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2,3-Dihydrofurans in the synthesis of heterocyclic compounds

M-G A Shvekhgeimer

Contents

Abstract. Published data on the synthesis of heterocyclic compounds based on 2,3-dihydrofuran and its derivatives are surveyed, described systematically, and analysed for the first time. The bibliography includes 206 references.

I. Introduction

2,3-Dihydrofuran and its derivatives are representatives of cyclic vinyl ethers (ethers of enols). They are highly reactive and readily undergo various chemical transformations. Vast information on the chemistry of 2,3-dihydrofuran and its derivatives is available; however, no review papers on this topic have been published so far. Only two monographs[1,2] contain some data concerning the chemistry of compounds of the 2,3-dihydrofuran series including a few examples of chemical transformations of 2,3-dihydrofurans.

2,3-Dihydrofuran and its derivatives incorporate a reactive double bond and, hence, they readily enter into various addition reactions. Among them, cycloaddition and addition of azoles or azines are especially interesting. Compounds obtained in these reactions, the molecules of which incorporate tetrahydrofuryl groups and residues of pyrimidine derivatives or derivatives of other nitrogen-containing heterocyclic systems, exhibit a broad spectrum of biological activity. Some of them have been found to be effective antitumour preparations.

Since 2,3-dihydrofurans are cyclic vinyl ethers, they readily undergo recyclisation reactions and are thus converted into other cyclic systems. It is also noteworthy that hydrogen atoms in 2,3-dihydrofurans are capable of being substituted by various fragments under mild conditions.

The data surveyed in our review are classified according to the types of reaction into which 2,3-dihydrofuran and its derivatives enter. In Section II, [2 + 1]-, [2 + 2]-, [3 + 2]-, [4 + 2]- and some other cycloaddition reactions involving compounds of the 2,3-dihydrofuran series are considered successively. Section III is devoted to the transformations of 2,3-dihydrofurans according to recyclisation reaction routes. The reactions involving substitution of hydrogen atoms in the molecules of 2,3-dihydrofuran and its derivatives are discussed in Section IV. Section V includes the available data on the addition of various reagents to the double bond in 2,3-dihydrofurans.

M-G A Shvekhgeimer A N Kosygin Moscow State Textile Academy,
ul. Malaya Kaluzhskaya 1, 117918 Moscow, Russian Federation.
Fax (7-095) 952 14 40. Tel. (7-095) 955 35 96

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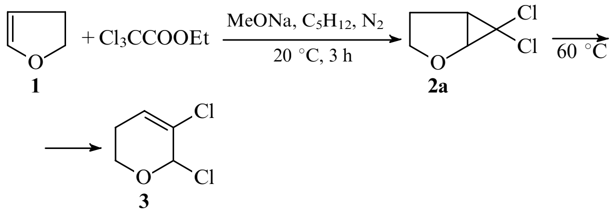
II. Cycloaddition reactions

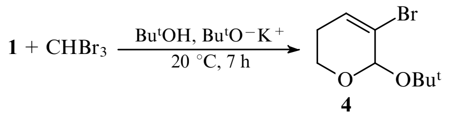
1. [2 + 1]-Cycloaddition

In the studies on the interaction of carbenes with 2,3-dihydrofuran and its derivatives two main methods are used for the generation of these highly reactive species (from gem-polyhalo-derivatives and from diazo compounds).

The reaction of 2,3-dihydrofuran **1** with ethyl trichloroacetate in the presence of sodium methoxide gives 6,6-dichloro-2-oxabicyclo[3.1.0]hexane **2a**, which is converted into 2,3-dichloro-5,6-dihydro-2*H*-pyran **3** on heating to 60 °C (yield 90%).[3]

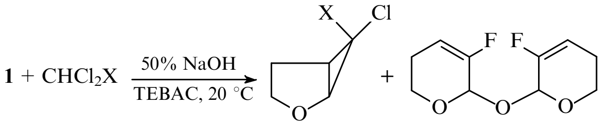


The reaction of the compound **1** with bromoform, carried out in *tert*-butyl alcohol in the presence of potassium *tert*-butoxide at 20 °C, afforded, instead of the expected 6,6-dibromo-2-oxabicyclo[3.1.0]hexane, the product of its isomerisation and interaction with the solvent, namely, 3-bromo-2-*tert*-butoxy-5,6-dihydro-2*H*-pyran **4** (yield 21%).[3]



The reaction of 2,3-dihydrofuran **1** with trihalomethanes in the presence of aqueous sodium hydroxide and benzyltriethylammonium chloride (BTEAC) (the Rodionov catalyst) has also been carried out.[4]

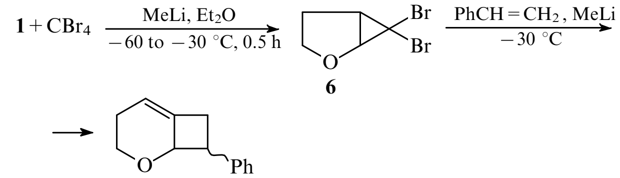
In the case where dichlorofluoromethane was used, in addition to the cyclopropane derivative **2b**, di(3-fluoro-5,6-dihydro-2*H*-pyran-2-yl) ether **5** arising from a rearrangement product similar to **3** was isolated in 40% yield.



2a,b **5**

X	Yield (%)
Cl	71 (**2a**)
F	30 (**2b**) + 40 (**5**)

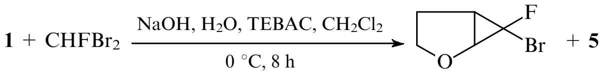
6,6-Dibromo-2-oxabicyclo[3.1.0]hexane **6**, formed upon treatment of 2,3-dihydrofuran **1** and carbon tetrabromide with methyllithium under an inert atmosphere, reacts with styrene to give a mixture of isomers of the cyclobuta[*b*]pyran derivative **7** (yield 24%).[5]



6

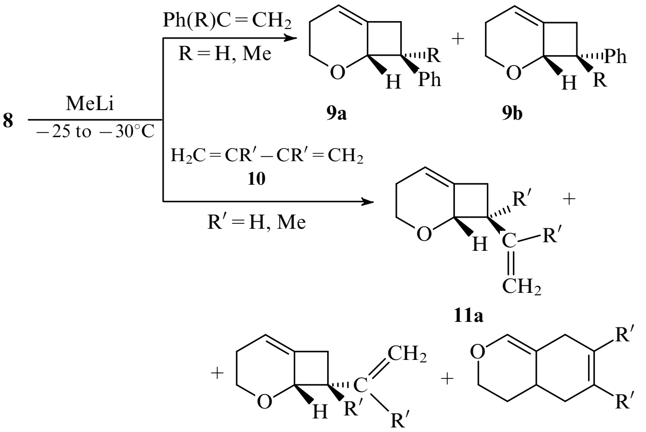
7

A mixture of *exo*-6-bromo-*endo*-6-fluoro-2-oxabicyclo[3.1.0]-hexane **8** (yield 25%) and the ether **5** (yield 35%) was obtained by the reaction of 2,3-dihydrofuran with dibromofluoromethane in the presence of sodium hydroxide and BTEAC.[5]

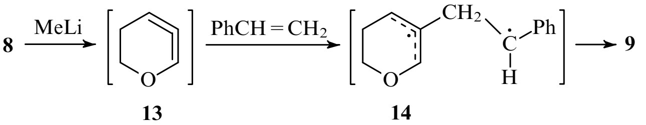


8

The bromofluoro-derivative **8** reacts with styrene or α-methylstyrene in the presence of methyllithium to give a mixture of *exo*- and *endo*-isomers **9a,b** (yield 54%), whereas the reaction of **8** with dienes **10** under the same conditions leads to a mixture of *exo*- and *endo*-isomers **11a,b** (yield 57% – 80%) and compound **12**.[5]

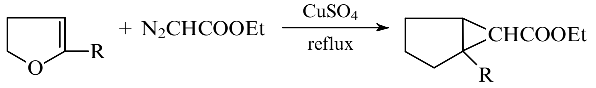


Christl and Braun[5] have proposed a scheme for the formation of the bicyclic systems **9** and **11** (using compounds **9** as an example) *via* the intermediate formation of cyclic 1,2-diene **13** and biradical **14**.



13 **14**

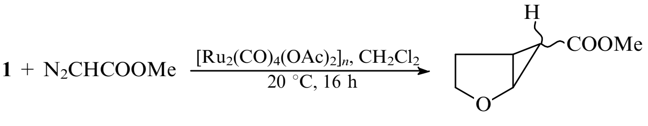
Refluxing of ethyl diazoacetate with an excess of 2,3-dihydrofuran **1** or 5-methyl-2,3-dihydrofuran **15** in the presence of copper(II) sulfate has led to 2-oxabicyclo[3.1.0]hexane derivatives **16** (yields 76% and 79%, respectively).[6]



1,15 **16**

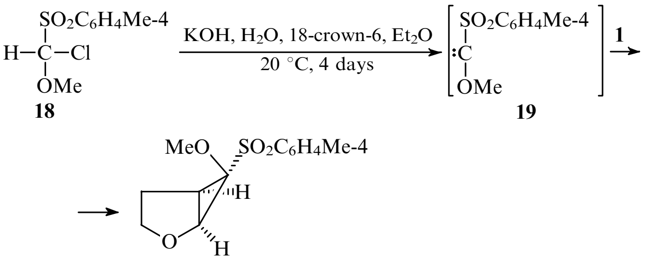
R = H, Me.

The compound **1** reacts with methyl diazoacetate in the presence of a ruthenium catalyst even at 20 °C to afford methyl 2-oxabicyclo[3.1.0]hexane-6-carboxylate **17** (yield 62%, *E* : *Z* isomer ratio 97 : 3).[7]



17

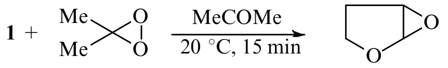
By treatment with aqueous potassium hydroxide in the presence of a crown ether, chloro(methoxy)methyl *p*-tolyl sulfone **18** has been converted into carbene **19**, which was introduced *in situ* into the reaction with 2,3-dihydrofuran **1**; *endo*-6-methoxy-*exo*-6-(tolyl-*p*-sulfonyl)-2-oxabicyclo[3.1.0]hexane **20** was thus synthesised in 48% yield.[8]



18 **19**

20

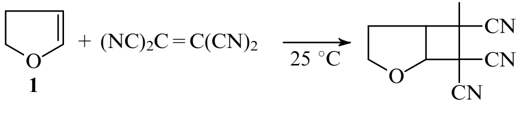
Oxidation of the enol ether **1** with dimethyldioxirane **21** at room temperature leading to 2,6-dioxabicyclo[3.1.0]hexane **22** can also be regarded formally as [2 + 1]-cycloaddition.[9]



21 **22**

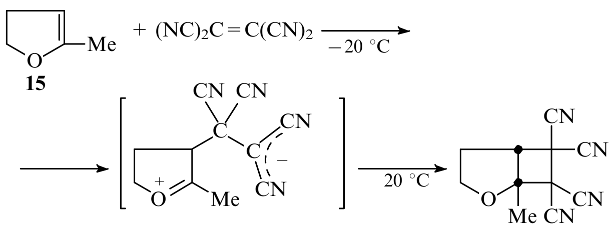
2. [2 + 2]-Cycloaddition

In 1973, Huisgen and Steiner[10] studied the reaction of 2,3-dihydrofuran **1** with tetracyanoethene and determined its rate constant ($k_2 \times 10^3$ = 22.6 litre mol^{-1} s^{-1}). They suggested that this reaction involves the intermediate formation of a biradical or a zwitterion.



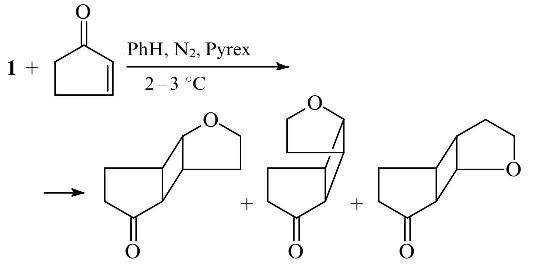
1

Fries and Gollinck[11] believe that the reaction of 5-methyl-2,3-dihydrofuran **15** with tetracyanoethene at −20 °C affords the zwitterion **23**, which is converted into the final adduct at 20 °C.



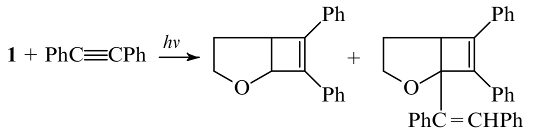
15 **23**

Photochemical reaction of the enol ether **1** with cyclopent-2-enone results in the formation of three products of [2+2]-cycloaddition: *exo*-**24** (head-to-tail), *endo*-**25** (head-to-tail) and *exo*-**26** (head to head), in 99% overall yield. The ratio of the isomers **24** : **25** : **26** = 75 : 3 : 22.[12]



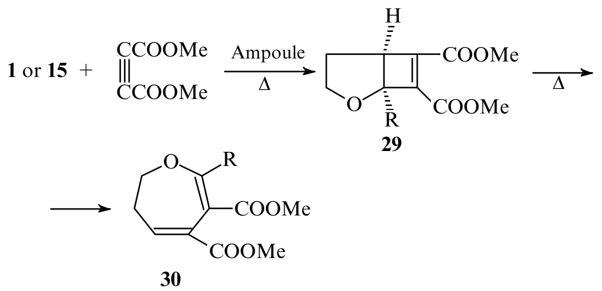
24 **25** **26**

When a mixture of the enol ether **1** and diphenylacetylene is irradiated with the light of a low-pressure mercury lamp for 3 days, two compounds are formed: 6,7-diphenyl-2-oxabicyclo[3.2.0]hept-6-ene **27** (yield 11%) and compound **28** resulting from the addition of the adduct **27** to the second diphenylacetylene molecule (yield 5%).[13]



27 **28**

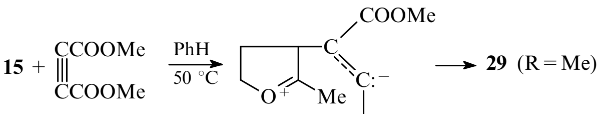
By thermal condensation of dihydrofurans **1** or **15** with dimethyl acetylenedicarboxylate, one can obtain [2+2]-cycloaddition products **29**, which are converted into 2,3-dihydrooxepine derivatives **30** on prolonged keeping at 200 °C.[14]



29 **30**

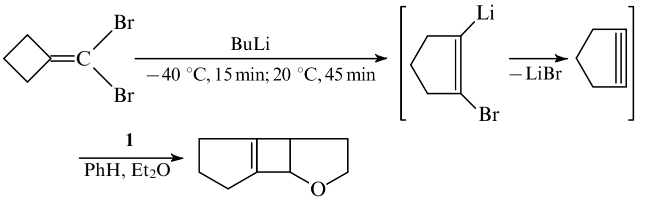
R	Catalyst	Solvent	T / °C	Time / h	Yield (%) 29	Yield (%) 30
H	Pr^i_2NEt	PhMe	110	1	39	–
Me	Pr^i_2NEt	PhMe	60	1	41	–
Me	Pr^i_2NEt	DMF	60	0.5	85	–
Me	Pr^i_2NEt	DMSO	60	0.5	95	–
Me	–	PhMe	200	12	–	85

In the opinion of Fries and Gollinck,[15] the reaction of enol ether **15** with dimethyl acetylenedicarboxylate is reversible and occurs *via* the formation of the intermediate bipolar ion **31**.



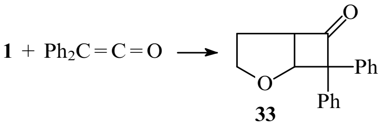
31

Treatment of dibromomethylenecyclobutane with butyllithium affords 1-lithio-2-bromocyclopentene, which eliminates lithium bromide under the reaction conditions being thus converted into cyclopentyne, which enters *in situ* into a [2+2]-cycloaddition reaction with the enol ether **1**; this leads to adduct **32** in 35% yield.[16]



32

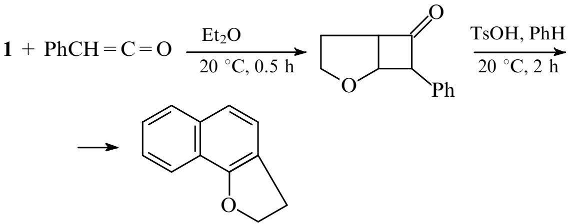
The compound **1** reacts smoothly with diphenylketene at 0 °C to give 7,7-diphenyl-2-oxabicyclo[3.2.0]heptan-6-one **33** in a quantitative yield.[17]



33

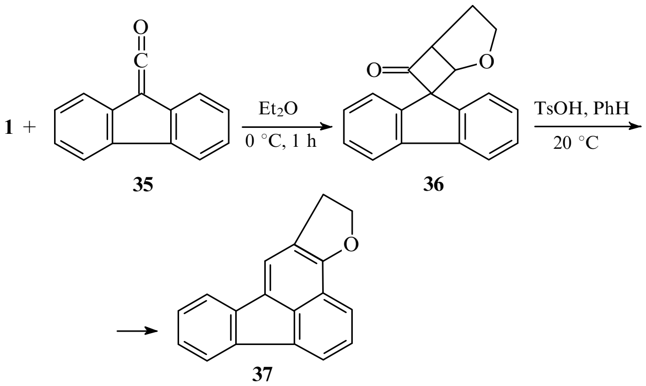
A study of the rate of [2+2]-cycloaddition of diphenylketene to various enol ethers has shown that the compound **1** reacts with the ketene 350 times faster than 2,3-dihydropyran and 20 times faster than ethyl vinyl ether.[18,19]

The enol ether **1** readily reacts with phenylketene to give 7-phenyl-2-oxabicyclo[3.2.0]heptan-6-one in 80% yield; the latter is converted into the naphthofuran derivative **34** (yield 30%) on treatment with toluene-*p*-sulfonic acid.[20]



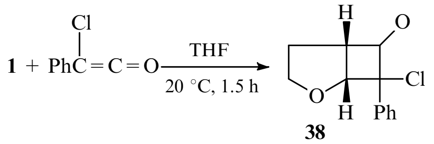
34

The reaction of the enol ether **1** with ketene **35** results in the formation of adduct **36** (yield 80%), treatment of which with toluene-*p*-sulfonic acid gives compound **37** in 70% yield.[20]



35 **36** **37**

Various heterocyclic compounds have been synthesised based on 7-chloro-7-phenyl-2-oxabicyclo[3.2.0]heptan-6-one **38**, which is formed in 75% yield upon [2 + 2]-cycloaddition of the enol ether **1** to chloro(phenyl)ketene **39**. For example, a mixture of lactones **40** and **41** was obtained in 45% overall yield, and bicyclic lactone **42** was prepared as a mixture of *cis*- and *trans*-isomers in a ratio of 1 : 1.6.



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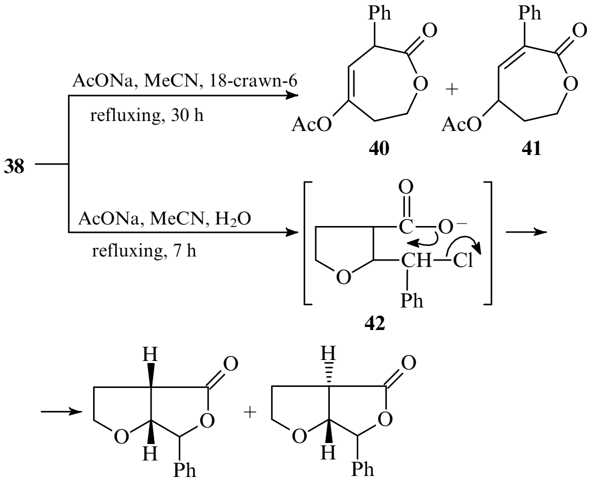
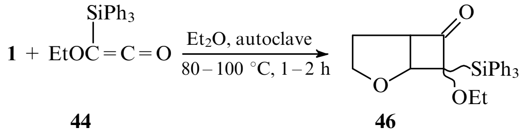
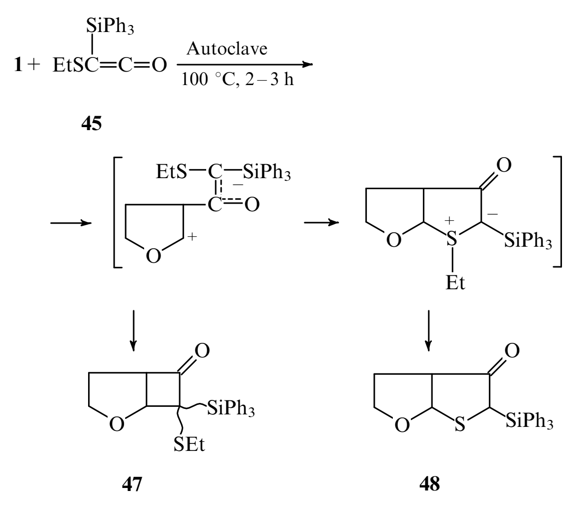


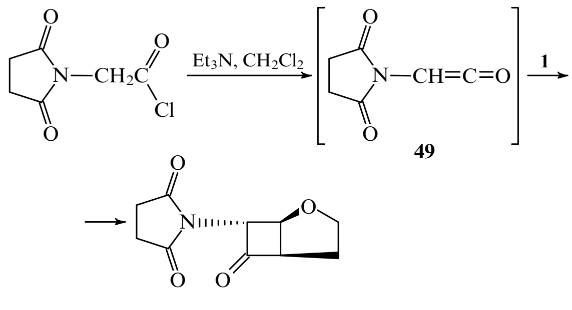
42 (65%)

The reactions of the enol ether **1** with ethoxy(triphenylsilyl)ketene **44** and its sulfur-containing analogue **45** follow essentially dissimilar pathways. Whereas the interaction of the enol ether **1** with the ketene **44** affords only the [2 + 2]-cycloaddition product **46** (yield 85%),[22] in the case of the ketene **45**, two compounds are formed: adduct **47** (yield 5%) and 7-triphenylsilyl-2-oxa-8-thiabicyclo[3.3.0]octan-6-one **48** (yield 14%).[23]

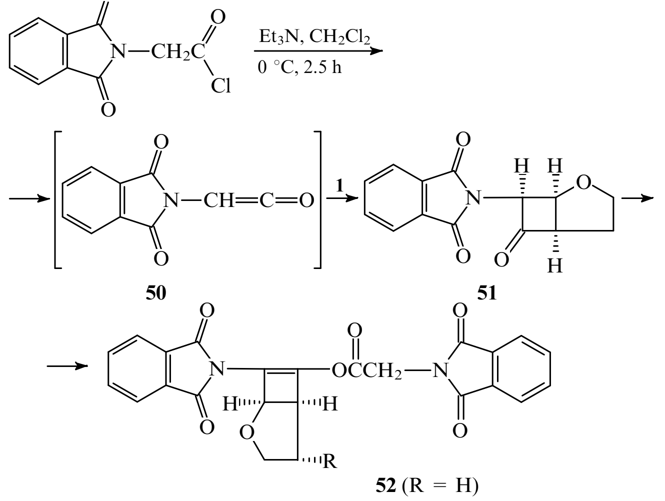




Ketene **49** arising upon treatment of succinimidoacetyl chloride with triethylamine enters into the [2 + 2]-cycloaddition reaction with the enol ether **1** leading to 7-succinimido-2-oxabicyclo[3.2.0]heptan-6-one.[24]

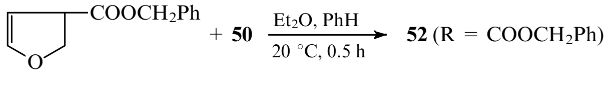


Two compounds have been obtained in the reaction of 2,3-dihydrofuran **1** with ketene **50**, prepared by treating phthalimidoacetyl chloride with triethylamine, namely, compound **51** resulting from [2 + 2]-cycloaddition (yield 40%) and 2-oxabicyclo[3.2.0]hept-6-ene derivative **52** (R = H, yield 7%) arising *via* acylation of the enol form of the adduct **51** with the initial acyl chloride.[25]

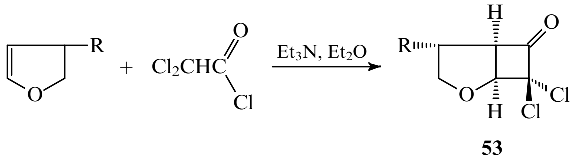


52 (R = H)

The reaction of 3-benzyloxycarbonyl-2,3-dihydrofuran with ketene **50** affords only compound **52** (R = COOCH$_2$Ph, yield 28%).[25]



As expected, the interaction of the enol ether **1** or 3-benzyloxycarbonyl-2,3-dihydrofuran with dichloroacetyl chloride in the presence of triethylamine gives only the products of [2 + 2]-cycloaddition **53**.[26]

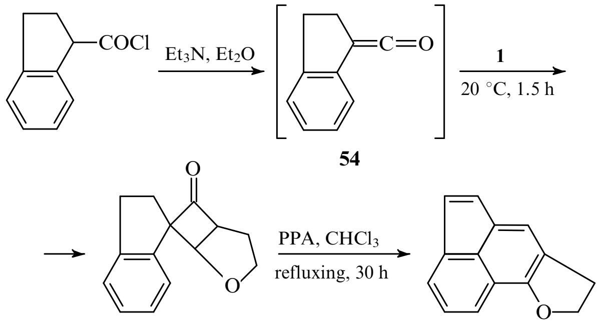


53

R	T / °C	Time / h	Yield (%)
H	20	2.5	55
COOCH$_2$Ph	0	1	53

Ketene **54** generated from indane-1-carboxylic acid chloride by treating it with triethylamine under an inert atmosphere has been made to react *in situ* with the enol ether **1** according to the [2 + 2]-cycloaddition route; this has led to the spiro-compound **55**.

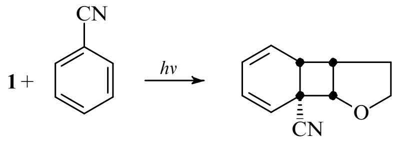
Prolonged refluxing of the cycloaddition product **55** in chloroform in the presence of polyphosphoric acid results in its recyclisation yielding compound **56**.[27]



54

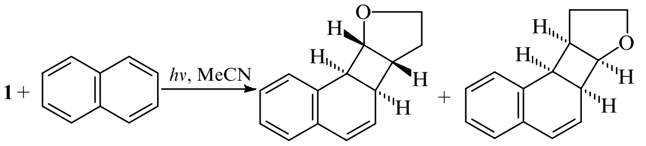
55 (90%) **56** (9%)

When the enol ether **1** and benzonitrile are irradiated with light from a 70-W low-pressure mercury lamp through a quartz filter under an inert atmosphere, [2+2]-cycloaddition reaction takes place giving rise to 1-cyano-3-oxatricyclo[5.4.0.0^{2,6}]undeca-8,10-diene **57** in 20% yield.[28]



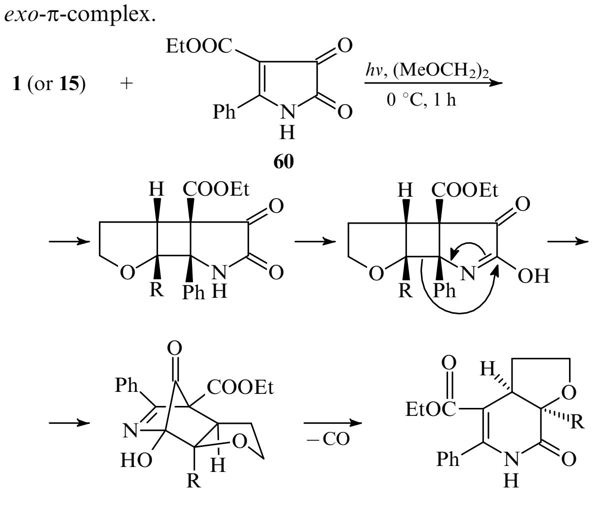
57

Gilbert *et al.*[29] managed to accomplish [2+2]-cycloaddition of the enol ether **1** to naphthalene by irradiating a mixture of the initial compounds with the light from a 125-W medium-pressure mercury lamp. Adducts **58** and **59** were obtained in this way in a low overall yield (5%).[29]



58 **59**

When compound **60** is exposed to the radiation of a high-pressure mercury lamp in the presence of compound **1** or **15**, a mixture of two products **61** and **62** is obtained in each case. The researchers[30] believe that the compounds **61** are formed *via* an intermediate *endo*-π-complex, whereas the compounds **62** arise *via* an *exo*-π-complex.



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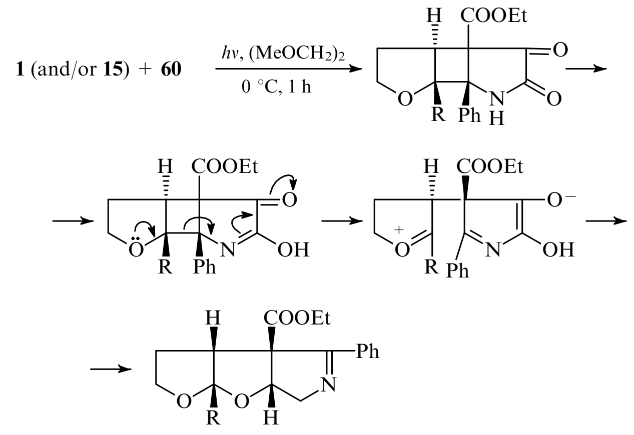
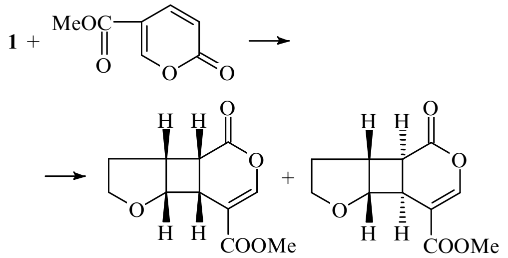
61



62

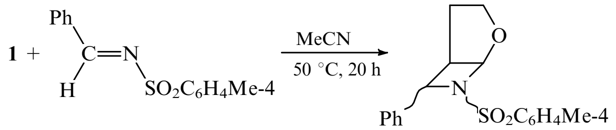
R	Yield (%)	
	61	**62**
H	2	8
Me	14	77

When the enol ether **1** is made to react with methyl 2-pyrone-5-carboxylate, two diastereomeric products of [2+2]-cycloaddition, **63a** and **63b**, are formed.[31]



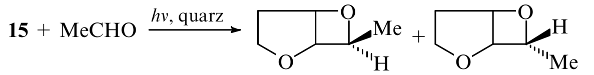
63a **63b**

At 50 °C and under a pressure of 12 kbar, *N*-tosylimine **64** undergoes [2+2]-cycloaddition to the enol ether **1**, which affords adduct **65** as a mixture of *cis*, *cis*-, *trans*, *cis*-, and *cis*, *trans*-isomers in 80% overall yield; the individual *cis*, *cis*-isomer was isolated from this mixture in a yield of 35%.[32]



64 **65**

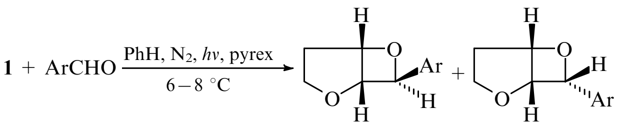
The irradiation of 5-methyl-2,3-dihydrofuran **15** and acetaldehyde with the light from a medium-pressure mercury lamp results in the formation of compound **66** as a mixture of isomers **66a** (yield 36%) and **66b** (yield 27%).[33]



66a **66b**

Japanese investigators[34] carried out [2+2]-cycloaddition of 2,3-dihydrofuran to benzaldehyde by irradiating the initial compounds with a high-pressure mercury lamp (450 W) under a nitrogen atmosphere at 0 °C for 6 h. They obtained a mixture of (1*SR*, 5*RS*, 7*SR*)- and (1*SR*, 5*RS*, 7*RS*)-7-phenyl-2,6-dioxabicyclo[3.2.0]heptanes (**67a,b**, Ar = Ph).

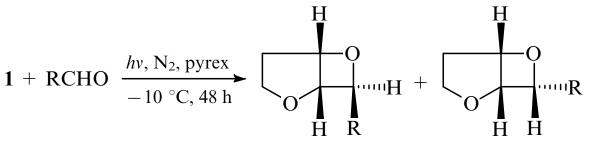
When this reaction has been carried out on exposure to the radiation of a 150-W high-pressure mercury lamp, the ratio of the isomers **67a** and **67b** has been found to depend on the nature of the aromatic aldehyde used.[35,36]


67a **67b**

Ar	Time / h	Yield (%)	Ratio **67a** : **67b**
Ph	11	50	7 : 1
2-MeC_6H_4	16	94	15 : 1
2,4,6-$Me_3C_6H_2$	8.5	97	20 : 1
2-Me-4,6-$(Bu^t)_2C_6H_2$	24	28	20 : 1

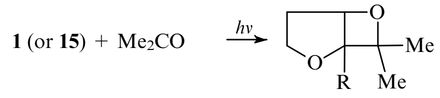
The rate and diastereoselectivity of the cycloaddition reaction involving the enol ether **1** were found to be higher than those in the case of cyclopentene.[35]

The diastereoselectivity of [2 + 2] cycloaddition of the enol ether **1** to aromatic aldehydes is completely reversed when the electronic configuration of the excited triplet form [3($n\pi^*$) − 3($\pi\pi^*$)] changes: in the case of 2,4,6-trimethylbenzaldehyde, the diastereomer **68a** is formed predominantly, while in the case of aldehydes of the naphthalene series, the diastereomer **68b** predominates.[37]

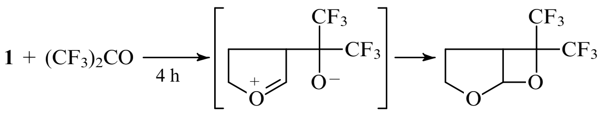

68a **68b**

R	Yield (%)	Ratio **68a** : **68b**
Me	76	55 : 45
2,4,6-$Me_3C_6H_2$	97	2 : 98
α-Naphthyl	55	98 : 2
β-Naphthyl	53	98 : 2

2,6-Dioxabicyclo[3.2.0]heptane derivatives **69** have been synthesised by [2 + 2]-cycloaddition of the enol ether **1** or **15** to acetone occurring on exposure to radiation of a medium-pressure mercury lamp.[33]


R = H (95%), Me (30%). **69**

A similar reaction involving hexafluoroacetone affords adduct **70**. It has been found that the reaction temperature and the nature of the solvent exert a substantial influence on the selectivity of the process, on the degree of conversion, and on the yield of the adduct **70**.[38]


70

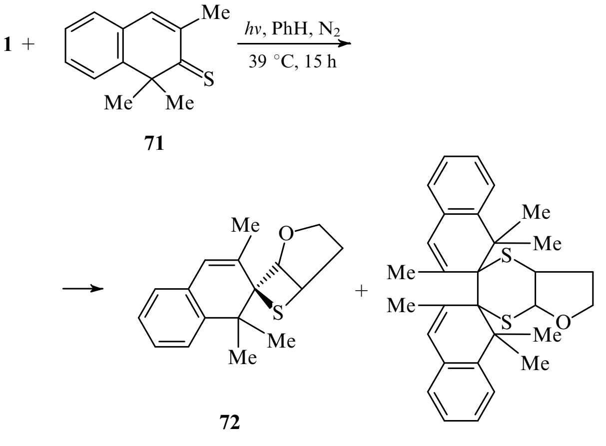
A. Temperature dependence of the selectivity and the yield of **70**.

T / °C	Yield (%)	Selectivity (%)	Conversion of **1** (%) (in heptane)
−5	39	39	100
−10	45	46	99
−15	56	75	74
−20	57	81	71
−62 (6 h)	62	62	100

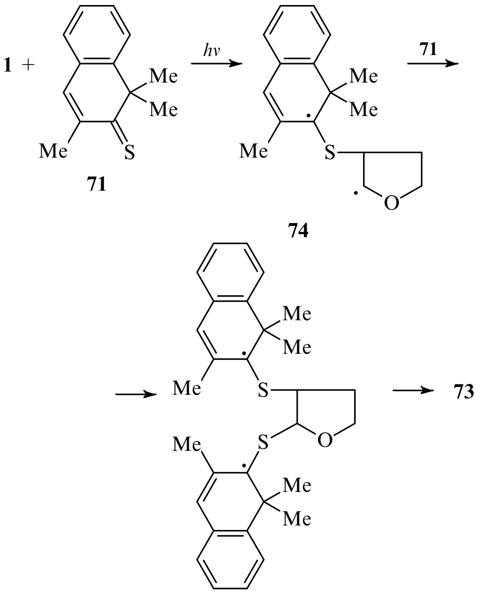
B. Solvent dependence of the selectivity and the yield of **70**.

Solvent	Yield (%)	Selectivity (%)	Conversion of **1** (%)
Et_2O	24	70	34
$CHCl_3$	27	27	100
PhMe	50	51	98
Heptane	57	81	71

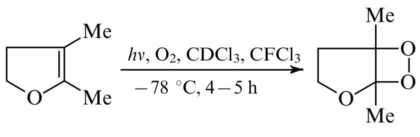
The irradiation of a mixture of the enol ether **1** and 1,3,3-trimethyl-1,2-dihydronaphthalene–2-thione **71** with an RPR lamp (λ = 350 nm) has led to two compounds: [2 + 2]-cycloaddition product **72** and compound **73** resulting from the interaction of one molecule of the enol ether **1** with two molecules of the initial naphthalene derivative **71**.[39]


71 **72** **73**

The formation of the compound **73** was explained[39] in terms of a scheme involving the generation of biradicals **74** and **75**.

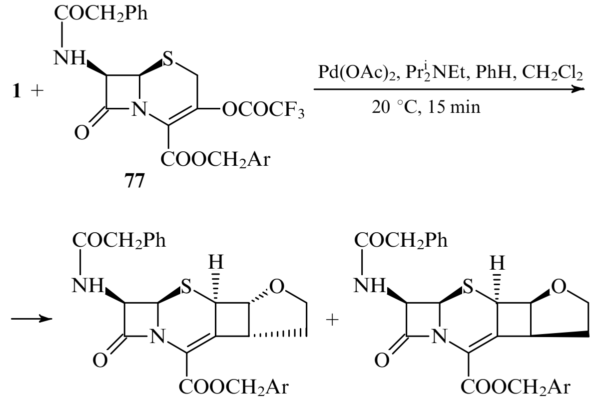

71 **74** **75**

4,5-Dimethyl-2,3-dihydrofuran has been photooxidised by irradiation with a filtered light (λ = 500 − 595 nm) of a 150-W lamp under an oxygen atmosphere in the presence of tetraphenylporphin or Bengal Rose. Among other products, 1,5-dimethyl-2,6,7-trioxabicyclo[3.2.0]heptane **76**, which can formally be regarded as resulting from the [2 + 2]-cycloaddition of oxygen to the double bond, is formed in 48% yield.



76

Cyclocondensation of the enol ether **1** with cephalosporin **77** in the presence of palladium acetate and ethyldiisopropylamine has led to compound **78**, which was separated into two isomers **78a** and **78b** (overall yield 73%, ratio of isomers 1.8 : 1).[41]



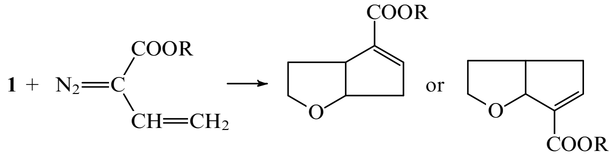
77

78a **78b**

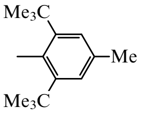
Ar = C_6H_4OMe-4.

3. [3 + 2]-Cycloaddition

Esters of 2-diazobut-3-enoic acid **79** decompose in the presence of various catalysts to give the corresponding carbenes; however, the primary products arising upon the addition of these carbenes to the double bond of 2,3-dihydrofuran **1** undergo a rearrangement affording regioisomers of 2-oxabicyclo[3.3.0]octene, which contain the ester group in the 6-position (**80a**) or in the 8-position (**80b**)[42,43] and are formally the products of [2 + 3]-cycloaddition of the diazo derivative **79** to dihydrofuran.

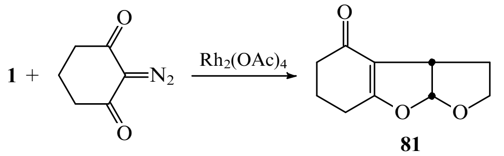


79 **80a** **80b**

R	Catalyst	Solvent	Yield (%)		Ref.
			80a	**80b**	
Me	$Rh_2(OC_8H_{17})_4$ Et_2AlCl	Pentane	66	–	42
	$Rh_2(OAc)_4$	CH_2Cl_2	–	40–42	42, 43

2,3-Dihydrofuran **1** reacts in a similar way with some other diazo compounds.

The influence of the reaction conditions on the yield of the product **81** resulting from the interaction of the enol ether **1** with 2-diazocyclohexane-1,3-dione in the presence of $Rh_2(OAc)_4$ has been studied.[44]

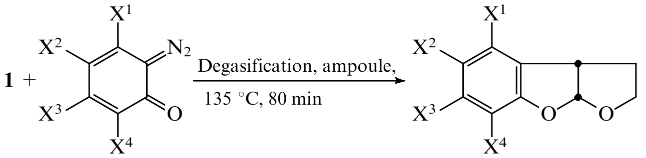


81

When the reaction is carried out without a solvent with boiling (2 h) or at 25 °C (4 h), compound **81** is formed in 84% yield. The nature of the solvent used in this reaction (25 °C, 24 h) has a substantial influence on the yield of the compound **81**.

Solvent	C_6H_5F	THF	PhH	CH_2Cl_2	MeCN
Yield of **81** (%)	70	61	48	43	20

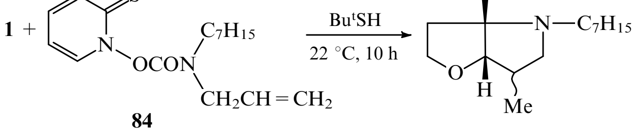
Thermal cyclocondensation of the enol ether **1** with diazo compounds **82** has given rise to furo[2.3-*b*]-2,3-dihydrobenzofuran derivatives **83** (yields 45% – 56%).[45]



82 **83**

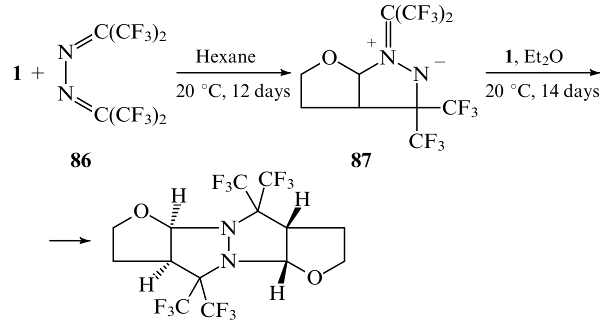
X^1	X^2	X^3	X^4
H	Cl	H	Cl
OMe	Cl	H	Cl
Br	H	Br	H

The reaction of the enol ether **1** with carbamate **84**, containing an allyl radical, in the presence of 2-methylpropane-2-thiol gave a mixture of *exo*- and *endo*-isomers of adducts **85** (in a ratio of 1 : 3) in 52% overall yield.[46]



84 **85**

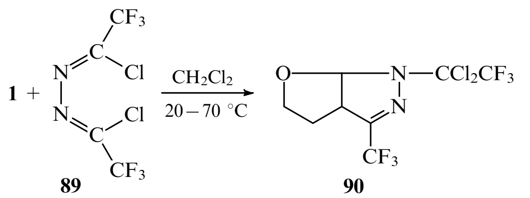
Perfluorinated heterodiene **86** reacts with the enol ether **1** at 20°C to give the stable bipolar ion **87** in a yield of 48%. The latter undergoes [3 + 2]-cycloaddition to a further molecule of the enol ether **1**, which affords a bis-adduct, namely, 7,7,14,14-tetrakis-(trifluoromethyl)-3,10-dioxa-1,8-diazatetracyclo[6.6.0.0$^{2.6}$0$^{9.13}$]-tetradecane **88** (yield 17%).[47]



86 **87**

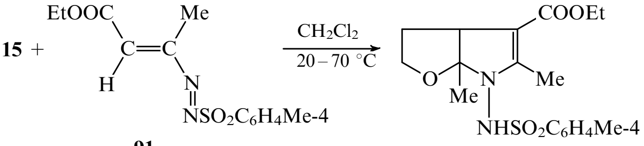
88

The [3 + 2]-cycloaddition of 2,3-dihydrofuran **1** to 1,4-dichloro-1,4-bis(trifluoromethyl)-2,3-diazabuta-1,3-diene **89** is accompanied by a rearrangement of this dichloroazine and yields compound **90** resulting from the 1,3-dipolar cycloaddition of the arising nitrilimine $CF_3\overset{+}{C}{=}N-\overset{-}{N}CCl_2CF_3$.[48]



89 **90**

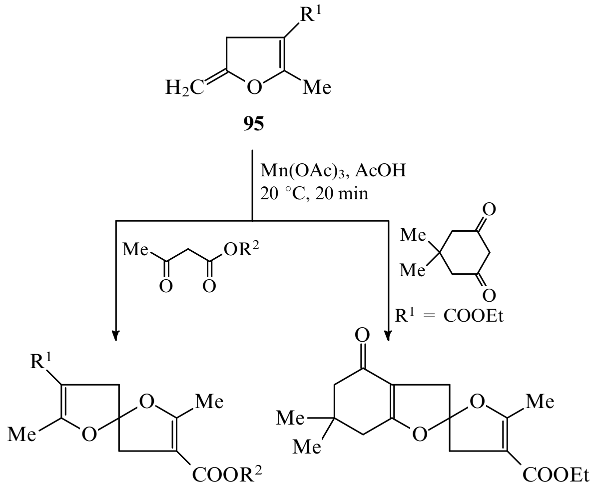
Clarke *et al.*[49] have suggested that the interaction of the compound **91** with 5-methyl-2,3-dihydrofuran **15** leads to the furanopyrrole derivative **92** (yield 35%). Apparently, this process also involves the intermediate formation of the corresponding nitrilimine.



91

92

The spiro-compounds **93** and **94**, containing each two dihydrofuran fragments, are formed in the condensation of dihydrofuran derivatives **95** with acetoacetates or with 5,5-dimethylcyclohexane-1,3-dione in the presence of manganese(III) acetate under an inert atmosphere.[50]

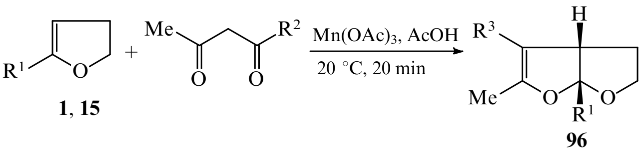


93

94

R^1	R^2	Yield **93** (%)
COOEt	Et	37
COOEt	CH_2Ph	40
SO_2Ph	Et	26

Enol ethers **1** or **15** react with acetoacetates or with pentane-2,4-dione under the same conditions to give compounds with a different structure — 1,5-dioxabicyclo[3.3.0]octane derivatives **96**.[50]

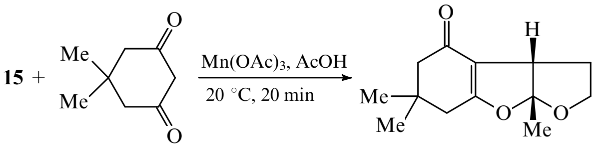


1, 15

96

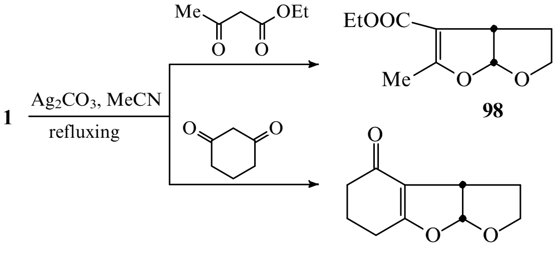
R^1	R^2	R^3	Yield **96** (%)
Me	OEt	COOEt	51
H	OEt	COOEt	53
H	OCH_2Ph	$COOCH_2Ph$	56
H	Me	MeCO	26

Tricyclic compound **97** has been obtained in 40% yield by cyclocondensation of the enol ether **15** with 5,5-dimethylcyclohexane-1,3-dione.[50]



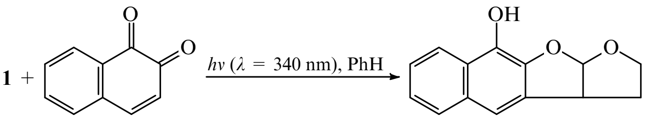
97

Kraus *et al.*[51] showed that the cyclocondensation of the compound **1** with esters of oxoacids or with cyclic diketones can be carried out in the presence of silver carbonate in boiling acetonitrile under an inert atmosphere. For example, compounds **98** (yield 50%) and **99** (yield 60%–76%) were prepared from the enol ether **1** and ethyl acetoacetate and cyclohexane-1,3-dione, respectively.



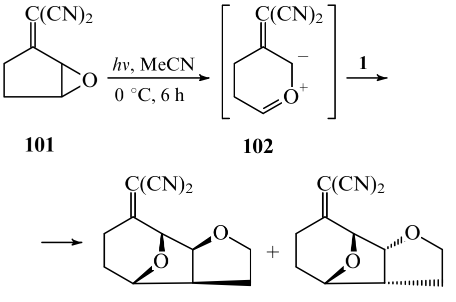
99

The yield of compound **100** resulting from the photochemical reaction (high-pressure mercury lamp) of 2,3-dihydrofuran **1** with 1,2-naphthoquinone depends markedly on the polarity of the solvent in which the process is conducted. In fact, in nonpolar benzene ($D = 0.00$), the yield of the compound **100** is only 6%, whereas in acetonitrile ($D = 3.37$), the yield reaches 58%.[52]



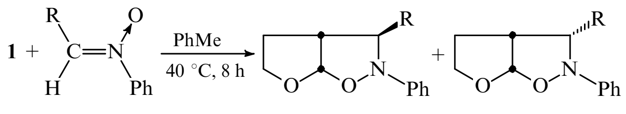
100

When epoxide **101** is irradiated with a low-pressure mercury lamp (60 W, λ = 254 nm) through a quartz filter under an inert atmosphere, it gives rise to carbonylylide **102**, which enters into 1,3-dipolar cycloaddition to 2,3-dihydrofuran **1** to give adducts **103a,b** as pairs of diastereomers (yields 21% and 5%, respectively).[53]



103a **103b**

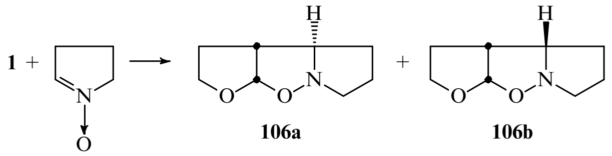
Reactions of [3+2]-cycloaddition of various 1,3-dipoles to 2,3-dihydrofurans have been studied fairly well. For example, 1,3-dipolar cycloaddition of the enol ether **1** to nitrones **104** proceeds according to the 'head-to-head' type and yields a mixture of *endo*- and *exo*-isomers **105a,b**.[54] The ratio of the isomers depends on the nature of the group R in the nitrone.



105a **105b**

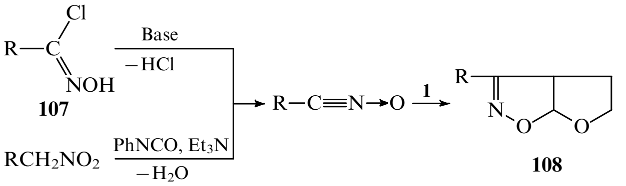
R	Ratio **105a** : **105b**
PhCO	52 : 48
Ph	22 : 78

Cycloaddition of the enol ether **1** to pyrroline *N*-oxide occurs stereoselectively; the reaction products consist predominantly of the diastereomer **106a** (yield 91%), only a small amount of the diastereomer **106b** being formed (yield 3%).[55]



106a **106b**

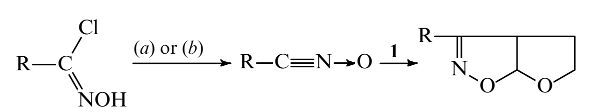
The first study devoted to the 1,3-dipolar addition of *N*-oxides of aliphatic, aromatic, and heterocyclic carboxylic acid nitriles to 2,3-dihydrofuran was published in 1962.[56] The nitrile *N*-oxides were generated by two methods: by treating hydroximoyl chlorides **107** with bases and by dehydration of primary nitro compounds through the action of phenyl isocyanate in the presence of triethylamine. Nitrile *N*-oxides were introduced *in situ* into the reaction with 2,3-dihydrofuran. The cycloaddition occurred according to the 'head-to-head' type and gave adducts **108**.



107 **108**

The conditions under which the nitrile *N*-oxides were generated and the yields of the adducts **108** are presented in Table 1.

Some 3*a*,4,5,6*a*-Tetrahydrofuro[2,3-*d*]isoxazoles **108** containing substituents in the 3-position have been synthesised by the cycloaddition of the enol ether **1** to the *N*-oxides of aliphatic carbonitriles, prepared by treatment of hydroximic acid chlorides **107** with sodium carbonate in water (*a*)[57] or with triethylamine in ether (*b*).[58–61]

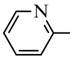
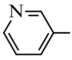
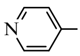


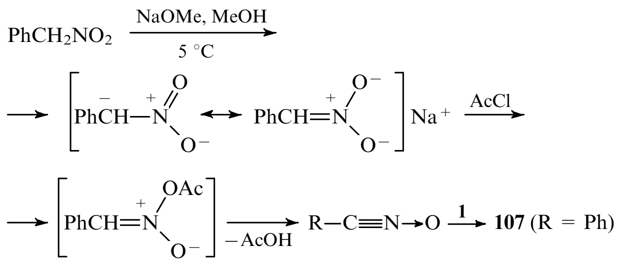
107 **108**

R	Yield (%)	Ref.
CN	25	57
COOEt	51	58, 59
Me	–	59
Ph	–	60
2,4-$Cl_2C_6H_3$	–	61

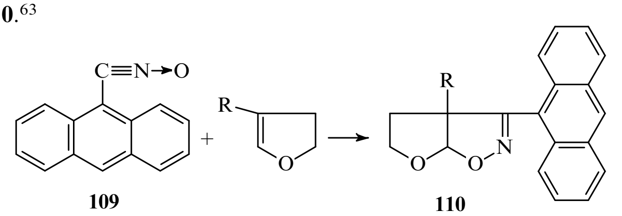
Harada *et al.*[62] described another method for the generation of benzonitrile *N*-oxide, which involves successive treatment of phenylnitromethane with sodium methoxide and acetyl chloride, and proposed a mechanism for this process. The resulting *N*-oxide was introduced *in situ* into the cycloaddition reaction with 2,3-dihydrofuran **1**.

Table 1. Conditions of reactions of 2,3-dihydrofuran **1** with nitrile *N*-oxides and yields of adducts **108**.

Substrate	Reaction conditions	Yield of **108** (%)
PhC(Cl) = NOH	NaOH, H_2O, 0 °C, 25 min	40
—C(Cl) = NOH	NaOH, H_2O, 20 °C, 1 h	65
—C(Cl) = NOH	Et_3N, Et_2O, $EtOCH_2CH_2OEt$, 20 °C, 40 min	42
—C(Cl) = NOH	Et_3N, Et_2O, $EtOCH_2CH_2OEt$, 20 °C, 40 min	59
PhC(O)C(Cl) = NOH	Et_2O, $EtOCH_2CH_2OEt$, pH 8 (citrate-phosphate buffer), 5 °C, 15 min	67
$MeCH_2NO_2$	Et_3N, PhNCO, PhH, refluxing, 1 h	66
$EtCH_2NO_2$	Et_3N, PhNCO, PhH, refluxing, 1 h	67
$PrCH_2NO_2$	Et_3N, PhNCO, PhH, refluxing, 1 h	71
$EtOCOCH_2NO_2$	Et_3N, PhNCO, PhH, 35 °C, 1 h	59
$MeOCO(CH_2)_3NO_2$	Et_3N, PhNCO, PhH, refluxing, 1 h	66



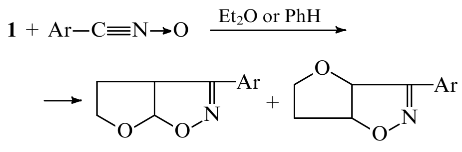
The 1,3-dipolar cycloaddition of anthracene-9-carbonitrile *N*-oxide **109** to 2,3-dihydrofuran **1** or to 4-methoxycarbonyl-2,3-dihydrofuran has been used to prepare the corresponding adducts **110**.[63]



109 **110**

R = H (61%), COOMe (31%).

Thorough investigation of 1,3-dipolar cycloaddition reactions involving 2,3-dihydrofuran **1** and benzonitrile and 2,4,6-trimethylbenzonitrile *N*-oxides has shown that these reactions are highly regioselective and that the 'head-to-head' coupling giving adducts **111** is the main reaction route. Only slight amounts of products **112** resulting from the 'head-to-tail' addition were isolated.[64]

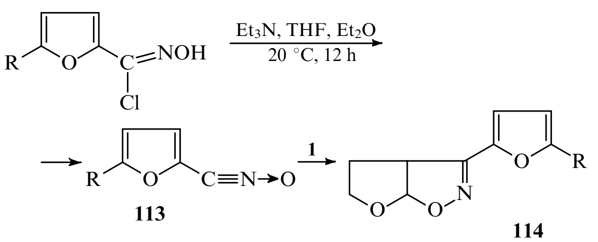


111 **112**

Ar	Ratio **111 : 112**
Ph	99.4 : 0.6
2,4,6-$Me_3C_6H_2$	99.5 : 0.5

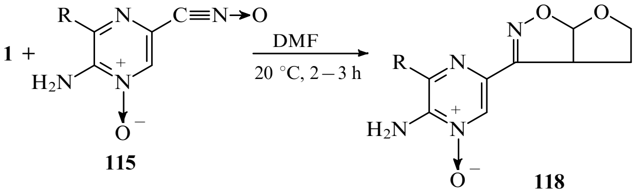
The same investigators[64] also found that the enol ether **1** reacts with nitrile *N*-oxides 1.8 times more rapidly than cyclopentene. They attributed this result to the resonance interaction of the double bond with the electron pair on the oxygen atom, which leads to an increase in the electron density on the carbon atom in the 4-position of the enol ether and to an increase in the electrophilicity of the double bond.

The carbonitrile *N*-oxides of the furan series **113** react with the enol ether **1** stereospecifically to give adducts **114** (yields 71% – 85%).[65]

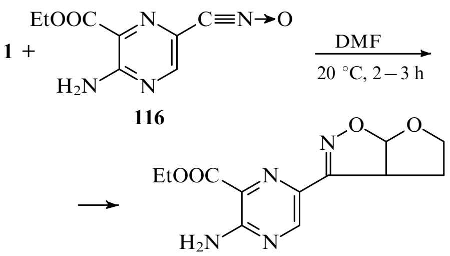


R = H, NO_2, 4-$O_2NC_6H_4$.

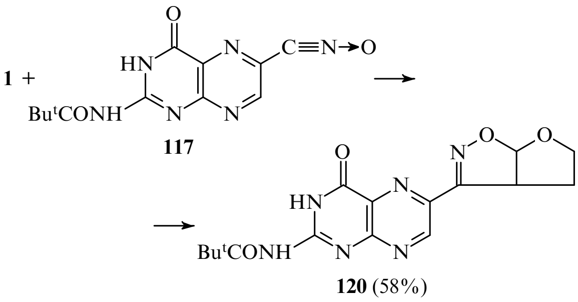
The 1,3-dipolar cycloaddition of 2,3-dihydrofuran **1** to the carbonitrile *N*-oxides of the pyrazine series (**115**, **116**) or of the pteridine series (**117**) has made it possible to synthesise adducts **118**, **119**, or **120**, respectively.[66] The reactions were carried out under an inert atmosphere.



R = COOEt (60%), CN (10%).

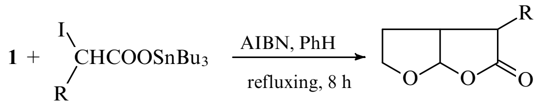


119 (55%)



120 (58%)

The enol ether **1** enters into cyclocondensation with tributylstannyl iodoacetate or α-iodopropionate **121** in the presence of azobisisobutyronitrile (AIBN) in boiling benzene to give 2,8-dioxabicyclo[3.3.0]octan-3-one **122** (R = H, yield 78%) or its 4-methyl-derivative **122** (R = Me, yield 72%). The latter compound is formed as a mixture of diastereomers in a ratio of 1 : 1.[67,68]

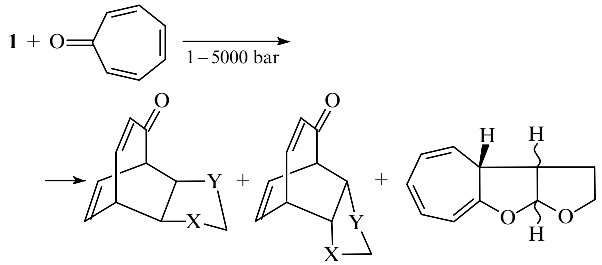


121 **122**

R = H, Me.

4. [4 + 2]-Cycloaddition

Two [4 + 2]-cycloaddition products as mixtures of two isomers (**123a,b** and **124a,b**) and [3 + 2]-cycloaddition product **125** have been obtained by the reaction of the enol ether **1** with tropolone under an elevated pressure. The product ratio (**123** + **124**) : **125** is pressure-dependent.[69]

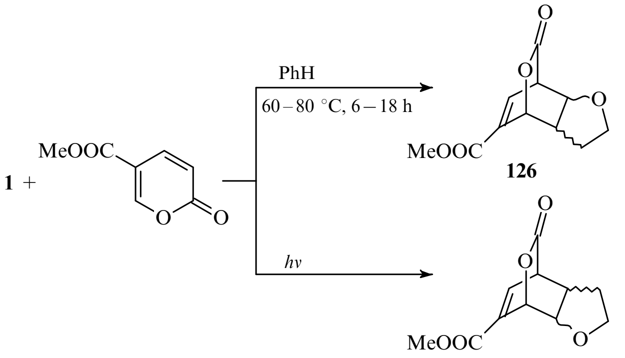


123 **124** **125**

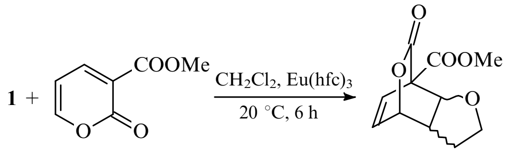
123a: X = O, Y = CH_2 ;
123b: X = CH_2 , Y = O.

Published studies indicate that [4 + 2]-cycloaddition of 2,3-dihydrofuran or its derivatives to esters of 2-pyronecarboxylic acids can be carried out under irradiation with actinic light, in the presence of catalysts, or it can be induced thermally.

The thermal condensation of the enol ether **1** with methyl 2-pyrone-5-carboxylate and the condensation induced by UV radiation afford different products. When the initial compounds were kept in benzene at 60 – 80 °C, methyl 9-oxo-3,8-dioxatricyclo[5.2.2.0^{2,6}]undec-10-ene-11-carboxylate **126** was obtained as a mixture of two isomers (*endo*, yield 25% and *exo*, yield 38%),[70] whereas the photochemical reaction, in which the orientation of the addends was opposite, afforded methyl 8-oxo-3,9-dioxatricyclo[5,2,2,0^{2,6}]undec-10-ene-10-carboxylate **127**.[31]



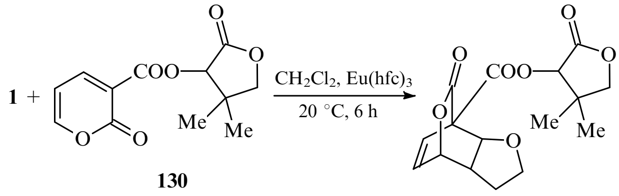
In the presence of lanthanide shift-reagents, the cycloaddition of enol ether **1** to methyl 2-pyrone-3-carboxylate occurs smoothly give products in high yields. When the reaction is carried out at 20 °C in the presence of Eu(hfc)$_3$, adduct **128** can be obtained in a yield of 93% – 96%.[71–73] In the reaction carried out at 0 °C for 0.5 h under an argon atmosphere in the presence of Yb(OTf)$_3$, the yield of the product was 93%.[74]



128

However, the thermal reaction (DMSO, 70–80 °C) in the absence of a shift-reagent afforded the adduct **128** in a yield of only 41%.[71]

Compound **129** is formed in 96% yield upon the [4+2]-cycloaddition of the enol ether **1** to the 2-pyrone derivative **130** in the presence of Eu(hfc)$_3$.[74]

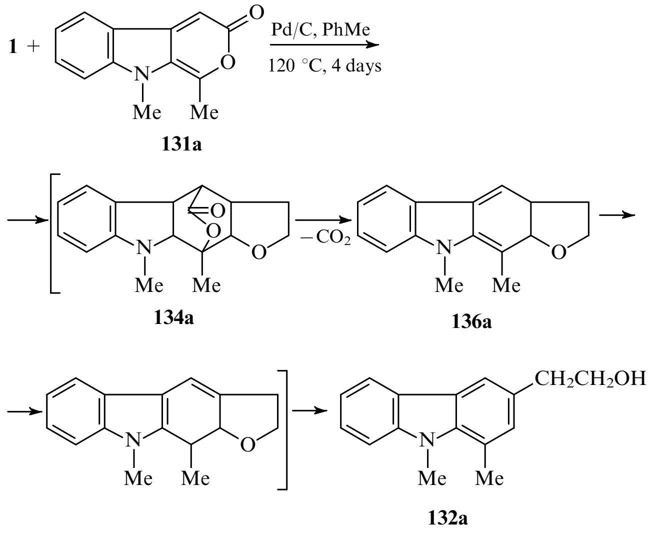


130 **129**

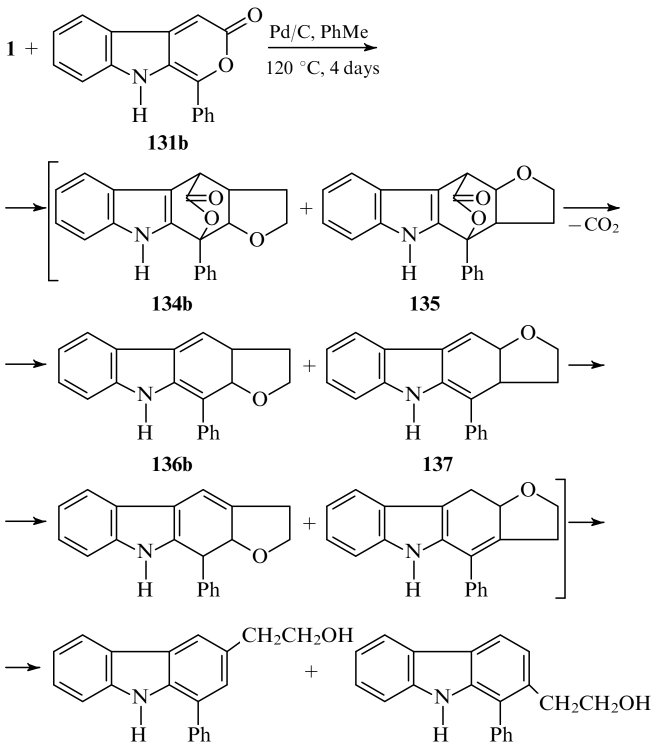
The kinetics of the [4+2]-cycloaddition of various unsaturated compounds to dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate have been studied.[75] It was found that the reaction involving the enol ether **1** occurs 180 times faster than that with 2,3-dihydropyran and 6 times faster than the reaction involving ethyl vinyl ether or cyclopentene.

Heating of the enol ether **1** with pyranono[3,4-*b*]indole **131a,b** in the presence of Pd/C in a sealed tube has given carbazole derivatives **132a** (from **131a**, yield 58%) or a mixture of isomers **132b** and **133** (from **131b**, yield 85%, ratio 5 : 4).

Evidently, the first stage of this process is [4+2]-cycloaddition, which is not regioselective in the case of the phenyl-substituted derivative **131b**. The resulting adducts **134a,b** and **135** lose a CO$_2$ molecule and thus generate indole-2,3-quinodimethane derivatives **136a,b** and **137**, which undergo a 1,5-sigmatropic H-shift, which leads (after cleavage of the tetrahydrofuran ring) to the final products **132a,b** or **133**.[76]

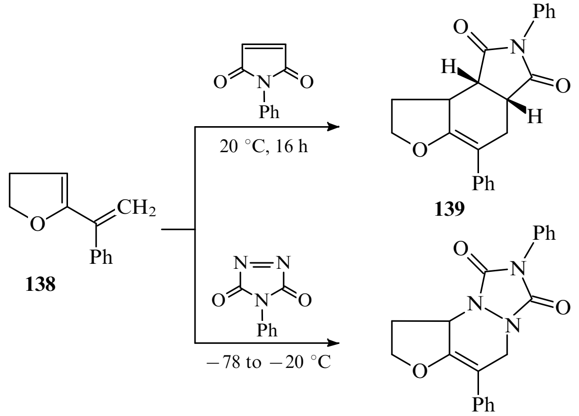


131a **134a** **136a** **132a**



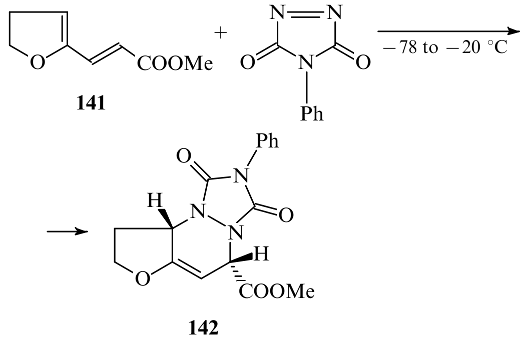
131b **134b** **135** **136b** **137** **132b** **133**

The Diels–Alder condensation of the vinyl-substituted dihydrofuran **138** with *N*-phenylmaleimide or with 4-phenyl-1,2,4-triazoline-3,5-dione has given the corresponding adducts **139** (yield 21%) or **140** (yield 38%).[77]



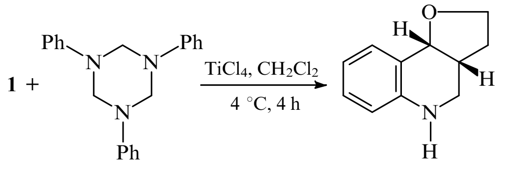
138 **139** **140**

The [4+2]-cycloaddition of methyl (*E*)-3-(2,3-dihydro-5-furyl)acrylate **141** to 4-phenyl-1,2,4-triazoline-3,5-dione is highly stereoselective and affords almost exclusively the *trans*-isomer of the adduct **142** (*E* : *Z* ⩾ 95 : 1, yield 88%).[77]



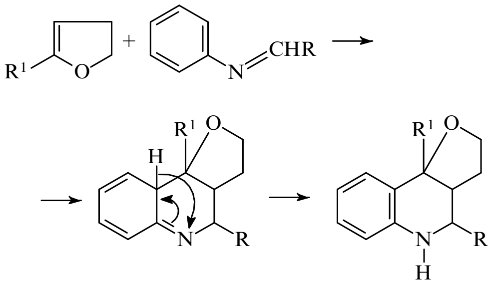
141 **142**

The cyclotrimer of *N*-methyleneaniline **143** reacts with 2,3-dihydrofuran in the presence of titanium(IV) chloride giving rise to 2,3,3*a*β,4,5,9*b*β-hexahydrofuro[3,2-*c*]quinoline **144** (yield 16.8%).[78]

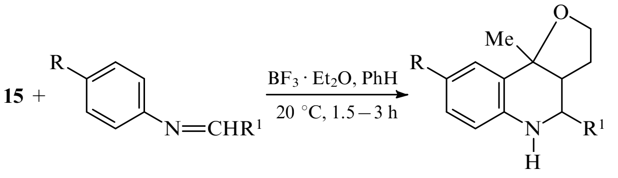


143 **144**

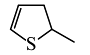
The first stage of the interaction of enol ethers with azomethines is obviously the [4 + 2]-cycloaddition involving the phenyl substituent. This is followed by the 1,3-shift of hydrogen, which restores the aromatic system and results in the formation of tetrahydroquinoline derivatives.

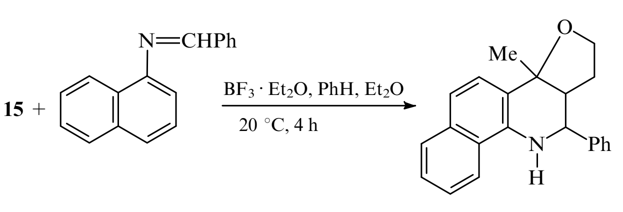


In the first study[79] devoted to the interaction of enol ethers with azomethines, the reaction of 5-methyl-2,3-dihydrofuran **15** with azomethines of the general formula $ArN=CHR_1$ in the presence of $BF_3 \cdot Et_2O$ was studied. The authors reported that this process is exothermic and is completed at ambient temperature. The reaction proceeds stereospecifically and affords compounds **145** or **146**.



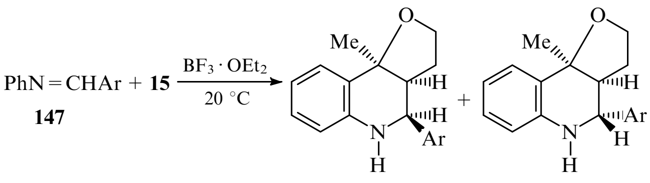
145

R	R^1	Yield (%)
H	Ph	81.3
MeO	Ph	70.3
H		61.5



146

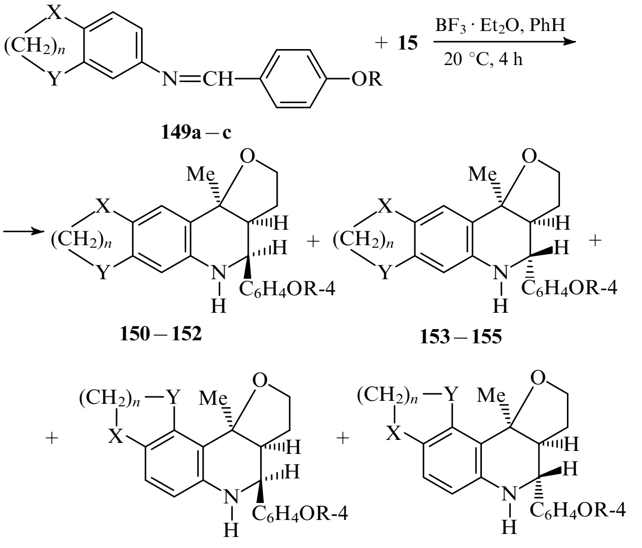
However, more recently,[80] it was shown that the reaction of the enol ether **15** with azomethines **147** is non-stereospecific and results in the formation of mixtures of diastereomers **148a,b** in a ratio of 1 : 1.



147 **148a** **148b**

Ar = Ph, 2-ClC$_6$H$_4$.

When the enol ether **15** reacts with the azomethines $PhN=CHC_6H_4NO_2$-2 in benzene in the presence of $BF_3 \cdot Et_2O$ at 20 °C for 4 h, a mixture consisting of equal amounts of *cis*-**148a** and *trans*-*dl*-2,3,3*a*,4,5,9*b*-hexahydro-9*b*-methyl-4-(*o*-nitrophenyl)furo[3,2-*c*]quinoline **148b** (Ar = $C_6H_4NO_2$-2) is also formed.[81] A detailed study of the reactions of the enol ether **15** with azomethines of the general formula $ArN=CHC_6H_4OR$ **149a – c** has shown that, depending on the nature of Ar, the process yields either one or two pairs of diastereomers.



149a – c

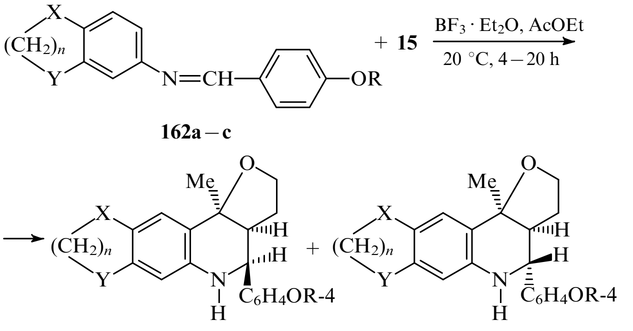
150 – 152 **153 – 155**

156 – 158 **159 – 161**

149a, **150**, **153**, **156**, **159**: X = Y = O, *n* = 2, R = Me;
149b, **151**, **154**, **157**, **160**: X = NAc, Y = CH$_2$, *n* = 2, R = H;
149c, **152**, **155**, **158**, **161**: X = Y = CH$_2$, *n* = 1, R = Me.

For example, two pairs of diastereomers are formed in the reactions of dihydrofuran **15** with each of compounds **149a**,[82] **149b**,[83] or **149c**. The overall yield of reaction products **150**, **153**, **156**, and **159** is 15%, that of **151**, **154**, **157**, and **160** is 48%, and that of **152**, **155**, **158**, and **161** is 64%.

On the other hand, the reactions between the enol ether **15** and the Schiff's bases **162a**,[82] **162b**,[83] or **162c**[83] resulted in the formation of only one diastereomer pair.



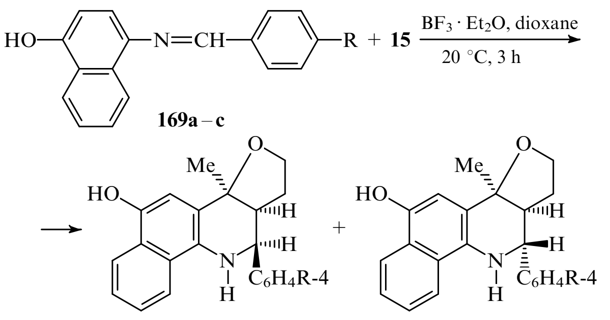
162a – c

163 – 165 **166 – 168**

162a, 163, 166: X = Y = O, *n* = 1, R = Me;
162b, 164, 167: X = CH$_2$, Y = NAc, *n* = 1, R = H;
162c, 165, 168: X = NAc, Y = CH$_2$, *n* = 1, R = H.

The overall yield of the two isomers **163** and **166** was 45%, that of the compounds **164** and **167** was 48%, and the yield of **165** and **168** was 45%.

Similar stereochemical results have been obtained in another study[84] of the interaction of the enol ether **15** with Schiff's bases **169a,b** and **176**.



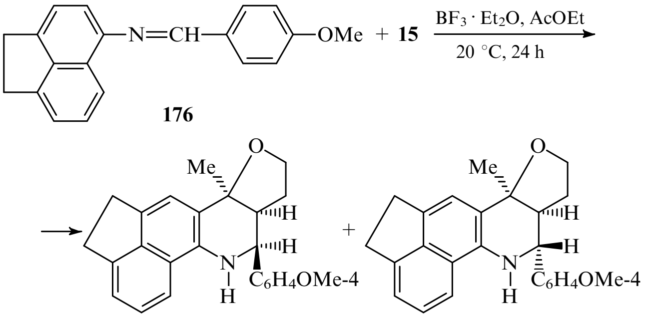
169a – c

170 – 172 **173 – 175**

169a, **170**, **173**: R = H; **169b**, **171**, **174**: R = OH; **169c**, **172**, **175**: R = OMe.

The overall yield of the diastereomers **170** and **173** was 81%, that of **171** and **174** was 47%, and the yield of **172** and **175** was 46%.

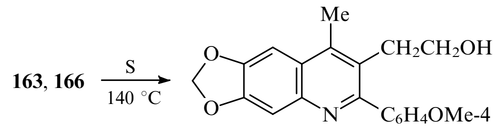
Acenaphthene derivatives **177a** and **177b** were obtained in an overall yield of 42%.



176

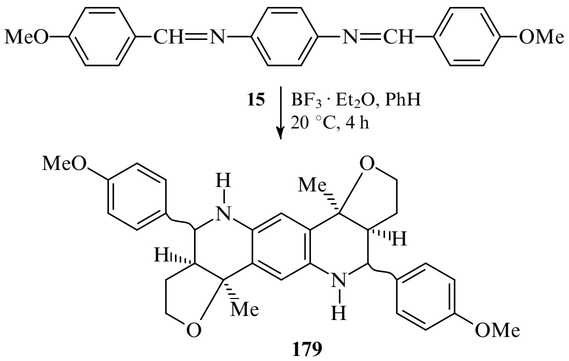
177a **177b**

On heating with sulfur, the diastereomers **163** and **166** are converted into the quinoline derivative **178** in 70% yield.[83]



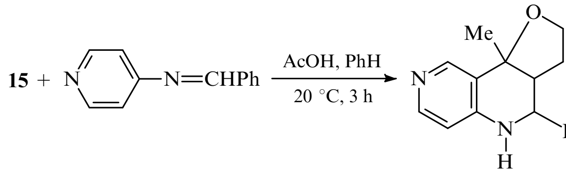
178

The reaction of N,N'-bis(p-methoxybenzylidene)-p-phenylenediamine with two moles of the enol ether **15** affords compound **179** in 32% yield.[83]



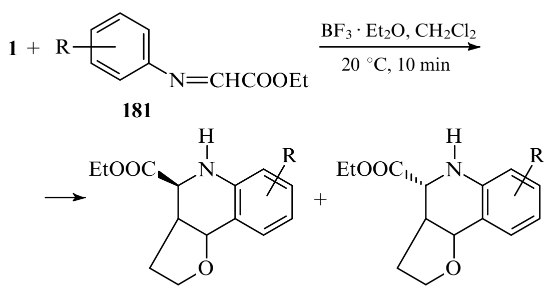
179

Adduct **180** has been synthesised in 33% yield by the cycloaddition of the enol ether **15** to N-benzylidene-4-aminopyridine in the presence of acetic acid at ambient temperature.[85]



180

The stereochemistry of the reaction of the enol ether **1** with azomethines **181**, containing various substituents in the 4- or 2-positions of the benzene ring, has been studied.[86] The results obtained imply that this reaction proceeds non-stereoselectively, the isomers **182a** being usually formed in somewhat larger amounts than the isomers **182b**. The nature of the substituents R in the 4-position of the benzene ring exerts only a slight influence on the ratio between the diastereomers **182a** and **182b**, except for azomethines in which R = 4-OMe and R = 2-NO$_2$. In the latter case, only one isomer was obtained.

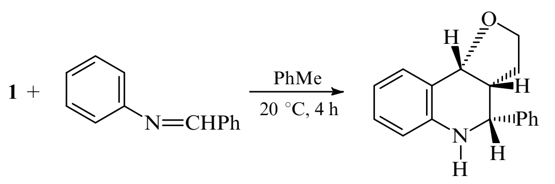


181

182a **182b**

R		Yield (%)	
181	**182**	**182a**	**182b**
H	H	31	23
4-Me	8-Me	27	26
4-OMe	8-OMe	15	33
4-Cl	8-Cl	38	31
4-NO$_2$	8-NO$_2$	36	31
2-NO$_2$	6-NO$_2$	41	–

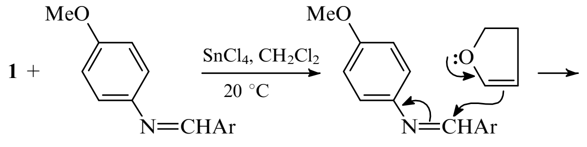
When various Lewis acids are used as catalysts in the reaction of the enol ether **1** with N-benzylideneaniline, the yields of the adducts **183** vary over a wide range.[87]



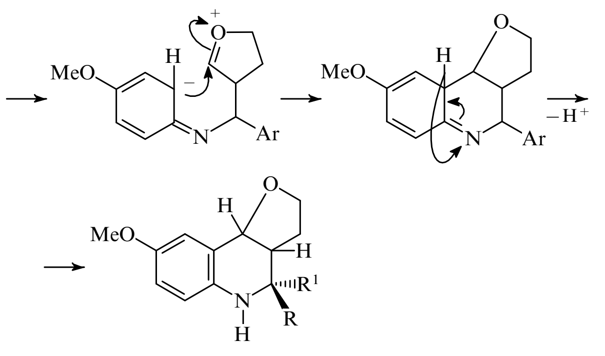
183

Catalyst	EtAlCl$_2$	ZnCl$_2$	SnCl$_4$	BF$_3$·Et$_2$O	AlCl$_3$	TiCl$_4$
Yield (%)	80	73.1	71.2	68.9	60.3	29.3

Japanese researchers[88] have studied the cycloaddition of the enol ether **1** to azomethines **184** in the presence of tin(IV) chloride and proposed a scheme for the formation of diastereomeric pairs of products **185**.



184

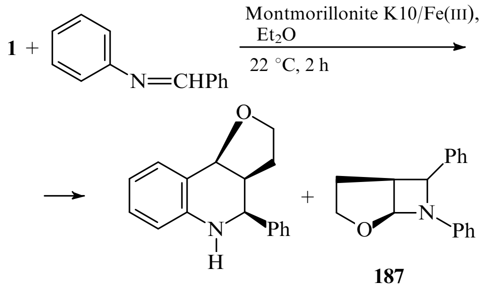


185a,b

185a: R = H, R¹ = Ar; **185b**: R = Ar, R¹ = H.

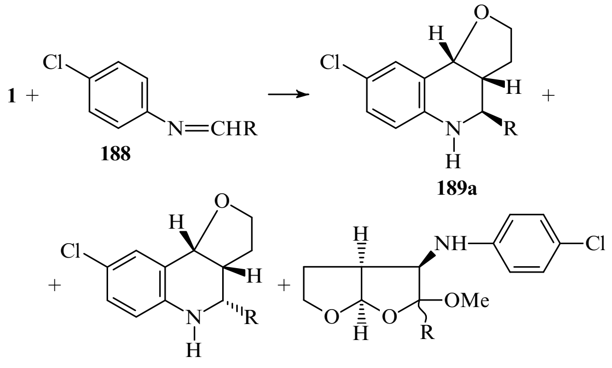
Ar	Time /h	Yield (%)	
		185a	**185b**
2-Furyl	25.5	4.5	13
2-Thienyl	42.5	8.1	8.3
2-Pyridyl	48	17	–

The reaction of the enol ether **1** with *N*-benzylideneaniline in the presence of montmorillonite K10/Fe(III) occurs ambiguously: apart from the normal cycloaddition product **186** (yield 81%), the [2 + 2]-cycloaddition product, namely, 6,7-diphenyl-2-oxa-7-aza-bicyclo[3.2.0]heptane **187** is formed (yield 7%).[89]



186 **187**

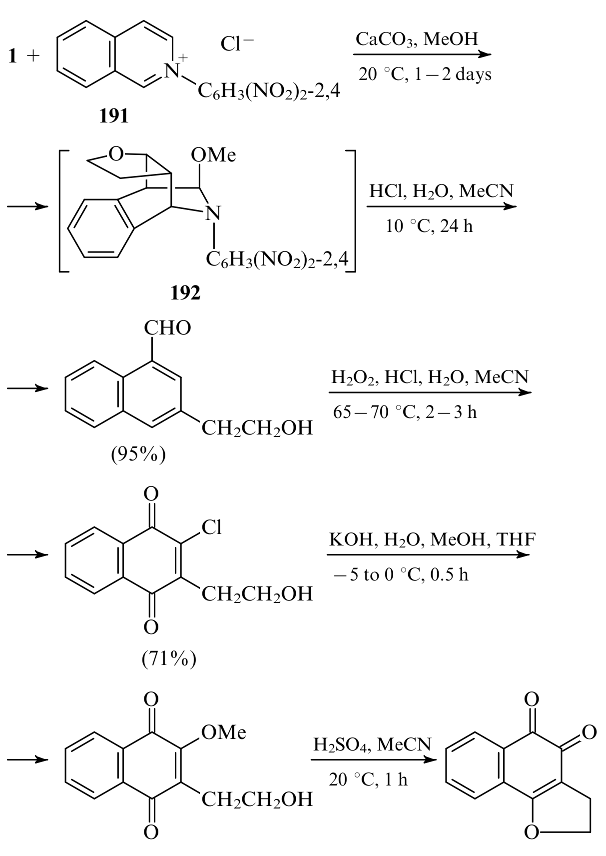
When the reaction of the compound **1** with azomethines **188** has been conducted in the presence of methanol and with Lewis acids as catalysts, together with the diastereomers **189a,b**, which are the normal reaction products, compounds **190** were obtained.[90]



188 **189a** **189b** **190**

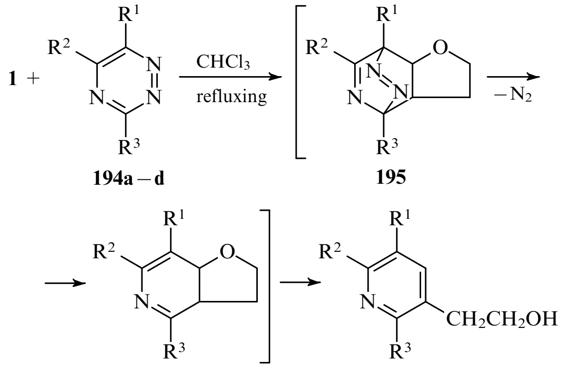
R = Ph, PhCO.

The reaction of isoquinolinium salt **191** and the enol ether **1** gave adduct **192**, which was converted into 4,5-dioxo-2,3,4,5-tetrahydronaphtho[1,2-*b*]furan **193** in four steps without isolation.[91]



191 **192** **193** (84%)

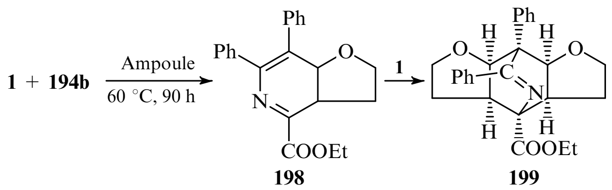
The interaction of the enol ether **1** with 1,2,4-triazine derivatives **194** begins with [4 + 2]-cycloaddition giving the corresponding adducts. Under reaction conditions (refluxing in chloroform), the adducts **195** formed in the first stage eliminate a nitrogen molecule and thus generate bicyclic compounds **196**, which then undergo cleavage of the five-membered ring and are converted into the pyridine derivatives **197**.[92]



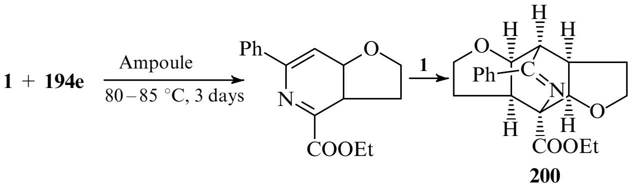
194a – d **195** **196** **197a – d**

Compound	R¹	R³	Time /h	Yield (%)
197a	COOEt	COOEt	49	77
197b	Ph	COOEt	46	55
197c	COOEt	NHCOMe	120	67
197d	COOEt	Me	45	80

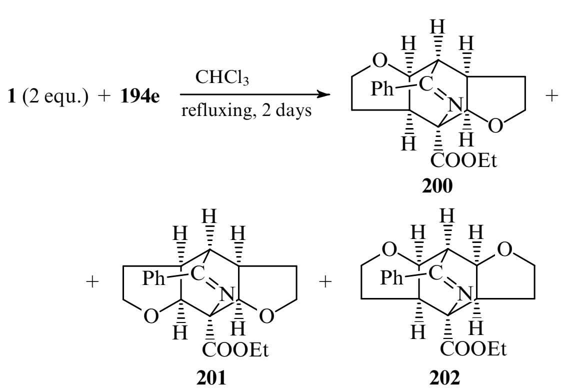
On heating in a sealed tube, the enol ether **1** reacts regioselectively with 1,2,4-triazine derivatives **194b** with the retention of the tetrahydrofuran ring to give compound **198**, which reacts regioselectively with another molecule of the enol ether **1** under the reaction conditions, and compound **199** is formed as the final reaction product (yield 69%).[92]



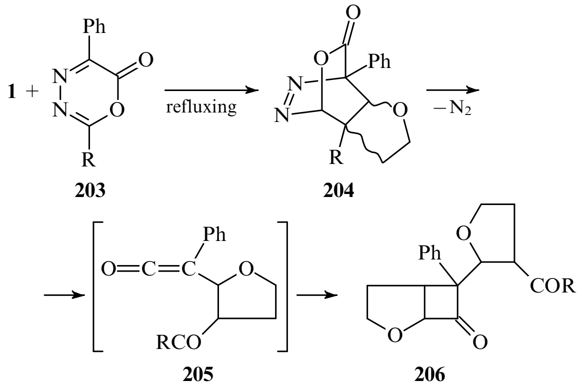
1,2,4-Triazine **194e** (R^1 = H, R^2 = Ph, R^3 = COOEt) also reacts with two molecules of the enol ether **1** when heated in a sealed tube; this reaction affords compound **200** in 68% yield. However, in this case, orientation of the first added molecule of the enol ether **1** is opposite.[92]



It is of interest that the same reaction carried out in boiling chloroform affords all three possible regioisomers **200**, **201**, and **202** in 64%, 10%, and 10% yields, respectively.[92]

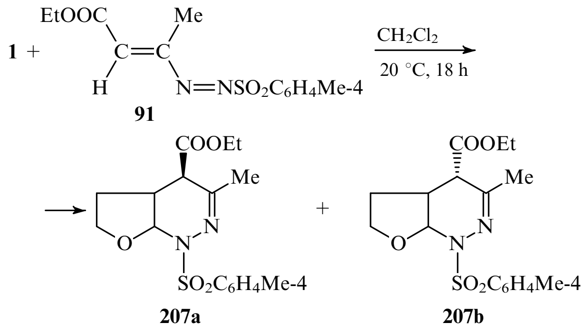


The adducts **204** obtained by heating the compound **1** with 1,3,4-oxadiazin-6-one derivatives **203** eliminate a nitrogen molecule under the reaction conditions, and the ketenes **205** thus generated react with a further molecule of the enol ether **1** giving finally bicyclo[3.2.0]heptan-6-one derivatives **206** as mixtures of diastereomers (yields 42% and 58%).[93]

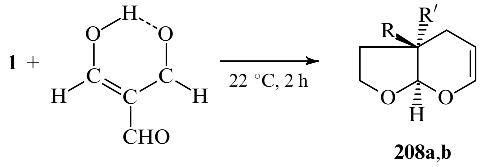


R = Ph, $PhCH_2$.

Ethyl *E*-3-(tolyl-*p*-sulfonylazo)but-2-enoate **91** reacts with 5-methyl-2,3-dihydrofuran **15** according to the [3 + 2]-cycloaddition reaction pattern.[49] However, the same heterodiene **91** reacts with 2,3-dihydrofuran also according to the [4 + 2]-cycloaddition scheme to give two diastereomers **207a,b**, one of which (**207b**) was isolated in a yield of 31%.[49]

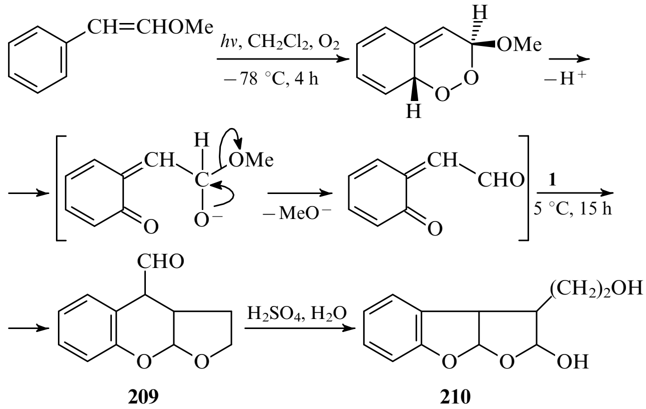


Triformylmethane enters into the reaction with the enol ether **1** at 20°C affording a mixture of isomeric 2,9-dioxabicyclo[4.3.0]non-3-ene derivatives **208a,b** (yield 73%, ratio **208a** : **208b** = 1 : 4).[94]

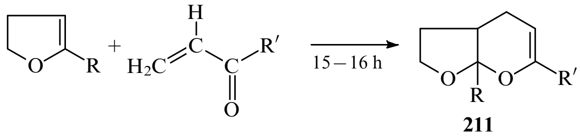


a: R = H, R′ = OH
b: R = OH, R′ = H

β-Methoxystyrene reacts with the enol ether **1** upon irradiation with the visible light in the presence of tetraphenylporphyrin to give aldehyde **209** (yield 13%), which is converted into the furobenzofuran derivative **210** on treatment with dilute sulfuric acid. Matsumoto and Kudora[95] proposed the following scheme for the formation of the compounds **209** and **210**:

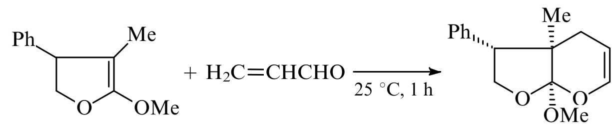


2,3,3*a*,7*a*-Tetrahydro-4*H*-furo[2.3-*b*]pyran and its derivatives **211** have been prepared by heating the enol ether **1** (or **15**) with acrolein or with methyl vinyl ketone in the presence of hydroquinone.[96]



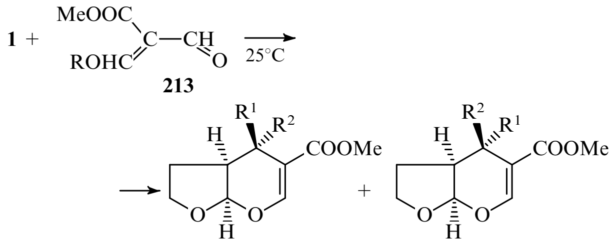
R	R′	*T*, °C	Yield (%)
H	H	140	60
Me	H	80	39
H	Me	160	25
Me	Me	140	25

The [4 + 2]-cycloaddition of 5-methoxy-4-methyl-3-phenyl-2,3-dihydrofuran **212** to acrolein has been carried out[97] at 25 °C, which has led to the *cis*-isomer of 1α-methoxy-6α-methyl-7-phenyl-2,9-dioxabicyclo[4.3.0]non-3-ene **213**.



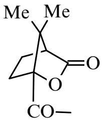
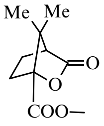
212 **213**

Diastereomeric compounds **214a,b** have been synthesised from the enol ether **1** and aldehydoesters at 25°C.[98]

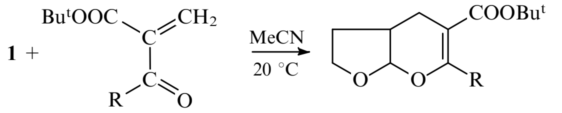


213

214a **214b**

R	R^1	R^2	Time /h	Yield (%)	Ratio **214a** : **214b**
H	H	OH	200	60	3 : 1
Ac	H	AcO	8–40	85	1 : 2
	H		40	86	1 : 2

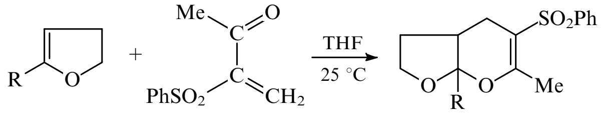
α,β-Unsaturated ketones **215** containing the bulky $COOBu^t$ group also react fairly readily with the enol ether **1** at 20 °C giving adducts **216**.[99]



215 **216**

R	Et	$PhCH_2CH_2$	C_6H_{11}	Ph	4-BrC_6H_4
Time /h	10	15	20	17	3
Yield (%)	40	36	54	70	79

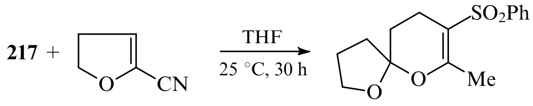
The reaction of the enol ether **1** or 5-(1-hydroxy-1-methylethyl)-2,3-dihydrofuran with 3-phenylsulfonylbut-3-en-2-one **217** has been reported.[100]



217

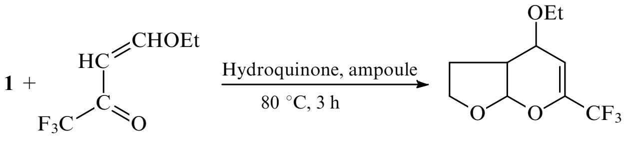
R	Time /h	Yield (%)
H	2.5	86
$C(Me)_2OH$	1	50

An unexpected result was obtained when the ketone **217** was made to react with 5-cyano-2,3-dihydrofuran **218**. Instead of a [4 + 2]-cycloaddition product, spiro-compound **219** was isolated in 35% yield.[100]



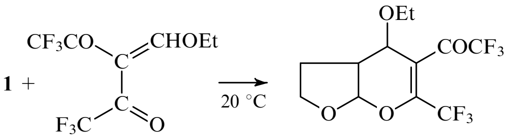
218 **219**

The reaction of 2,3-dihydrofuran **1** with 4-ethoxy-1,1,1-trifluorobut-3-en-2-one **220** occurs regioselectively but non-stereoselectively; this reaction leads to a mixture of diastereomers of 4-ethoxy-6-trifluoromethyl-2,3,3*a*,7*a*-tetrahydro-4*H*-furo[2,3-*b*]pyran **221** in 68% yield.[101]



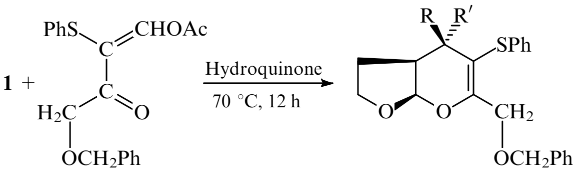
220 **221**

The [4 + 2]-cycloaddition product **222** has been synthesised in 86% yield by the reaction of the compound **1** with heterodiene **223**.[102]



223 **222**

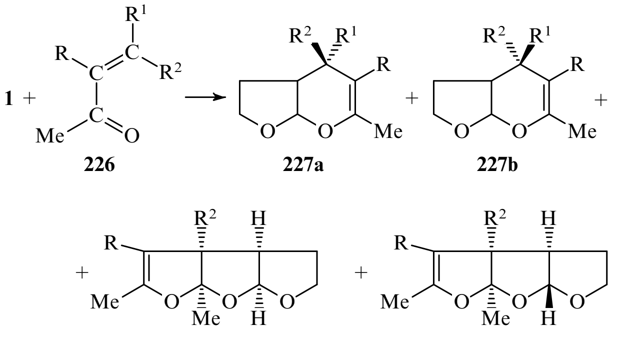
Heating of the enol ether **1** with heterodiene **224** has given compound **225** as a mixture of diastereomers.[103]



224 **225**

R	R′	Yield (%)
OAc	H	50
H	OAc	12.5

A more complex picture is observed when the enol ether **1** is introduced into the reaction with unsaturated ketones **226**. Depending on the nature of substituents in the ketone molecule, the process gives either adduct **227a** or a mixture of adducts **227a** and **227b** and compounds **228a** and **228b** resulting from their transformations.[104]

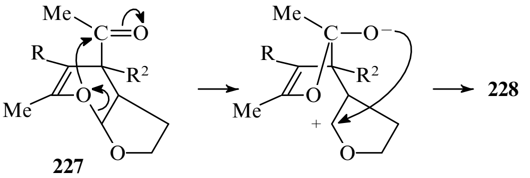


226 **227a** **227b**

228a **228b**

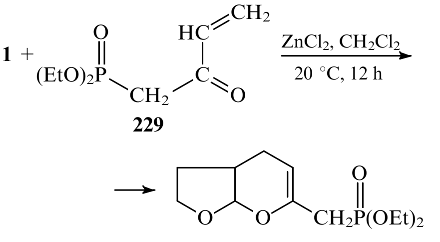
R	R^1	R^2	T /°C	Time /h	Yield (%)
Ac	Ac	Ac	55	6	54 (**227a**) + 36 (**228a**)
H	H	Ac	85	29	90 (**227a**)
COOEt	Ac	COOEt	55	8	32 (**227a**) + 49 (**227b**) + + 8 (**228a**) + 4 (**228b**)

The researchers cited[104] explained the formation of the compounds **228** from the adducts **227** in terms of the following scheme:



227

The reaction of the enol ether **1** with methyl vinyl ketone **229** in the presence of zinc chloride proceeds *endo*-selectively and gives rise to compound **230** (yield 89%).[105]

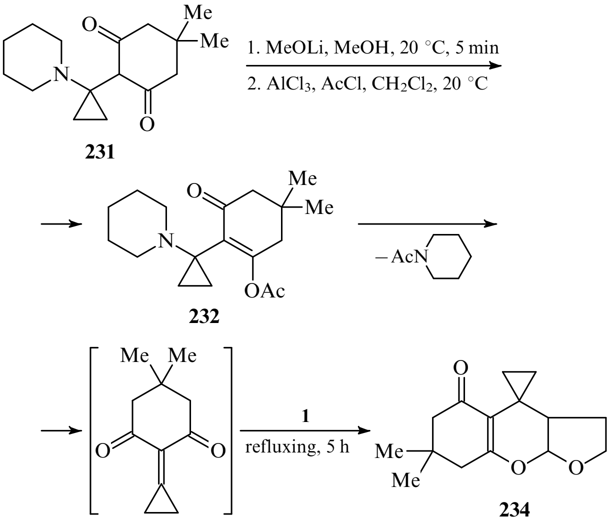


229

230

In the absence of zinc chloride, this reaction needs to be carried out in a sealed tube at 85 °C for 20 h.

Treatment of diketone **231** with lithium methoxide and then by acetyl chloride affords the *O*-acetyl derivative **232**; on boiling in the enol ether **1**, this compound eliminates *N*-acetylpiperidine and is thus converted into a new diketone, compound **233**, which reacts with the enol ether **1** giving tricyclic compound **234** (yield 48%).[106]



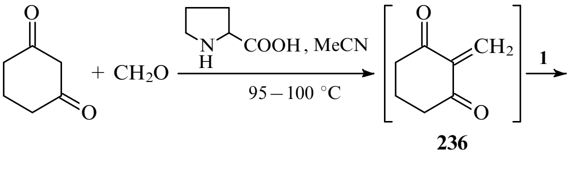
231

232

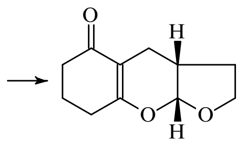
233

234

Compound **235** has been prepared by condensing the enol ether **1** with cyclohexane-1,3-dione and formaldehyde in the presence of proline. It is clear that the interaction of the diketone and formaldehyde results in the intermediate formation of heterodiene **236**, which undergoes [4+2]-cycloaddition to the enol ether.[107]

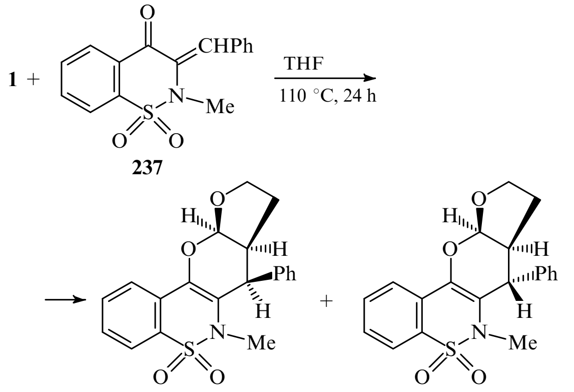


236



235

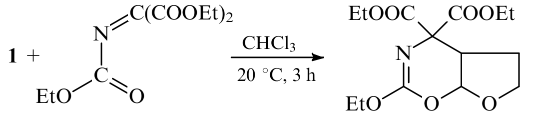
When heterodiene **237** is heated with the enol ether **1** in a sealed tube for a long period, two diastereomeric adducts **238a** and **238b** are produced (yields 60% and 10%).[108]



237

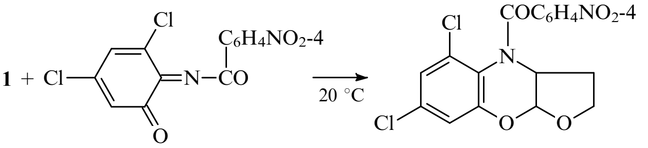
238a **238b**

The [4+2]-cycloaddition of the enol ether **1** to compound **239** has led to adduct **240** (yield 61%).[109]



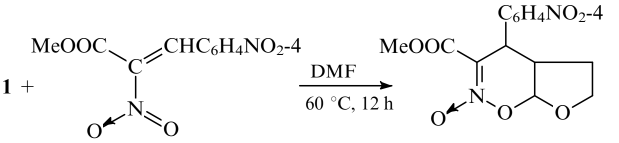
239 **240**

Of the two heterodiene systems, present in the compound **241**, C=N–C=O and N=C–C=O, the system that incorporates the carbon–oxygen semicyclic double bond is involved in the cycloaddition with the enol ether **1** affording adduct **242** in 90% yield.[110]



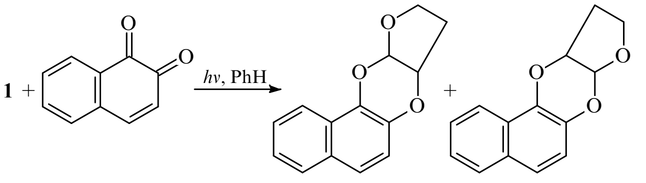
241 **242**

Nitroalkene **243** enters into Diels–Alder condensation with 2,3-dihydrofuran **1** on heating in DMF, the [4+2]-cycloaddition product **244** being formed in 80% yield.[111]



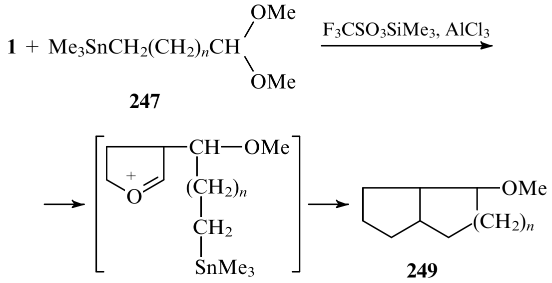
243 **244**

2,3-Dihydrofuran **1** and 1,2-naphthoquinone exposed to the radiation of a high-pressure mercury lamp (λ = 340 nm) interact following the [4+2]-cycloaddition pattern; this affords a mixture of two isomeric adducts **245** and **246**. A crucial influence on the yield of the adducts is exerted by the polarity of the solvent used. When the reaction is conducted in non-polar benzene (D = 0.00), the overall yield of the compounds **245** and **246** is 55%; in the case where acetonitrile (D = 3.37) is used, the overall yield of the adducts is only 4%.[52]



245 **246**

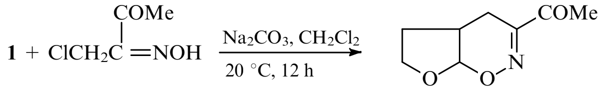
The reaction of the compound **1** with dimethyl acetals **247** in the presence of trimethylsilyl trifluoromethanesulfonate and aluminium chloride involves the intermediate formation of the oxonium ions **248**, which are converted into the diastereomers of compound **249** under the reaction conditions.[112] This process can only formally be classified as cycloaddition.



247 **248** **249**

n	1	2	3
Yield (%)	60	56	48

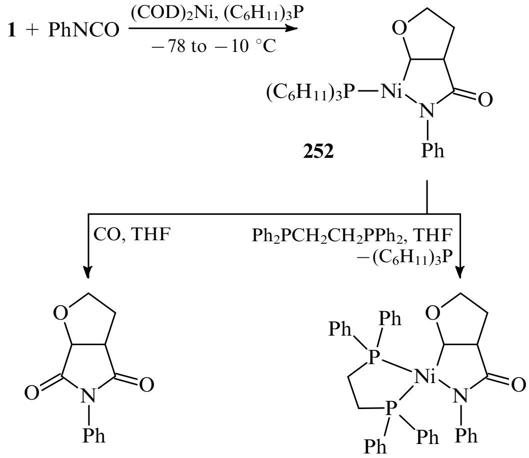
Similarly, 'formal cycloaddition' of the enol ether **1** to oxime **250** (treatment with sodium carbonate at room temperature) affords 3-acetyl-4*a*,5,6,7*a*-tetrahydro-4*H*-furo[3,2-*e*]-1,2-oxazine **251**.[113]



250 **251**

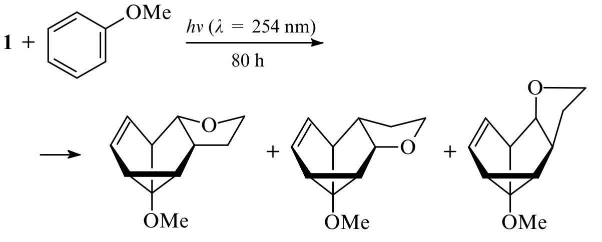
5. Other cycloaddition reactions

2,3-Dihydrofuran **1** has been made to react with phenyl isocyanate in the presence of bis(cyclooctadiene)nickel $(COD)_2Ni$ and tricyclohexylphosphine at a low temperature; this gave organometallic compound **252** in 93.5% yield. The latter reacts with carbon monoxide or with 1,2-bis(diphenylphosphino)ethane resulting in the formation of furopyrrole derivative **253** or organometallic compound **254** (yields 63.8% or 62%, respectively).[114]



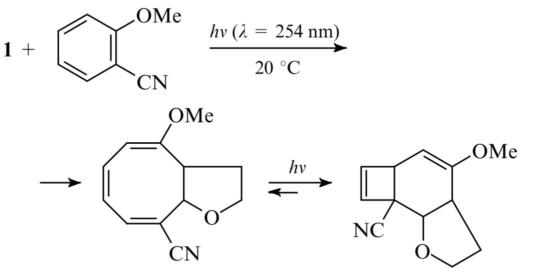
253 **254**

Three compounds: *exo*-isomer **255**, *exo*-isomer **256**, and *endo*-isomer **257**, have been isolated in 2 : 1 : 3 ratio from the products of the photochemical reaction of 2,3-dihydrofuran **1** with anisole.[115]



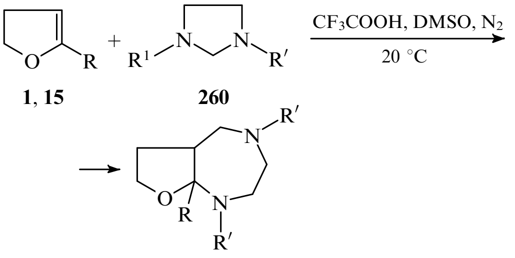
255 **256** **257**

A totally different picture is observed in a photochemical reaction of 2,3-dihydrofuran **1** with the anisole derivative containing an electron-withdrawing cyano-group in the 2-position. The bicyclo[6.3.0]undecatriene derivative **258** is the primary reaction product, which isomerises upon irradiation into tricyclic compound **259**. An equilibrium shifted toward the compound **259** is established under the reaction conditions. The latter compound is converted into the bicyclic compound **258** on heating.[116]



258 **259**

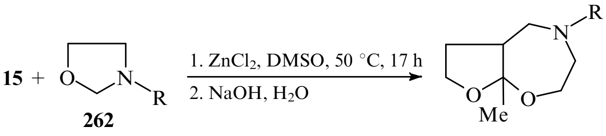
The reaction of 1,3-dialkylimidazolidines **260** with the enol ethers **1** or **15** in the presence of trifluoroacetic acid has led to octahydrofuro[3,2-*f*]-1,4-diazepine derivatives **261**.[117]



261

R	R′	Time /h	Yield (%)
H	Me	22	41
H	Bu	139	35
Me	Me	23	20

The reaction of 5-methyl-2,3-dihydrofuran **15** with 3-substituted oxazolidines **262** in the presence of Lewis acids is accompanied by expansion of the oxazolidine ring and results in the formation of 4-R-8a-methylperhydrofuro[3.2-*f*]-1,4-oxazepines **263** in 50% – 75% yields.[118, 119]

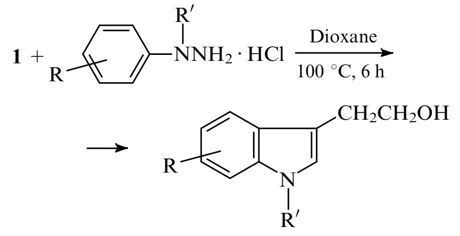


263

R = Me, $PhCH_2$.

III. Recyclisation reactions

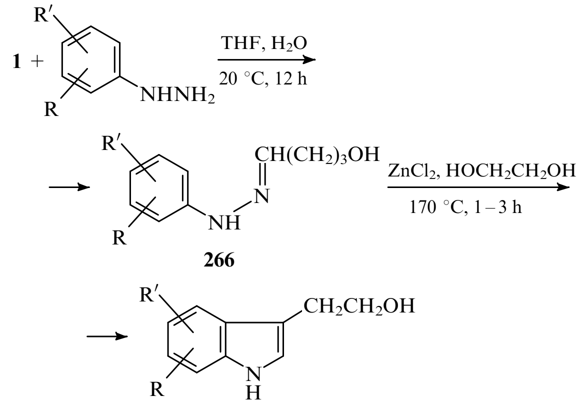
Two methods have been proposed for the synthesis of tryptophol derivatives **264**. The first method involves heating of a mixture of the enol ether **1** and arylhydrazine in dioxane for 6 h. The indole derivatives **264** are obtained without isolation of the intermediate hydrazones.[120–122]



264

R	R′	Yield (%)	Ref.
H	H	30	55
5-Me	H	40	55
7-Me	H	20	55
7-MeO	H	25	55
H	Me	32	55
H	Ph	45	56
7-cyclo-C_3H_5	H	25	56
7-Et	H	–	57

According to the second method, tryptophol derivatives **265** are prepared in two stages. Arylhydrazones **266** are obtained initially from the enol ether **1** and the corresponding arylhydrazines; then the arylhydrazones are cyclised by heating in the presence of zinc chloride under an inert atmosphere to give the target compounds **265**.[123–125]

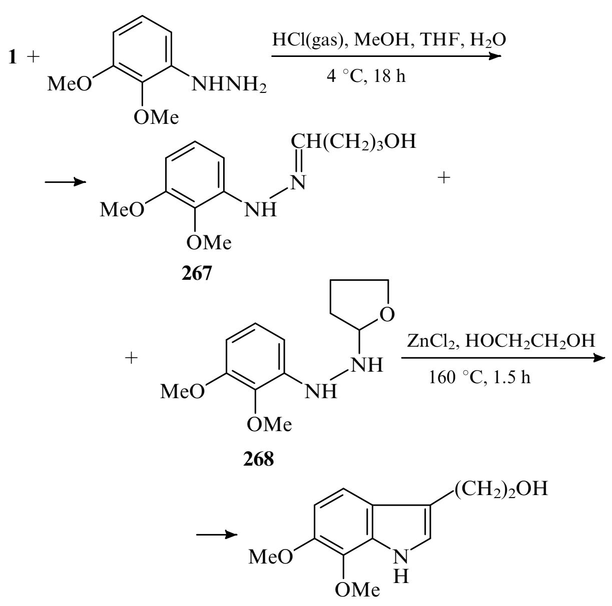


265

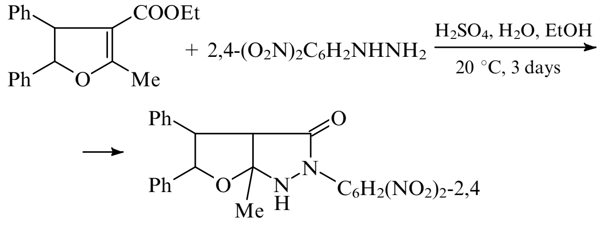
R	R′	Yield of **265** (%)	Ref.
H	7-I	48	123
6-F	7-I	–	124
6-F	7-Br	48	125

It has been shown[126] that the reaction of the compound **1** with 2,3-dimethoxyphenylhydrazine in the presence of hydrogen chloride at 4 °C affords two products, namely, arylhydrazone **267** (yield 42.5%) and the hydrazine derivative **268** (yield 42.5%).

When the resulting mixture of **267** and **268** is heated under an inert atmosphere in the presence of zinc chloride, the compounds cyclise leading to only one product, 3-(2-hydroxyethyl)-6,7-dimethoxyindole, its yield being as low as 10%.[126]

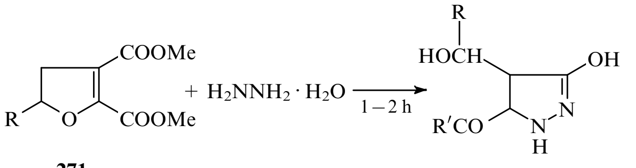


Cyclocondensation of ethyl 5-methyl-2,3-diphenyl-2,3-dihydrofuran-4-carboxylate with 2,4-dinitrophenylhydrazine in the presence of H_2SO_4 at 20 °C has led to 2-(2,4-dinitrophenyl)-6*a*-methyl-4,5-diphenyl-hexahydrofuro[2,3-*c*]pyrazol-3-one **269** in 18% yield.[127]



269

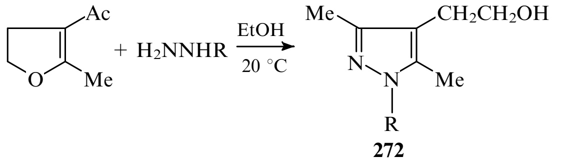
The pyrazole derivatives **270** have been prepared by recyclisation of 4,5-bis(methoxycarbonyl)-2,3-dihydrofurans **271** with hydrazine hydrate.[128]



271 **270**

R	R′	Reaction conditions	Yield (%)
H	OMe	20 °C	59
H	$NHNH_2$	boiling	90
Me	$NHNH_2$	boiling	77
Et	$NHNH_2$	boiling	87

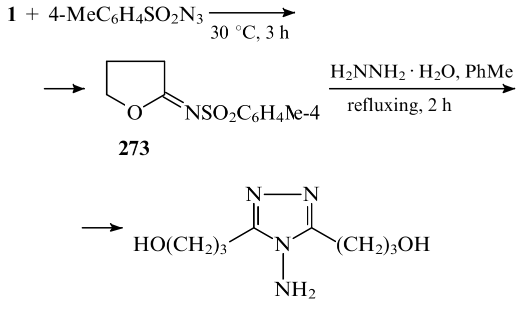
The reaction of 4-acetyl-5-methyl-2,3-dihydrofuran with hydrazine, phenylhydrazine, or tosylhydrazine has led to compounds of the pyrazole series **272**.[129]



272

R	H	Ph	$SO_2C_6H_4Me$-4
Yield (%)	54	47	62

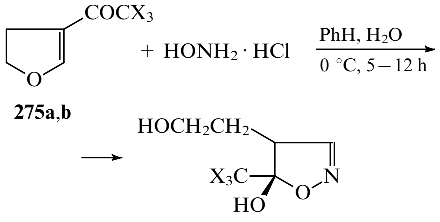
The reaction of the enol ether **1** with toluene-*p*-sulfonyl azide affords imine **273**, which is recyclised to 4-amino-3,5-bis(3-hydroxypropyl)-1,2,4-triazole **274** (yield 88%) on heating with hydrazine hydrate in toluene.[130]



273

274

4-(Trihalomethylcarbonyl)-2,3-dihydrofurans **275** recyclise on treatment with hydroxylamine in the presence of pyridine even at 0 °C to give 5-hydroxy-4-(2-hydroxyethyl)-5-trihalomethyl-2-isoxazolines **276**.[131]



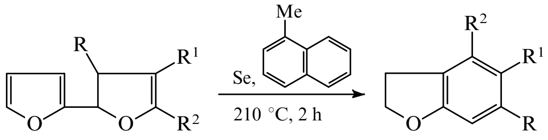
275a,b

276a,b

X = F (**a**), Cl (**b**).

The trifluoroacetyl derivative **275a** is more reactive. Its reaction is completed over a period of 5 h giving rise to compound **276a** in 90% yield. The compound **275b** reacts over a period of 12 h to give **276b** in 85% yield.[131]

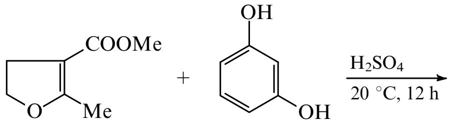
On heating with selenium in 1-methylnaphthalene, compounds **277** containing both furan and 2,3-dihydrofuran rings are converted into benzofuran derivatives **278**.[132]



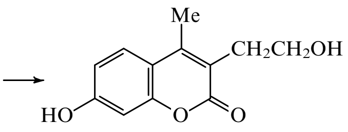
277 **278**

R	R^1	R^2	Yield (%)
H	H	H	70
Me	H	H	70
H	Me	H	35
H	Me	Me	70

Condensation of methyl 5-methyl-2,3-dihydrofuran-4-carboxylate **279** with resorcinol in the presence of sulfuric acid gives 7-hydroxy-3-(2-hydroxyethyl)-4-methylcoumarin **280**.[133]

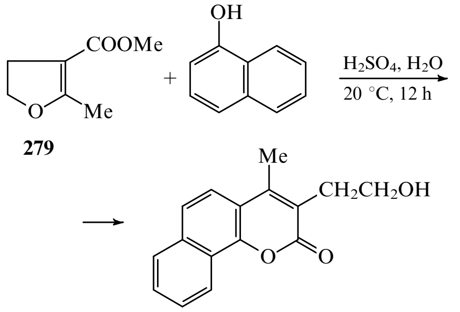


279



280

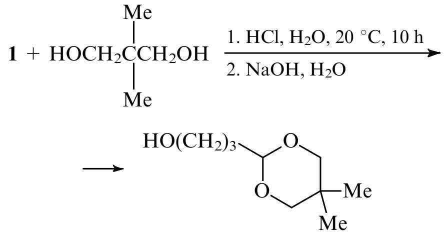
The 2,3-dihydrofuran **279** reacts with 1-naphthol in the presence of 80% sulfuric acid to afford the benzocoumarin derivative **281**.[133]



279

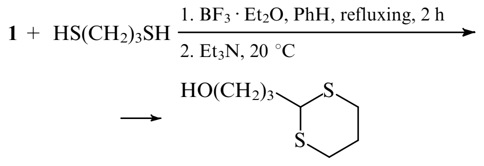
281

In the presence of hydrochloric acid, 2,3-dihydrofuran **1** reacts with 2,2-dimethylpropane-1,3-diol at room temperature, and the 1,3-dioxane derivative **282** is formed in 83% yield.[134]



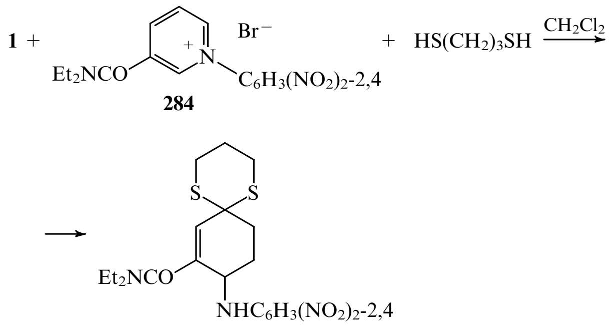
282

A sulfur-containing analogue of the compound **282** (compound **283**) has been synthesised in 43% yield by the reaction of the compound **1** with propane-1,3-dithiol in the presence of boron trifluoride etherate followed by treatment of the reaction product with triethylamine.[135]



283

It has been reported[136] that the reaction of the salt **284** with 2,3-dihydrofuran **1** and propane-1,3-dithiol leads to compound **285**.

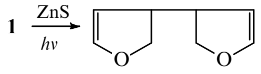


284

285

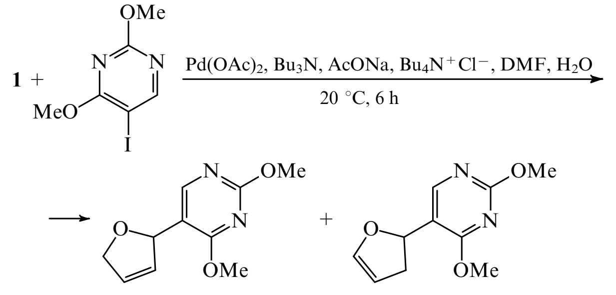
IV. Substitution of hydrogen atoms in 2,3-dihydrofurans

Photocatalytic heterogeneous dehydrodimerisation of the enol ether **1** in the presence of zinc sulfide and water results in the formation of bi(2,3-dihydrofuran-3-yl).[137]



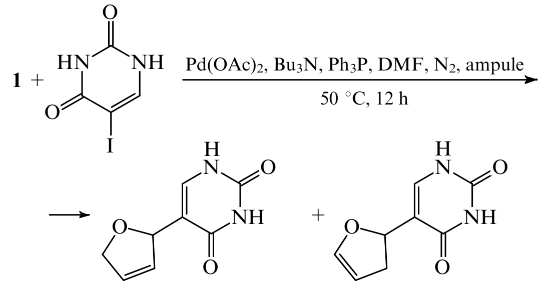
When 2,3-dihydrofuran **1** reacts with 5-iodo-2,4-dimethoxypyrimidine in the presence of palladium acetate, tributylamine, sodium acetate, and a phase transfer catalyst, the hydrogen atom in the 2-position of the enol ether is substituted, and the double bond in the dihydrofuran ring partly isomerises.

This gives two compounds **286** (yield 55%) and **287** (yield 26%).[138]



286 **287**

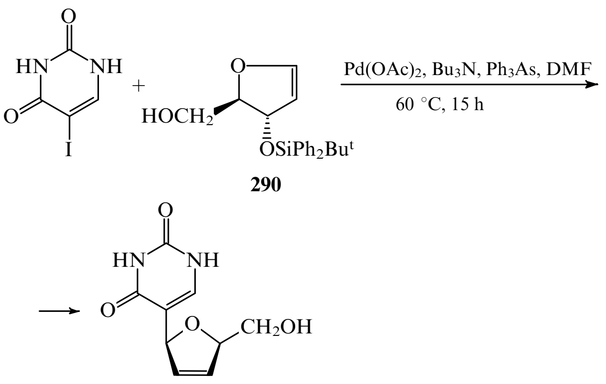
Two compounds **288** and **289** in an overall yield of 68% and in a ratio of 3 : 4 have also been synthesised by the reaction of the dihydrofuran **1** with 5-iodouracil in the presence of palladium acetate, tributylamine, and triphenylphosphine.[138]



288 **289**

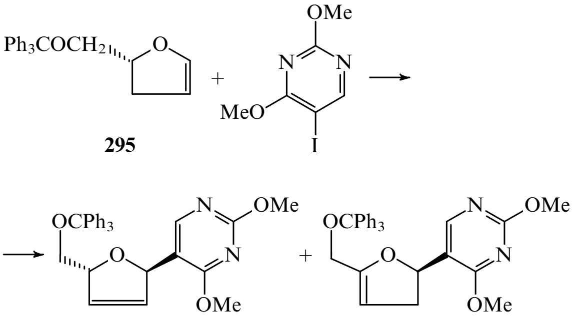
If triphenylarsine is used in this reaction instead of triphenylphosphine, the compounds **288** and **289** are formed over a period of 3 h at 50 °C in 58% overall yield and in a 2 : 3 ratio.[138]

The reaction of 5-iodouracil with the 2,3-dihydrofuran derivative **290** in the presence of $Pd(OAc)_2$, Bu_3N, and Ph_3As under an inert atmosphere occurs stereoselectively and affords 5-(5-hydroxymethyl-2,5-dihydrofuran-2-yl)uracil **291** in 58% yield.[138]



291

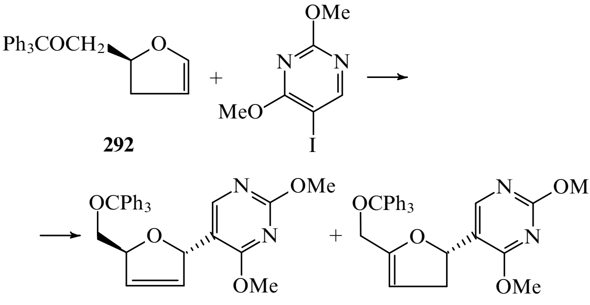
In order to prepare initial compounds for the synthesis of 2′,3′-deoxy-*C*-nucleosides, the reaction of 5-iodo-2,4-dimethoxypyrimidine with 2(*R*)-(triphenylmethoxymethyl)-2,3-dihydrofuran **292** has been studied. By varying reaction conditions, Zhang and Daves[139] prepared compounds **293** and **294** in various proportions.



296 **297**

Reaction conditions	Yield (%)	
	293	**294**
$Pd(OAc)_2$, Et_3N, $Bu_4N^+Cl^-$; H_2O, DMF, N_2, 20 °C, 20 h	56	31
$Pd(OAc)_2$, Ph_3As, Et_3N, MeCN, N_2, 75 °C, 10 h	18	59

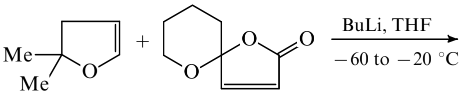
The reaction of 5-iodo-2,4-dimethoxypyrimidine with 2(*S*)-(triphenylmethoxymethyl)-2,3-dihydrofuran **295** also led to two isomers **296** and **297**, the ratio between them being dependent on the reaction conditions.[139]



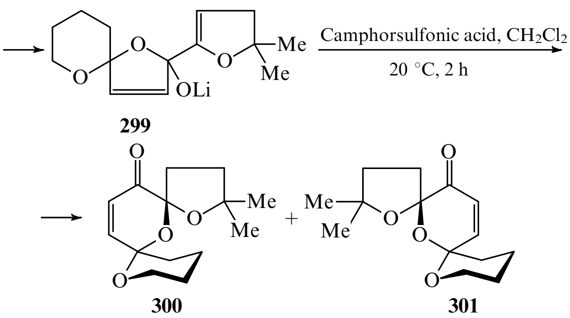
293 **294**

The reactions involving the compound **295** were carried out under the same conditions as those with the isomer **292**. The compounds **296** and **297** were obtained in the following yields: in water and DMF at 20 °C, 53% and 30%; in MeCN at 75 °C, 20% and 58%. When the reaction of the isomer **295** with the iodo-derivative was carried out in the presence of $Pd(OAc)_2$, Ph_3P, and Ag_2CO_3 in MeCN at 75 °C for 10 h under a nitrogen atmosphere, only the isomer **296** was formed in 40% yield.[139]

In the presence of butyllithium, 2,2-dimethyl-2,3-dihydrofuran reacts with 1,6-dioxaspiro[4.5]dec-3-en-2-one **298** to give the lithium derivative **299** arising due to the substitution of the hydrogen atom in the 5-position of 2,2-dimethyl-2,3-dihydrofuran. In the presence of camphorsulfonic acid, the lithium derivative **299** undergoes a rearrangement being thus converted into two compounds **300** and **301** (overal yield 15%, ratio 1 : 1).[140]

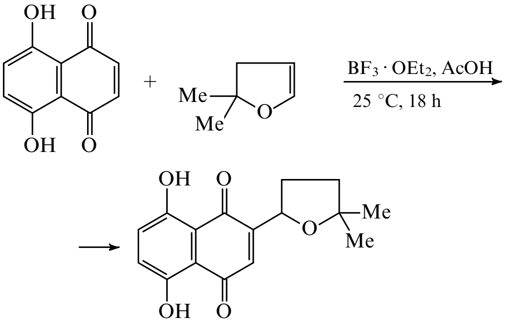


298



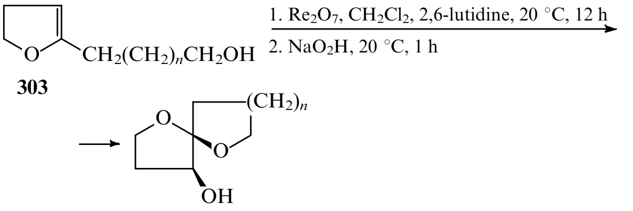
V. Addition to the double bond in 2,3-dihydrofurans

The addition product **302** has been synthesised in 40% yield by the reaction of 5,8-dihydroxy-1,4-naphthoquinone with 2,2-dimethyl-2,3-dihydrofuran in the presence of boron trifluoride etherate in acetic acid.[141]

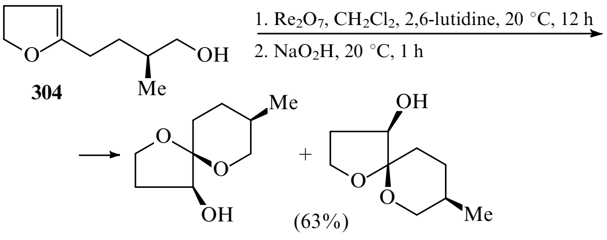


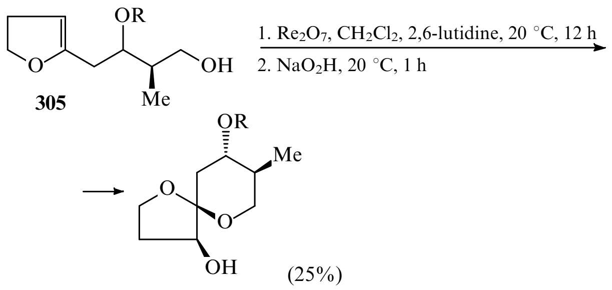
302

The 2,3-dihydrofuran derivatives **303**–**305** containing ω-hydroxyalkyl groups in the 5-position undergo spirocyclisation under the conditions of intramolecular addition–oxidation in the presence of Re_2O_7 under an inert atmosphere followed by treatment with sodium peroxide.

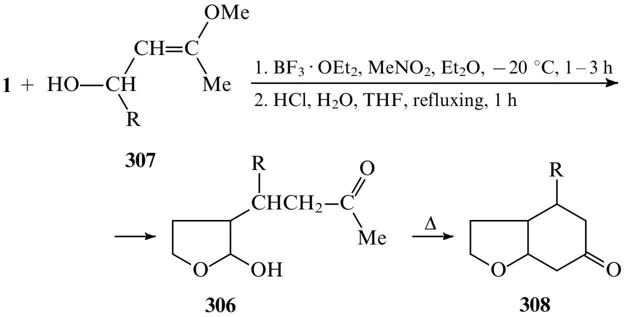


n	1	2
Yield (%)	18	48



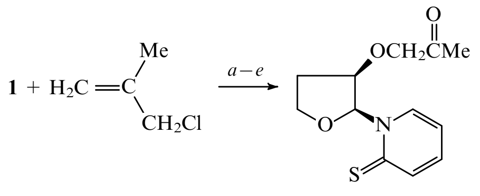


Ketones **306**, which are the addition products formed from the enol ether **1** and compounds **307**, are converted on heating into the perhydrobenzofuran-6-one derivatives **308** (yields 48%–50%).[143, 144]



R = H, Me.

The tetrahydrofuran derivative **309** has been prepared from the enol ether **1**, 1-chloro-2-methylprop-2-ene, and di(2-pyridyl) disulfide (yield 6%).[145]



309

a) $3\text{-}ClC_6H_4CO_3H$; *b*) KH, THF, $Bu_4N^+I^-$;
c) O_3, CH_2Cl_2, Ph_3P, −78 °C; *d*) H^+, MeCN, H_2O;
e) $(2\text{-}C_5H_4NS)_2$, Bu_3P, CH_2Cl_2, 0 to −20 °C, 1.5 h.

The reactions of 2,3-dihydrofuran **1** with uracil or its derivatives **310** containing various substituents in the 5-position have been studied in most detail. The influences of the substituents in the 5-position, of the catalysts and solvents used, and of the reaction temperature and time on the yields of the addition products have been studied. Table 2 presents the substituents R in the initial and final compounds, conditions under which the reactions were conducted, and the yields of the resulting compounds **311**.

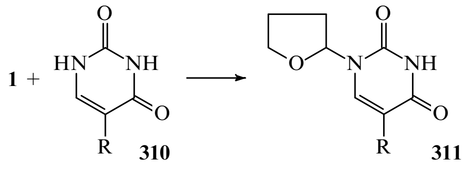
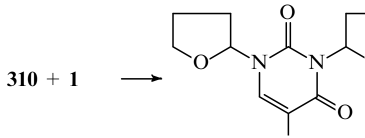


Table 2. Conditions of reactions[a] of uracil derivatives **310** with 2,3-dihydrofuran **1** and yields of addition products **311**.

R	Reaction conditions	Yield (%)	Ref.
H	Py, 170 °C, 5 h	25	146
H	Py, 180 °C, 18 h	80	147
F	150 – 200 °C	82 – 88	148, 149
F	Py, THF, $TiCl_4$	90	150
F	Py, 180 °C, 3 h	85	147
F	$AlCl_3$, DMF, $CHCl_3$, 60 °C, 12 h	70.2	151
F	$MgCl_2$, DMF, 120 °C, 3 h	71	152
F	Py, 4-$MeC_6H_4SO_3H$, 120 °C, 21 h	71	153
F	MeCOEt, 180 °C, 2 h	79	154
F	$PdCl_2(PhCN)_2$, $MgCl_2$, 18-crown-6, PhH, 80 °C, 7 h	54	155
F	PCl_5, $(Me_2N)_3PO$, 20 °C, 1 h	74.7	156
F	$Et_3N \cdot HCl$, DMF, 100 °C, 8 h	65	157
F	AcOH, 90 – 95 °C, 5 h, dioxane	70	158
F	LiCl, 120 °C, 4 h	95	159
F	$AlCl_3$, Na_2CO_3, DMF, 130 °C, 4 h	60	160
F	DMF, 35 °C, 40 min	81.5	161
F	Py, F_3CCOOH, 60 °C, 6 h	73.9	162
F	$AlCl_3$, tris(3,6-dioxaheptyl)amine, MeCN, refluxing, 2 h	80	163
F	1. Py, AcOH, 120 °C, 24 h; 2. AcONa, 70 °C, 4.5 h	45	164
F	Py, H_2O (ethanol), 185 °C, 3 h	73	165
F	$SiCl_4$, DMF, CH_2Cl_2, 20 °C, 5 h	82	166
Cl	Py, 150 °C, 6 h	85	147
Br	Py, 150 °C, 16 h	74	147
Me	Py, 180 °C, 8 h	90	147
COOMe	Py, 180 °C, 8 h	–	147
CN	Py, 150 °C, 6 h	65.7	147
I	Py, 170 °C, 5 h	–	146

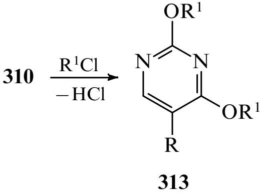
[a] At temperatures above 100 °C, the reactions were carried out in an autoclave.

Under certain conditions, the reactions of the uracil derivatives **310** with excess enol ether **1** have led to the corresponding 1,3-di(tetrahydrofuran-2-yl)uracil derivatives **312** (Table 3).



312

Yet another approach to the synthesis of the compounds **311** and **312** has been developed. According to this approach, 2,3-dihydrofurans **1** and bis-ethers **313**, prepared from the corresponding uracil derivatives **310**, are used as the initial compounds (Table 4).



313

R^1 = CMe_3, SiR^2_3, SnR^2_3 (R^2 = Alk).

The reaction of equimolar amounts of the dihydrofuran **1** and the compound **310** with Me_2SiCl_2 in DMF and CH_2Cl_2 at 20 °C for 6 h gives adduct **311** (R = F) in 84% yield. If the compounds **310** and **1** in a ratio of 1 : 2 react at 20 °C for 30 h, the reaction leads to a mixture of the compounds **311** (R = F) and **312** (R = F), their yields being 40% and 41%, respectively.[186] The interaction of 5-fluorouracil with the compound **1** and Me_2SiCl_2 in the presence of triethylamine in CH_2Cl_2 at 20 °C for 6 h affords the compound **311** (R = F) in 98% yield.[187]

Table 3. Conditions of reactions of uracil derivatives **310** with 2,3-dihydrofuran[a] and yields of compounds **312.**

R	Reaction conditions	Yield (%)	Ref.
H	Py, 180 °C, 20 h	82.1	147
F	LiCl, $Cl_2CHCHCl_2$, refluxing, 4.5 h	78.4	167
F	DMF, 135 °C, 20 h	42	168
F	$AlCl_3$, Py, 130 °C, 3 h	70	169
F	Py, 160 °C, 18 h	90	147
F	150 °C, 6 h	65	170
F	$SiCl_4$, DMF, CH_2Cl_2, 20 °C, 5 h	75	171
Cl	Py, 150 °C, 15 h	86.6	147
Br	Py, 150 °C, 15 h	86.8	147
Me	Py, 180 °C, 15 h	91.9	147
$CONH_2$	Py, 150 °C, 15 h	93.2	147
COOMe	Py, 140 °C, 6 h	11	147

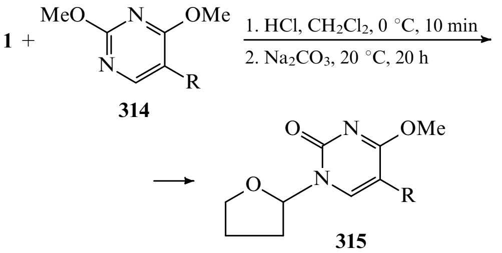
[a] Excess 2,3-dihydrofuran was used.

Table 4. Conditions of reactions of bis-ethers **313** with 2,3-dihydrofuran **1** and yields of compounds **311**.

R	R^1	Reaction conditions	Yield (%)	Ref.
F	$SiMe_3$	4-$MeC_6H_4SO_3H$, CH_2Cl_2, refluxing, 4 h	86.2	172
F	$SiMe_3$	$AlCl_3$, LiI, I_2, H_2O, 70 °C, 3.5 h	80	171
F	$SiMe_3$	$SnCl_4$, CH_2Cl_2, refluxing 3 h	79.4	173
F	$SiMe_3$	SO_2Cl_2, THF, 20 °C, 15 h	50	174
F	$SiMe_3$	2,4-lutidine, CH_2Cl_2, refluxing, 2 h	92.3	175
F	$SiMe_3$	$PyH \cdot HCl$, MeCN, 20 °C, 5 h	89.6[a]	176
F	$SiMe_3$	$SnCl_4$	90	177
F	$SiMe_3$	Amberlite IR-120, CH_2Cl_2, refluxing, 6 h	83	178
F	$SiMe_3$	H_3BO_3, $AlCl_3$, PyH, refluxing, 1 h	65	179
F	$SiMe_3$	4-$MeC_6H_4SO_3H$, MeCN, 130 °C, 40 min	71	180
F	$SiMe_3$	HCl, CH_2Cl_2, EtOH, 0 °C, 0.5 h	80	181
F	CMe_3	$PyH \cdot HCl$, PyH, refluxing, 3 h	65	182
F	$SnMe_3$	$AlCl_3$, MeCN, H_2O, 60 °C, 3 h	70	183
Br	$SiMe_3$	HCl, CH_2Cl_2, EtOH, 0 °C, 0.5 h	75	181
I	$SiMe_3$	NaI, CH_2Cl_2, refluxing, 3.5 h	79.6	184
Me	$SiMe_3$	HCl, CH_2Cl_2, EtOH, 0 °C, 0.5 h	70	181
COMe	$SiMe_3$	Na_2CO_3, CH_2Cl_2, 20 °C, 18 h	66	185

[a] Compound **312**.

By successive treatment of a mixture of dimethoxy-derivatives **314** and the dihydrofuran **1** with hydrogen chloride and with sodium carbonate, compounds **315** have been prepared.[188]



314

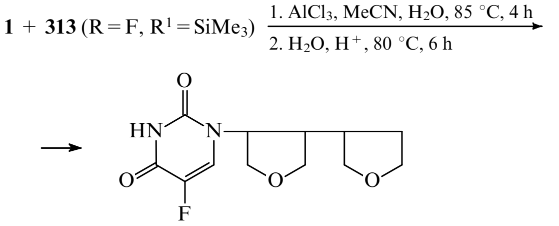
315

R	H	Me	Br	I
Yield (%)	86	40	31	33

5-Fluorothiouracil **316** adds to the compound **1** in the presence of triethylamine hydrochloride in boiling acetone giving 5-fluoro-1-(tetrahydrofuran-2-yl)thiouracil **317** in 65% yield.[189]

316 **317**

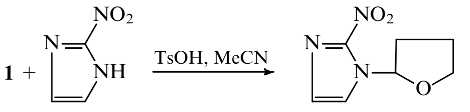
A method for the synthesis of 3-[4-(5-fluorouracil-1-yl)tetrahydrofuran-3-yl]tetrahydrofuran **318** (yield 16%) has been patented.[190] The method involves the reaction of the dihydrofuran **1** with the bis-ether **313** ($R = F$, $R^1 = SiMe_3$) in the presence of aluminium chloride followed by treatment of the reaction product with water at pH 4.[190]



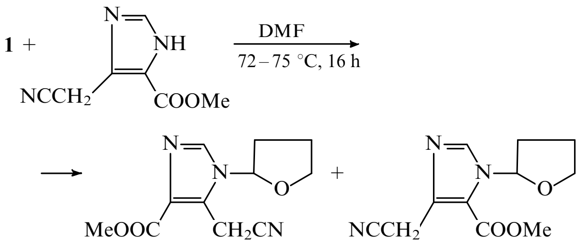
318

2-Morpholinotetrahydrofuran has been obtained by the addition of morpholine to the compound **1** in the presence of the $Pd(SCN)_2/P(OPh)_3$ catalyst at 20 °C for 15 h.[191]

2-Nitroimidazole adds to the compound **1** in the presence of toluene-*p*-sulfonic acid.[192]



The addition of methyl 5-cyanomethylimidazole-4-carboxylate di(*p*-nitrophenyl) phosphate to 2,3-dihydrofuran **1** on heating in an autoclave occurs non-regioselectively and gives two compounds **319** and **320** (yields 50% and 20%).[193]

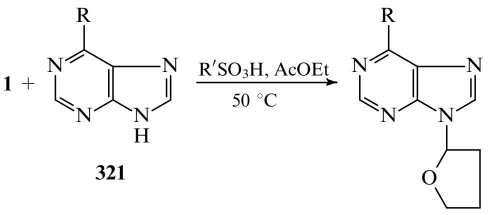


319 **320**

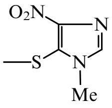
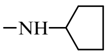
2-(1,2,4-Triazol-1-yl)tetrahydrofuran has been prepared in 90% yield by the reaction of the dihydrofuran **1** with 1,2,4-triazole in the presence of $4\text{-}MeC_6H_4SO_3H$ in DMF.[194]

2-(Benzotriazol-1-yl)tetrahydrofuran has been obtained in a quantitative yield by refluxing the compound **1** with benzotriazole in tetrachloromethane for 5 h.[195]

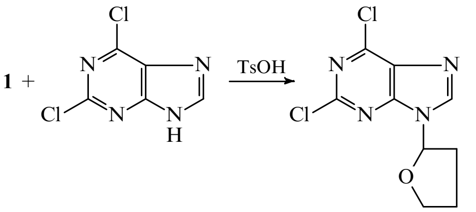
Purine derivatives **321** containing substituents in the 6-position have been made to react with dihydrofuran **1** in the presence of organic sulfonic acids; this reaction afforded addition products **322**.[196–198]



321 **322**

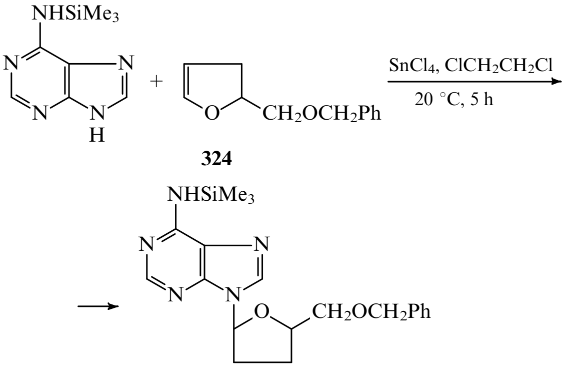
R	R′	Time /h	Yield (%)	Ref.
	$4\text{-}MeC_6H_4$	24	86	196
$-SMe$	$4\text{-}MeC_6H_4$	12	71.4	197
	Et	12	31	198
$-NH_2$	Et	12	28	198

2,6-Dichloropurine adds to the dihydrofuran **1** in the presence of toluene-*p*-sulfonic acid to give 2,6-dichloro-9-(tetrahydrofuran-2-yl)-9*H*-purine **323** in 88% yield.[199]



323

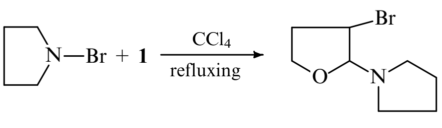
By the reaction of 2-benzyloxymethyl-2,3-dihydrofuran **324** with 6-(trimethylsilylamino)purine at ambient temperature in the presence of tin(IV) chloride, compound **325** has been synthesised in 53% yield.[200]



324

325

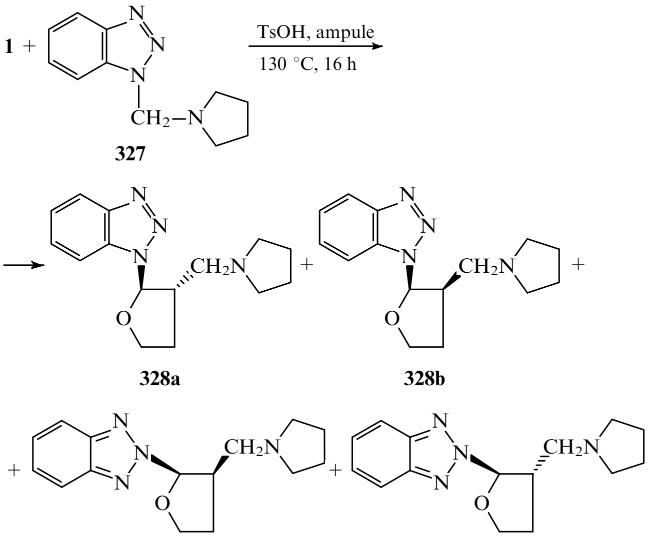
Refluxing of the compound **1** with 1-bromopyrrolidine in tetrachloromethane leads to 3-bromo-2-pyrrolidinotetrahydrofuran **326** in 29% yield.[201]



326

A fairly complex picture has been observed when 2,3-dihydrofuran **1** has been introduced in the reaction with 1-substituted benzotriazole derivatives.

When the enol ether **1** is heated with 1-pyrrolidinomethylbenzotriazole **327** in the presence of toluene-*p*-sulfonic acid in a sealed tube, a mixture of two pairs of diastereomers **328a,b** (yields 19% and 24%) and **329a,b** (yields 3% and 53%) is formed.[202]

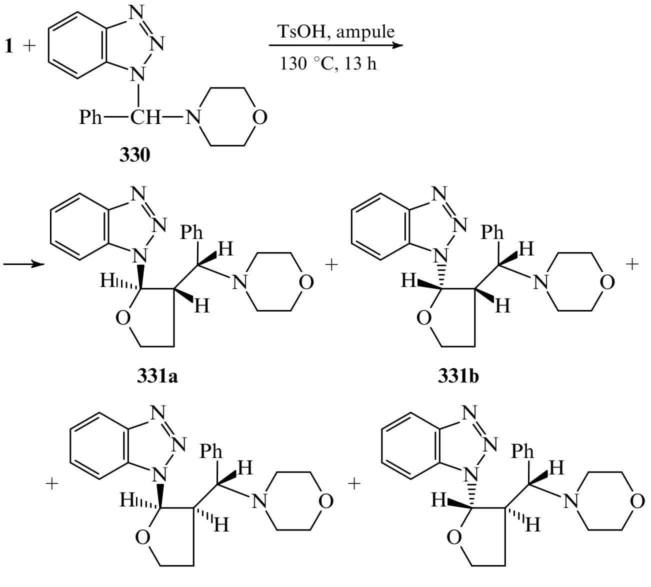


327

328a **328b**

329a **329b**

The reaction of 2,3-dihydrofuran **1** with benzotriazole derivatives **230** under the same conditions gives rise to the normal addition product as a mixture of four isomers (2*R*, 3*S*, 6*R*)-**331a**, (2*S*, 3*S*, 6*R*)-**331b**, (2*R*, 3*R*, 6*R*)-**331c**, and (2*S*, 3*R*, 6*R*)-**331d**.[202]

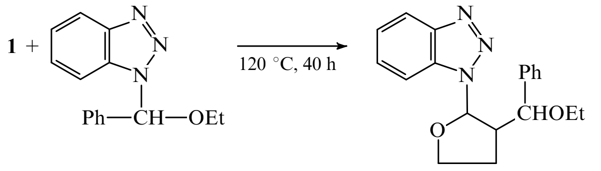


330

331a **331b**

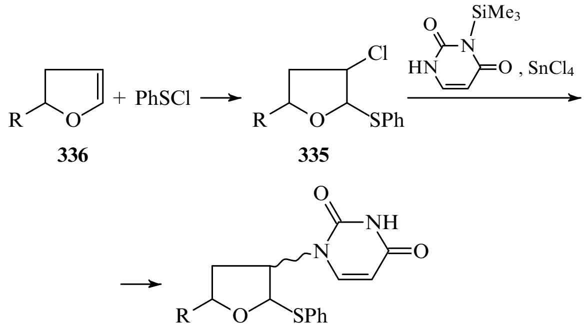
331c **331d**

A mixture of four isomers of compound **332** has been obtained by heating the dihydrofuran **1** with 1-(α-ethoxybenzyl)benzotriazole **333** in a sealed tube.[203]



333 **332**

Tetrahydrofuran derivatives **334**, containing an uracil residue in the 4-position, have been synthesised by treating the adducts **335**, prepared by the addition of phenylsulfenyl chloride to dihydrofurans **336**, with *N*-trimethylsilyluracil in the presence of tin(IV) chloride.[204]

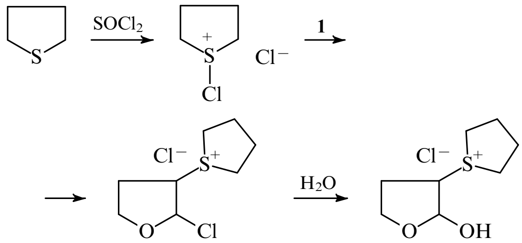


336 **335**

334

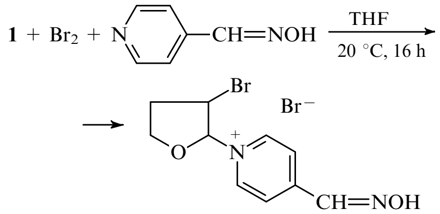
R = H, $CH_2OSiPh_2Bu^t$.

The reaction of 2,3-dihydrofuran with tetrahydrothiophene and thionyl chloride in sulfur dioxide has led to salt **337**, which was converted into the chloride of the hydroxy-derivative **338** through the action of water; the compound **338** was characterized as the corresponding picrylsulfonate (yield 19.5%).[205]



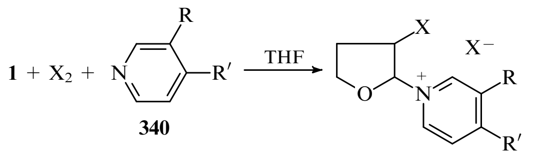
337 **338**

4-Formylpyridine oxime reacts with the compound **1** and bromine in THF to give the pyridinium salt **339** (yield 74%).[206]



339

A similar interaction of pyridine derivatives **340** with halogens and the dihydrofuran **1** resulted in the formation of salts **341**.[206]



340 **341**

X	R	R′
Cl	H	H
Br	CH=NOH	H
I	Me	H

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