives

Witaykran *et al.*[89] developed an efficient method, which met the green chemistry principles, for preparing 5,6-dihydroxybenzo[*b*]furans by reacting pyrocatechols with 1,3-dicarbonyl compounds. Pyrocatechols **291** and **292** are oxidized by the laccase enzyme to *o*-quinones, which are then added to scandium triflate-activated 1,3-dicarbonyl compounds by the Michael reaction. The resulting products are 5,6-dihydroxybenzo[*b*]furans **293** – **295** (Scheme 57). The reaction

Scheme 57

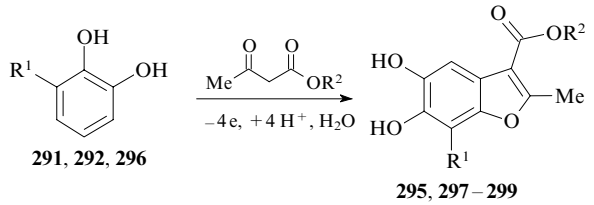


R^1 = H (**291**): R^2 = Me (**293**, 66% yield); R^1 = Me (**292**): R^2 = Me (**294**, 79%), Et (**295**, 48%)

occurs only in neutral media, as laccase has its activity strongly reduced in alkaline media, and at pH 4.5, acetylacetone ionization inhibits the Michael reaction with *o*-quinone.

A similar result was obtained with the electrochemical synthesis of 5,6-dihydroxy-2-methylbenzo[*b*]furan-3-carboxylates from pyrocatechols. Pyrocatechols **291**, **292** and **296** are oxidized in water to *o*-quinones, which are then made to react with acetoacetic acid esters (Scheme 58).[90] Michael 1,4-addition yields 5,6-dihydroxy-2-methylbenzo[*b*]furan-3-carboxylic acid esters **295**, **297**–**299** in good yields.

Scheme 58



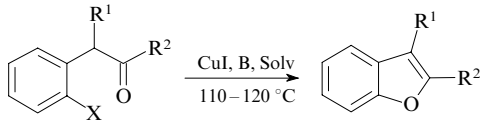
291, **292**, **296** **295**, **297**–**299**

R^1 = H (**291**): R^2 = Et (**299**, 65% yield);
R^1 = Me (**292**): R^2 = Et (**295**, 72%), Me (**297**, 70%);
R^1 = OMe (**296**): R^2 = Et (**298**, 60%)

IV.3. Cyclization of α-(*o*-halophenyl) ketones to yield benzofurans

In order to prepare benzo[*b*]furans, Chen and Dormer[91] used the cyclization of *o*-halobenzyl ketones. *o*-Bromo- and *o*-iodobenzyl ketones **300**–**302** in dimethylformamide in the presence of potassium carbonate undergo copper(I)-catalyzed intramolecular cyclization to form benzo[*b*]furans **303**–**305**. A similar process is suitable for preparing 2-unsubstituted benzo[*b*]furan-3-carboxylates.[92] In the presence of ligands, *o*-chlorobenzyl ketones also enter a similar heterocyclization reaction.[93] Later, this method was implemented with high efficiency in aqueous medium (the yield of desired product amounted to 99%); the base and ligand was *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) (Scheme 59).[94]

Scheme 59



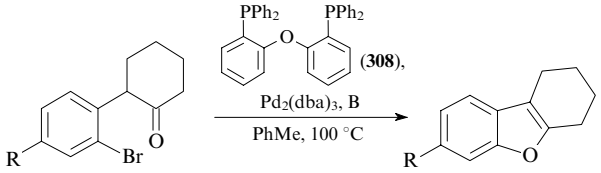
300–**302** **303**–**305**

B isbase, Solv is solvent

Compounds	X	R^1	R^2	Yield (%)
300, **303**	I	Me	4-$MeOC_6H_4$	87
301, **304**	Br	CO_2Et	Ph	88
302, **305**	Br	H	2-$H_2NC_6H_4$	99

Buchwald–Hartwig intramolecular reaction appeared to be efficient for similar cyclization of α-(*o*-haloaryl)cyclohexanones **306** and **307** with $Pd_2(dba)_3$ as the catalyst and ligand **308**.[95] Benzo[*b*]furans **309** and **310** fused with a cyclohexane moiety were prepared in this way (Scheme 60). The product yield strongly depended on the base, so the reaction parameters were varied to prepare a series of benzo[*b*]furan derivatives with various functionalities, which somewhat limits the versatility of this method.

Scheme 60

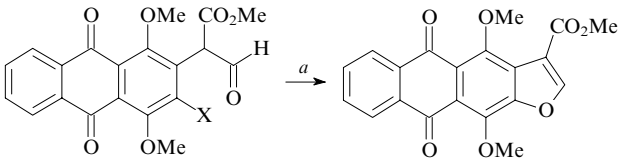


306, **307** **309**, **310**

B = Cs_2CO_3: R = H (**306**; **309**, 95% yield);
B = Bu^tONa: R = F (**307**; **310**, 81%)

This heterocyclization method was adapted to prepare derivatives of 2-unsubstituted 5,10-dioxoanthra[2,3-*b*]-furan-3-carboxylic acid. Heating of 2-(3-haloanthraquinon-2-yl)formylacetic esters **311** and **312** in *N*,*N*-dimethylacetamide in the presence of K_3PO_4 or Na_2CO_3 and catalytic amounts of CuI affords methyl 4,11-dimethoxy-5,10-dioxo-5,10-dihydroanthra[2,3-*b*]furan-3-carboxylate (**313**) (Scheme 61).[96]

Scheme 61

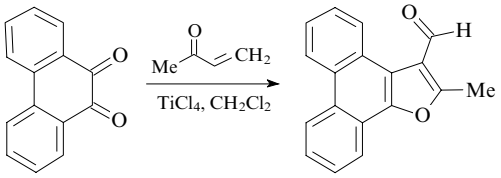


311, **312** **313** (35%–43%)

(*a*) Na_2CO_3, CuI, DMA, 95–115 °C; X = Cl (**311**), Br (**312**)

For phenanthrenes, several approaches to the annelation of furan ring are described with the use of phenanthrene-9,10-dione (**314**) as the substrate. An efficient route to prepare phenanthro[9,10-*b*]furans is the reaction of compound **314** with alkenes substituted at the α-position (Baylis–Hillman reaction). Phenanthrene-9,10-dione (**314**) is condensed with methyl vinyl ketone under titanium tetrachloride catalysis; subsequent intramolecular cyclization produces 2-methylphenanthro[9,10-*b*]furan-3-carbaldehyde (**315**) in good yield (Scheme 62).[97] Basavaiah *et al.*[97] explained the appearance of formyl group by the halogenation of the initial compounds followed by the hydrolysis of cyclization product.

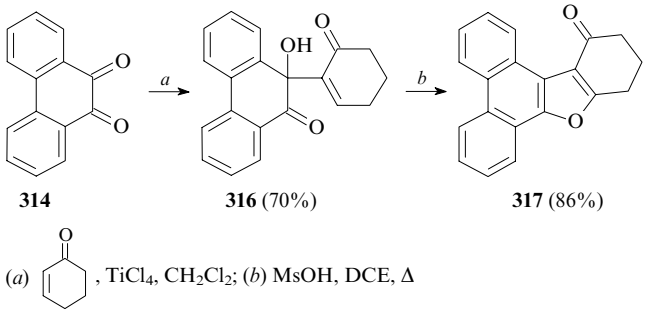
Scheme 62



314 **315** (70%)

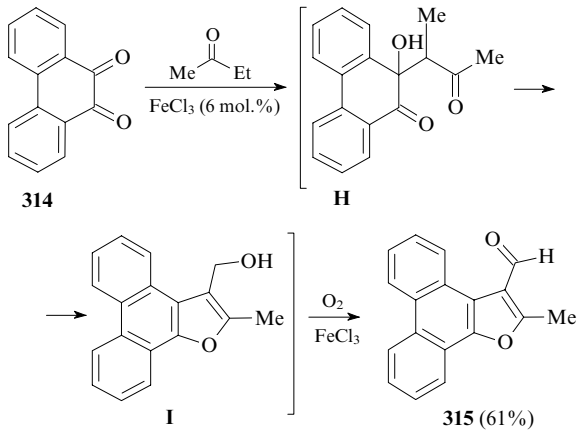
Later, a two-stage modification of this method was proposed for use to prepare fused systems containing a furan ring. At the first stage, phenanthrene-9,10-dione (**314**) and cyclohex-2-en-1-one react to yield 9-hydroxy-10-oxophenanthrene **316**. At the second stage, derivative **316** is converted to phenanthro[9,10-*b*]furan (**317**) in high yield under the action of methanesulfonic acid (MsOH) in dichloroethane (DCE) (Scheme 63).[98]

Scheme 63



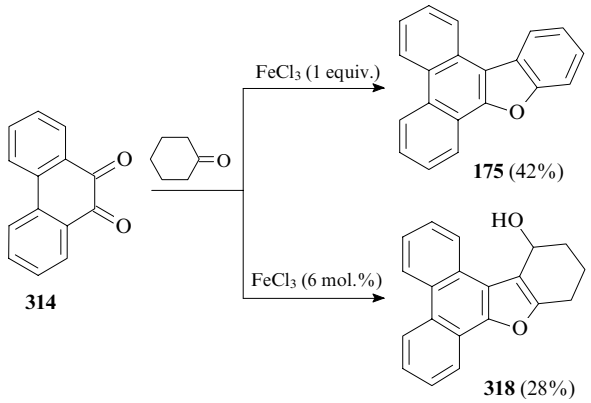
Rao and Vijjapu[99] developed a method for preparing phenanthro[9,10-*b*]furans through the iron(III) chloride-catalyzed aldol condensation of phenanthrene-9,10-dione (**314**) with ketones, followed by heterocyclization. In the presence of catalytic amounts of $FeCl_3$, compound **314** reacts with methyl ethyl ketone to yield 2-methylphenanthro[9,10-*b*]-furan-3-carbaldehyde (**315**). Likely, the initially formed intermediate **H** yields 2-methylphenanthro[9,10-*b*]furan-3-ylmethanol **I** as a result of dehydration followed by cyclization and rearrangement, and the oxidation of **I** by atmospheric oxygen *in situ* yields product **315** (Scheme 64).

Scheme 64



Noteworthy, the result of the reaction of phenanthrene-9,10-dione (**314**) with cyclohexanone under similar conditions depends on the iron(III) chloride amount. In the presence of catalytic amounts of $FeCl_3$, the heterocyclization product is hydroxy derivative **318**; with an equimolar ratio of iron(III) chloride to phenanthrene-9,10-dione (**314**), the reaction with cyclohexanone produces phenanthro[9,10-*b*]benzofuran (**175**) (Scheme 65).[100]

Scheme 65

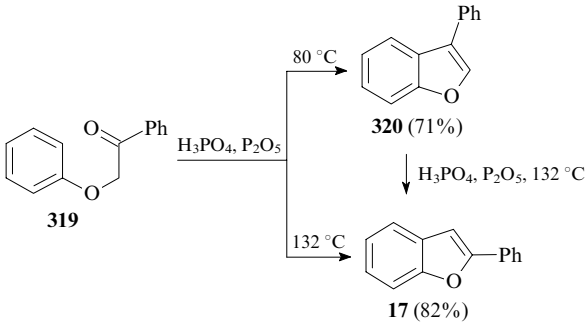


V. Annelation of the furan ring *via* generation of C(3)–C(3a) bond

The generation of C(3)–C(3a) bond is the basis of one of the first methods for preparing benzo[*b*]furan as described in the late 19th century by Stoermer.[101] Stoermer discovered that small amounts of benzo- and naphthofurans were formed when aryloxyacetaldehydes were treated with glacial acetic acid in the presence of zinc chloride. An extensive study of the synthetic potentials of this type of heterocyclization culminated in the development of some efficient preparative methods for the production of benzo[*b*]furan derivatives. The initial compounds used in these reactions are aryloxy ketones and their analogues.

The annelation of the furan ring through the cycloisomerization of aryloxy ketones was first described in 1958.[102] This method makes it possible to regioseletively prepare 2- or 3-substituted benzo[*b*]furans by varying reaction parameters. When α-phenoxyacetophenone (**319**) is heated to 80 °C in polyphosphoric acid, it is cyclized to 3-phenylbenzo[*b*]furan (**320**). When the process temperature increases to 132 °C, the cyclization of compound **319** in polyphosphoric acid is accompanied by rearrangement and yields 2-phenylbenzofuran (**17**) (Scheme 66).

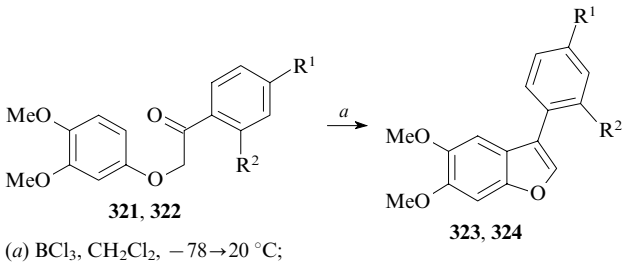
Scheme 66



Soft Lewis acids, for example, boron trichloride, are useful to convert aryloxy ketones to benzofurans. Compounds **321** and **322** experience intramolecular cyclization under the action of boron trichloride, followed by dehydration and formation of benzo[*b*]furans **323**, **324** (Scheme 67).[103]

This strategy also applies to the preparation of naphthofurans. α,β-Naphthyloxy ketones **325** and **326** under

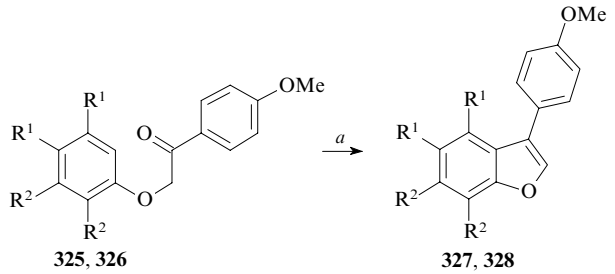
Scheme 67



(*a*) BCl_3, CH_2Cl_2, −78→20 °C;
R^1 = OMe, R^2 = H (**321**; **323**, 91% yield); R^1 = H, R^2 = OMe (**322**; **324**, 86%)

similar conditions are converted to isomeric angular naphtho[*b*]furans **327** and **328** in high yields (Scheme 68).[103]

Scheme 68

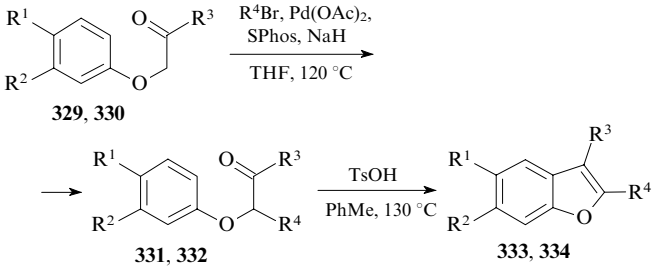


325, **326** **327**, **328**

(*a*) BCl_3, CH_2Cl_2, −78→20 °C;
R^1–R^1 is benzo, R^2 = H (**325**; **327**, 83% yield);
R^1 = H, R^2–R^2 is benzo (**326**; **329**, 85%)

The above-described strategy was successfully modified and supplemented with the stage comprising preliminary palladium-catalyzed α-arylation of initial aryloxy ketones, which made it possible to synthesize benzofurans having an additional aryl group in position 2. The cross-coupling of aryloxy ketones **329** and **330** with aryl bromides catalyzed by the $Pd(OAc)_2$–SPhos–NaH system (SPhos is 2,6-dimethoxy-2′-dicyclohexylphosphinobiphenyl) yielded arylation products **331** and **332**, which were heterocyclized to 2,3-diarylbenzofurans **333** and **334** when heated with TsOH (Scheme 69).[104]

Scheme 69

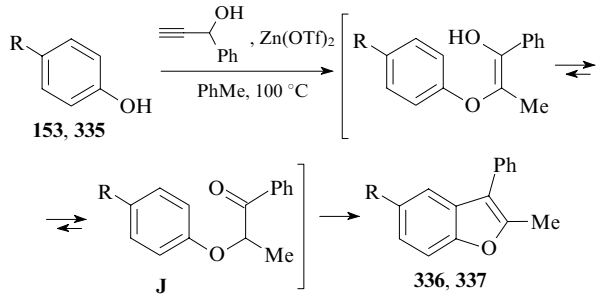


329, **330** **331**, **332** **333**, **334**

R^1 = Bu^t, R^2 = H, R^3 = Ph (**329**): R^4 = 4-$MeOC_6H_4$ (**331**, 83% yield; **333**, 63%); R^1 = H, R^2 = OMe, R^3 = 4-$MeOC_6H_4$ (**330**): R^4 = 4-ClC_6H_4 (**332**, 64%; **334**, 94%)

Phenols having no substituents in the *ortho*-position also find use in the synthesis of benzo[*b*]furans. For example, phenol (**153**) or *p*-hydroxyanisol (**335**) reacts with 1-phenylpropargyl alcohol under $Zn(OTf)_2$ catalysis in toluene at

Scheme 70



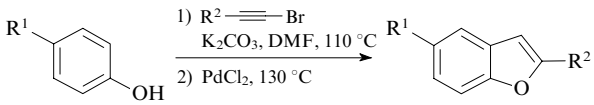
153, **335** **J** **336**, **337**

R = H (**153**; **336**, 86% yield); OMe (**335**; **337**, 91%)

100 °C to produce 2-methyl-3-phenylbenzofurans **336** and **337** in high yields (Scheme 70).[105] The heterocyclization scheme includes nucleophilic addition at the triple bond of the propargyl alcohol to yield aryloxy ketones **J**. Furan ring annelation is due to the cycloisomerization of the *in situ* obtained adduct induced by catalytic amounts of zinc(II) triflate.

The synthesis of 2-substituted benzofurans based on the metal-catalyzed C–H-activation of phenols having free *ortho*-positions was developed by Wang *et al.*[106] At the first stage, there is nucleophilic addition of phenols **153** and **338** to bromoalkyne in the presence of a base. Then, the intermediate is subjected to palladium-catalyzed intramolecular cross-coupling to produce 2-substituted benzofurans **17**, **339** and **340** in high yields (Scheme 71). *p*-Nitrophenol (**338**) was noticed to be more reactive than unsubstituted phenol (**153**) or its derivatives, which have electron-withdrawing groups in *para*- and *meta*-positions.

Scheme 71



153, **338** **17**, **339**, **340**

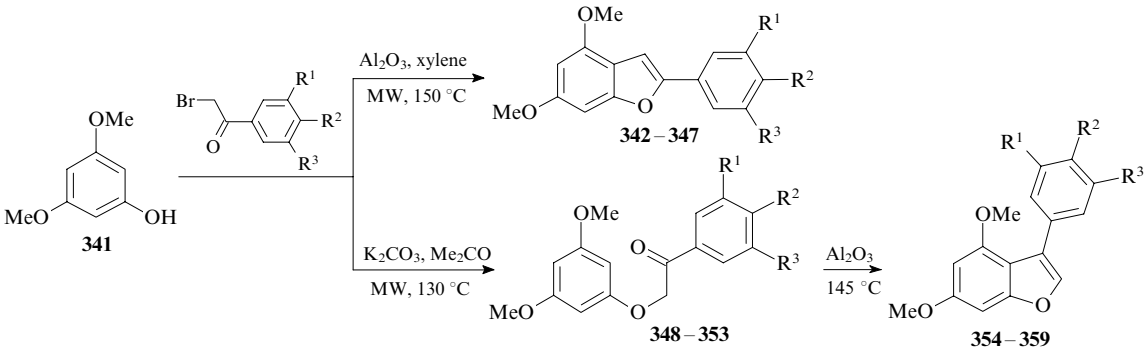
R^1 = H (**153**): R^2 = Ph (**17**, 73% yield), 2-ClC_6H_4 (**339**, 71%);
R^1 = NO_2 (**338**): R^2 = Ph (**340**, 91%)

Another example of the use of *ortho*-unsubstituted phenols for the regioselective preparation of 2- or 3-substituted benzo[*b*]furans is provided by Cossio *et al.*[107] In the presence of Al_2O_3, 3,5-dimethoxyphenol (**341**) adds to the carbonyl group of an α-bromoacetophenone, and the subsequent intramolecular cyclization of the adduct under microwave exposure yields 2-substituted benzofurans **342**–**347**. In order to obtain 3-substituted benzo[*b*]furans, the synthesis is carried out in two stages with the isolation and purification of intermediates. At the first stage, compound **341** is alkylated by α-bromoketones under alkaline conditions to produce aryloxy ketones **348**–**353** in high yields. Subsequent Friedel–Crafts intramolecular reaction in the presence of Al_2O_3 yields 3-substituted benzofurans **354**–**359** (Scheme 72).

A method proposed for the synthesis of natural benzo[*b*]furans derived from *Calea* plants was based on the Lewis acid-catalyzed intramolecular cyclization of methyl-2-aryloxy-3-dimethylaminoacrylate derivatives and their keto analogues. First, phenols **360** and **361** are alkylated by α-chlorocarbonyl compounds in the presence of bases (NaOH, K_2CO_3) in water or acetone to produce esters **362** and **363** in high yields (Scheme 73).[107] The condensation of derivatives **362** and **363** with dimethylformamide dimethylacetal (DMA–DMF) under long-term heating (24 h) or under microwave activation yields enamines **364** and **365**, whose $ZnCl_2$-catalyzed intramolecular heterocyclization yields benzo[*b*]furan **366** and caleprunin A (**5**) (Scheme 74).[108]

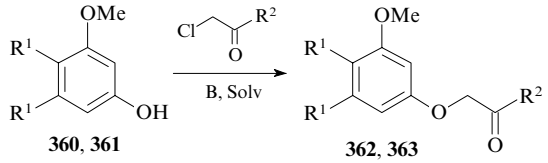
The Lewis acid-catalyzed cycloaddition of oxiranes to benzoquinones **367**–**369** appeared to be an efficient route to prepare 2,3-substituted benzofurans. Under the action of boron trifluoride etherate, *trans*-2,3-diphenyloxirane (**370**) generates a cation that is attacked by the carbonyl oxygen atom of the quinone from the side that is least sterically hindered. Subsequent proton migration and the intramolec-

Scheme 72



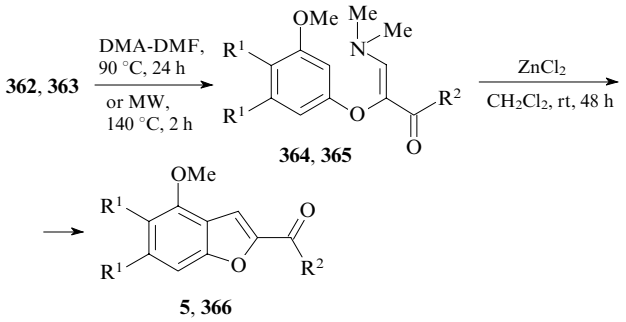
Compound	R^1	R^2	R^3	Benzofuran yield (%)	Compound	R^1	R^2	R^3	Benzofuran yield (%)
342	H	OMe	H	50	**348**, **354**	H	OMe	H	70
343	OMe	H	OMe	86	**349**, **355**	OMe	H	OMe	50
344	OMe	OMe	OMe	75	**350**, **356**	OMe	OMe	OMe	50
345	H	NO_2	H	44	**351**, **357**	OBn	H	OBn	26
346	H	CN	H	24	**352**, **358**	H	CN	H	42
347	F	H	F	46	**353**, **359**	F	H	F	68

Scheme 73



R^1 = H (**360**, **362**), OMe (**361**, **363**); R^2 = OMe (**362**, 81% yield), Me (**363**, 92%)

Scheme 74



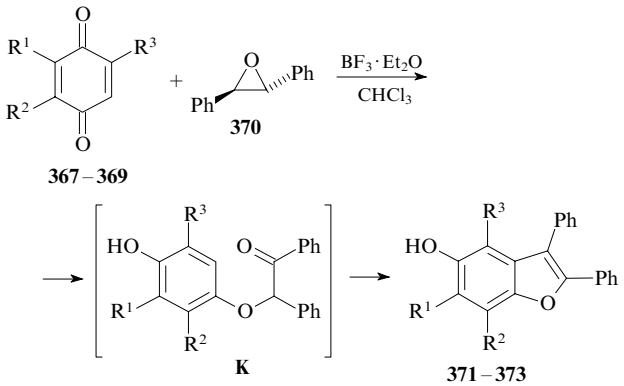
R^1 = H, R^2 = OMe (**364**; **366**, 62% yield); R^1 = OMe, R^2 = Me (**365**; **5**, 61%)

ular Friedel – Crafts reaction of the thus-prepared adduct **K** produce 2,3-diphenylbenzofurans **371** – **373** in moderate yields (Scheme 75).[109]

VI. Conclusion

During the last decade, some new preparative strategies have been developed and classical routes to annelate the furan ring to arenes improved. These strategies make it possible to prepare polyfunctional derivatives of benzofuran and its analogues, which are of interest for medicinal chemistry and other fields of chemistry. One general trend

Scheme 75



R^2 = H: R^1 = R^3 = Me (**367**; **371**, 77% yield), OMe (**368**; **372**, 47%); R^1 = R^2 = OMe, R^3 = Me (**369**; **373**, 76%)

in the types of heterocyclizations we consider in this survey is to use catalytic reactions, which allow increasing synthesis efficiency and attaining high yields of desired products.

Metal-catalyzed cross-coupling of 2-halophenol derivatives with terminal alkynes and alkenes, followed by the heterocyclization of intermediates, may be classified with the very important and versatile strategies. Further, schemes comprising the condensation of salicylaldehyde and its analogues with α-haloketones and α-haloacetates are efficient for preparing polysubstituted benzofurans. These schemes use available initial compounds and chemicals and make it possible to modify substituents efficiently both in positions 2 and 3 of the heterocycle and in the carboaromatic ring. Some schemes have been approved in preparing furan-containing polyaromatic systems (naphtho[1,2-*b*]furan, phenanthro[2,3-*b*]furan, anthra[2,3-*b*]furan-5,10-dione, *etc.*) which have biological activities. Catalytic cyclization methods provide higher product yields, reduce the number of synthesis steps, and minimize wastes.[110] Some methods meet the green chemistry principles, thereby acquiring more merits to serve as the

base for environmentally friendly low-waste or waste-free technologies.

Despite these advances, further development and a search for new versatile methods for annelating the furan ring to arenes still remain a topical problem, whose future solution will expand the application potentials of this series of compounds.

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