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METHODS FOR THE SYNTHESIS OF HETEROARYL-SUBSTITUTED 1,4-BENZO- AND 1,4-NAPHTHOQUINONES (REVIEW)

N. G. Batenko, G. Karlivans, and R. Valters

Methods for the synthesis of heteroaryl-substituted 1,4-benzo- and 1,4-naphthoquinones with a C–C bond between the heterocycle and quinone fragments are reviewed.

Keywords: heteroaryl-1,4-benzoquinones, heteroaryl-1,4-naphthoquinones, synthesis.

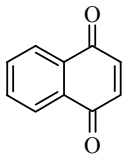
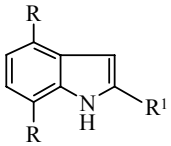
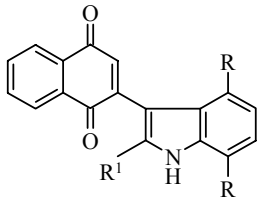
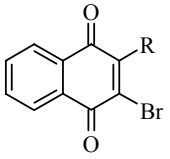
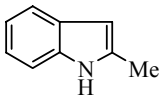
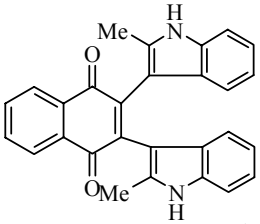
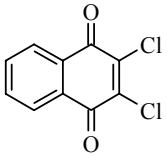
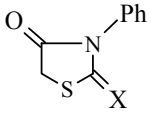
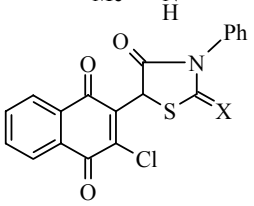
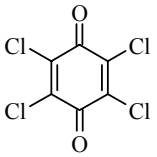
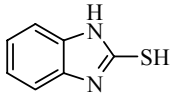
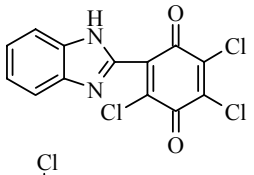
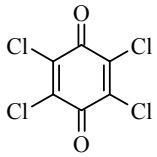
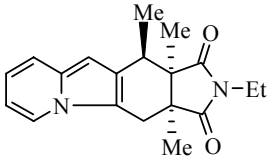
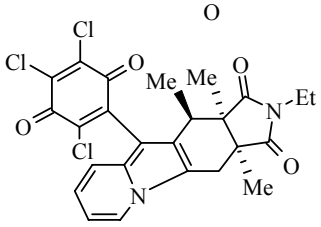
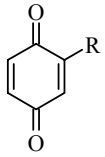
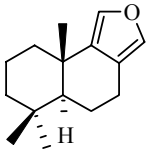
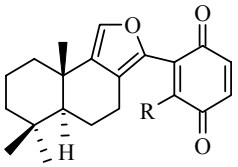
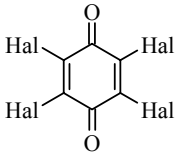
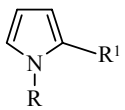
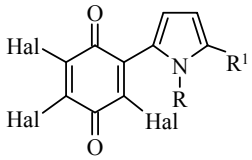
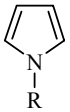
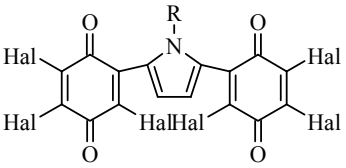
Benzoquinones and their derivatives are widely used in organic synthesis as synthons and reagents [1, 2]. They are used as electron-accepting components for the production of charge-transfer complexes and radical-ion salts [3, 4]. Derivatives of benzoquinones, isolated from natural sources, are subunits in many biological processes, such as electron transport, the photosynthesis of plants, the coagulation of blood, and cell respiration [1, 2, 5]. Reviews have been published on the synthesis of hydroxyquinones [6] and 1,4-benzoquinones condensed with heterocycles [7, 8], but methods for the synthesis of heteroaryl derivatives of 1,4-benzoquinones and 1,4-naphthoquinones where the fragments of the heterocycle and the quinone are linked by a C–C bond have not so far been reviewed. Heteroaryl-substituted benzoquinones have demonstrated anticancer [9-11], antifungal, and antibacterial characteristics [11] and antidiabetic activity [12]. The present review is devoted to the analysis and classification of methods for the production of these compounds. Methods for the synthesis of heteroaryl derivatives of quinones can be divided into three groups: The formation of a C–C bond between the quinone and the heterocycle, construction of the heterocycle on the basis of the quinone, and construction of the quinone on the basis of the heterocycle.

1. METHODS WITH C–C BOND FORMATION

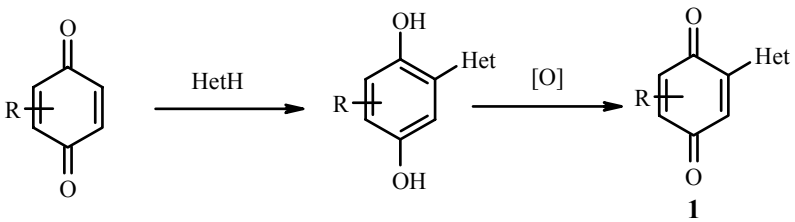
1.1. Noncatalytic Formation of the Carbon–Carbon Bond

This process can take place as addition or substitution. In the case of addition the quinone is transformed into the hydroquinone, which is oxidized by the excess of the quinone or by special oxidizing agents. Heteroaryl derivatives obtained by this method are shown in the following table.

Riga Technical University, Riga, Latvia; e-mail: rvalters@latnet.lv. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 803-833, June, 2005. Original article submitted February 13, 2005.

Quinone	Heterocycle	Product	Method*	References
	 R = H, OH; R^1 = H, Me, CHO, CO_2H		A	[13]
 R = Br, OMe			A	[14, 15]
	 X = S, O		B	[16]
			B	[17]
			A	[18]
 R = COMe, CO_2Me, NO_2			B	[19, 20]
 Hal = Cl, Br	 R = H, Me R^1 = H, Ar, CO_2H		B	[21–23]
	 R = H, Me		B	[21, 23]

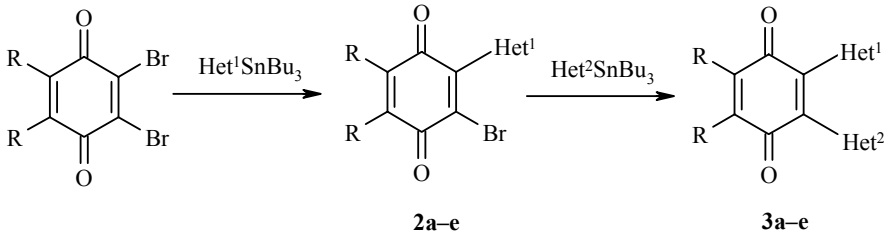
* The reaction is carried out with heat (A) or at room temperature (B).



R = H, Alk, OAlk, Hal

1.2. Reactions of Haloquinones with Heteroarylstannanes, Catalyzed by Palladium

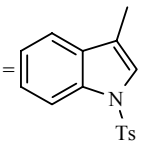
The reaction of dibromoquinones with tributylstannylheteroarenes is carried out under the conditions of the Stille reaction. The reaction between organotin compounds and various electrophiles takes place under neutral conditions in the presence of catalytic amounts of palladium [24] and has a high degree of selectivity. Both symmetricaly [25, 26] and unsymmetrically substituted quinones [26] can be obtained by this method. The usual catalyst is $Pd(PPh_3)_4$. Symmetrical 2,3-diheteroaryl-1,4-benzoquinones are produced by the reaction of 1 eq. of 2,3-dibromoquinone with 2 eq. of tributylstannylheteroarene with yields of ~70%. Diheteroaryl-benzoquinones **3** with various substituents at positions 2 and 3 are produced according to the following scheme [25, 26]:

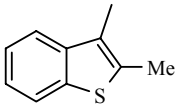


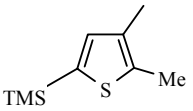
2a–e **3a–e**

2,3 a-c R = Me, **d**, **e** R + R = benzo; **a-c** Het^1 = 2-cyano-1,5-dimethylpyrrol-4-yl;

2 d Het^1 = 2-phenyl-4-furyl, **e** Het^1 = 1-methyl-2-phenylpyrrol-4-yl;

3 a Het^2 = 

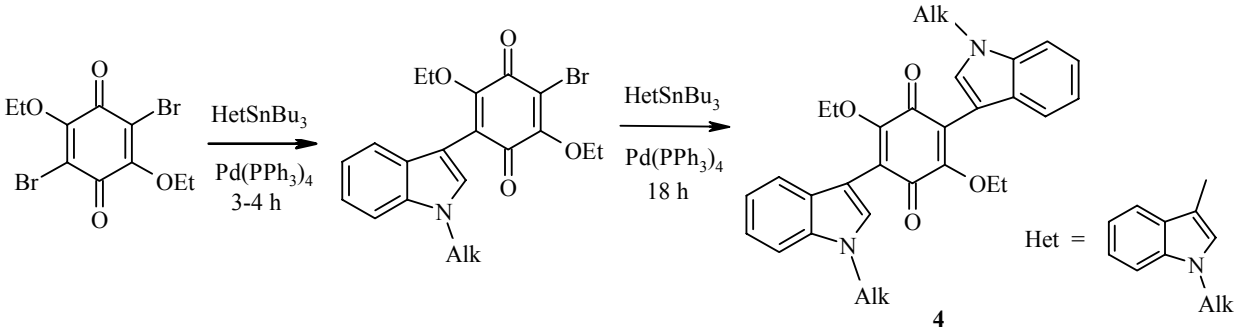
, **b** Het^2 = 

, **c** Het^2 = 

,

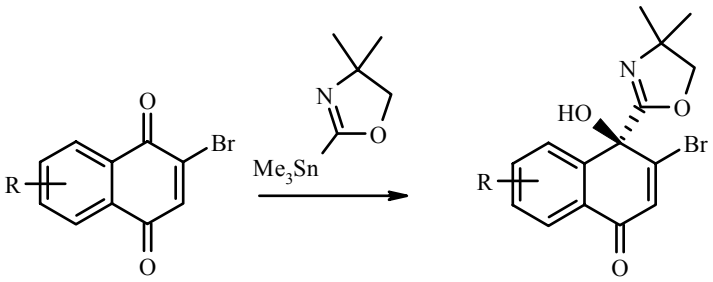
d,e $Het^1 = Het^2$

In the reaction of 2,5-dibromobenzoquinone with an excess of 3-indolylstannane under the standard conditions for the Stille reaction the monosubstituted product is formed initially, and the 2,5-disubstituted benzoquinone **4** is then formed more slowly [27]. By this two-stage method it is possible to obtain 2,5-bisindolylquinones with various alkyl substituents at the nitrogen atom.



4

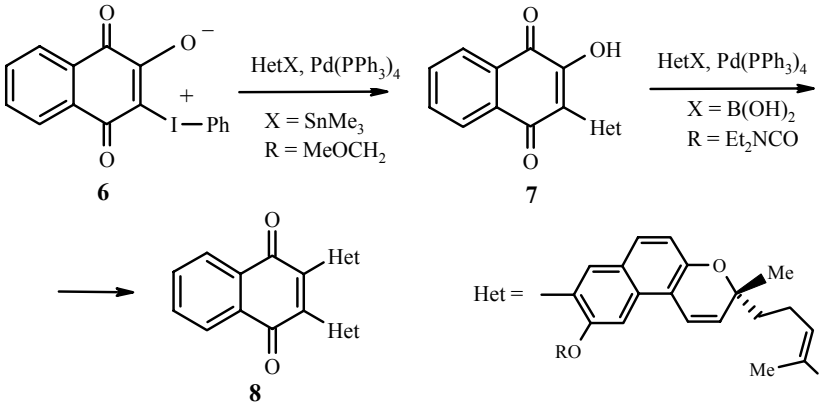
A similar reaction takes place between pyranylstannane and 2-bromo-1,4-naphthoquinone in boiling toluene [28, 29]. The formation of the carbon–carbon bond requires the presence of 5% of $Pd(PPh_3)_4$. When the reaction conditions were optimized, it was found that the addition of CuBr to the $Pd(PPh_3)_4$ increased the yield of the final product and/or reduced the reaction time.



R = H, OMe **5**

The use of analogous reaction conditions for the production of oxazolin-2-yl-1,4-naphthoquinone did not give a positive result. The authors [30] therefore rejected the use of a catalyst, and this led to addition of the oxazoline at the vicinal carbonyl group in relation to the bromine atom. The reaction takes place regioselectively with the formation of a single product **5**. It is notable that addition takes place at the sterically more hindered carbonyl group.

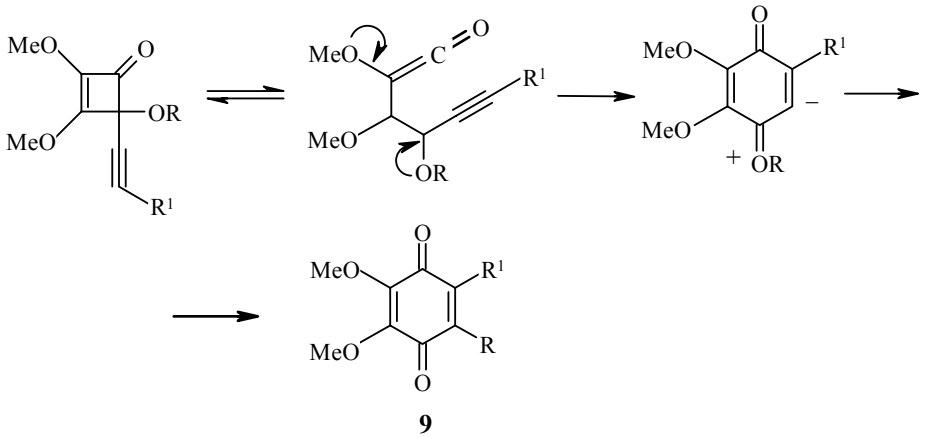
In the reaction of naphthopyranylstannane with the betaine **6** [31] the naphthoquinone **7** is formed with a yield of 75%. We note that the introduction of an analogous substituent at position 3 under the conditions of the Stille reaction [$Pd(PPh_3)_4$/LiCl/dioxane/60°C] is more complicated and gives lower yields. However, if the conditions of the Suzuki reaction are used [$Pd(PPh_3)_4/K_3PO_4$/DMF/60°C] are used, the yield of the 2,3-disubstituted quinone **8** is increased to 20%.



6 **7** **8**

1.3. Reaction of Stannylquinones with Heteroaryl Iodides Catalyzed by Palladium

The tributylstannylquinones **9** are produced by the recyclization of 4-alkynylcyclobutenones [32, 33]:



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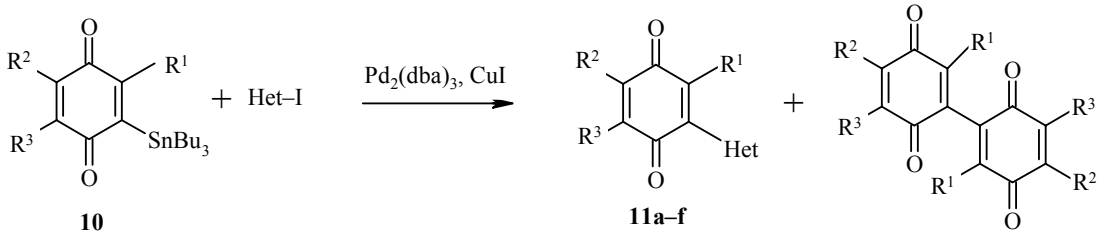
R = H, $SnBu_3$, $SiMe_3$; R^1 = Me, Bu, $SiMe_3$

2-Tributylstannyl-1,4-naphthoquinones were also produced in the reactions of 2-bromo-1,4-naphthoquinones with butylstannanes at a palladium catalyst [34].

In the reactions of stannyl derivatives of quinones **10** with heteroaryl iodides compound **11** is formed as main product, and the symmetrical quinone dimer **12** is formed as side product [35]. We note that in order to reduce the formation of the quinone dimer 2 eq. of the heteroaryl iodide was first added to the palladium catalyst, and only then was the stannylquinone **10** added. The catalyst consisted of 2.5 mole % of $Pd_2(dba)_3$ (dba = dibenzylideneacetone), 50 mol % of CuI, and 20 mol % of Ph_3As (as required).

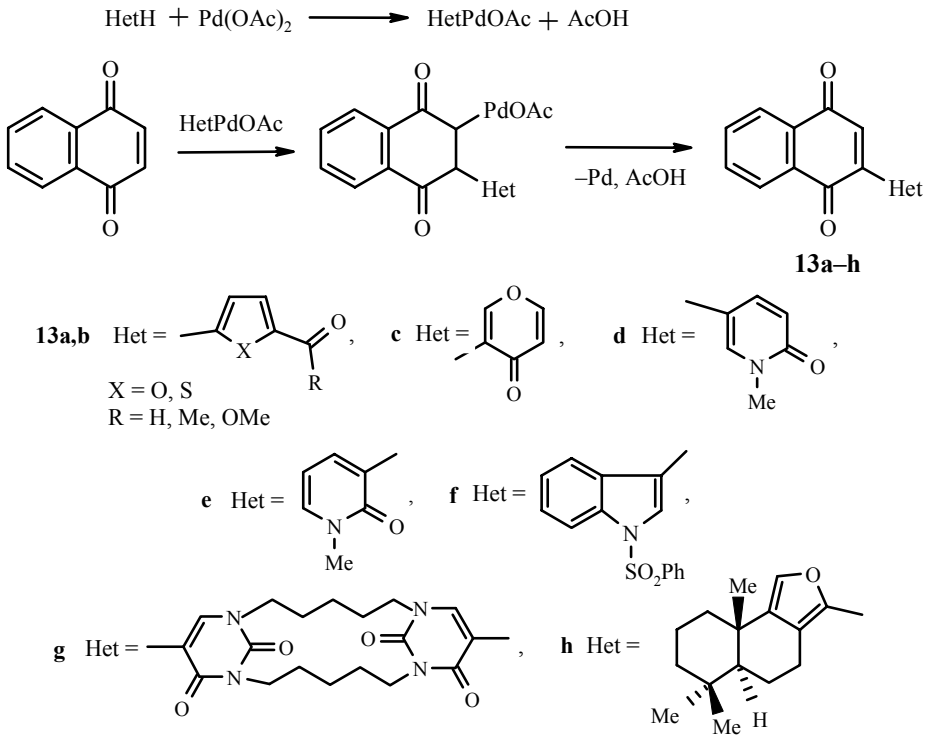


10 **11a–f** **12**

11a-d $R^1 = R^2 = R^3$ = Me; **a** Het = 2-thienyl; **b** Het = 5-pyrimidyl,
c Het = 4-(1-methoxymethyl)pyrazolyl, **d** Het = 2-pyridyl; **e** R^1 = Bu, R^2 = Me,
R^3 = OMe, Het = 5-pyrimidyl; **f** $R^1 = SiMe_3$, $R^2 + R^3$ = benzo, Het = 5-pyrimidyl

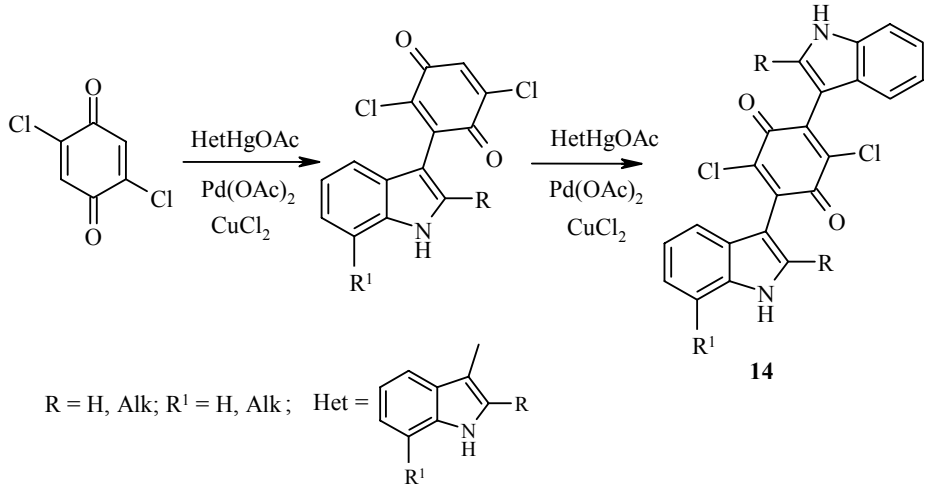
1.4. Oxidative Coupling of 1,4-Naphthoquinones with Heteroarenes by the Action of Palladium Acetate

Heteroaryl-substituted 1,4-naphthoquinones can be obtained by oxidative coupling. Examples of reactions between heteroarenes and olefins in the presence of palladium acetate are well known [36]. This method was used for the production of substituted 1,4-naphthoquinones **13a-f** [11], **13g** [37], and **13h** [38].



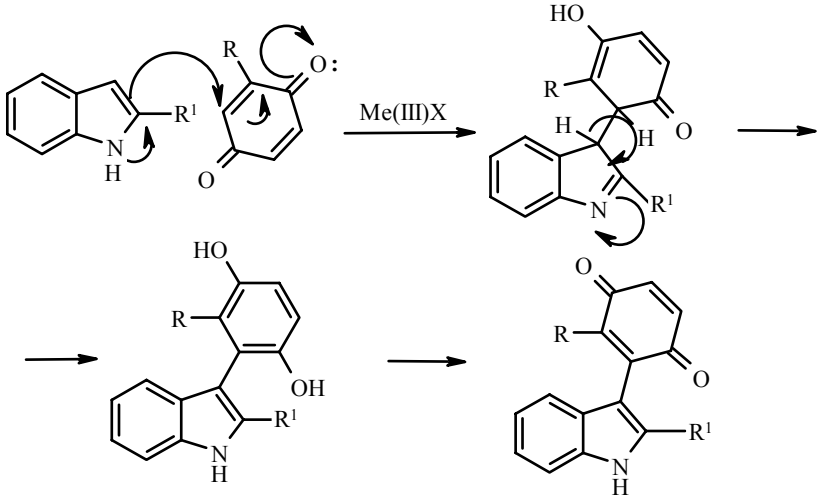
According to data in [11], oxidative coupling between naphthoquinone and thiophene or furan does not occur under these conditions. However, the reaction can be realized if the furan and thiophene contain a formyl, acetyl, or ester group as substituent at position 2. The process leads to the formation of an initial heteroarylpalladium intermediate, which in turn readily reacts with 1,4-naphthoquinone. The final heteroarylnaphthoquinones **13** are formed after boiling in acetic acid with yields of 18-79%, depending on the heterocycle used.

It was also possible to obtain 2,5-bis(3-indolyl)-1,4-benzoquinones **14** by this method. In this case the formation of the C–C bond is preceded by the substitution of AcOHg by AcOPd at position 3 of the sterically hindered indoles. However, since the initial condensation product is relatively unstable, the yield of the final benzoquinone **14** was less than 10% [27].



1.5. The Formation of a C–C Bond between the Quinone and the Heterocycle Catalyzed by Acids

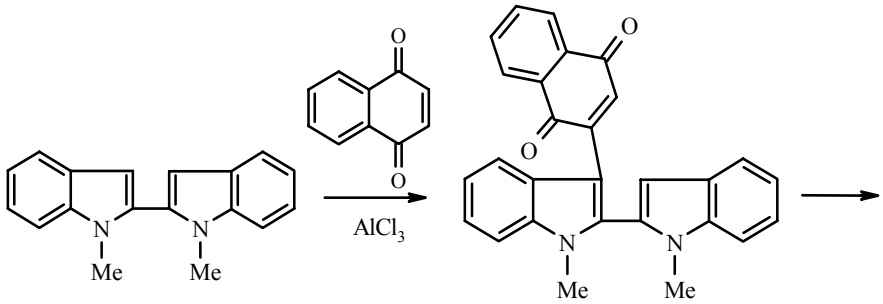
Lewis Acids. Lewis acids have recently been used widely for the synthesis of heteroarylbenzoquinones. A series of communications have been published on the synthesis of indolylbenzoquinones [39-42], benzopyranylbenzoquinones [43], and tetrahydrofuryl- and tetrahydropyranylbenzoquinones [44].



15

Me(III)X = $InBr_3$, $Bi(OTf)_3$; R = H, Me, Cl; R^1 = H, Me

The formation of the indolylbenzoquinone **15** [39, 41] probably involves addition of the indole to the quinone activated by the Lewis acid. The product tautomerizes to the hydroquinone, which is soon oxidized by a second equivalent of 1,4-benzoquinone. The method can be used for indoles containing both electron-donating and electron-withdrawing substituents. During the reaction of 2,2'-bisindole **16** with naphthoquinone in the presence of aluminum trichloride a racemic mixture of symmetrical atropoisomers **17** is formed.



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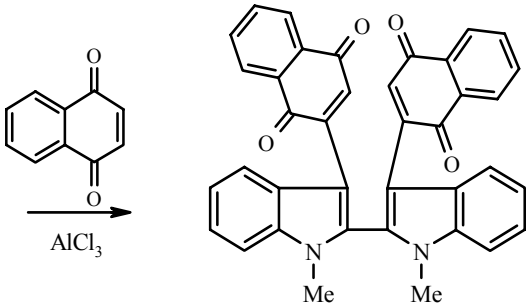

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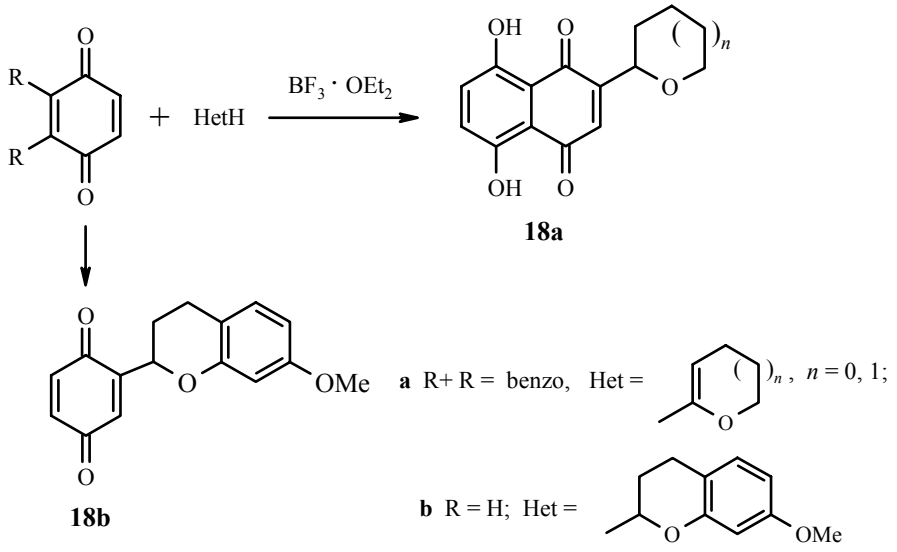
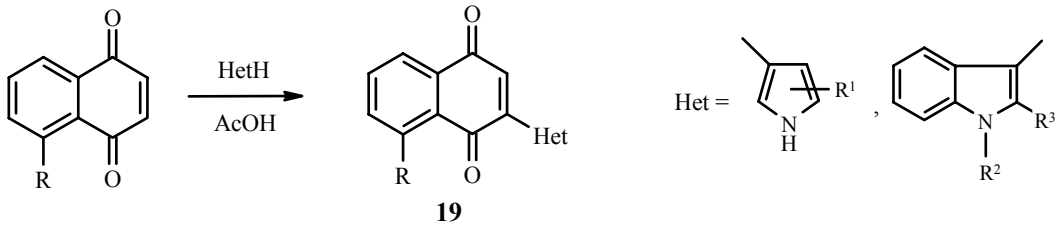


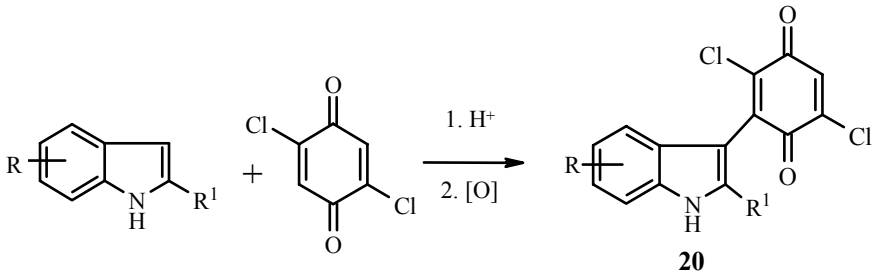
In the reaction of dihydrofuran or dihydropyran with 5,8-dihydroxy-1,4-naphthoquinone (naphthazarin) initial attack occurs at the hydroquinone ring. On account of the presence of the two hydroxyl groups at positions 5 and 8 the naphthazarin forms a tautomeric system. The reaction product tautomerizes to the more stable form **18a** [44], in which the substituent is already in the quinone ring. The reaction of chromene with benzoquinone in the presence of BH_3 and subsequent oxidation by atmospheric oxygen lead to the quinone **18b** [43].

Acetic Acid. In the reactions of 1,4-naphthoquinones with alkyl-substituted pyrroles [45] or indoles [46, 47] in the presence of acetic acid 2-heteroaryl-1,4-naphthoquinones **19** are formed.



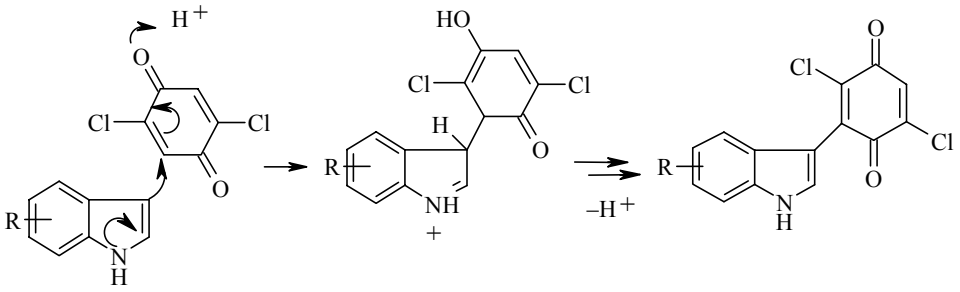
R = H, OH; R^1 = H, Alk, OAlk, Ac; R^2 = H, Alk; R^3 = H, Me

Mineral Acids. The condensation of indoles with 2,5-dichloro-1,4-benzoquinones, catalyzed by HCl or H_2SO_4, was used for the synthesis of a large group of substituted indol-3-yl-1,4-benzoquinones **20** [10, 48, 49].



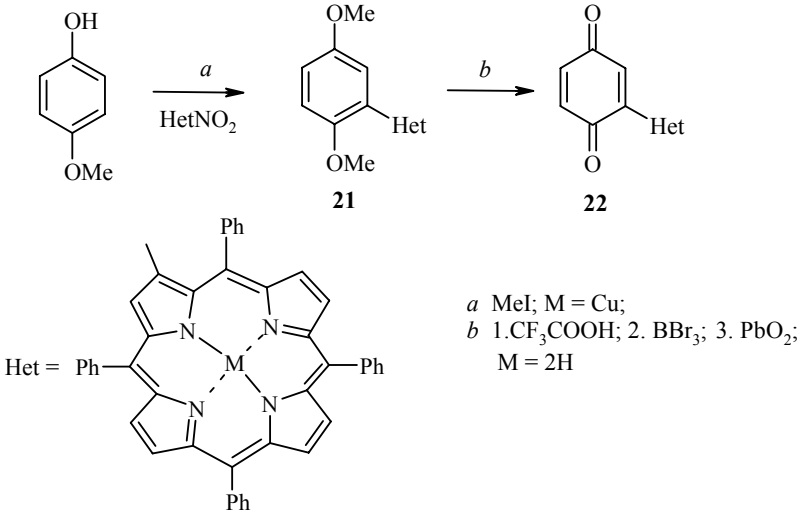
R = H, Alk, OAlk, Ar, OAr, Hal; R^1 = H, Alk, Ar

In the proposed mechanism for the formation of indol-3-ylquinones the proton activates the unsubstituted position of the quinone, to which the indole is then added. The initial addition product tautomerizes to the hydroquinone and is then oxidized to the final product **20** [10, 49].



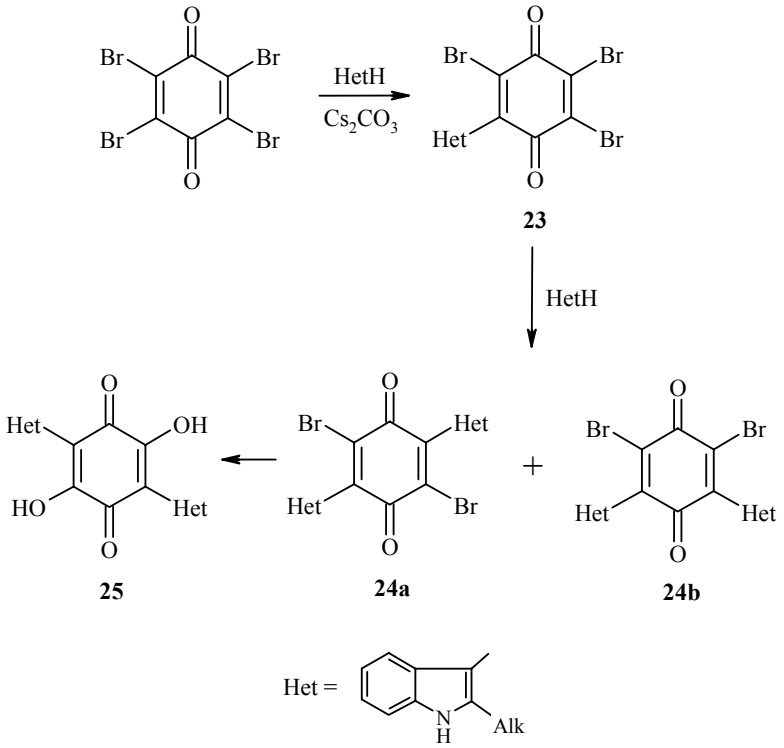
The reaction takes place more readily between benzoquinone and alkyl-substituted indoles than with halogen-substituted indoles, which give lower yields. The presence of a substituent at position 4 of the indole has a negative effect on the reaction, and this is clearly due to steric screening of the reaction center.

Other Catalysts. When copper 2-nitro-5,10,15,20-tetraphenylporphyrinate is boiled in *p*-methoxyphenol in the presence of sodium hydroxide, a bond is formed between the benzene ring and the β-carbon atom of one of the pyrrole rings. Further methylation leads to 1,4-dimethoxybenzene (**21**), while subsequent demethylation and oxidation lead to the covalently bonded porphyrin–quinone system **22** [50].



A method was described [9] for the effective and fast synthesis of 2,5-bis(indol-3-yl)-3,6-dihydroxy-1,4-benzoquinones in the reaction of *p*-bromoanil with 2-alkylindoles. The treatment of 1 eq. of *p*-bromoanil with 2 eq. of indole in the presence of cesium carbonate in acetonitrile at room temperature leads to a mixture of regioisomers **24a** (46%) and **24b** (44%). The monoadduct **23** is formed more quickly (~2 h) than the second equivalent of indole is added (~22 h). Hydrolysis of the quinone **24a** by boiling in a water–alcohol solution of

potassium hydroxide leads to a 78% yield of 2,5-bisindolyl-3,6-dihydroxybenzoquinone. We note that it was not possible to hydrolyze the quinone **24b** in a similar manner. The dihydroxyquinone **25** can be obtained without previous isolation of the regioisomers by hydrolysis of their mixture.

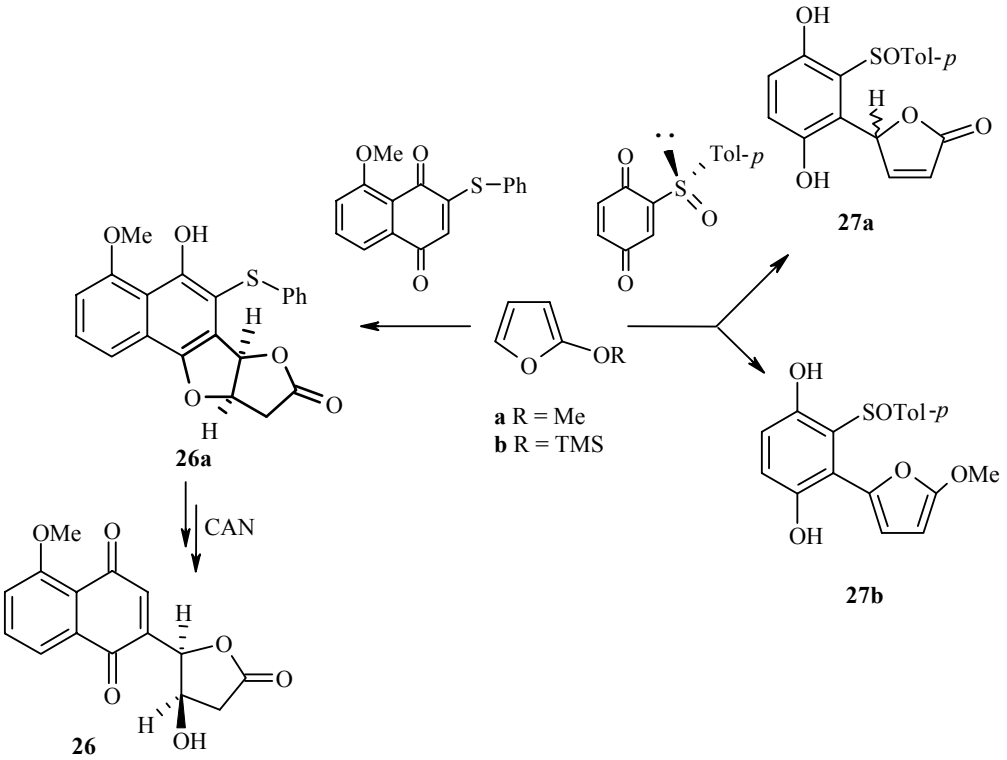


Asterriquinones (2,5-bisindol-3-yl-3,6-dimethoxy-1,4-benzoquinones in which the indole fragments have 3-methylbut-2-enyl or 1,1-dimethylprop-2-enyl substituents at positions 1 and 2 of the indole) are a group of compounds isolated from *Aspergillus terreus* and have anticancer, antidiabetic, and antiviral activity [27]. A series of modifications of both the alkyl substituents of the indole [51] and the hydroxy groups of the quinone [52, 55] have been made in order to investigate the relation between the chemical structure and the biological activity.

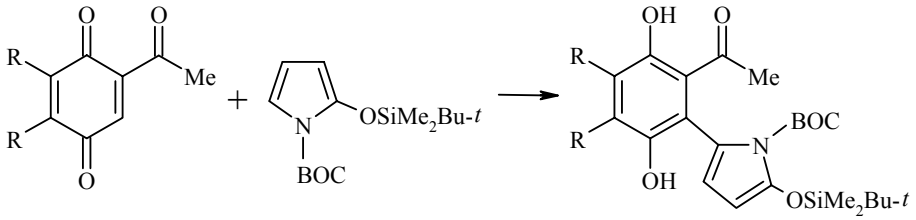
1.6. Reaction of Heterocycles with Activated Quinones

The reaction of 2-trimethylsiloxyfuran with activated naphthoquinone gives the adduct **26a**, which then undergoes oxidative cleavage with cerium ammonium nitrate (CAN). Further transformations lead to the naphthoquinone derivative **26** (juglomycin A) [54].

The formation of compounds **27a** and **27b** [55] results from the reaction of furan substituted at position 2 with activated benzoquinone. The nucleophilic C-5 atom of the furan is first attacked by the electrophilic C-3 atom of the benzoquinone, and the initial intermediate is then aromatized.



If the electron-deficient 2-acetyl-substituted 1,4-benzo- or 1,4-naphthoquinones are used, the product **28** results from electrophilic substitution at the C-5 atom of the pyrrole [56, 57].

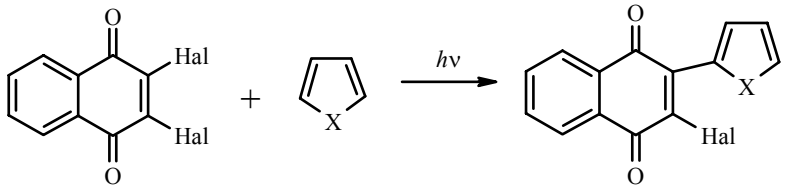


a R + R = benzo; **b** R = H

28a,b

1.7. Formation of the C–C Bond in Homolytic Reactions

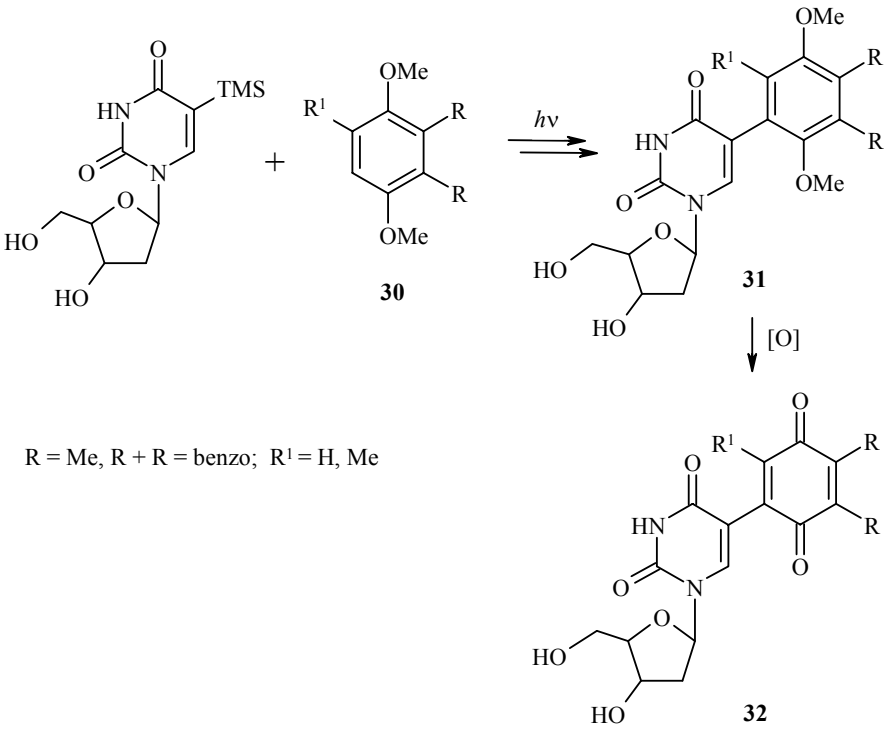
Photochemical Reactions. Photochemical reactions between halo-1,4-naphthoquinones and thiophene [58] or furan [59] can be initiated by photoelectron transfer from the heterocycle to the naphthoquinone with the formation of the product **29**.



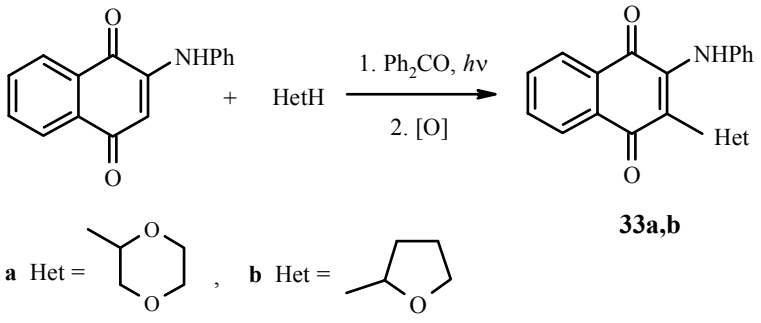
X = O, S; Hal = Cl, Br

29

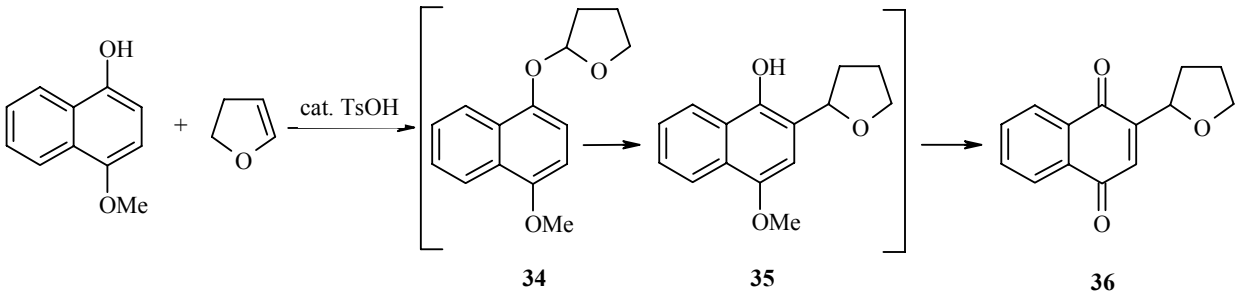
In [60] the following method was proposed for the synthesis of 2'-deoxyuridin-5-yl-1,4-benzoquinone **32**. A solution of substituted 1,4-dimethoxybenzene or naphthalene **30** and 5-trimethylsilyl-2'-deoxyuridine was irradiated at 254 and 310 nm. In the case of 1,4-dimethoxynaphthalene a mixture of isomers consisting of compound **31** and the products from substitution in the benzene ring of the 1,4-naphthoquinone is formed. Oxidative demethylation takes several minutes with an aqueous solution of CAN. Compound **32** can also be obtained by the reaction of compound **30** and 4-O-trimethylsilyl-5-iodo-2'-deoxyuridine in the presence of palladium.



Irradiation of a solution of 2-anilino-1,4-naphthoquinone containing an excess of THF or dioxane and 2 eq. of benzophenone leads to the formation of a mixture of 1,4-naphthoquinone and 1,4-dihydroxynaphthalene. Further oxidation leads to compounds **33** [61].



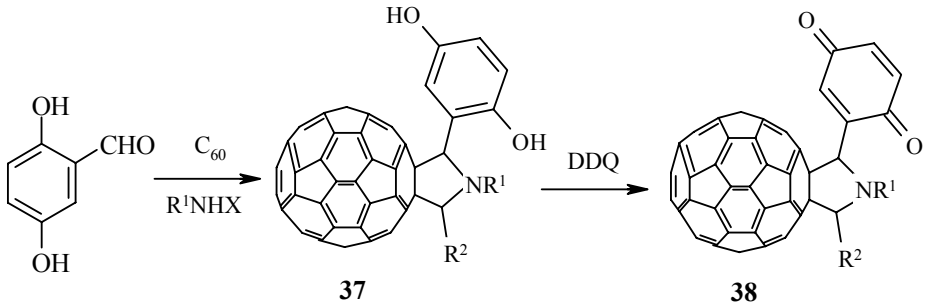
Anodic Oxidation. The anodic oxidation of 4-methoxy-1-naphthol [62, 63] in the presence of dihydrofuran leads initially to compound **34**. This is then followed by O→C migration of the tetrahydrofuryl group with the formation of compound **35**, which after two-electron oxidation gives a 79% yield of the naphthoquinone **36**.



2. METHODS OF CONSTRUCTION OF THE HETEROCYCLE BASED ON QUINONE

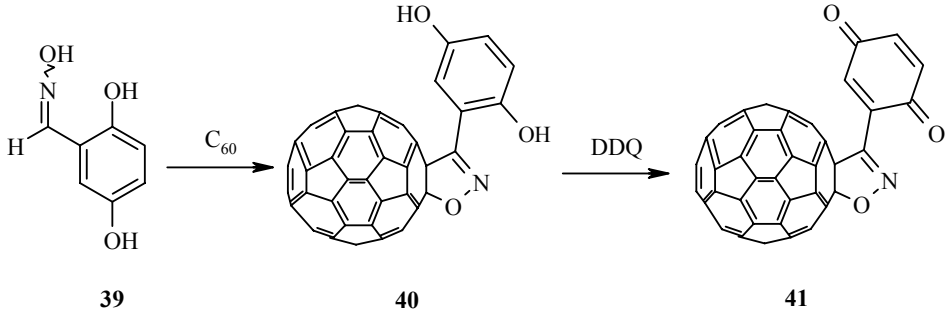
Heterocycles differ in chemical nature, and it is therefore difficult to develop general methods for the construction of heterocycles based on quinones. Special methods for the synthesis of individual heterocyclic systems are described in this section.

The fullerene derivatives **38**, containing annelated pyrrolidine covalently bonded to 1,4-benzoquinone, can be obtained as a result of the direct reaction of C_{60} with 2,5-dihydroxybenzaldehyde and substituted amines [64]. Since the hydroquinones **37** are poorly soluble in most organic solvents, the oxidation of dichlorodicyanobenzoquinone (DDQ) was carried out in a mixture of toluene and ethyl acetate.

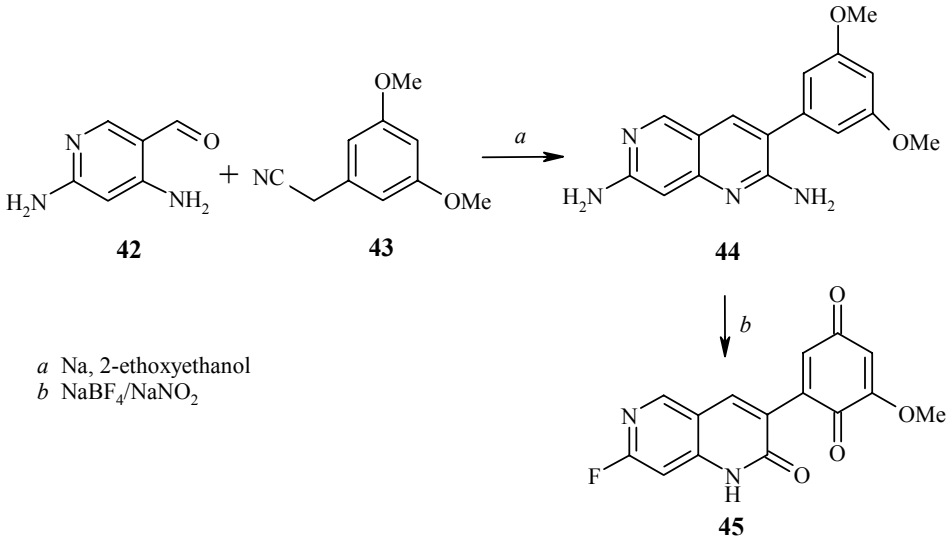


a X = Ph(CH–)$SiMe_3$, R^1 = H, R^2 = Ph; **b** X = CH_2COOH, R^1 = Me, R^2 = H

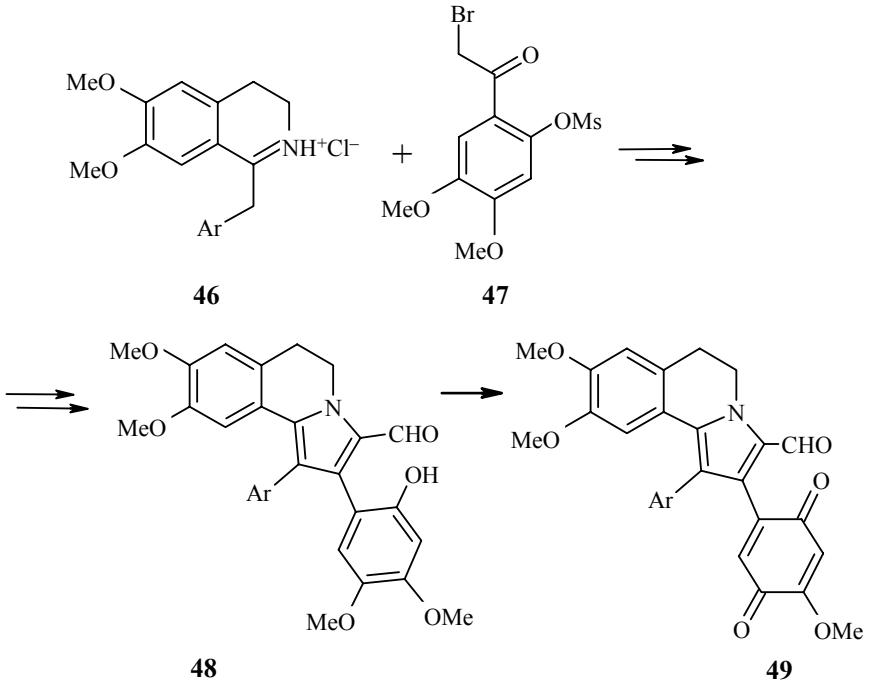
The reaction of 2,5-dihydroxybenzaldehyde oxime with C_{60} and N-chlorosuccinimide in the presence of pyridine and triethylamine leads to the formation [65] of the hydroquinone **40** with a low yield (8%). The quinone **41** [65], attached to isoxazole annelated with the fullerene, is produced by oxidation of the hydroquinone **40**.



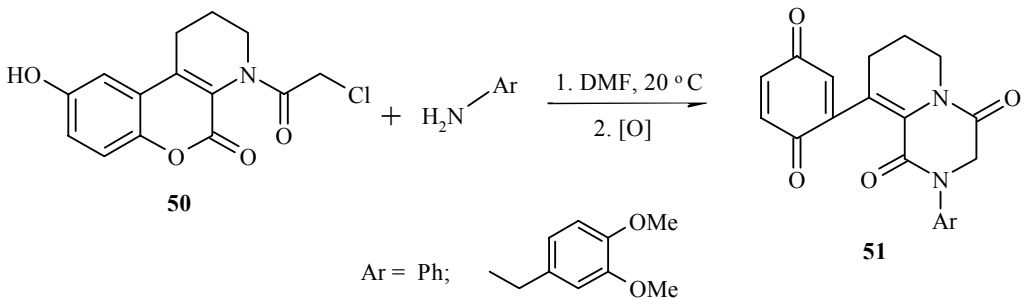
The reaction of 4,6-diaminonicotinaldehyde **42** with phenylacetonitrile **43** in the presence of metallic sodium in 2-ethoxyethanol leads to the formation of the benzoquinone derivative **45** [66].



The following scheme was proposed for the production of the natural alkaloid lamellarin G [67]. The condensation of 3,4-dihydropapaverine hydrochloride **46** with phenacyl bromide **47** in acetonitrile in the presence of potassium carbonate leads to the substituted pyrrolo[2,1-*a*]isoquinoline (the Knorr reaction), into the molecule of which a formyl group is inserted in the following stages, while the mesyl group is removed. Two reactions can occur during oxidation of the obtained isoquinoline **48**: Closure of a hemiacetal ring by the intramolecular addition of hydroxyl to the aldehyde group and oxidation of the hemiacetal to a lactone, leading to the lamellarin G system, and also oxidation of the phenol ring with the formation of the quinone **49**. Lamellarin G was obtained with a yield of 80% during the oxidation of **48** with a $Pd(OAc)_2/PPh_3/K_2CO_3$/PhBr mixture in DMF.

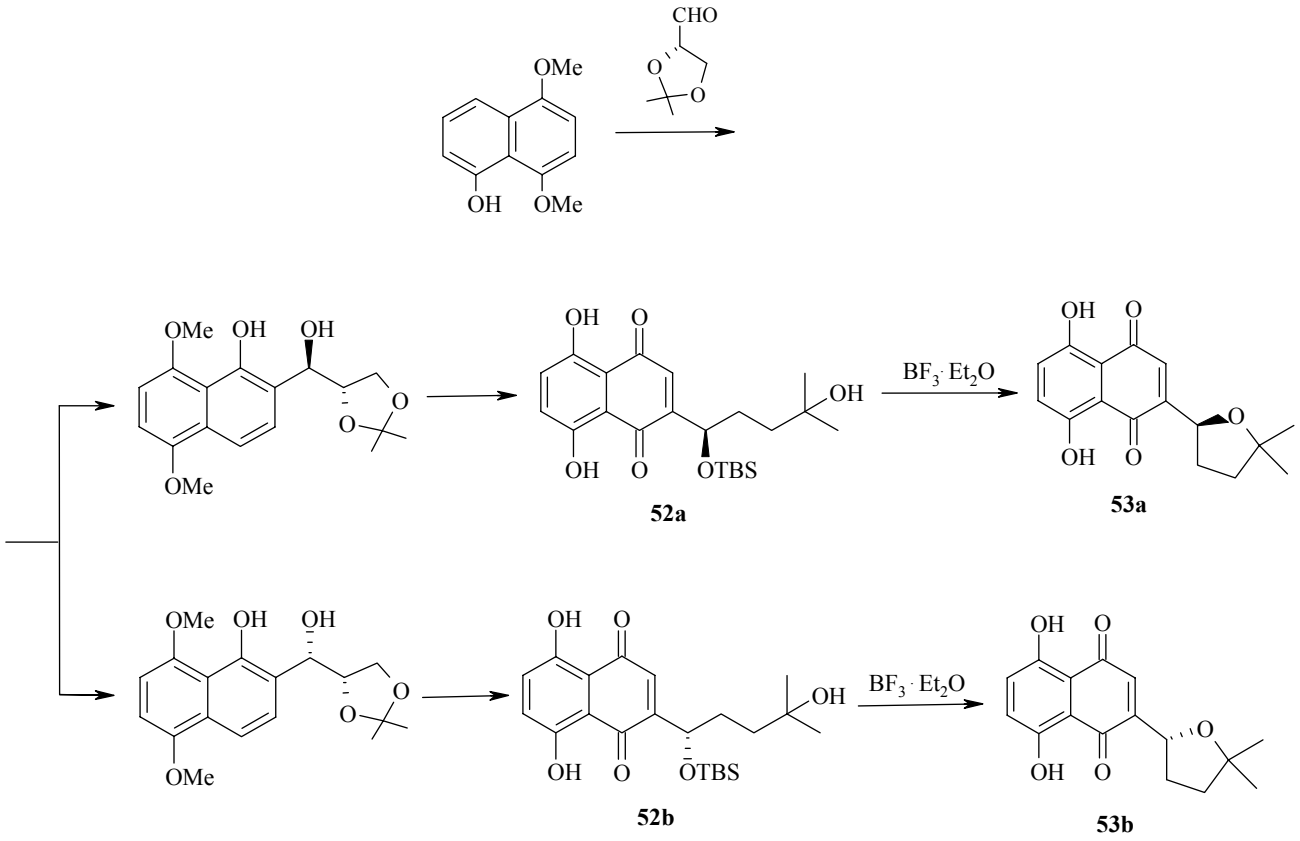


Reaction of the N-chloroacetyl derivative of chromeno[3,4-*b*]pyridine **50** with primary arylamines followed by oxidation leads to an unusual recyclization with the formation of pyridopyrazinedione **51**, which is C–C-bonded with the benzoquinone fragment [68].

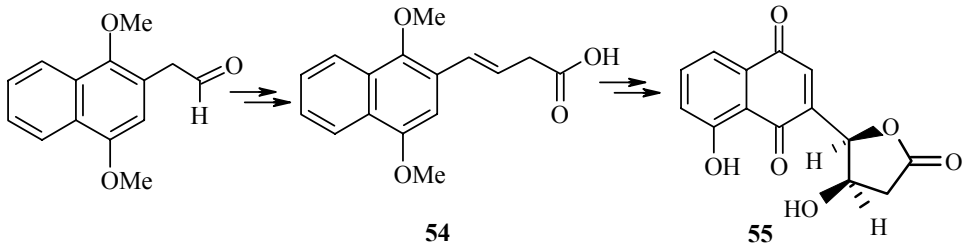


50 **51**

Optically active derivatives of 5,8-dihydroxynaphthoquinone **53a**,**b** were synthesized in order to produce telomerase inhibitors [69]. The chiral center is formed during the direct C-arylation of *D*-2,3-isopropylideneglyceraldehyde with 5,8-dimethoxynaphthol in the presence of Ti(OPr-*i*)$_3$ or MeMgBr. The *erythro* isomer is formed with MeMgBr and the *threo* isomer with Ti(OPr-*i*)$_3$. After oxidation of the naphthol system, construction of the side chain, and removal of the *tert*-butyldimethylsilyl group (TBS) the cycloalkanin **53a** and cycloshikonin **53b** were obtained.

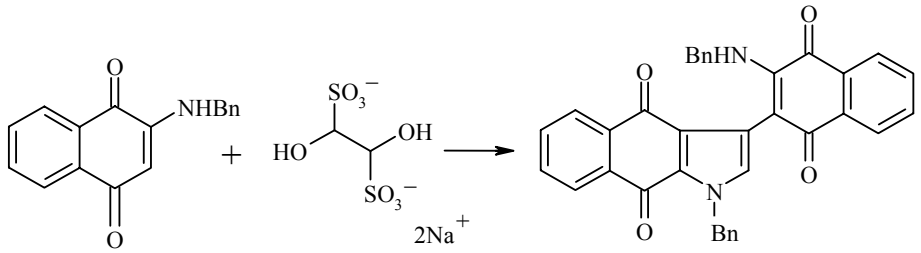


Asymmetric dihydroxylation of the *E*-isomer of 4-(1,4-dimethoxy-2-naphthyl)buten-3-oic acid (**54**) followed by oxidation with CAN leads to the quinone (**55**) [70].



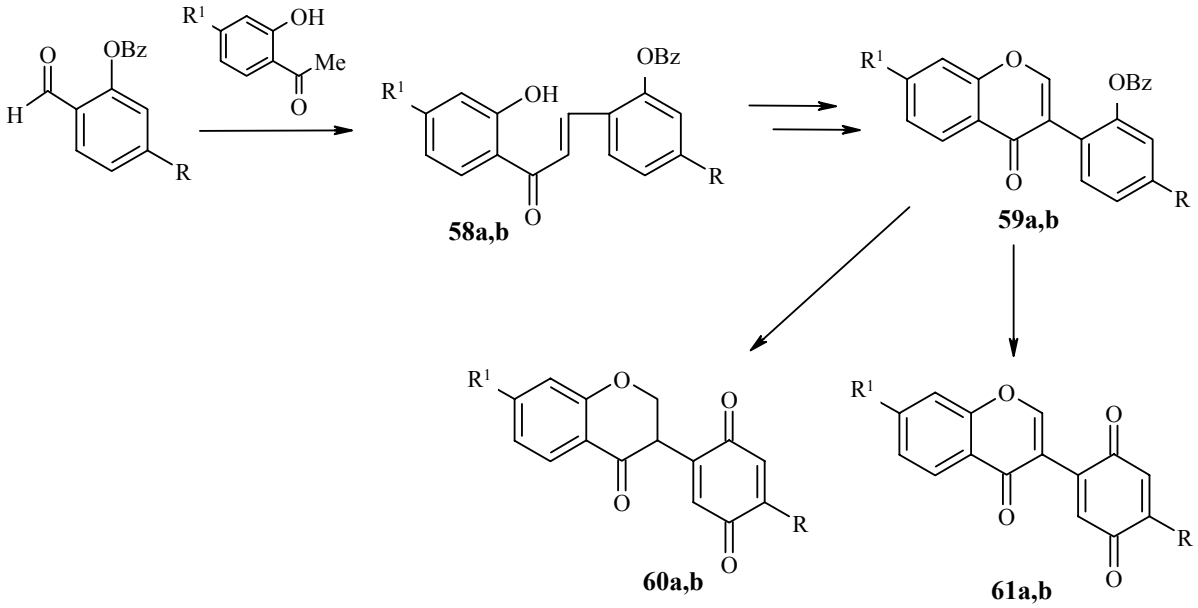
54 **55**

Reaction of the disodium slat **56** (the bisulfite derivative of glyoxal) with an excess of 2-benzylamino-1,4-benzoquinone in the presence of potassium carbonate leads to 2-benzylamino-3-(1-benzyl-1H-benzo[*f*]indole-4,9-dion-3-yl)-1,4-naphthoquinone (**57**) [71].



56 **57**

The isoflavan- and isoflavon-3-yl-1,4-benzoquinones **60** and **61** were synthesized [72] according to the scheme:

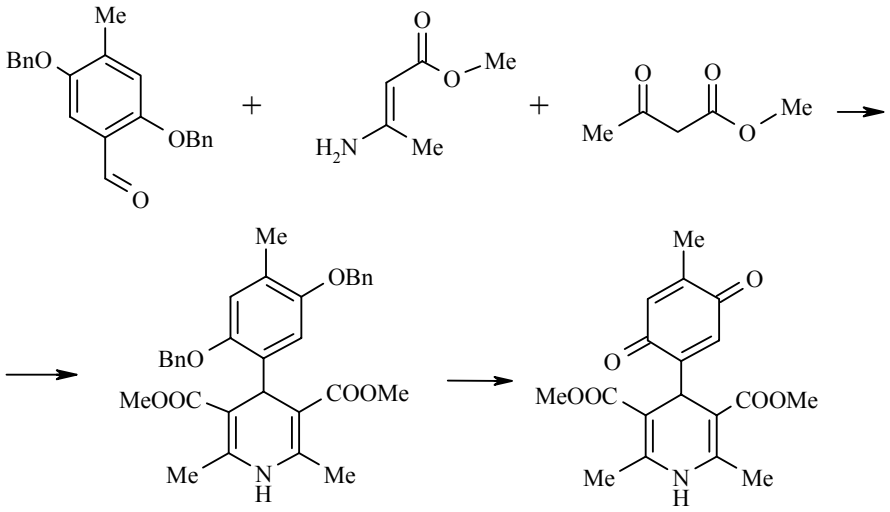


58a,b **59a,b** **60a,b** **61a,b**

a R = OMe, R^1 = H; **b** R = H, R^1 = OMe

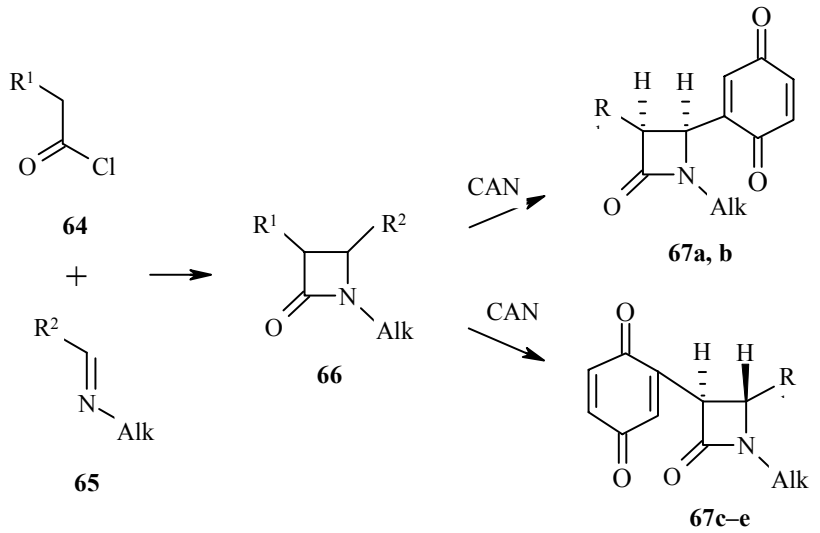
In reaction with 2-hydroxy-4-substituted acetophenone in the presence of alkali 4-substituted 2-benzyloxybenzaldehyde forms the chalcone **58**. Acylation and treatment with $Tl(NO_3)_3/CH(OMe)_3$ and dilute hydrochloric acid then give the isoflavone **59**, the hydrogenation and subsequent oxidation of which with Fremy's salt lead to the quinone **60**. Debenzylation of the isoflavone **59** with HBr followed by oxidation gives the quinone **61**.

The dihydropyridine **62** was synthesized [73] by a modification of the Hantsch method according to the scheme given below. After removal of the protecting groups and oxidation with Ag_2O the quinone **63** was obtained.



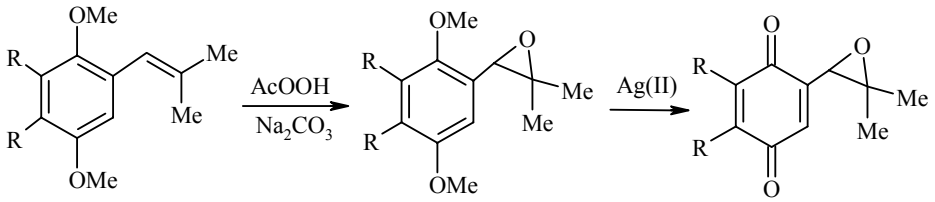
62 **63**

A method was proposed for the synthesis of *cis*- and *trans*-β-lactams **67** with a quinone substituent at the C-3 and C-4 atoms [74]. The 2,5-dimethoxyphenyl-substituted β-lactam **66a** was obtained in the form of the *cis* diastereomer as a result of ketene–imine [2+2] cycloaddition of the chloride **64** and the corresponding imine **65** in the presence of triethylamine. The enantiomerically pure 2-azetidinone (+)-**66b** is formed if (*S*)-4-phenyl-2-oxazolidin-3-ylacetyl chloride is used. Compounds **66c-e** were synthesized as the *trans* diastereomers. The final quinones were obtained by oxidative demethylation with CAN in aqueous acetonitrile.



a R^1 = OMe, R^2 = 2,5-dimethoxyphenyl; **b** R^1 = (*S*)-4-phenyl-2-oxooxazolidin-3-yl, R^2 = 2,5-dimethoxyphenyl; **c** R^1 = 2,5-dimethoxyphenyl, R^2 = 2-furyl; **d** R^1 = 2,5-dimethoxyphenyl, R^2 = 3-furyl; **e** R^1 = 2,5-dimethoxyphenyl, R^2 = 3-thienyl

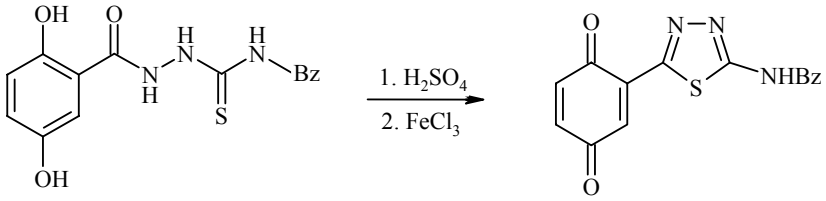
Oxiranyl-1,4-benzoquinone and oxiranyl-1,4-naphthoquinone **69** were obtained by epoxidation of the sterically hindered double bond of 1,4-dimethoxyarene **68** followed by oxidative demethylation [75].



68 **69**

R = Me, OMe; R+ R = benzo

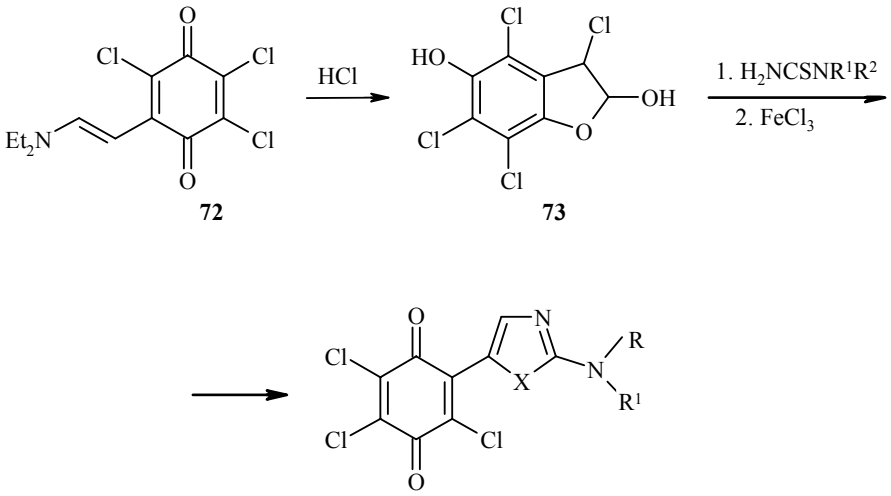
Cyclization of the side chain of the hydroquinone **70** in an acidic medium followed by oxidation gives 1,3,4-thiadiazol-2-yl-1,4-benzoquinone **71** [76].



70 **71**

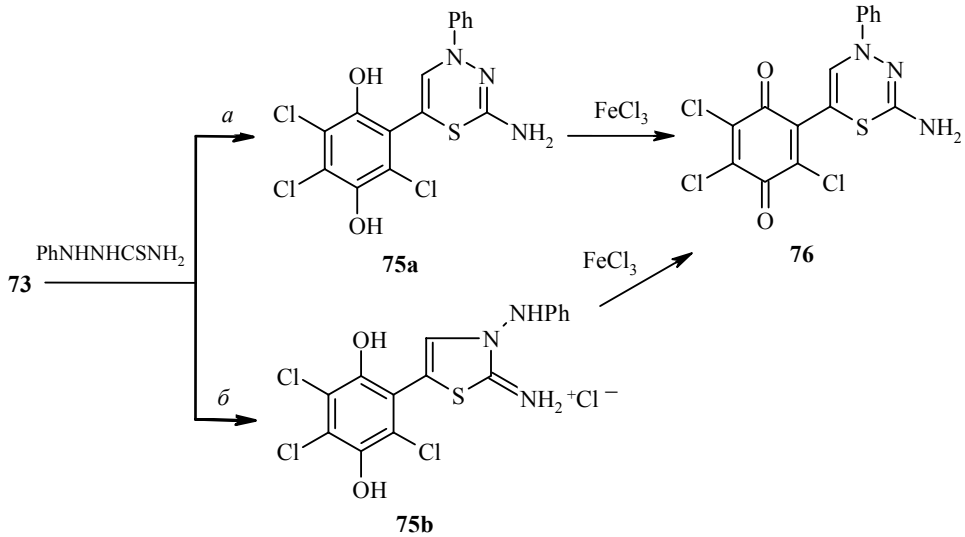
The most general method for the construction of a heterocycle based on a quinone is the method described in [77]. Here, during construction of the heterocycle 2,5-dihydroxy-3,4,6,7-tetrachloro-2,3-dihydrobenzo[*b*]furan **73** is used as universal synthon (the 2,3-*trans* configuration predominates). This is the cyclic tautomeric form of the aryl-substituted α-chloroacetaldehyde and is formed in the reaction of vinylquinone **72** with HCl in dioxane solution [78]. The heterocycle was constructed by the reaction of benzofuran **73** with bifunctional nucleophilic reagents. Nucleophilic substitution of the chlorine atom occurs at the first stage, the product then undergoes recyclization with the formation of a trichlorohydroquinonyl-substituted heterocycle, and at the end the hydroquinone fragment is oxidized to quinone. A limitation of this method is the fact that the reaction only takes place successfully if one of the nucleophilic centers is a sulfur (or selenium) atom, which as a rule carries out the initial attack at the electrophilic center of C–Cl. In some cases after nucleophilic substitution the formation of a tricyclic condensed benzo[*b*]furan derivative, resulting from ring closure by intramolecular substitution of the hydroxy group, was observed instead of cyclization [79-82].

In the reactions of benzo[*b*]furan **73** with thiourea and its substituted derivatives and also with selenoureas followed by oxidation of the obtained hydroquinones it was possible to synthesize a whole series of (2-aminothiazol-5-yl)-1,4-benzoquinones [83-86] and (2-aminoselenazol-5-yl)-1,4-benzoquinones **74** [87]. The benzoquinones **74** (X = S) were also obtained with lower yields [83, 88] by reaction of the vinylquinone **72** with thioureas in the presence of HCl and subsequent oxidation, i.e., without isolating the benzo[*b*]furan **73**. In the reactions with N,N'-disubstituted thioureas the corresponding derivatives of 3-alkyl-2-iminothiazolines were obtained.



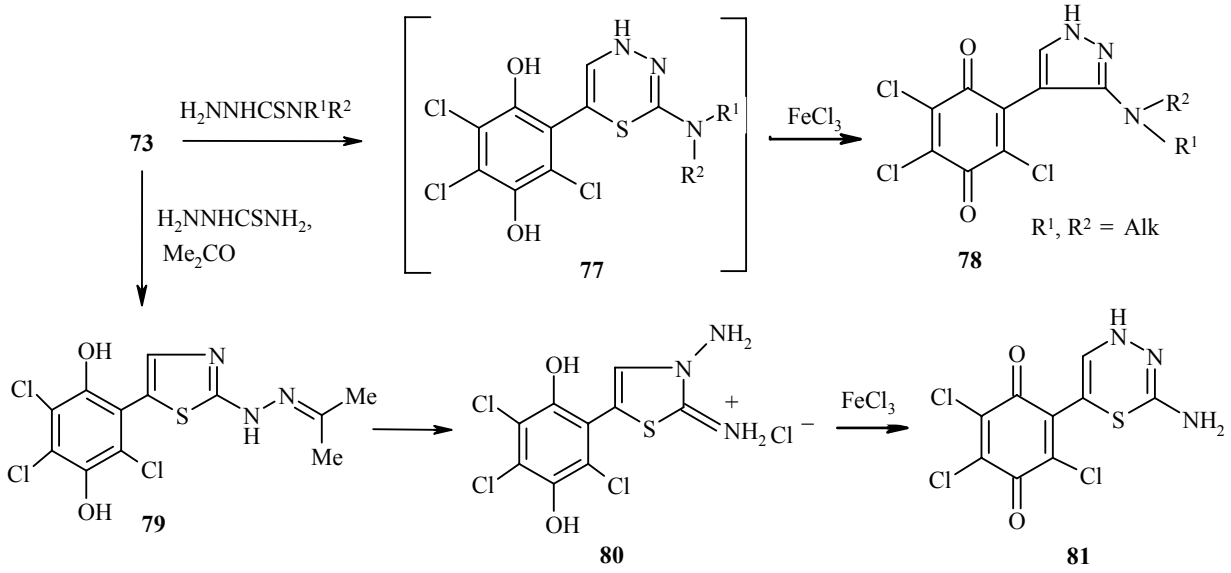
a $R^1 = R^2$ = H, Me, $(CH_2)_5$, $(CH_2)_6$, $(CH_2)_2O(CH_2)_2$; R^1 = H, R^2 = Me, COMe, Ph, CH_2=CHMe; X = S; **b** R^1 = H, R^2 = H, Ph, X = Se

The reaction between benzo[*b*]furan **73** and 1-phenylthiosemicarbazone leads to the hydroquinone **75a** when carried out in ethanol and to the hydroquinone **75b** after heating in acetone. The oxidation of both hydroquinones leads to the quinone **76** [89].



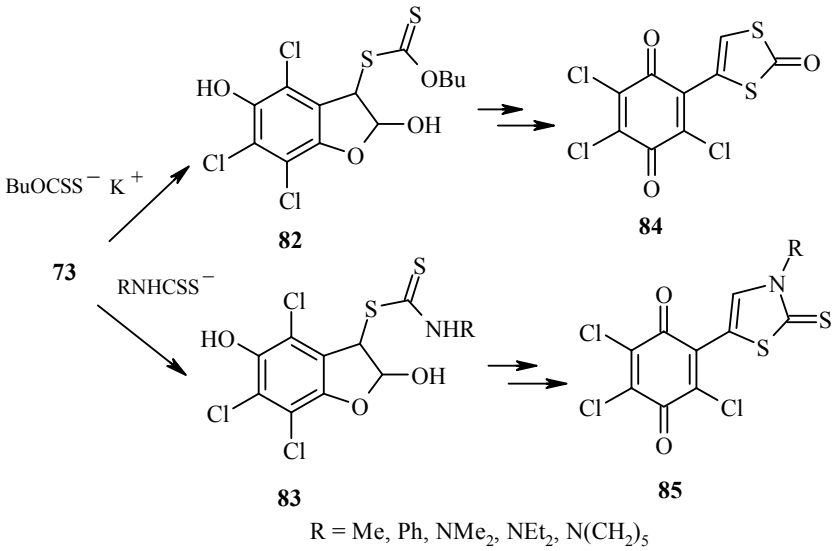
a EtOH, 78°C;
b Me_2CO, 56°C

The reaction of benzo[*b*]furan **73** with 4,4-dialkylthiosemicarbazide leads to the formation of the intermediate 1,3,4-thiadiazine **77**, from which the pyrazole derivative **78** is formed after extrusion of the sulfur atom and oxidation [89, 90].

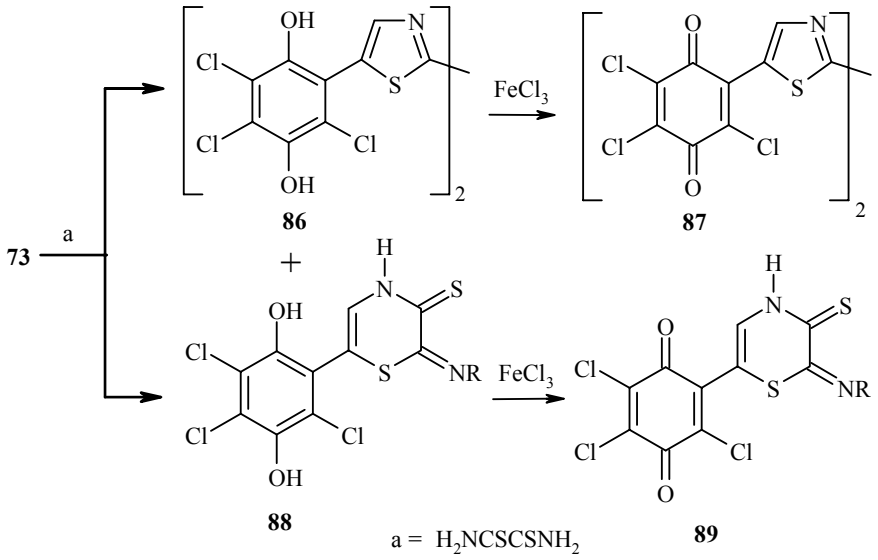


The reaction between benzo[*b*]furan **73** and thiosemicarbazide in acetone gives the thiazole **79**, the subsequent acid hydrolysis of which leads to removal of the isopropylidene group. As a result the more stable 2-iminothiazoline ring of compound **80** is formed. Oxidation takes place with simultaneous isomerization of the heterocycle and leads to the formation of (2-amino-4H-1,3,4-thiadiazin-6-yl)trichlorobenzoquinone **81** [91].

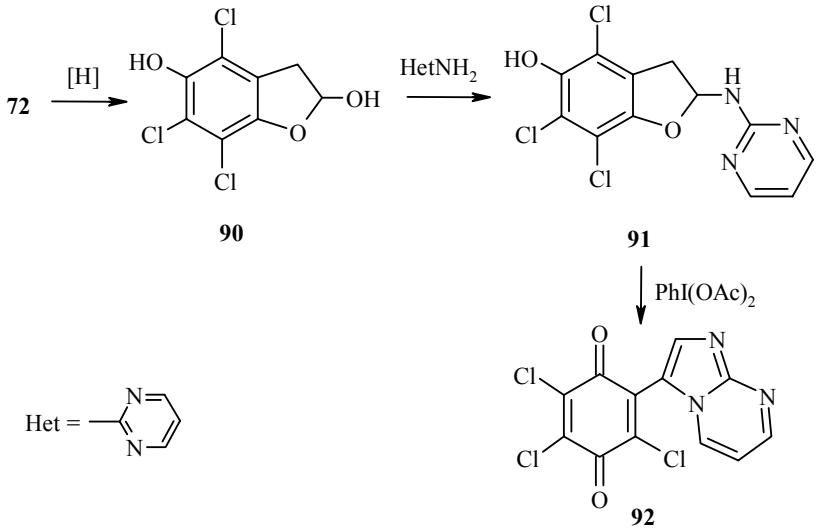
The reaction of benzo[*b*]furan **73** with potassium O-butyl xanthate [81], triethylammonium N-methyl- or N-phenyl dithiocarbamates [92], and the N,N-dialkylhydrazinium salts of the N,N-dialkylhydrazides of dithiocarbonic acid [82] leads to substitution of the chlorine atom at position 3 and the formation of the corresponding derivatives **82** and **83**. When heated in the presence of concentrated sulfuric acid or hydrochloric acid, the products undergo recyclization with the formation of a 1,3-dithiol-2-one [81] or thiazoline-2-thione [82, 92] ring. The corresponding quinones **84** and **85** were obtained during oxidation of the hydroquinone fragment.



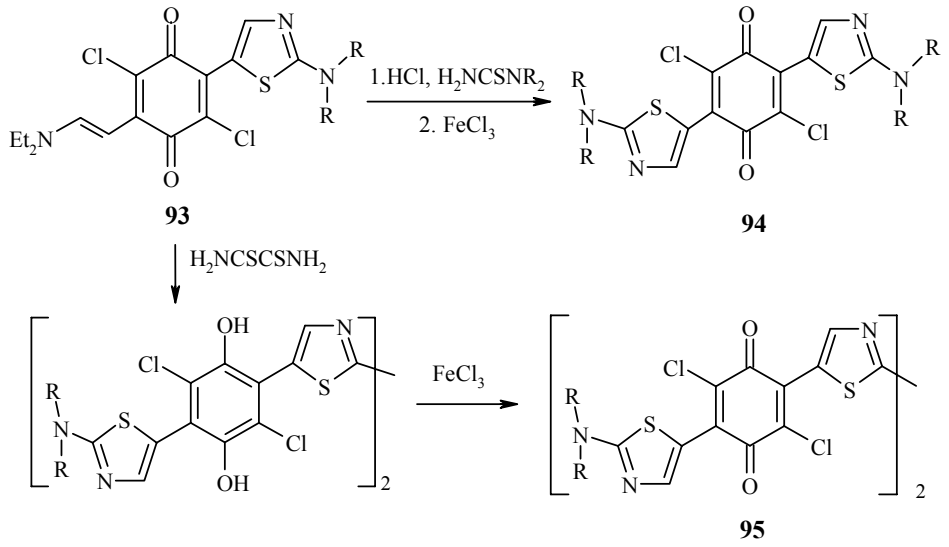
The reaction of benzo[*b*]furan **73** with dithiooxamide (rubeanic acid) in acetic acid gave 2,2'-bi[5-(2,5-dihydroxy-3,4,6-trichlorophenyl)thiazole] **86**, which is readily oxidized to the quinone (**87**) [93, 94]. A side product of the reaction of benzo[*b*]furan **73** with rubeanic acid is 2-imino-3,4-dihydro-4H-1,4-thiazine-3-thione **88**, which is also oxidized to the quinone **89**.



The reduction of the vinylquinone **72** with sodium dithionite or stannous chloride gave dihydrobenzo[*b*]furan **90** [95], which in reaction with 2-aminopyrimidine formed the substitution product **91**. The oxidation of the substituted dihydrobenzo[*b*]furan **91** with phenyl iodosodiacetate led to oxidative recyclization with the formation of the benzoquinone **92** [96].



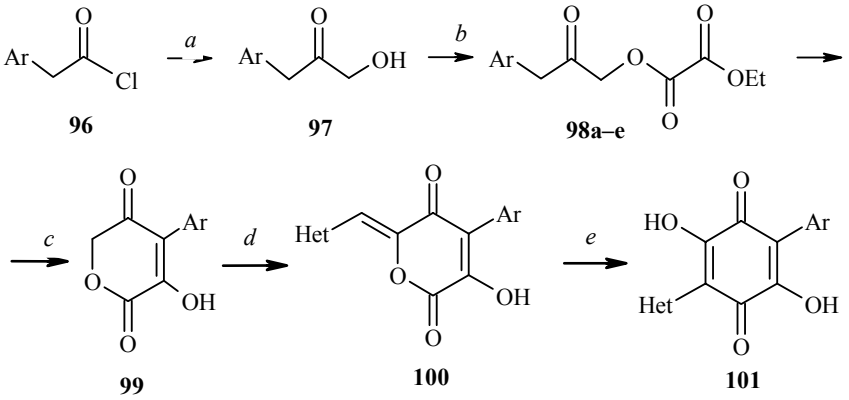
The quinones **94** and **95** were obtained [97, 98] on the basis of vinylquinone **93**, which was synthesized by the method in [99, 100] from benzoquinones **74** (X = S). The 2,5 position of the heteroaryl substituents in the molecule of the quinone **94** was confirmed by ^{13}C NMR spectroscopy [97].



94 R = H, Alk; **95** R = Me, R+ R = $(CH_2)_5$

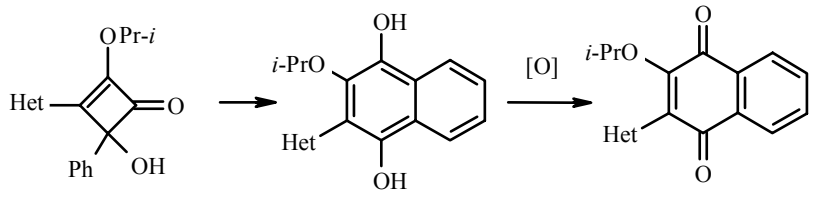
3. CONSTRUCTION OF THE QUINONE ON THE BASIS OF A HETEROCYCLE

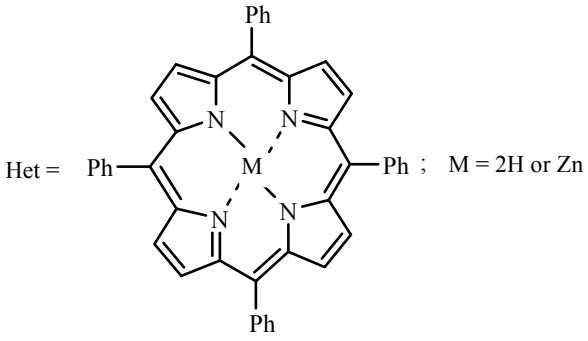
Various heteroaryl-substituted 1,4-benzoquinones were obtained according to a scheme developed for the synthesis of natural asterriquinone B1. The reaction of the acyl chloride **96** with tri(trimethylsilyloxy)ethylene in the presence of catalytic amounts of $TiCl_4$ [101] or $SnCl_4$ [102] followed by hydrolysis and decarboxylation leads to the α-hydroxy ketone **97** with a yield of 70%. Acylation of compound **97** with ethoxalyl chloride gives the oxalate **98**, which undergoes cyclization with 2 eq. of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in DMF. In this reaction the key pyrandione **99** is formed with a yield of 65%. The yield of the product from condensation of the pyrandione **99** with heteroarenecarbaldehyde in the presence of ammonium acetate amounts to 75%. The rearrangement catalyzed by sodium methoxide takes place at room temperature, and the yield of the quinones amounts to 98%.



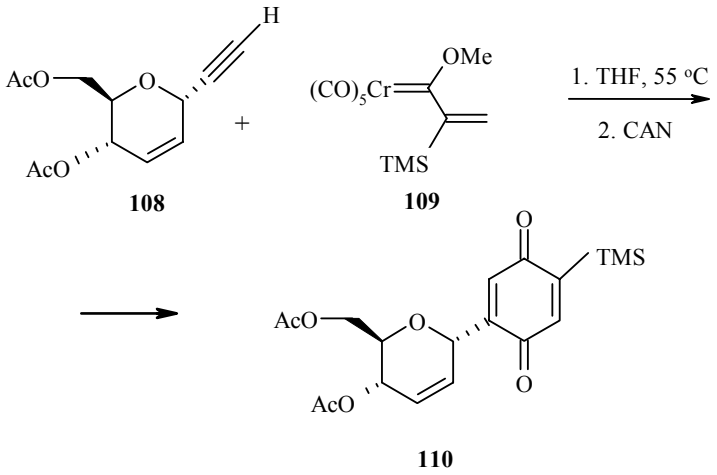
a 1. TMSO, OTMS, TMSO, 2. HCl; *b* EtOCOCOCl, Et_3N; *c* DBU;
d HetCHO/HCl, AcOH; *e* NaOMe, MeOH;
98 a-d Ar = Ph; **a** Het = 3-indolyl, **b** Het = 1-methyl-3-indolyl, **c** Het = 3-benzothienyl,
d Het = 3-benzofuryl; **e** Ar = 7-methyl-3-indolyl, Het = 3-indolyl

The Stille reaction can be used to obtain compounds in which the quinone fragment is attached to porphyrin [103, 104]. The initial 3-isopropoxy-4-tributylstannylcyclobutene-1,2-dione **102** reacts with bromotetraphenylporphyrin and forms the corresponding 4-heteroaryl-3-isopropoxycyclobutene-1,2-dione **103**. The catalyst was $Pd_2(dba)_3/AsPh_3$. The reaction of compound **103** (M = Zn) with phenyllithium in THF at -78°C takes several minutes and gives an 89% yield of compound **104**. Isolation and purification of the product **104** are not essential for the synthesis of the final naphthoquinone **105**. Thermal rearrangement of compound **104** through the intermediate hydroquinone leads to the expected porphyrin-substituted naphthoquinone **105** with a yield of 82%. The addition of 1.5 eq. of vinylmagnesium bromide to a solution of compound **103** (M = Zn) in THF gives the intermediate vinylcyclobutenone **106**, which rearranges to the hydroquinone when heated. DDQ is used for the oxidation of hydroquinone and the production of the quinone **107**. The possibility of using this sequence of reactions for the production of the quinone–porphyrin–quinone triad was noted.





During benzannelation of the dihydropyran ethynyl derivative **108** and the alkenylcarbene **109** followed by oxidation the quinone **110** was formed with a yield of 61% [105].



108 **109** **110**

REFERENCES

1. S. Patai (editor), *The Chemistry of the Quinonoid Compounds*, Pt. 1 and 2, Wiley, London et al. (1974), 1274 pp.
2. S. Patai and Z. Rappoport (editors), *The Chemistry of the Quinonoid Compounds*, Vol. 2, Pt. 1 and 2, Wiley, Chichester (1988), 1711 pp.
3. C. Vazquez, J. C. Calabrese, D. A. Dixon, and J. S. Miller, *J. Org. Chem.*, **58**, 65 (1993).
4. O. Ya. Neilands, *Latv. PSR ZA Vestis. Fiz. un tehn. zin. ser.*, No. 6, 63 (1981).
5. R. H. Thompson, *Naturally Occurring Quinones*, Vol. 1-3, Chapman and Hall., London.
6. S. Spyroudis, *Molecules*, **5**, 1291 (2000).
7. P. R. W. Middleton and J. Patrick, in: S. Patai and Z. Rappoport (editors), *The Chemistry of the Quinonoid Compounds*, Vol. 2, Pt. 2, Wiley, Chichester et al. (1988), p. 1099.
8. M. Tisler, *Adv. Heterocycl. Chem.*, **45**, 37 (1989).
9. G. D. Harris, A. Nguyen, H. App, P. Hirth, G. McMahon, and C. Tang, *Org. Lett.*, **1**, 431 (1999).
10. M. C. Pirrung, K. Park, and Z. Li, *Org. Lett.*, **3**, 365 (2001).
11. T. Itahara, *J. Org. Chem.*, **50**, 5546 (1985).
12. B. Zhang, G. Salituro, D. Szalkowski, Z. Li, Y. Zhang, I. Royo, D.Vilella, M. T. Diez, F. Pelaez, C. Ruby, R. L. Kendall, X. Mao, P. Griffin, J. Calaycay, J. R. Zierath, J. V. Heck, R. G. Smith, and D. E. Moller, *Science*, **284**, 974 (1999).
13. V. K. Tandon, R. V. Singh, S. Rai, R. B. Chor, and Z. Khan, *Boll. Chim Farm.*, **141**, 304 (2002).
14. J.-C. Henrion, B. Jacquet, M. Hocquaux, G. Barre, and C. Lion, *Bull. Soc. Chim. Belg.*, **103**, 163 (1994).
15. J.-C. Henrion, B. Jacquet, M. Hocquaux, C. Lion, and M. Hedayatullah, *Bull. Soc. Chim. Belg.*, **105**, 409 (1996).
16. A. K. El-Shafei, A. M. El-Sayed, A. Sultan, and H. Abdel-Ghany, *Gazz. Chim. Ital.*, **120**, 197 (1990).
17. A. A. Hassan, N. K. Mohamed, E. H. El Tamany, B. A. Ali, and A. E. Mourad, *Monatsh. Chem.*, **126**, 653 (1995).
18. F. Siberdt and J. Nasielski, *Bull. Soc. Chim. Belg.*, **106**, 85 (1997).
19. J. A. Valderrama, J. Benites, M. Cortes, D. Pessoa-Mahana, E. Prina, and A. Fournet, *Tetrahedron*, **58**, 881 (2002).
20. J. A. Valderrama, J. Benites, M. Cortes, D. Pessoa-Mahana, M. Preite, and J. Benites, *Tetrahedron Lett.*, **41**, 3563 (2000).

21. J. M. Ribo and C. Acero, *Liebigs Ann. Org. Bioorg. Chem.*, 509 (1995).
22. C. Lion, R. Baudry, M. Hedayatullah, L. Da Conceicao, M. Hocquaux, S. Genard, and J. Maignan, *J. Heterocycl. Chem.*, **37**, 1635 (2000).
23. H. Laatsch, B. Renneberg, U. Hanefeld, M. Kellner, H. Pudleiner, G. Hamprecht, H.-P. Kraemer, and H. Alike, *Chem. Pharm. Bull.*, **43**, 537 (1995).
24. D. R. Mckean, G. Parrinello, A. F. Renaldo, and J. K. Stille, *J. Org. Chem.*, **52**, 422 (1987).
25. X. Deng and L. S. Liebeskind, *J. Am. Chem. Soc.*, **123**, 7703 (2001).
26. S. Yoshida, H. Kubo, T. Saika, and S. Katsumura, *Chem. Lett.*, 139 (1996).
27. M. C. Pirrung, Z. Li, K. Park, and J. Zhu, *J. Org. Chem.*, **67**, 7919 (2002).
28. N. Tamayo, A. M. Echavarren, and M. C. Paredes, *J. Org. Chem.*, **56**, 6488 (1991).
29. A. M. Echavarren, N. Tamayo, and D. J. Cardenas, *J. Org. Chem.*, **59**, 6075 (1994).
30. K. W. Stagliano, H. C. Malinakova, and J. S. Harwood, *J. Org. Chem.*, **66**, 7530 (2001).
31. K. W. Stagliano and H. C. Malinakova, *J. Org. Chem.*, **64**, 8034 (1999).
32. J. O. Karlsson, N. V. Nguyen, L. D. Poland, and H. W. Moore, *J. Am. Chem. Soc.*, **107**, 3392 (1985).
33. L. D. Poland, J. O. Karlsson, S. T. Perri, R. Schwabe, S. L. Xu, S. Patil, and H. W. Moore, *J. Am. Chem. Soc.*, **Ill**, 975 (1989).
34. G. Bringmann, R. Gotz, P. A. Keller, R. Walter, M. R. Boyd, F. Lang, A. Garcia, J. J. Walsh, I. Tellitu, K. V. Bhaskar, and T. R. Kelly, *J. Org. Chem.*, **63**, 1090 (1998).
35. L. S. Liebeskind and S. W. Riesinger, *J. Org. Chem.*, **58**, 408 (1993).
36. R. Asano, I. Moritani, Y. Fujiwara, and Sh. Teranishi, *Bull. Chem. Soc. Jpn.*, **46**, 663 (1973).
37. T. Itahara, *Bull. Chem. Soc. Jpn.*, **69**, 3239 (1996).
38. J. A. Valderrama, J. Benites, M. Cortes, H. Pessoa-Mahana, E. Prina, and A. Fournet, *Bioorg. Med. Chem.*, **11**, 4713 (2003).
39. J. S. Yadav, B. V. S. Reddy, and T. Swamy, *Synthesis*, **1**, 106 (2004).
40. A. V. Reddy, K. Ravinder, T. V. Goud, P. Krishnaiah, T. V. Raju, and Y. Venkateswarlu, *Tetrahedron Lett.*, **44**, 6257 (2003).
41. J. S. Yadav, B. V. S. Reddy, and T. Swamy, *Tetrahedron Lett.*, **44**, 9121 (2003).
42. U. Pindur, Y.-S. Kirn, and D. Schollmeyer, *J. Heterocycl. Chem.*, **31**, 377 (1994).
43. G. A. Kraus and I. Kim, *J. Org. Chem.*, **68**, 4517 (2003).
44. Y. Tanoue, A. Terada, H. Taniguchi, T. Okuma, H. Kaai, M. Anan, Y. Kakara, M. Doi, and Sh.-i. Morishita, *Bull. Chem. Soc. Jpn.*, **66**, 3712 (1993).
45. C. Lion, R. Baudry, M. Hedayatullah, L. Conceicao, S. Genard, and J. Maignan, *J. Heterocycl. Chem.*, **39**, 125 (2002).
46. J.-C. Henrion, B. Jacquet, M. Hocquaux, G. Barre, M. Hedayatullah, and C. Lion, *Bull. Soc. Chim. Belg.*, **105**, 557 (1996).
47. J.-C. Henrion, B. Jacquet, M. Hocquaux, C. Lion, and G. Barre, *Bull. Soc. Chim. Belg.*, **104**, 521 (1995).
48. J. Sohn, B. Kiburz, Z. Li, L. Deng, A. Safi, M. C. Pirrung, and J. Rudolph, *J. Med. Chem.*, **46**, 2580 (2003).
49. M. C. Pirrung, L. Deng, Z. Li, and K. Park, *J. Org. Chem.*, **67**, 8374 (2002).
50. A. Sen and V. Krishnan, *Tetrahedron Lett.*, **37**, 8437 (1996).
51. H. B. Wood, Jr., R. Black, G. Salituro, D. Szalkowski, Z. Li, Y. Zhang, D. E. Moller, B. Zhang, and A. B. Jones, *Bioorg. Med. Chem.*, **10**, 1189 (2000).
52. A. Kaji, K. Kimura, M. Teranishi, N. Kiriyama, M. Nomura, and K.-i. Miyamoto, *Chem. Pharm. Bull.*, **46**, 1325 (1998).
53. A. Kaji, R. Saito, Y. Hata, and N. Kiriyama, *Chem. Pharm. Bull.*, **47**, 77 (1999).
54. M. A. Brimble and E. Ireland, *J. Chem. Soc., Perkin Trans. 1*, 3109 (1994).
55. M. C. Carreno, J. L. Garcia Ruano, A. Urbano, C. Z. Remor, and Y. Arroyo, *Tetrahedron: Asymmetry*, **10**, 4357 (1999).

56. M. A. Brimble, C. Burgess, R. Halim, and M. Petersson, and J. Ray, *Tetrahedron*, **60**, 5751 (2004).
57. M. A. Brimble, R. Halim, and M. Petersson, *Tetrahedron Lett.*, **43**, 4777 (2002).
58. K. Maruyama and H. Tamiaki, *Bull. Chem. Soc. Jpn.*, **60**, 1847 (1987).
59. M. Yamaji, M. Kurumi, H. Kimura, and H. Shizuka, *Phys. Chem. Chem. Phys.*, **1**, 1859 (1999).
60. L. A. Al-Razzak, D. Schwepler, Ch. J. Decedue, J. Balzarini, E. De Clercq, and M. P. Mertes, *J. Med. Chem.*, **30**, 409 (1987).
61. K. Kobayashi, M. Suzuki, H. Takeuchi, A. Konishi, H. Sakurai, and H. Suginome, *J. Chem. Soc., Perkin Trans. 1*, 1099 (1994).
62. G. A. Kraus and I. Kirn, *Tetrahedron*, **59**, 7935 (2003).
63. H. R. El-Seedi, S. Yamamura, and S. Nishiyama, *Tetrahedron*, **58**, 7485 (2002).
64. M. Iyoda, F. Sultana, A. Kato, M. Yoshida, Y. Kuwatani, M. Komatsu, and S. Nagase, *Chem. Lett.*, 63 (1997).
65. B. M. Illescas and N. Martin, *J. Org. Chem.*, **65**, 5986 (2000).
66. A. M. Thompson, H. D. H. Showalter, and W. A. Denny, *J. Chem. Soc., Perkin Trans. 1*, **12**, 1843 (2000).
67. S. Ruchirawat and T. Mutarapat, *Tetrahedron Lett.*, **42**, 1205 (2001).
68. V. M. Lyubchanskaya, S. A. Savina, L. M. Alekseeva, and V. G. Granik, *Mendeleev Commun.*, **13**, 29 (2003).
69. Q. Lu, W. Liu, J. Ding, J. Cai, and W. Duan, *Bioorg. Med. Chem Lett.*, **12**, 1375 (2002).
70. H. R. Mohan and A. S. Rao, *Synthetic Comm.*, **23**, 2579 (1993).
71. M. A. Rerghot, *Rev. Roum. Chim.*, **48**, 197 (2003).
72. C.-Y. Chang, L.-J. Huang, J.-P. Wang, C.-M. Teng, S.-C. Chen, and S.-C. Kuo, *Chem. Pharm. Bull.*, **48**, 964 (2000).
73. U. Kucklaender, P. Ulmer, and G. Zerta, *Arch. Pharm.*, **322**, 437 (1989).
74. B. Alcaide, P. Almendros, and N. R. Salgado, *Tetrahedron Lett.*, **42**, 1503 (2001).
75. K. Kloc, J. Mlochowski, L. Syper, and M. Mordarski, *J. Prakt. Chem.*, **328**, 419 (1986).
76. M. A. Hassan, A. O. Maslat, M. Abussaud, I. Ch. Ahmed, and A. S. AlKofahi, *Arch. Pharm.*, **331**, 385 (1998).
77. R. Valters, G. Karlivans, J. Gulbis, M. Utinans, and A. Bace, *Phosphorus, Sulfur, and Silicon*, **95-96**, 457 (1994).
78. R. E. Valter, E. E. Liepin'sh, G. A. Karlivan, V. R. Zin'kovska, and M. F. Utinan, *Zh. Org. Khim.*, **21**, 436 (1985).
79. G. A. Karlivan, R. E. Valter, A. E. Batse, and Yu. V. Gulbis, *Khim. Geterotsikl. Soedin.*, 463 (1996).
80. R. Valters, G. Karlivans, A. Bace, and J. Gulbis, *Phosphorus, Sulfur, and Silicon*, **120-121**, 411 (1997).
81. G. A. Karlivan, R. E. Valter, and Yu. V. Gulbis, *Khim. Geterotsikl. Soedin.*, 1055 (1998).
82. Yu. V. Gulbis and R. E. Valters, *Khim. Geterotsikl. Soedin.*, 1556 (2001).
83. M. F. Utinan, R. E. Valter, G. A. Karlivan, E. E. Liepin'sh, and A. S. Edzhinya, *Khim. Geterotsikl. Soedin.*, 692 (1988).
84. R. E. Valter, G. A. Karlivan, M. F. Utinan, and Yu. V. Gulbis, *Sib. Khim. Zh.*, No. 4, 39 (1992).
85. M. Utinans, J. Gulbis, R. Valters, E. Liepins, G. Karlivans, and A. Edzina, *Khim. Geterotsikl. Soedin.*, 410 (1991).
86. M. F. Utinan, Yu. V. Gulbis, R. E. Valter, and G. A. Karlivan, *Khim. Geterotsikl. Soedin.*, 427 (1992).
87. M. F. Utinan, R. E. Valter, and G. A. Karlivan, *Khim. Geterotsikl. Soedin.*, 1430 (1989).
88. G. A. Karlivan, R. E. Valter, and M. F. Utinan, *Khim. Geterotsikl. Soedin.*, 849 (1985).
89. G. Karlivans, J. Gulbis, R. Valters, A. Bace, and R. Kampare, *Latvian J. Chem.*, 99 (1994).
90. Yu. V. Gulbis, M. F. Utinan, G. A. Karlivan, and R. E. Valter, *Khim. Geterotsikl. Soedin.*, 424 (1992).
91. G. A. Karlivan, R. E. Valter, A. E. Batse, and Yu. V. Gulbis, *Khim. Geterotsikl. Soedin.*, 1424 (1996).
92. Yu. V. Gulbis, R. E. Valter, G. A. Karlivan, and M. F. Utinan, *Khim. Geterotsikl. Soedin.*, 111 (1994).

93. R. Valters, G. Karlivans, J. Gulbis, and A. Bace, *Phosphorus, Sulfur, and Silicon*, **153-154**, 411 (1999).
94. G. A. Karlivan, R. E. Valter, and A. E. Bace, *Khim. Geterotsikl. Soedin.*, 988 (1999).
95. G. Karlivans and R. Valters, *Khim. Geterotsikl. Soedin.*, 1837 (2003).
96. G. A. Karlivans and R. E. Valters, *Khim. Geterotsikl. Soedin.*, 939 (2004).
97. N. G. Batenko, R. E. Valter, and G. A. Karlivan, *Khim. Geterotsikl. Soedin.*, 835 (2000).
98. N. Batenko, R. Valters, and G. Karlivans, *Scientific Proceedings of RTU. Material Science and Applied Chemistry*, **1**, 99 (2003).
99. D. Buckley, H. Henbest, and P. Slade, *J. Chem. Soc.*, 4891 (1957).
100. M. Alnabari and S. Bittner, *Synthesis*, **8**, 1087 (2000).
101. K. Liu, L. Xu, D. Szalkowski, Z. Li, V. Ding, G. Kwei, S. Huskey, D. E. Moller, J. V. Heck, B. B. Zhang, and A. B. Jones, *J. Med. Chem.*, **43**, 3487 (2000).
102. K. Liu, H. B. Wood, and A. B. Jones, *Tetrahedron Lett.*, **40**, 5119 (1999).
103. X. Shi, Sk. R. Amin, and L. S. Liebeskind, *J. Org. Chem.*, **65**, 1650 (2000).
104. X. Shi and L. S. Liebeskind, *J. Org. Chem.*, **65**, 1665 (2000).
105. S. R. Pulley and J. P. Carey, *J. Org. Chem.*, **63**, 5275 (1998).