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FURAN DERIVATIVES OF GROUP I ELEMENTS (REVIEW)

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1. ORGANOLITHIUM DERIVATIVES

1.1. Synthesis

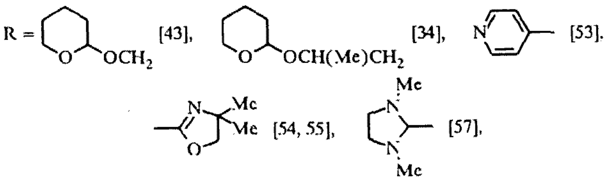
The organolithium derivatives of furan are highly reactive compounds in reactions with various electrophiles and are widely used in organic synthesis for the production of functional derivatives of furan and also for the introduction of 2- and 3-furyl groups into the molecules of organic compounds. There are two main methods for the synthesis of lithium derivatives in which the metal is attached to one of the ring carbon atoms, i.e., substitution of the hydrogen atom by direct metallation of unsubstituted furan and its mono-, di-, and trisubstituted derivatives and substitution of halogen atoms (bromine, iodine) by lithium.

2-Furyllithium is formed readily and with a high yield during the metallation of furan in inert solvents or their mixtures (hexane, ether, tetrahydrofuran) in an inert atmosphere at −20 to +5°C. n-Butyllithium has most often been used as metallating agent [1-23], and ethyllithium [24], tert-butyllithium [25], phenyllithium [16, 26, 27], or poly-p-lithiostyrene [28] have been used more rarely. Both when the metallating agent is added to the furan and when the initial substances are mixed in the reverse order, when an excess of RLi is created in the reaction mixture, the formation of the monolithium derivative is observed.

R = Et, *n*-Bu, *t*-Bu, Ph, $(C_6H_4CH{-}CH_2)_n$

The lithium derivatives of a series of 2-substituted furans containing groups inert toward metallating agents can also be obtained in a similar way.

R = Me [10, 20, 21, 23, 29—43], $PhCH_2CH_2$ [42], *c*-C_6H_{11} [44], $CH_2{=}CH$ [45], MeO [43], *t*-$BuMe_2SiOCH_2$ [43, 46], $MeOCH_2$, $EtOCH_2$ [47], $PhCH_2OCH_2$ [43], Me_3Si [15,17,48], Me_3Ge [48], $(RO)_2CH$ [49—52], RN=C(OMe) [56]



For all the 2-substituted furans discussed above (except the last [57], where traces of the C-4 metallation product are formed) metallation takes place at position 5 of the furan ring.

The metallation of derivatives containing functional groups that enter into reaction with butyllithium takes place in a more complicated way. Thus, treatment of 2-furaldoxime with a twofold quantity of n-butyllithium at −78°C in the presence of N,N,N′,N′-tetramethylethylenediamine gives the following dianion [58, 59]:

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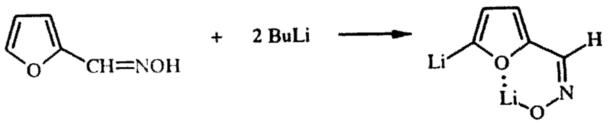
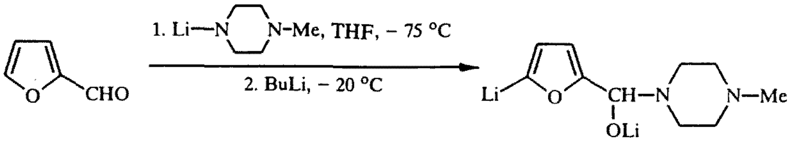
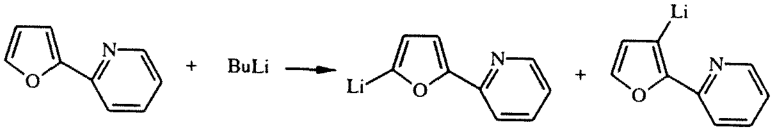


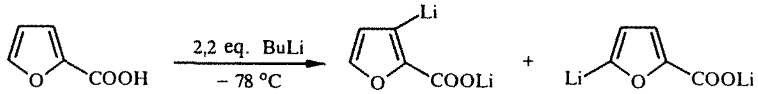
If the aldehyde function of furfural is blocked with lithium N-methylpiperazide, it is possible to metallate position 5 of the furan ring selectively by the action of n-butyllithium and s-butyllithium [60].



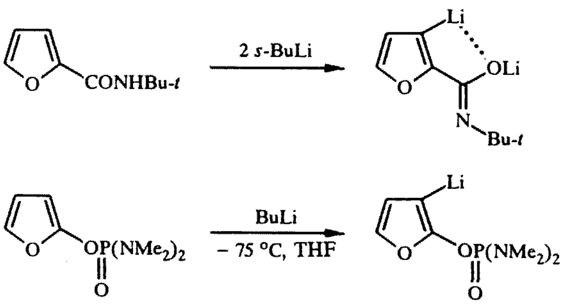
Unlike 4-(2-furyl)pyridine [53], 2-(2-furyl)pyridine is metallated at positions 3 and 5 of the furans ring. The nature of the solvent has the greatest effect on the direction of the reaction: the 3-isomer is formed preferentially in THF, and the 5-substituted product is formed preferentially in ether [61].



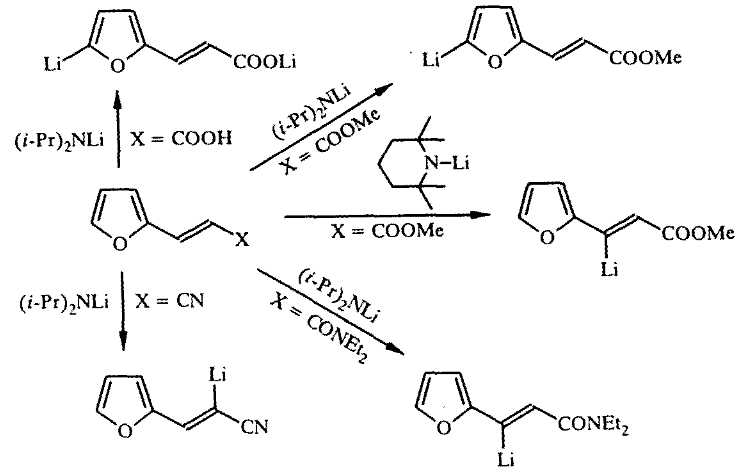
The metallation of 2-furancarboxylic acid also does not take place in a well defined manner [62], and a mixture of the 3- and 5-isomers in a ratio of 5:3 is formed. Selective metallation at position 5 of the ring in 2-furancarboxylic acid can be achieved if butyllithium is replaced by the milder lithium diisopropylamide.



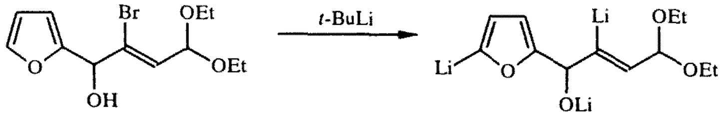
A mixture of isomers is also formed during the metallation of N-tert-butyl-2-furancarboxamide. Quantitative metallation at position 3 was observed in dimethoxyethane at −10°C and in tetrahydrofuran at −78°C. The authors [63] consider that this is achieved as a result of the maximum stabilization of the lithium dianion. The tetramethyldiamidophosphate substituent is very effective for the introduction of a lithium atom at position 3 of the furan ring [64]:



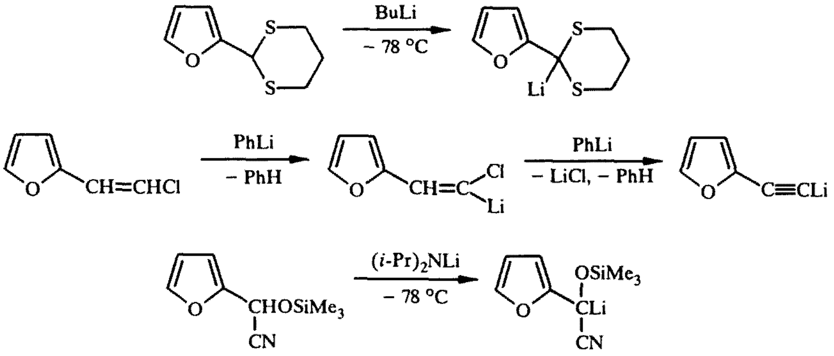
For some 2-furyl derivatives, containing a double bond in the substituent, metallation takes place not only in the ring but also at the carbon atoms of the vinyl group [65, 66]. For instance, the direction of the reaction with the 2-furylacryl derivative is determined by the nature of the carboxylate substituent X and the metallating agent [65]:



The reaction of lithium 1-(2-furyl)-2-bromo-4,4-diethoxy-2-buten-1-olate with three equivalents of tert-butyllithium also leads to deprotonation of the ring and replacement of the bromine by a lithium atom [66].

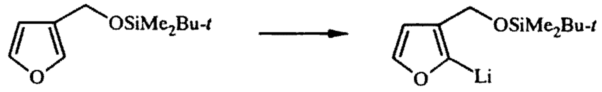


The reactions of 2-(2-furyl)-1,3-dithiane with n-butyllithium in tetrahydrofuran at −78°C [67], of 2-(2-furyl)vinyl chloride with phenyllithium in ether [68], and of 2-(trimethylsilyloxycyanomethyl)furan with lithium diisopropylamide in tetrahydrofuran at −78°C [69, 70] take place without the participation of the furan ring.



The metallation of some 3-substituted furans was realized [3, 60, 71-81]. Most of them are deprotonated by n-butyl- and sec-butyllithium and lithium diisopropylamide at the second position, and a mixture the 2- and 5-substituted isomers was only formed in isolated cases [60, 80, 81].

[78]



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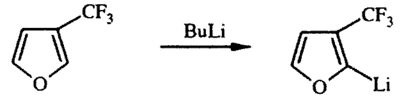
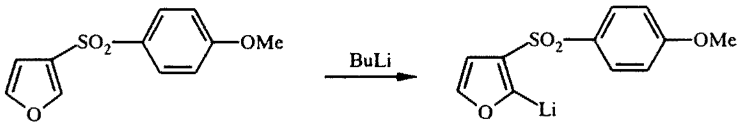


[75, 76]



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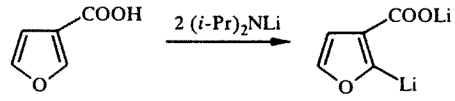

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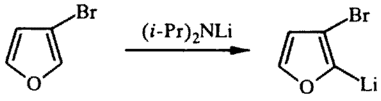
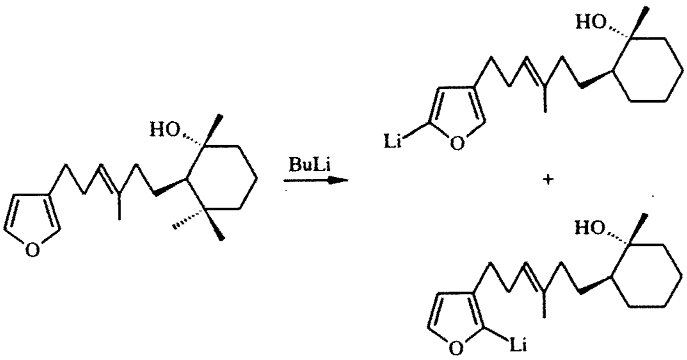
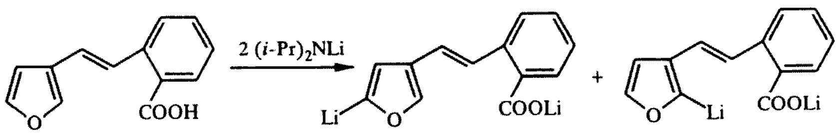
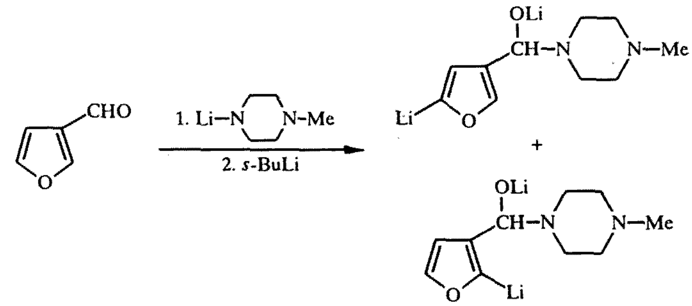


[3, 79]





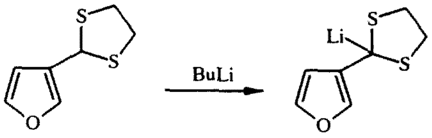
The direction of metallation of 3-furancarbaldehyde, in which the aldehyde group was blocked by lithium N-methylpiperazide, depends on the metallating agent [60]. The action of butyllithium leads to selective reaction at position 2 of the ring, while sec-butyllithium gives mainly the 5-isomer with 70-82% regioselectivity.



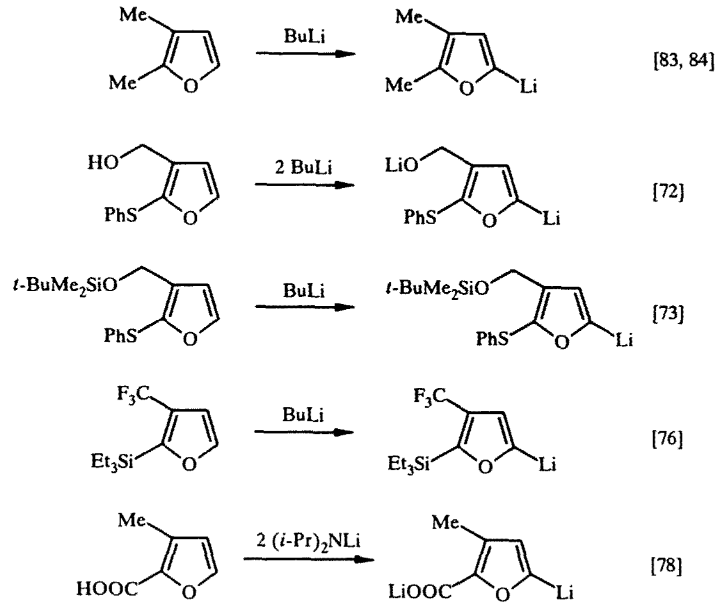
The regioselectivity of metallation at position 5 of the 3-furancarbaldehyde ring, blocked by lithium morpholide, also increases in the transition from butyllithium to sec-butyllithium [71].

During the metallation of 3-bromofuran by lithium diisopropylamide in ether or THF at −80 to −70°C [3, 79] the usual substitution of bromine by a lithium atom, which is observed during the reaction with ethyl- and butyllithium and will be discussed below, does not occur. The hydrogen atom at position 2 of the ring is substituted.

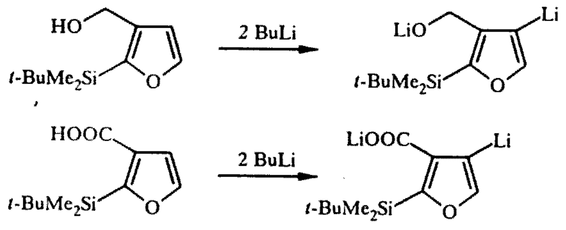
Like 2-(2-furyl)-1,3-dithiane [67], 2-(3-furyl)-1,3-dithiolane [82] is not metallated in the ring by n-butyllithium.



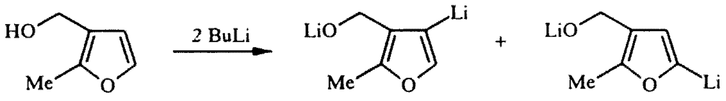
Under the influence of lithium compounds 2,3-substituted furans form the 5-substituted products.



Only 2-dimethyl(tert-butyl)silyl-3-hydroxymethylfuran [85-88] and 2-dimethyl(tert-butyl)silyl-3-furancarboxylic acid [89] are metallated regioselectively at position 4 of the furan ring. Thus, when treated with 2.2 equivalents of n-butyllithium in dimethoxyethane at 0°C for 15 min, the hydroxymethyl derivative [85-88] is converted into the 4-substituted lithium derivative. The yield of the latter, according to data from subsequent electrophilic substitution of the lithium atom (D_2O, MeI, Me_3SiCl, R_3SnCl, ClCOOMe), amounts to 57-92%.



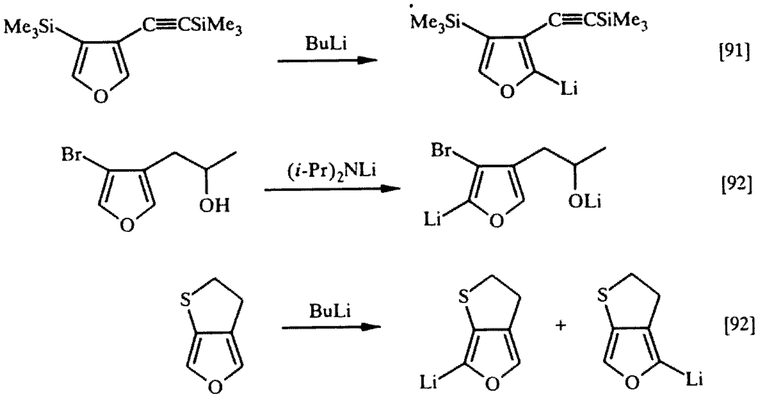
Replacement of the dimethyl(tert-butyl)silyl group by the less bulky methyl group leads to loss of selectivity and to the formation of a mixture of products from substitution at positions 4 and 5 of the furan ring in a ratio of 2:1 [85].



3,4-Dimethoxyfuran [90] and 3,4-di(trifluoromethyl)furan [75] enter readily into reaction with n-butyllithium.

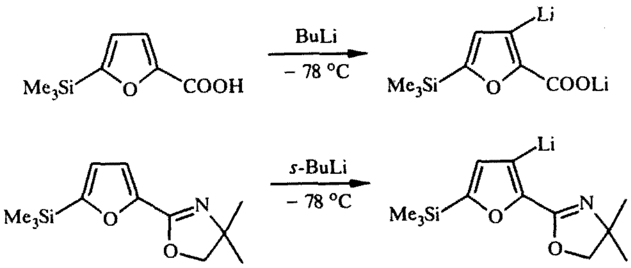
R = MeO [90], CF_3 [75]

Under the influence of metallating agents unsymmetrical 3,4-disubstituted furans give both one isomer [91, 92] and two isomers, as in the case of the condensed compound 2,3-dihydrothieno[2,3-c]furan [92].

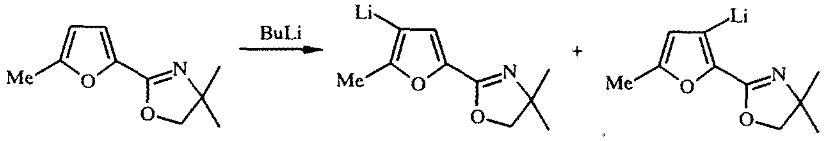


Unlike 3-trimethylsilyl-4-trimethylsilylethynylfuran [91], 3-trimethylsilyl-4-ethynylfuran is not deprotonated at the ethynyl group by n-butyllithium in THF at 0°C [93].

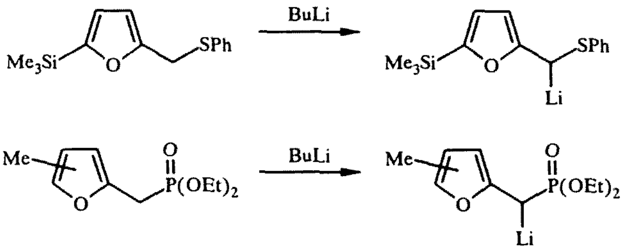
The direct metallation of the ring in the 2,5-disubstituted derivatives of furan has been investigated little [54, 62, 94, 95]. 2-(5-Trimethylsilyl)furancarboxylic acid is deprotonated by the action of n-butyllithium in THF at −78°C [62] and of lithium diisopropylamide [94] with the formation of a single isomer. The reaction of 4,4-dimethyl-2-[(5-(trimethylsilyl)-2-furyl]oxazoline with sec-butyllithium takes place similarly [54].



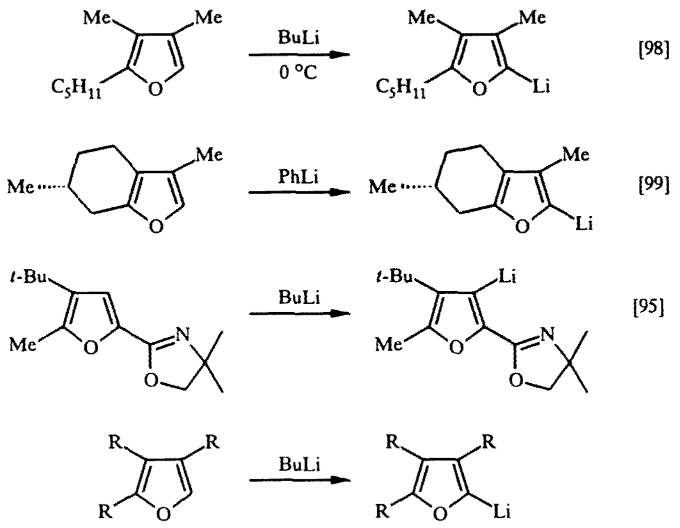
The direction of metallation of 4,4-dimethyl-2-(5-methyl-2-furyl)oxazoline depends on the reaction time and on the ratio of the reagents [95]. If equimolar amounts of the reagents are used, the 4-substituted product is formed after 15 min; an excess of the metallating agent and an eightfold increase in the reaction time lead to the formation of the 3-isomer.



If, however, the 2,5- and 2,4-disubstituted furans contain a phenylthiomethyl [96] or diethoxyphosphorylmethyl [97] group at position 2, metallation of the ring does not occur, and substitution of the more active hydrogen of the methylene groups is observed.

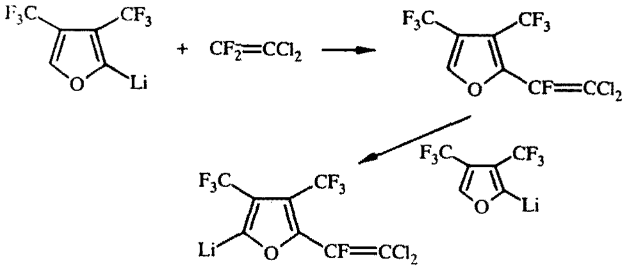


Metallation of a series of trisubstituted furan compounds at the free position of the ring was realized [75, 95, 98-101].

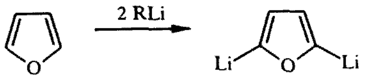


R = CF$_3$ [100], F [101]

The metallation of 2-(2,2-dichloro-1-fluorovinyl)-3,4-di(trifluoromethyl)furan, formed in the reaction of the lithium derivative of 3,4-di(trifluoromethyl)furan with 1,1-difluoro-2,2-dichloroethylene, takes place in an unusual way, since the unreacted lithium substrate is the metallating agent [75].

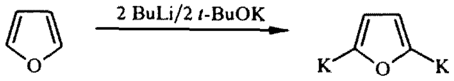


A number of authors have studied the possibilities of simultaneous introduction of two lithium atoms into the furan ring [23, 36, 90, 102, 103].

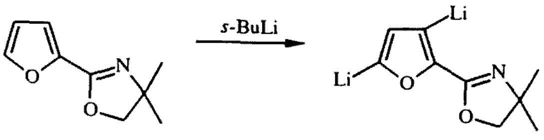


Such compounds make it possible to eliminate the multistage character during the synthesis of di-, tri-, and tetrasubstituted furans. The effects of various factors (the ratio of furan and n-butyllithium, the reaction time and temperature, the solvent, additions of N,N,N',N'-tetramethylethylenediamine) on the dimetallation of furan and its derivatives were studied [23]. Increase in the ratio of furan and n-butyllithium to 1:2.5 leads to a substantial increase in the dilithium derivative. (The ratio of the mono- and disubstituted products amounts to 9:91 and 5:57, depending on the reaction time.) Further increase in the amount of the n-butyllithium leads to appreciable polymerization of the reaction mixture. Increase in the reaction time (to 3 h) and temperature (25°C) is also accompanied by an increase in the yield of the 2,5-dilithium compound. The solvent has a significant effect on its formation; 2,5-dilithiofuran can be obtained in hexane, and only 2-furyllithium is formed in ether. The presence of N,N,N',N'-tetramethylethylenediamine has a complicated effect on the dimetallation of furan — with the butyllithium and furan in a ratio of 2.5:1 it leads to an increase in the yield of the disubstituted product. In the absence of an excess of the metallating agent N,N,N',N'-tetramethylethylenediamine increases the proportion of 2-furyllithium [23]. The highest yield of 2,5-dilithiofuran was obtained during metallation in hexane at room temperature with a 2,5-fold excess of n-butyllithium [23] or sec-butyllithium [104] in the presence of N,N,N',N'-tetramethylethylenediamine.

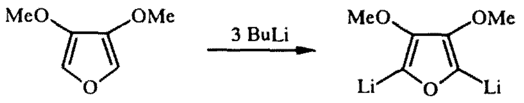
Furan is dimetallated by two equivalents of n-butyllithium under the influence of a strong base (potassium tert-butoxide) at −25°C in pentane [103]. It was, however, considered [103] that transmetallation occurred under these conditions and that 2,5-dipotassiofuran was formed.



The maximum dilithiation of 2-(2-furyl)oxazoline is obtained during its treatment with 3.3 equivalents of sec-butyllithium in THF at −78°C for 2 h in the presence of 3.3 equivalents of N,N,N',N'-tetramethylethylenediamine [102].

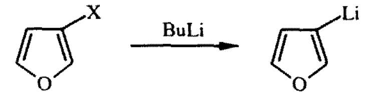


3,4-Dimethoxyfuran is easily dilithiated with a three times the amount of n-butyllithium [36, 90]:



The second method for the synthesis of lithium derivatives of furan involves the substitution of halogen atoms (bromine or iodine) by lithium not, as in alkyl halides, by the action of metallic lithium but by an exchange reaction with the alkyllithium derivatives. The high reactivity of the halogen compared with hydrogen in metallation reactions makes it possible in many cases to extend the possibilities substantially for the synthesis of the functional derivatives of furan and of the 3-substituted derivatives in particular.

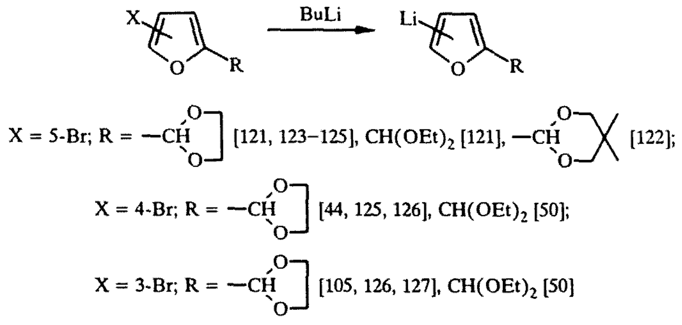
3-Bromofuran [13, 105-111] and 3-iodofuran [105, 112-115] are the most suitable starting reagents for the synthesis of 3-furyllithium. The general procedure for its preparation includes the metallation of halogenofurans at −78 to −70°C with ethyllithium [105, 114] or n-butyllithium [106-111, 113, 115] in most cases in a mixture of ether and hexane.



X = Br, I

As noted earlier [3, 79], the milder metallating agent lithium diisopropylamide does not react at the C−Br bond of 3-bromofuran but deprotonates position 2 of the ring. The metallation of a series of alkylbromo- and alkyliodofurans (2-methyl-4-bromofuran [116], 2-ethyl-4-bromofuran [116], 2-bromo-3-isopropylfuran [117, 118], 2,5-dimethyl-3-iodofuran [119], 2-[2-(2-thienyl)ethyl]-3-bromofuran [120]) with ethyl- and butyllithium takes place selectively at the C−halogen bond.

The metallation of various acetals of furfural has been studied most widely in the series of monohalogen-substituted derivatives of furan [44, 50, 105, 121-127].

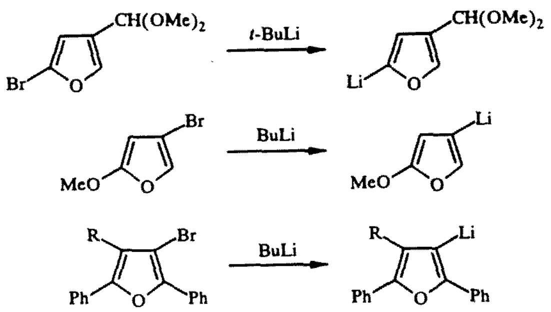


X = 5-Br; R = [121, 123–125], CH(OEt)$_2$ [121], [122];

X = 4-Br; R = [44, 125, 126], CH(OEt)$_2$ [50];

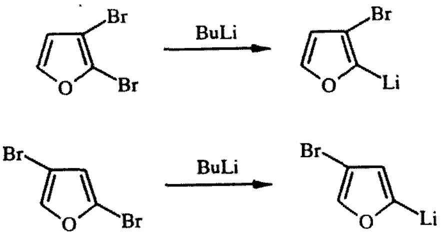
X = 3-Br; R = [105, 126, 127], CH(OEt)$_2$ [50]

The reaction gives a high yield and takes place exclusively at the bromine atom. The reactions of 2-bromo-4-(dimethoxymethyl)furan with tert-butyllithium [128] and of 2-methoxy-4-bromofuran [129] and 2,5-diaryl- and 2,4,5-triaryl-3-bromofurans [130] with n-butyllithium take place in a similar way.

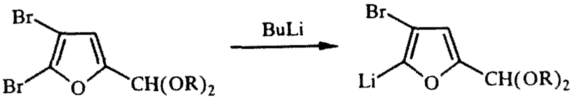


R = H, Ph

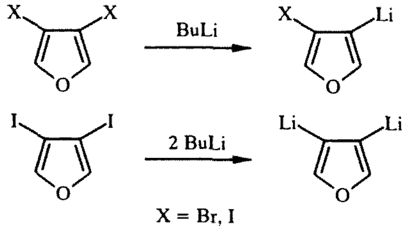
The lithiation of a series of dibromofurans [50, 92, 105, 131-136], tribromofurans [131], diiodofurans [92, 105], and triiodofurans [137] has been carried out. With an equimolar amount of n-butyllithium 2,3-dibromofuran [50, 105, 131] and 2,4-dibromofuran [131] are only metallated at the bromine atom at position 2 of the ring.



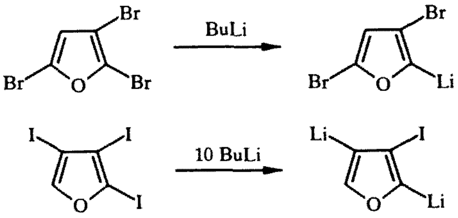
The reactions of 2,3-dibromofurfural acetals take place in a similar way [50, 132-136].



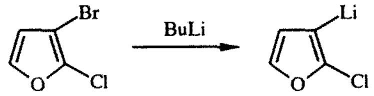
In the reaction of equimolar amounts of 3,4-dibromofuran [92] or 3,4-diiodofuran [92, 105] and n-butyllithium [92, 105] only one halogen atom is substituted; the substitution of two iodine atoms is observed during the treatment of 3,4-diiodofuran with twice the amount of n-butyllithium [105].



The reactions of 2,3,5-tribromofuran [131] and 2,3,4-triiodofuran [137] with n-butyllithium take place according to the following schemes:

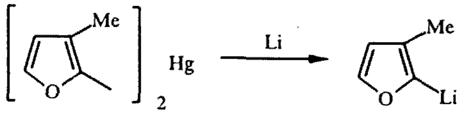


It was established that the chlorine atom of 2-chloro-3-bromofuran was inactive [128] and that 2-chloro-3-furyllithium was formed by the action of n-butyllithium.

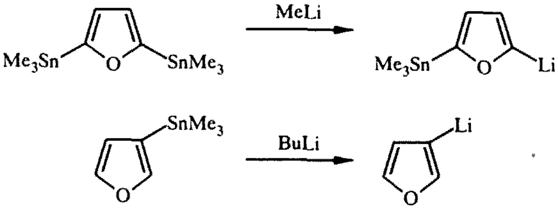


Apart from the methods for the synthesis of organolithium derivatives examined above there are data in the literature on the metallation of the organomercury [139, 140], organotin [104, 141], and organoselenium [142] compounds of furan.

3-Methyl-2-furyllithium is formed by the action of a suspension of lithium in ether on bis(3-methyl-2-furyl)mercury at −20°C [139, 140].

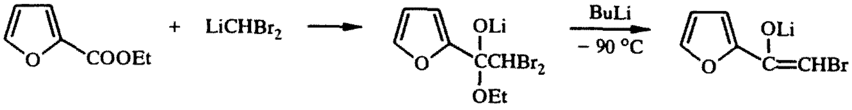


At low temperatures (−78°C) in THF methyllithium [104] and n-butyllithium [141] cleave the C−Sn bond in 2,5-bis(trimethylstannyl)furan [104] and 3-tributylstannylfuran [141].



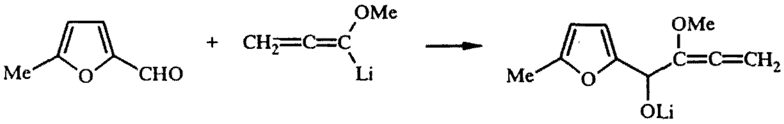
2-Methylselenofuran also gives 2-furyllithium, i.e., the product from cleavage of the Se−C(furyl) bond, as a result of reaction with n-butyllithium in ether at room temperature [142].

Earlier it had already been noticed that lithium salts [62, 78, 81] and alcoholates [72, 73, 87] are formed together with the products from substitution of hydrogen of the ring during the metallation of furan derivatives with functional groups (COOH, OH). In a number of cases the reactions with lithium compounds only take place at the oxygen atom of the functional groups [143-145]. Ethyl 2-furancarboxylate reacts with dibromomethyllithium at −90°C, and the reaction takes place at the C═O group [143].

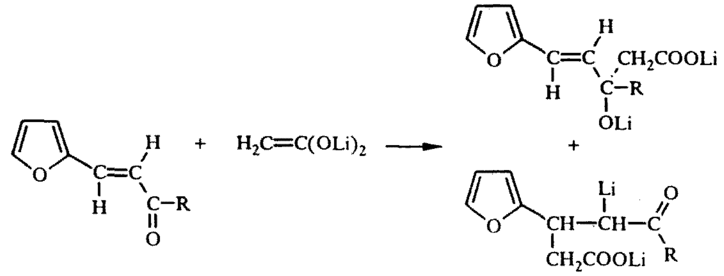


By treating the dibromo derivative it is then possible to obtain the lithium enolate.

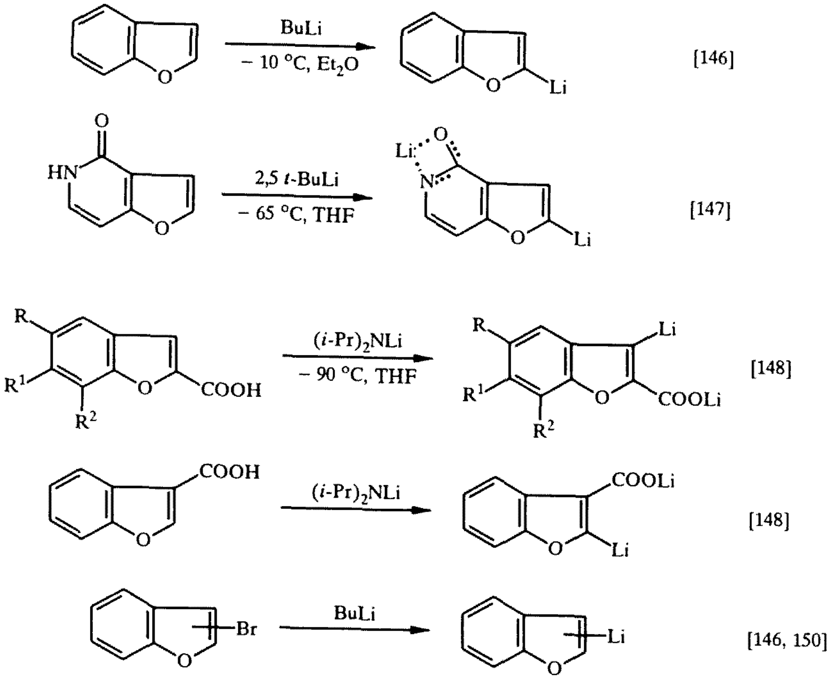
5-Methylfurfural reacts with the lithium derivative of methoxyallene at the carbonyl group [144].



The reaction of the α,β-substituted ketones of furan with a lithium diolate in THF at $-50°C$ was investigated. The yield for the derivative with R = Ph amounted to 57%, and the ratio of the products was 3:2 [145].

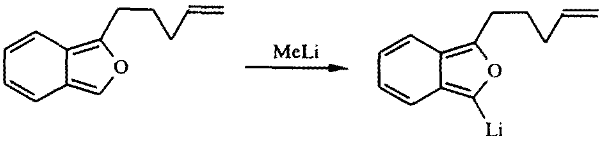


On the whole methods similar to the methods for the production of furan derivatives are used for the synthesis of benzofuran derivatives and of certain compounds containing a furan ring condensed with other heterocycles through the $C_{(2)}-C_{(3)}$ bond, i.e., the substitution of hydrogen atoms [28, 146-149] or bromine atoms [146, 150, 151] by lithium with metallating agents.

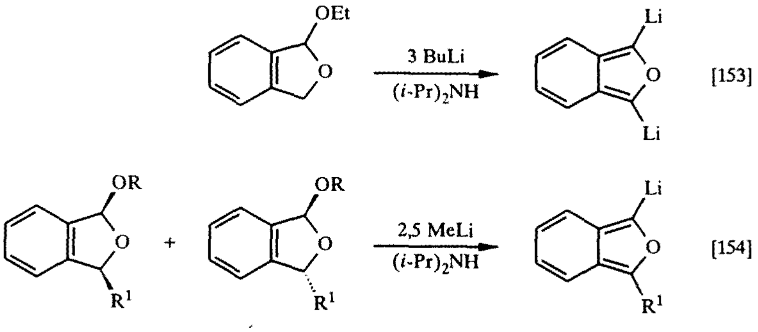


With 2,3-dibromobenzofuran and butyllithium in a ratio of 1:1 at $-75°C$ the 2-monolithium derivative is mainly formed [146, 151]. With a fivefold excess of n-butyllithium a mixture of the dilithium (60%) and monolithium (40%) products is formed [146].

The metallation of 1-(4-pentenylisobenzofuran with methyllithium in the presence of catalytic amounts of diisopropylamine takes place at the free position of the furan ring [152].

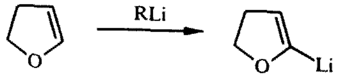


1,4-Elimination has also been used for the synthesis of the lithium compounds of isobenzofuran [153, 154].



R = Me, Et; R^1 = Ph, Me

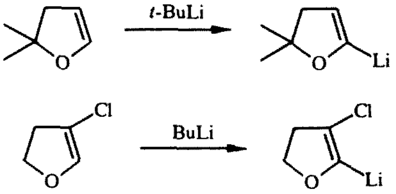
The possibilities for the synthesis of the lithium derivatives of 2,3-dihydrofuran have been studied in a number of papers [155-168]. The metallation of 2,3-dihydrofuran was conducted with n-butyllithium [155, 156, 159-161], sec-butyllithium [155], and tert-butyllithium [155, 156, 162-166]. It was noticed that the most complete deprotonation was observed when a small excess (0.1 eq.) of tert-butyllithium was used at −78°C [155]. In the presence of N,N,N′,N′-tetramethylethylenediamine the reaction can be carried out at 0°C [161].



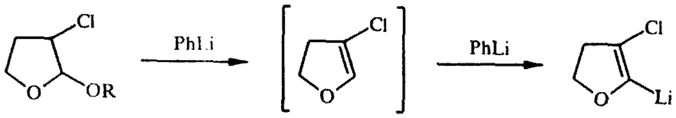
R = Bu, s-Bu, t-Bu

According to data in [156], however, side processes occur when the product from metallation of 2,3-dihydrofuran with n-butyllithium is kept at 25°C for 24 h, since the products from subsequent silylation contain disilylketene in addition to the silyl derivative of 2,3-dihydrofuran. The authors [156] consider that ring opening with the elimination of ethylene and the formation of lithium the alkynolate takes place in the 2,3-dihydro-5-furyllithium molecule.

2,2-Dimethyl-2,3-dihydrofuran [165] and 4-chloro-2,3-dihydrofuran [167] react with tert-butyllithium in pentane and with n-butyllithium in hexane respectively at −78°C and give high yields of the lithium compounds. 2,2-Dimethyl-2,3-dihydrofuran reacts similarly with tert-butyllithium in THF at −20°C in 30 min [166].



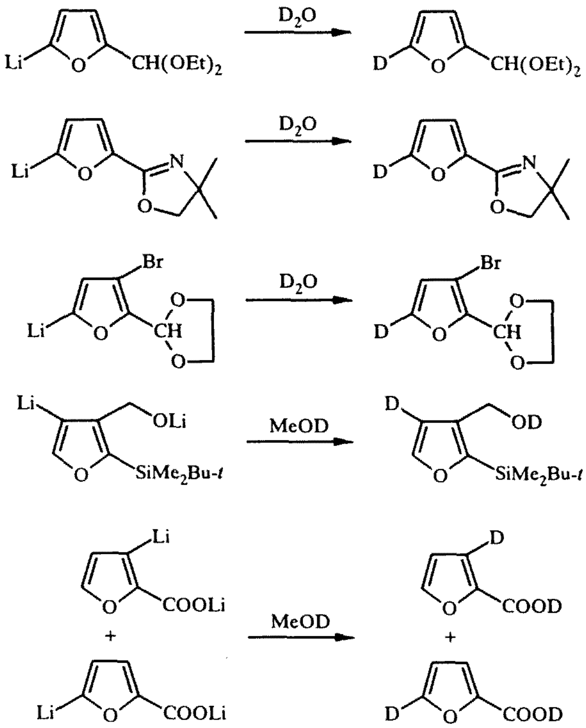
In addition to the direct metallation of the double bond of 2,3-dihydrofurans, the dealkoxylation of 2-alkoxy-3-chlorotetrahydrofurans with phenyllithium has also been used for the synthesis of the lithium derivatives [168].



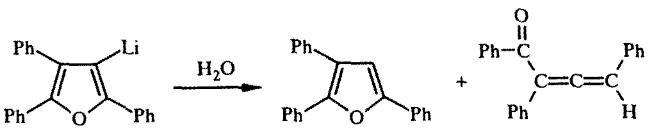
1.2. Chemical Properties

The organolithium derivatives of furan are highly reactive substances and enter into reaction with widely varying electrophiles (water, alcohols, carbon dioxide, acids, esters, nitriles, halogenoalkanes, halogenosilanes, halogenogermanes, halogenostannanes, etc.). As a rule the reactions take place readily an give high yields.

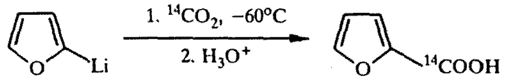
The lithium derivatives are easily decomposed by water [49, 50, 55, 59, 78, 79, 85, 130, 131, 136]. The reaction with deuterated water and also with deuteromethanol CH_3OD [61, 62, 85] is widely used to establish the direction of metallation of furan compounds. It is possible to judge the structure of the initial furyllithium from the position of the deuterium atom in the ring, determined by NMR spectroscopy.



Sometimes the reaction with water is accompanied by side processes. For example, in reaction with water 2,4,5-triphenyl-3-furyllithium gives not only 2,3,5-triphenylfuran but also allene, which is a ring opening product. Their ratio depends on the solvent and on the temperature. In benzene at room temperature the allene is mainly formed (60%), and only 30% of the triphenylfuran is formed. In ether the furan compound and only traces of the allene (5%) are formed [130].



The carbonyl group, which is easily introduced by reaction with carbon dioxide, is very often used as an indicator group [1, 2, 23, 57, 62, 90, 98-102, 105, 110, 113, 121, 131, 135, 137, 138, 141, 146, 151, 169, 170].



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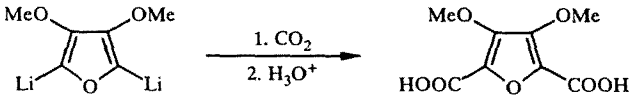
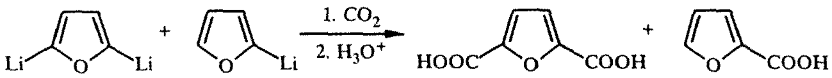
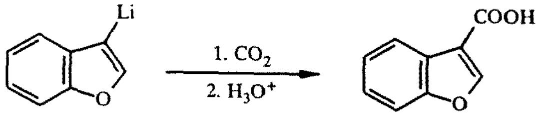


[90]

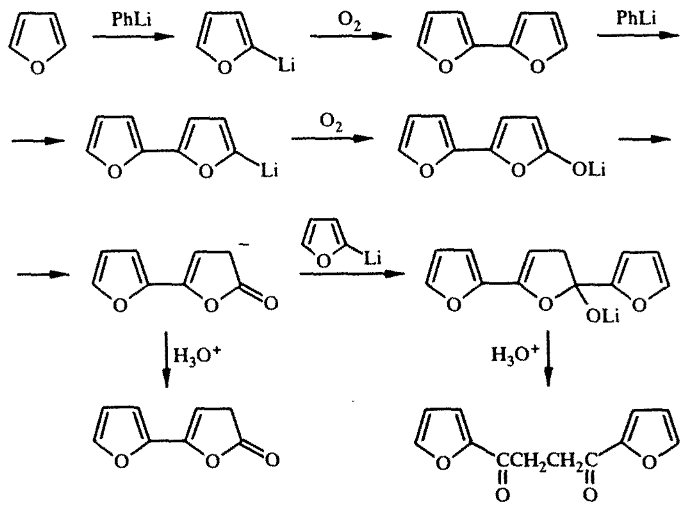


[23]

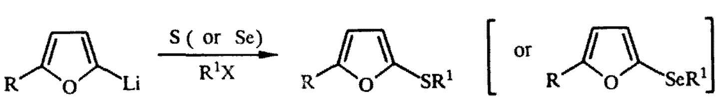


[146]

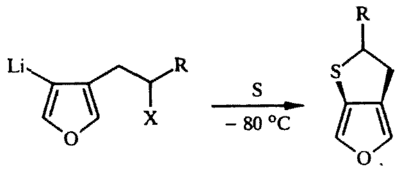
Attempts were made to oxidize 2-furyllithium with oxygen [26, 27, 32] and tert-butyl hydroperoxide [32]. However, very strong resinification of the reaction mixture was observed [32]. Only in [26, 27] was it possible to isolate 1,4-di(2-furyl)butane-1,4-dione (15%) and 5-(2-furyl)-2,3-dihydrofuran-2-furanone (13%), which are probably formed according to the following scheme:



In reaction with elemental sulfur or selenium the unsubstituted and substituted derivatives of furyllithium form hydrosulfides [21, 37, 92, 171-174] or hydroselenides [171, 175, 176] respectively, which are converted into sulfides by the action of alkyl halides usually without isolation from the mixture. Phosphates [37, 171] and a 2-furylselenothiocarbamate [176] were synthesized similarly.

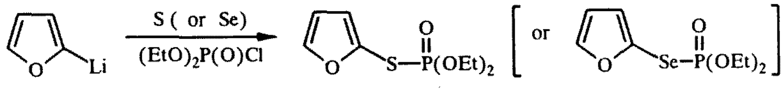


[21, 175]

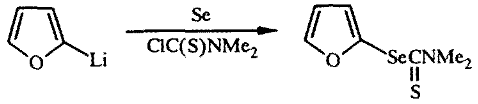


X = Br, I; R = H, Me

[92]

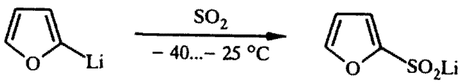


[171]

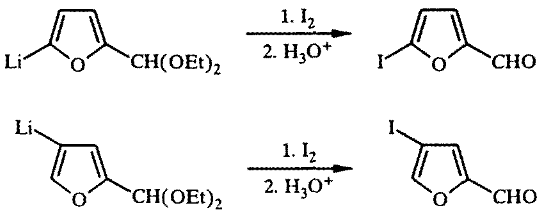


[176]

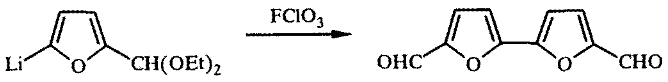
The reaction of 2-furyllithium and sulfur dioxide gave a 48% yield of lithium 2-furansulfinate [177-179].



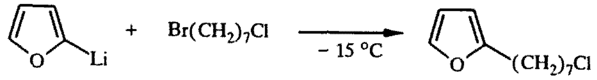
The reactions of the lithium derivatives of furan with halogens do not have practical significance, and the reaction with iodine has extremely limited use [51, 131].



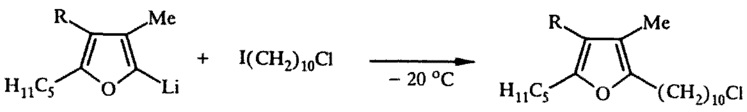
It was not possible to fluorinate the lithium derivative of furfural diethyl acetal, since 5,5'-bifurfural is formed [51].



The reactions of the lithium compounds with alkyl halides have been studied quite widely [1, 3, 4, 25, 30, 34, 38, 46, 57, 59, 61, 62, 64-66, 78, 90, 98, 146, 155, 157, 161-163, 167, 180-182]. The alkyl iodides are most reactive. The alkyl bromides and particularly the alkyl chlorides are significantly less reactive.



[4]

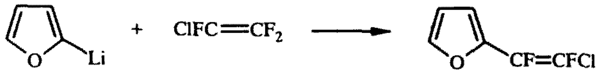


R = H, Me

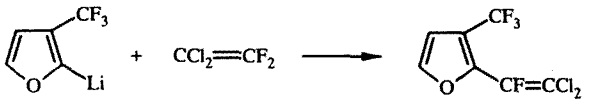
[98]

Allyl bromides [3, 34] and benzyl bromides [34, 38, 161, 181] with a more mobile bromine atom than in the alkyl bromides react with the lithium substrates under mild conditions and give fairly high product yields (60-80%).

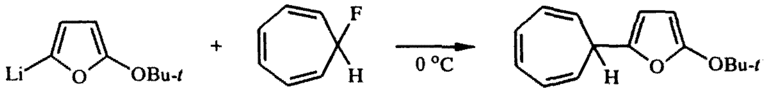
In some compounds the fluorine atom proved very reactive toward 2-furyllithium derivatives [75, 183, 184].



[183]

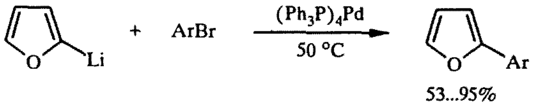


[75]

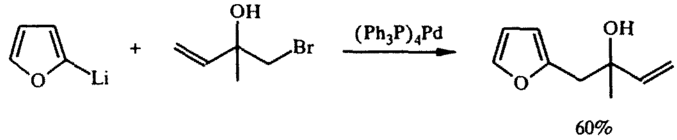


[184]

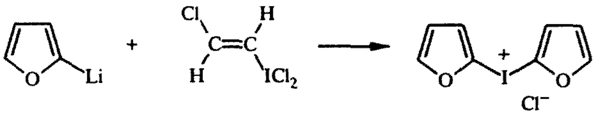
The series of aryl bromides [185], alkenyl bromides [186], and also isoprene bromohydrin [187] proved inactive in reactions with 2-furyllithium. It was possible to realize the coupling of these substrates with the phosphine complex of palladium $(Ph_3P)_4Pd$ as catalyst [188, 189].

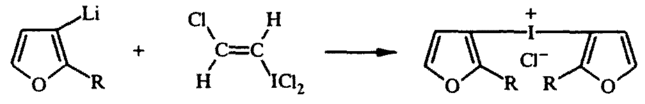


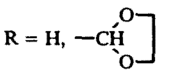
Ar = Ph, 4-MeC_6H_4, 3-MeC_6H_4, 4-$MeOC_6H_4$, 3-$MeOC_6H_4$, 2,4-$(MeO)_2C_6H_3$, 4-$O_2NC_6H_4$



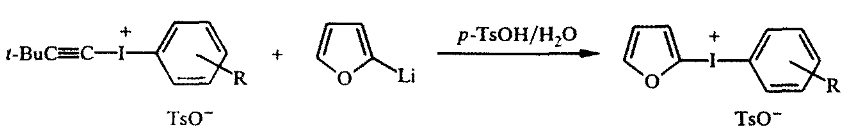
The reactions of 2-furyl- and 3-furyllithium with trans-chlorovinyliodine dichloride were used for the production of the iodonium salts of furan [111, 127, 190]. According to the data in [111], the yields of di(2-furyl)- and di(3-furyl)iodonium chlorides were 35 and 54% respectively.





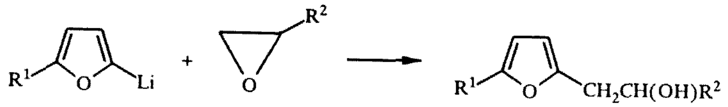


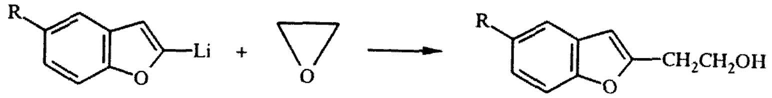
Unsymmetrical furyl-containing compounds were obtained by substitution of the ethynyl group in aryl(tert-butylethynyl)iodonium and phenyl(phenylethynyl)iodonium tosylates by furyl with 2-furyllithium [191]. However, the yields of the products of this reaction were low (21-32%).



R = 2-Me, 3-Me, 4-Me, 2-F

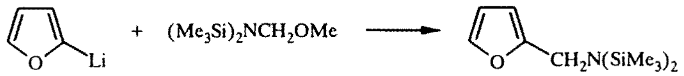
2-Furyllithium [9, 10, 17, 34], its 5-substituted derivatives [10, 15, 34, 40, 45, 192], and 2-benzofuryllithium derivatives [193] readily open the epoxide ring of oxiranes.



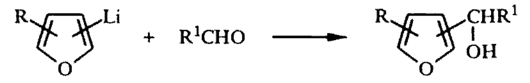


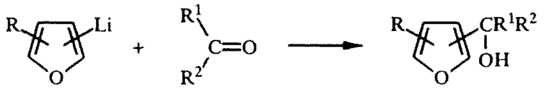
These reactions are useful for the synthesis of furylethyl alcohols, which are used in turn for the production of acetyl derivatives [9, 45], tetrahydropyranyl ethers [34], and phosphonates and phosphates [17].

In the presence of magnesium bromide at room temperature 2-furyllithium cleaves the C–O bond of N,N-bis(trimethylsilyl)methoxymethylamine [194].

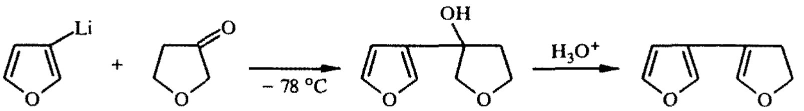


The reaction of the lithium derivatives of furan with carbonyl-containing compounds (aldehydes and ketones) has been studied very comprehensively and is a simple and convenient method for the production of furfuryl alcohols [1, 3, 5-8, 11, 33, 41, 43, 44, 51, 59, 64, 76, 78, 83, 107-109, 112, 115-118, 122, 125, 126, 129, 165, 195-205].

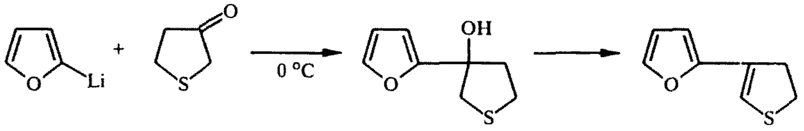




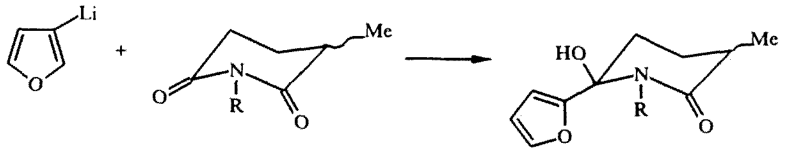
Some biheterocycles were synthesized by the reaction of furan compounds with heterocyclic ketones [112, 195, 200, 201].



[112]

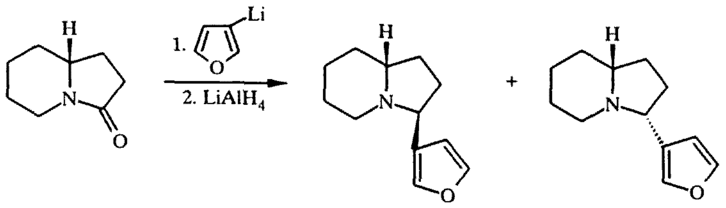


[201]

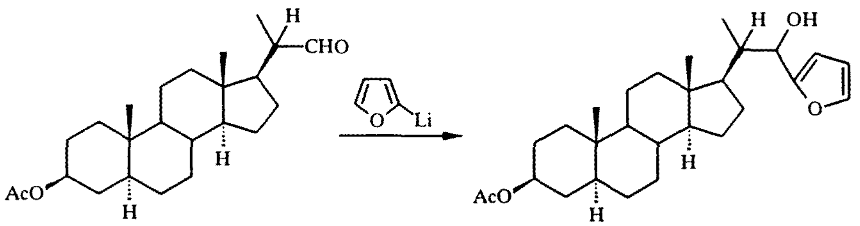


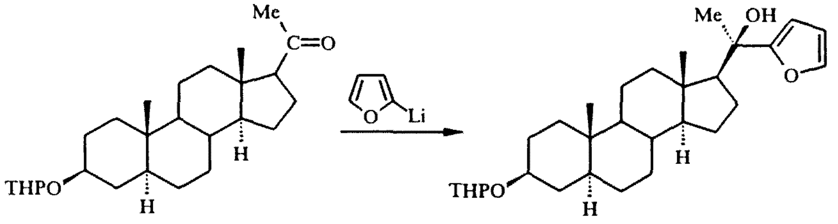
[200]

R = H, CH_2Ph

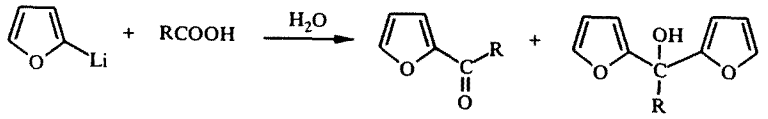


Furyllithium compounds have been used very widely in the production of furyl-containing steroids. Subsequent transformations of the furan ring make it possible to obtain the most varied biologically active compounds of this type [7, 117, 118, 155, 196].



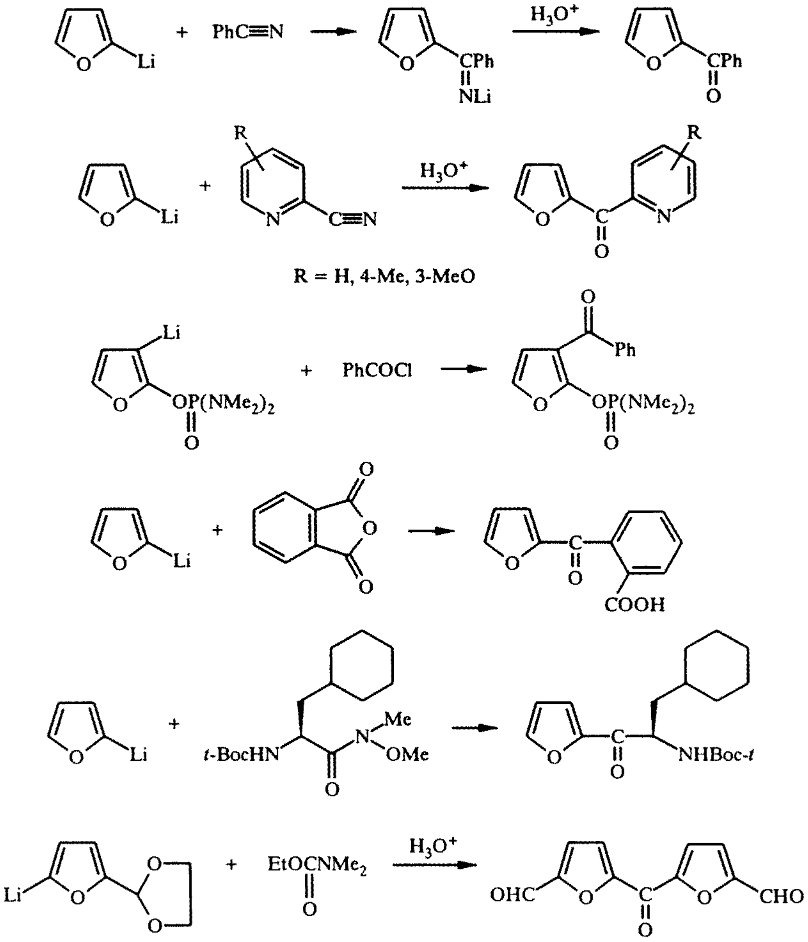


The reaction of the lithium compounds of furan with carboxylic acids and some of their derivatives were investigated [1, 64, 123, 124, 206-214]. A convenient method for the production of α-furyl ketones under nonacidic conditions is the condensation of 2-furyllithium with acids followed by treatment of the reaction mixture with water. However, it should be noted that the yield of the ketones is rather low on account of the formation of difurylcarbinols [206].

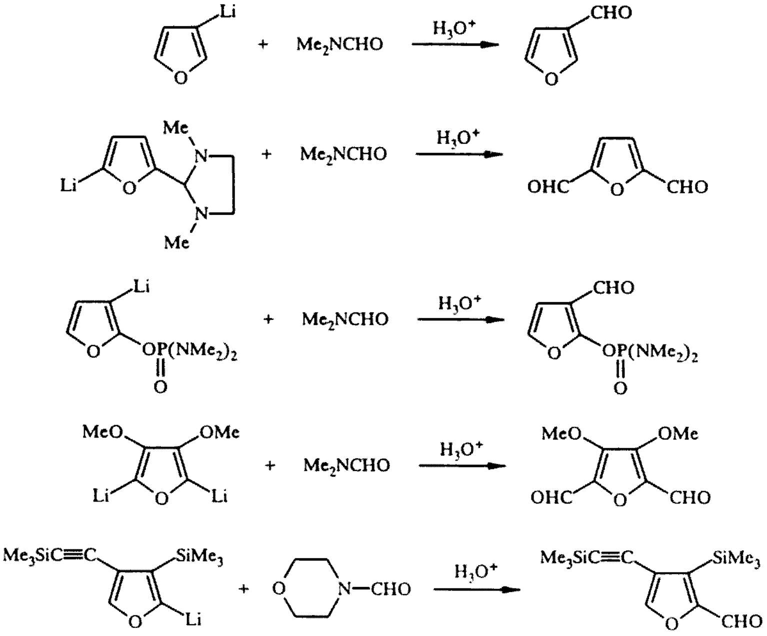


R = Me, Et, *i*-Pr, *t*-Bu, Ph

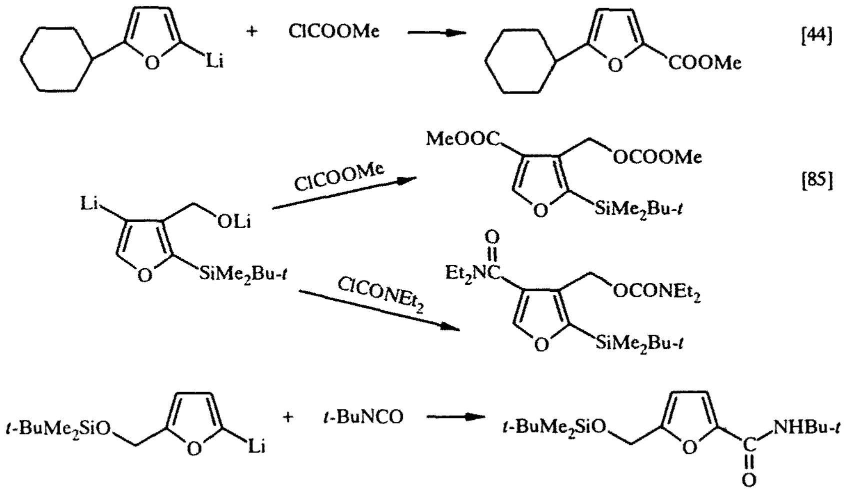
α-Furyl ketones can also be obtained by the reaction of lithium derivatives with nitriles [1, 207-211], acid chlorides [64], phthalic anhydride [214], and amides [212]. Difuryl ketones can be obtained in reaction with carbamates [123, 124].



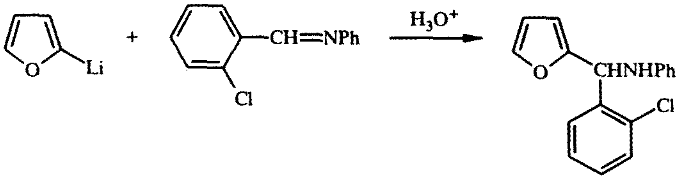
Formylation of the furan ring can be realized most simply in the reaction of lithium derivatives with dimethylformamide [57, 64, 90, 103, 105, 113, 114, 131, 132, 135, 138, 147] or 4-formylmorpholine [91].



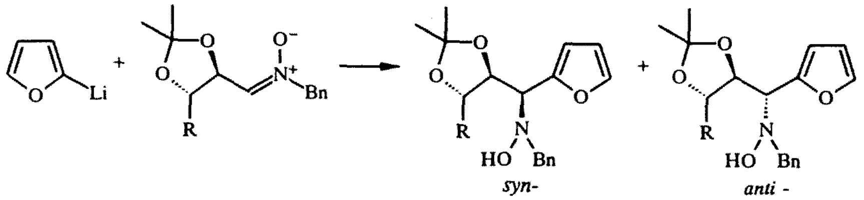
The yields of furancarbaldehydes by this method amount to 60-80%. Methyl furancarboxylates were obtained by the treatment of the lithium products with methyl chloroformate [44, 85], while the amides were obtained with N,N-diethylchloroformamide [85] or tert-butyl isocyanate [46].



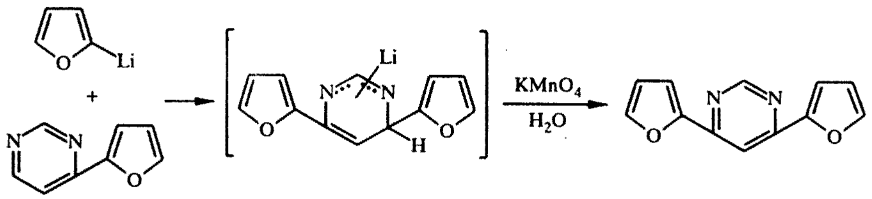
There is data in the literature on the production of furfurylamines from Schiff bases [14]. 2-Furyllithium reacts at the C=N double bond of N-(o-chlorobenzylidene)aniline with the formation of N-(o-chlorophenylfurylmethyl)aniline.

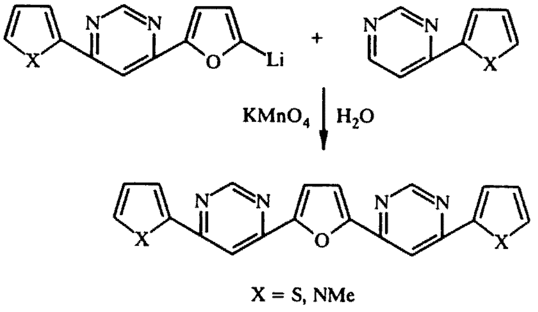


β-Alkoxy-α-hydroxylamino-2-alkylfurans were obtained with high yields and with syn selectivity in the reaction of N-benzylnitrones with 2-furyllithium. The analogous reaction in the presence of diethylaluminum chloride takes place with high anti selectivity [215].

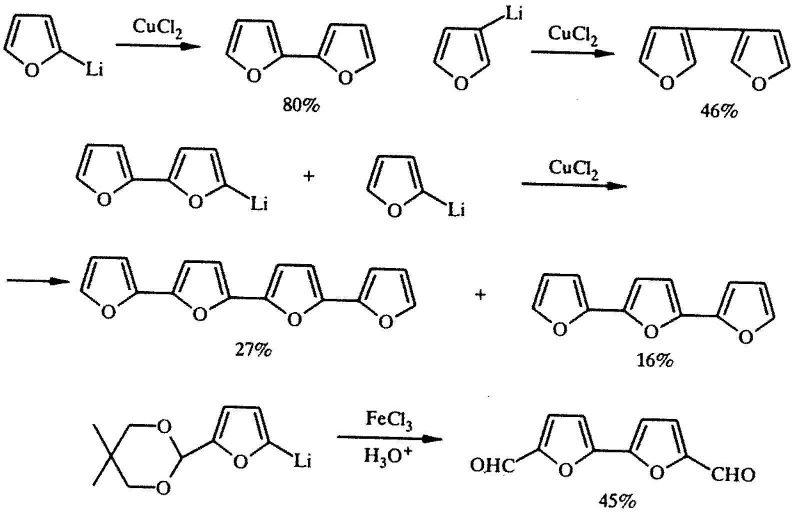


The reaction of 2-furyllithium with pyrimidine derivatives was used for the synthesis of polyheterocyclic systems [216].



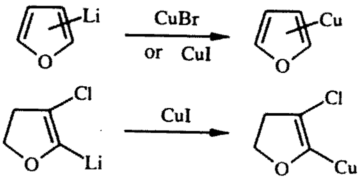


It is also possible to obtain bi-, tri-, and tetrafurans by the oxidative coupling of organometallic derivatives under the influence of copper [12], iron [51, 217], and nickel and cobalt [51] chlorides. Analogous coupling was mentioned above [51] during the action of perchloryl fluoride on 5-lithio-2-diethoxymethylfuran.

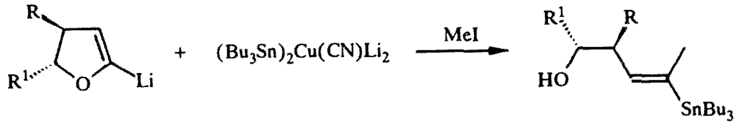


The organolithium derivatives have been used successfully not only in organic synthesis but also in the production of organometallic and heteroorganic compounds of copper, cadmium, boron aluminum, silicon, germanium, tin, zirconium, phosphorus, sulfur, nickel, and iridium.

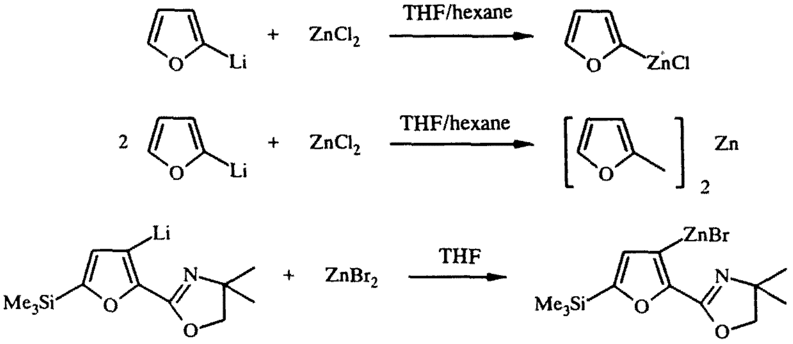
2-Furylcopper [218-221] and 3-furylcopper [218, 222] and also 5-(4-chloro-2,3-dihydrofuryl)copper [223] were obtained from the corresponding lithium derivatives and copper bromide or iodide in the range of −70-0°C.



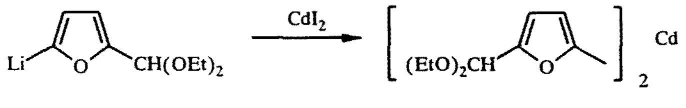
Lithium di(2-furyl)cuprate is formed during the treatment of a suspension of the complex of copper bromide and dimethyl sulfide in THF with 2-furyllithium [5]. Lithium di(3-furyl)cuprate can be obtained in a similar way or by the action of 3-furyllithium on copper iodide in ether at −78°C [224]. However, in some reactions, for example, with the series of oxiranes greater reactivity was exhibited not by lithium di(3-furyl)cuprate but by its complexes with two equivalents of 3-furyllithium $(3\text{-furyl})_4CuLi_3$ and $(3\text{-furyl})_4CuLi_3 \cdot Me_2S$ [225, 226]. Cuprates containing a cyano group $(5\text{-R-2-furyl})_2Cu(CN)Li_2$ (R = H [227, 228], R = Me_3Si [228]) were synthesized by the reaction of cuprous cyanide with two equivalents of 2-furyllithium [227, 228]. In the reaction of the lithium derivatives of 2,3-dihydrofuran with various cyanocuprates the products from opening of the dihydrofuran ring were obtained [164, 229].



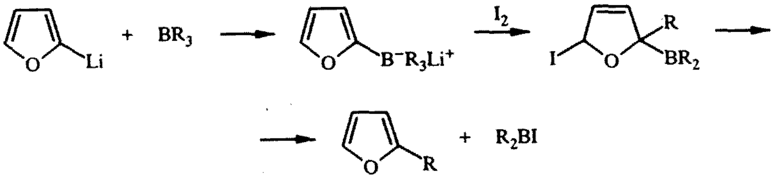
Methods for the production of furylzinc [54, 230, 231] and di(2-furyl)zinc [232] halides are given without sufficient detail. They were synthesized by the treatment of the lithium derivatives of furan with zinc chloride or bromide.



Attempts to obtain acylfurfurals from 5-lithio-2-diethoxymethylfuran by the action of acid chlorides did not give positive results [51]. If, however, the lithium derivative was first treated with an ether solution of cadmium iodide, the organocadmium compound was formed, and this was acylated easily and with a good yield.

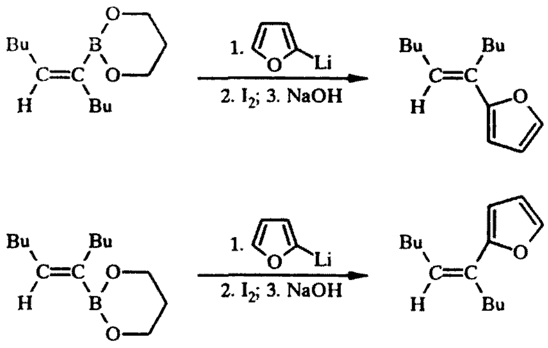


Organolithium compounds have found use in the synthesis of organic derivatives of boron, which are in turn used in further chemical transformations [119, 233-239]. The reaction of 2-furyllithium with trialkylboranes was investigated [233, 234]. The obtained alkylborate at-complexes are fairly stable at temperatures below 0°C. They react readily with iodine and form alkylfurans. The product yields in this method exceed 90%.

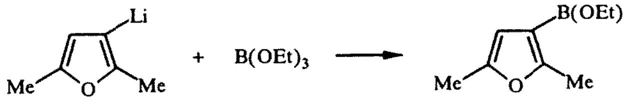


R = $n\text{-}C_6H_{13}$, *s*-Bu, *i*-Bu

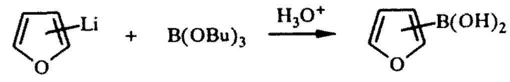
The at-complexes of E- and Z-5-(5-decenyl)-1,3,2-dioxaborinanes with 2-furyllithium were used for stereospecific synthesis. The iodination of these complexes in methanol at −78°C followed by deiodoboronation with alkali gave 2-furyldecenes with high yields (78-80%) and with stereochemical purity.



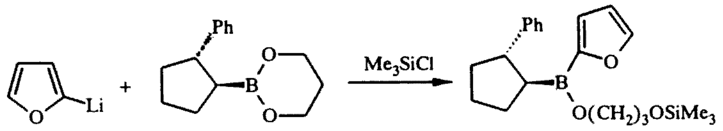
With triethyl [119] and tributyl [236, 237] borates and also with optically active boronates [238] the lithium derivatives of furan cleave the B−O bond and form the boronates and borinates respectively.



[119]

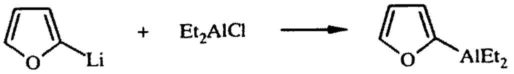


[236]

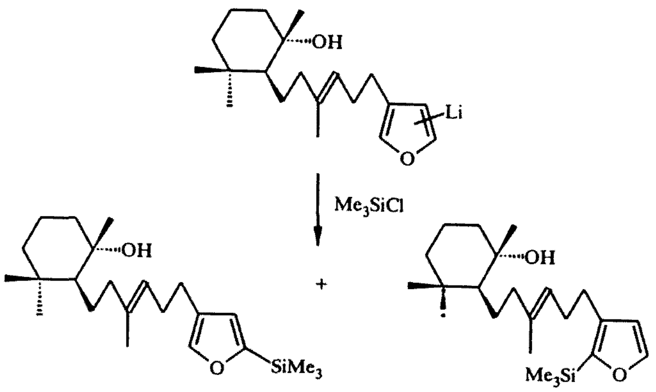


[238]

There are data on the production of diethyl(2-furyl)aluminum from 2-furyllithium and diethylaluminum chloride [240].



Of the heteroorganic derivatives of group IVB the most widely studied are the reactions of chlorosilanes with organolithium compounds. By the silylation of lithiofurans with trimethylchlorosilane together with deuteration with D_2O and carbonylation with carbon dioxide it is possible to determine the direction of metallation from the position of the trimethylsilyl group in the ring [52-54, 57, 59-62, 64, 71-73, 76, 80, 89, 128, 148, 149, 152-154].



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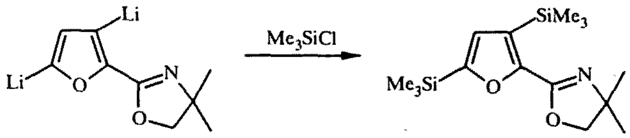
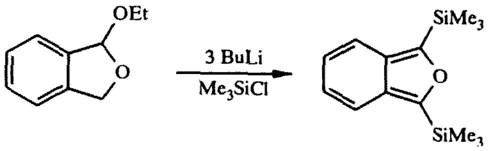
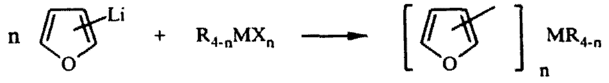


[102]

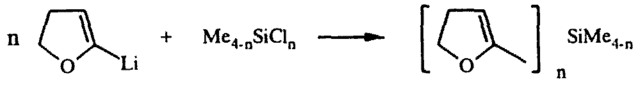


[154]

The lithium method of synthesis is the most general for the production of mono-, di-, and tetrafurylsilanes and the corresponding germanes and stannanes [15-17, 19, 24, 241-247].

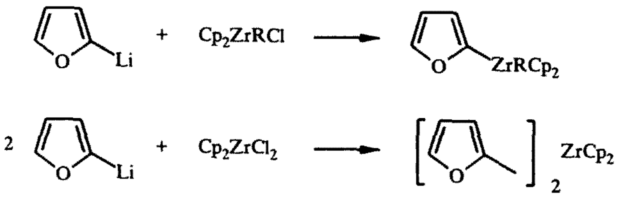


M = Si, Ge, Sn; n = 1...4; R = Me, Et, Ph

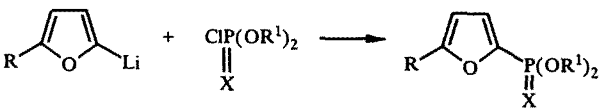


This method was used for the synthesis not only of the alkyl- and arylsilyl derivatives but also of compounds containing hydrogen [31, 160, 248], halogen [242, 249], and vinyl [250, 251], chloromethyl [248, 250], or ethoxy [18, 252] groups in addition to the furan ring at the group IVB element and also furfuryltriorganosilanes [15, 18, 253], and 2,5-disilyl-, 2,5-silylgermyl-, and 2,5-germylstannylfurans [48, 254]. Furylsilanes and germanes containing acetal [128, 255, 256], oxime [59], carboxyl [62], tetramethyldiamidophosphate [64], pyridine [53, 61], and certain other functional groups in the ring were obtained in a similar way.

A few compounds with a $C_{furyl}-Zr$ bond were synthesized by the reaction of 2-furyllithium with the halogen derivatives of zirconocene [257].

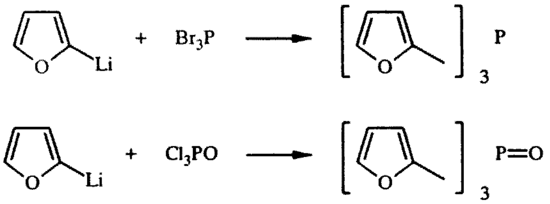


A series of phosphorus compounds were also synthesized by the reaction of 5-substituted 2-lithiofurans with various chlorine derivatives of phosphorus [17, 20, 258, 259].

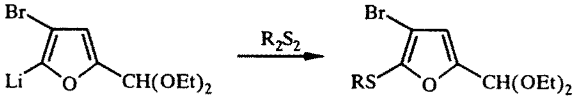


R = H, Me [20, 258], R_3Si [17]; R^1 = Me, Et; X = O, S

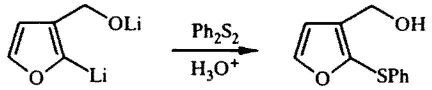
According to data in [20], the substitution of one or two alkoxy groups was observed in addition to substitution of the chlorine atom. Tri(2-furyl)phosphine was obtained in the reaction of 2-furyllithium with phosphorus tribromide, while its oxide was obtained in the reaction with phosphorus oxychloride [259].



As already mentioned above, certain sulfur-containing furan compounds are easily formed during the action of sulfur or sulfur trioxide on the lithium derivatives of furan. Furyl alkyl [36, 57, 102, 114, 135] and furyl phenyl [64, 72, 73] sulfides can also be obtained from dialkyl and diphenyl disulfides.

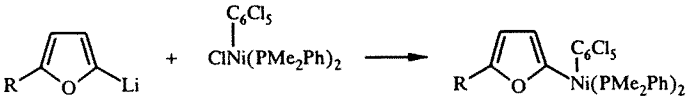


[135]

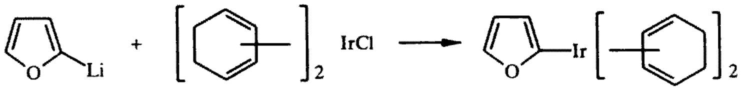


[72, 73]

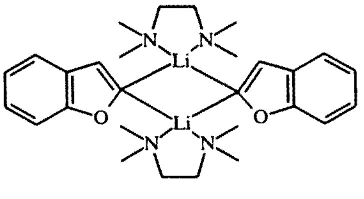
Compounds with $C_{furyl}-Ni$ and $C_{furyl}-Ir$ bonds were synthesized from trans-chloro(pentachlorophenyl)bis(dimethylphenylphosphine)nickel [260] and chloro[bis(η^4-1,3-cyclohexadiene)]iridium [261] at 0°C with yields of 58 and 50% respectively according to the following schemes:



R = H, Me



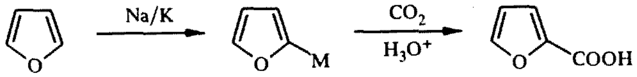
Investigations into the physicochemical properties of the furan derivatives of lithium are extremely limited on account of their high reactivity. The molecular structure of the tetramethylethylenediamine complex of 2-benzofuryllithium was investigated by x-ray crystallographic analysis. In the crystalline state the complex is dimeric, the two benzofuryl rings are attached to the two lithium atoms, and the tetramethylethylenediamine is a ligand at the metal atoms. The angle formed by the benzofuryl rings and the Li–Li vector is significant (39.1°), and this leads to a short Li–O distance (2.09 Å). The lengths of the Li–C bonds are 2.39 and 2.33 Å respectively [262].



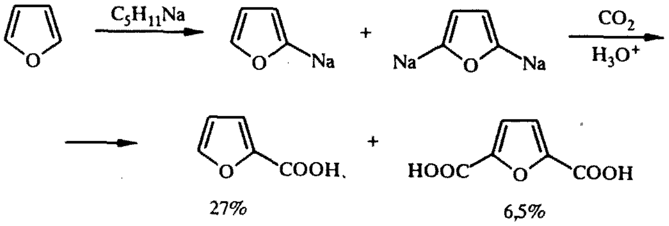
2. FURAN DERIVATIVES OF SODIUM, POTASSIUM, AND COPPER

Whereas the methods for the synthesis of organolithium compounds have been studied well, the organometallic derivatives of other elements of group I with a $C_{furyl}-M$ bond have been studied to a lesser degree.

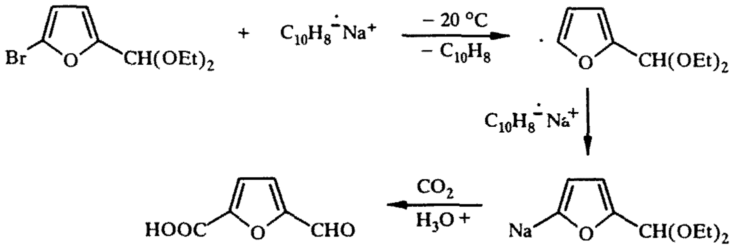
Sodium and potassium proved completely unreactive toward furan, methylfuran [263], and chloro- and bromofuran [264]. With liquid sodium–potassium alloy, however, furan forms 2-furylsodium and 2-furylpotassium [263].



Furan is also metallated by ethyl-, phenyl-, and triphenylsodium, but the yield of 2-furancarboxylic acid, obtained in the reaction of 2-furylsodium with carbon dioxide, is small (15-58%) [263]. In the reaction of furan with pentylsodium a small amount of 2,5-disodiofuran is formed in addition to the monosodium derivative [265].

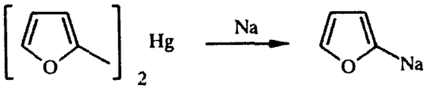


5-Sodio-2-diethoxymethylfuran is formed as a result of the reaction of 5-bromo-2-diethoxymethylfuran with naphthylsodium at −20°C in THF. Since naphthylsodium can only give one electron, located in the lowest antibonding π orbital, in the opinion of the authors the reaction takes place through two one-electron transfers [266].

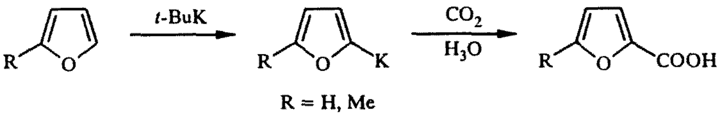


The sodium derivative is formed during the action of phenylsodium on the initial 5-bromo-2-diethoxymethylfuran, but this reaction is complicated by side processes.

2-Furylsodium was also obtained by the transmetallation of di(2-furyl)mercury with metallic sodium [263].

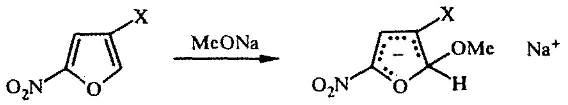


The metallation of furan and sylvan by tert-butylpotassium takes place at −75 and −60°C [267]. However, to judge from the yields of the corresponding furancarboxylic acids (17-28%) the yields of 2-furylpotassium and 5-methyl-2-furylpotassium are small.



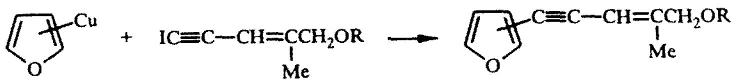
As mentioned above [103], the dipotassium derivative of furan is, possibly, formed from 2,5-dilithiofuran by the action of potassium tert-butoxide.

The reaction of 2-nitrofuran and its derivatives with sodium methoxide in methanol at 25°C was studied by NMR spectroscopy [268, 269]. The obtained Meisenheimer products have the following structure:

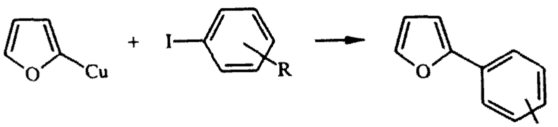


The synthesis of the organocopper derivatives of furan with a C_{furyl}–copper bond was discussed earlier during analysis of the chemical transformations of organolithium compounds [5, 218-228], and only the chemical properties will be summarized in this section.

2-Furyl- and 3-furylcopper react readily with iodoalkynes [218, 222] and aryl iodides [219, 220, 270]. With 1,3,5-trinitrobenzene at −10-0°C 2-furylcopper forms a Meisenheimer salt [221].

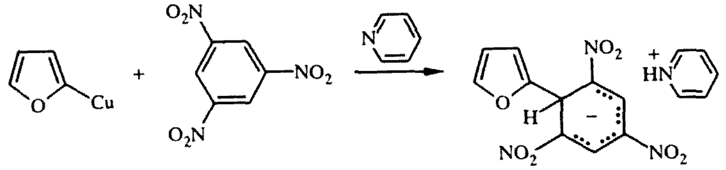


[218, 222]



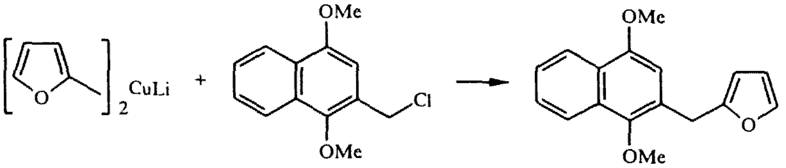
[219, 220, 270]

R = 2-COOMe, 4-OMe, 4-OSiMe$_3$

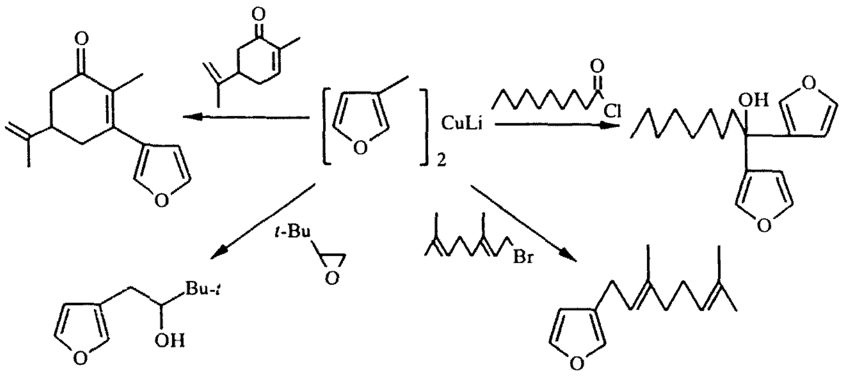


[221]

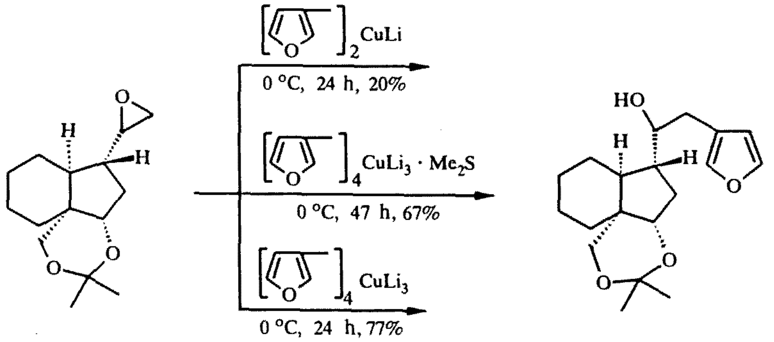
Lithium di(2-furyl)cuprate [5] and di(3-furyl)cuprate [224, 271, 272] enter into reactions with electrophiles.



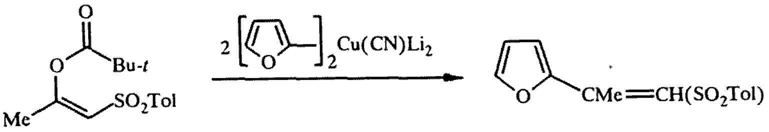
[5]



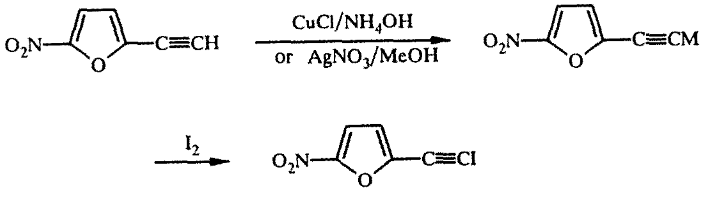
Its complexes with 3-furyllithium and dimethyl sulfide have higher reactivity than lithium 3-furylcuprate in reactions with certain oxiranes [225, 226].



Dilithium 2-furylcyanocuprate reacts with vinyl esters containing a sulfonyl substituent in the vinyl group. Cleavage of the C−O bond takes place after 10-30 min at −78°C in THF. A 1:40 mixture of the Z- and E-vinyl sulfones is formed as a result of the reaction [227].



In addition to the compounds with a $C_{furyl}-Cu$ bond, derivatives in which the metal was not directly attached to the furan ring were also obtained. 2-Ethynyl-5-nitrofuran reacts with an ammoniacal solution of copper chloride with the formation of the corresponding furylacetylide. Silver furylacetylide was synthesized similarly by the action of a solution of silver nitrate in methanol. Treatment of the acetylides with iodine gave the corresponding iodides [273].



M = Cu, Ag

Other investigated organometallic derivatives of group I elements are the alcoholates of furfuryl alcohols [274, 275] or the salts of furancarboxylic acids [276-279]. The compounds were obtained by traditional methods of synthesis and were used in further transformations [224-277], while the rubidium salts [278, 279] were investigated by x-ray crystallographic analysis.

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