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WITTIG REARRANGEMENT OF ALLYL FURFURYL AND ALLYL THIENYL ETHERS AND SULFIDES AND THEIR BENZO-DERIVATIVES

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Treatment of allyl furfuryl ethers and sulfides with butyllithium results in metallation at the free α-position of the heterocycle, with partial Wittig rearrangement to the isomeric alcohols and sulfides and ring opening. With the benzo-derivatives, Wittig rearrangement and ring opening takes place.

The possibility of using the Wittig rearrangement in the synthesis of unsaturated hydroxy- and mercapto-derivatives of the aromatic series has demonstrated in the treatment of benzyl allyl ethers and sulfides with strong bases [1, 2]. The extension of this reaction to furans and thiophens provides a convenient method for the functionalization of these systems.

For this purpose, we examined the reactions of some allyl furfuryl and allyl thienyl ethers and sulfides, together with their benzo-derivatives, with the strong base butyllithium, which is widely employed for the generation of anionoid species.

It would be expected from the results of basic deuterium exchange experiments carried out with some of the starting compounds as a preliminary, (Table 1), that deprotonation on treatment with bases would take place for the most part at the methylene group between the heterocycle and the hetero-atom, and at the free α-position of the heterocyclic system.

The principal pathway in the reactions of 2-allyloxy-methyl- and 2-allylthiomethylbenzofurans (I) and (II) with butyllithium is metallation at the free 5-position of the furan ring, giving following silylation the 5-trimethylsilylfurans (III) and (VII). Additionally, deprotonation takes place at the methylene group located between the heterocycle and the hetero-

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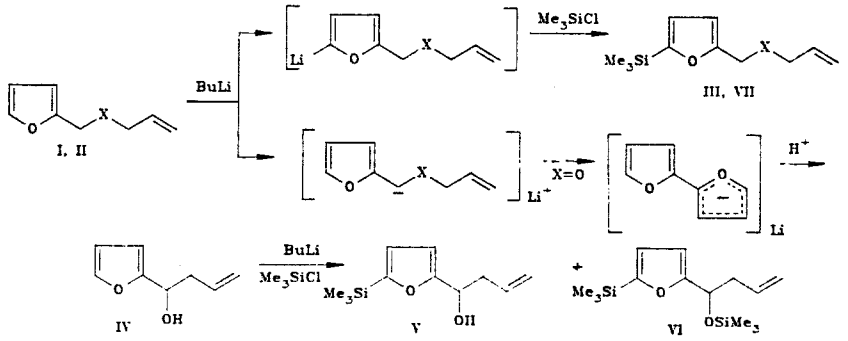
TABLE 1. Deuterium Exchange in Furfuryl and Benzofurfuryl Allyl Ethers and Sulfides

Compound	T, °C	Deuterium exchange rate constants in different positions of the substrates			
		$K \cdot 10^5$ sec^{-1}			
		$-CH_2X-$	$-XCH_2-$	α-H*	β-H*
I	64	1.0	0.4	1.5	0.3
	85	1.9	0.7	1.6	0.5
	130	9.8	2.3	6.9	2.0
II	64	1.1	0.6	1.2	0.5
	85	2.8	0.8	3.7	1.3
	110	6.0	1.2	3.6	1.9
	130	8.3	1.5	5.7	3.2
		$K \cdot 10^6$ sec^{-1}			
		$-CH_2X-$	$-XCH_2$		β-H
XIX	110	4.9	No exchange		2.0
	130	6.2			2.2
3-Methyl-2-allyloxymethylbenzothiophen	110	2.0	0.3		No exchange
	130	4.6	1.2		

*Hydrogen atoms in the heterocycle.

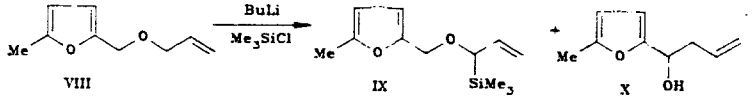
atom. The intermediate formed from the ether (I) gives the Wittig rearrangement products (IV-VI), together with ring opening, but the sulfide (II) undergoes ring opening only:



I, III X=O; II, VII X=S

An increase in the reaction temperature above −5°C usually results in considerable reinification as a result of the preferential opening of the heterocycle. This complex reaction sequence for (I) and (II) results in low yields of the Wittig rearrangement products (no greater than 36%, Table 2), and the selectivity is poor.

When 2-allyloxymethyl-5-methylfuran reacts with butyllithium (VIII), the selectivity of the [2,3]-sigmatropic rearrangement is greater as a result of the exclusion of metallation at the second α-position of the furan ring. From the reaction mixture obtained by the successive treatment of the ether (VIII) with butyllithium and trimethylchlorosilane there were isolated (IX) and (X), the structures of which indicate the possibility of deprotonation of both methylene groups in the side chain of the ether (VIII).

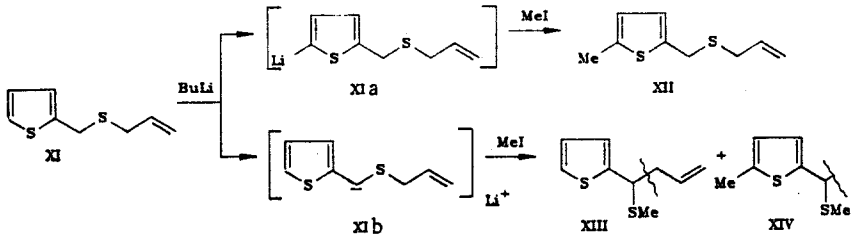


The reaction of 2-allylthiomethylthiophen (XI) with butyllithium is similar to that of the furan compound, metallation taking place at the free α-position of the heterocycle and the methylene group between the heterocycle and the surfur atom. The addition of an electrophile (methyl iodide) to the mixture results in the formation of a mixture of compounds (XII-XIV):

TABLE 2. Reactions of Furfuryl and Thenyl Allyl Ethers and Sulfides with Butyllithium in Diethyl Ether

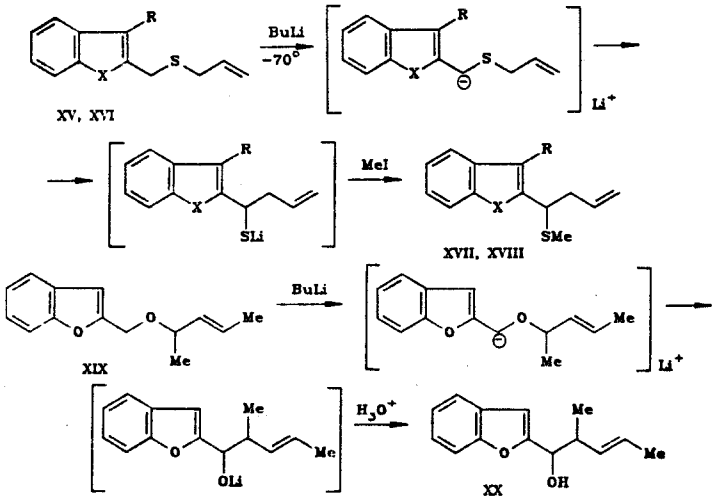
Starting compound	T_{expt}, °C	Reaction time, min	Composition of reaction mixture, %			
			products of [2,3]-sigmatropic rearrangement	2,5-disubstituted furans (thiophens)	products of cleavage of heterocycle	starting ether (sulfide)
I	−5	5	10	40	12	38
	−20	5	10	45	5	40
	−30	90	—	—	19	81
VIII	−5	5	10	15*	5	70
II	−5	5	—	23*	10	67
	−30	150	—	—	22	78
XI	−30	150	—	—	14	86
	−10	40	36	24	—	40

*Products of substitution in the allyl group of the original ether and sulfide.



The formation of the sulfide (XII) is due to metallation of the free 5-position in the thiophen ring in the sulfide (XI), sulfide (XIII) resulting from [2,3]-sigmatropic rearrangement of the anion (XIb), formed by deprotonation of the α-methylene group, and (XIV) from the occurrence of both of these reactions. Successive treatment of 2-allylthiomethylthiophen (XI) with butyllithium and methyl iodide failed to give compounds with a methyl group in the allyl chain, in good agreement with the deuterium exchange data for (XI), according to which the hydrogen atoms in the allyl group are less labile than those of the α-methylene group adjacent to the heterocycle.

The presence of an annelated benzene ring in benzofurfuryl and benzothienyl allyl ethers and sulfides increases their stability toward strong bases. In the case of (XV), (XVI), and (XIX) the reaction with butyllithium (Table 3) is much more selective than with their noncondensed precursors. The principal products of the reaction of the benzo-compounds (XV), (XVI), and (XIX) with butyllithium are the isomeric alcohols (XX) (from XIX) and thiols [isolated as the more stable sulfides (XVII) and (XVIII)], formed by [2,3]-sigmatropic rearrangement of the corresponding anions:



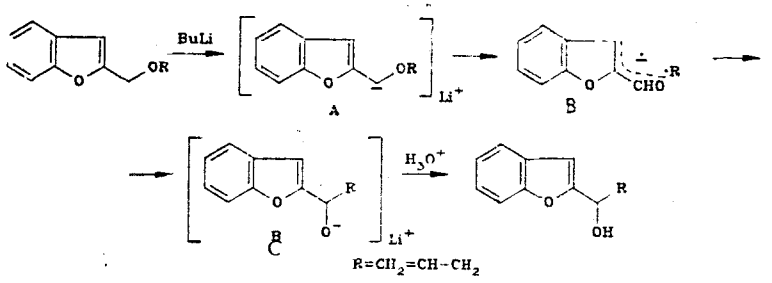
XV, XVII X=O, R=H; XVI, XVIII X=S, R=Me

TABLE 3. Reaction of Benzofurfuryl and Benzothienyl Allyl Ethers and Sulfides with Butyllithium in Diethyl Ether (Substrate—Base Ratio, 1:1.2)

Starting compound	Reaction time, min	T_{expt}, °C	Compositon of reaction mixture, %		
			[2,3]-sigmatropic rearrangment product	products of cleavage of heterocycle	starting ether (sulfide)
XV	18	−55	22	28	50
	35	−70	32	—	68
XVI	30	−70	37	—	63
XIX	40	−35	10	10	80
	60	−55	21	5	74
	60	−65	15	5	80

Ring opening products were obtained from (XV), (XVI), and (XIX) in lower yields than from the ethers (I), (II), and (VIII), and no metallation of the heterocyclic system was observed.

From the composition of the [2,3]-sigmatropic rearrangement products of 2-(2-butenyloxymethyl)benzofuran on treatment with butyllithium, it has been suggested [3] that the reaction proceeds in parallel by concerted and stepwise mechanisms. An examination of the products of the reaction of 2-allyloxymethylbenzofuran with butyllithium by the CIDNP method demonstrated the absence in the PMR spectrum of the reaction mixture of signals for polarized products, which does not however exclude the possibility of a stepwise mechanism involving radicals. The absence of signals for polarized products could be due to rapid recombination of the initial cell pair B without escape of the radicals formed from the solvent cell. If such escape does take place, however, the radicals could undergo secondary recombination to form the polarized reaction products C:



The absence of CIDNP signals for polarized products in the reactions of benzofurfuryl ethers could also be due to the short relaxation times of such large aggregated species as lithium alkoxides formed in the Wittig rearrangement [4].

EXPERIMENTAL

PMR spectra were obtained on a Varian T-60 spectrometer in CCl_4, internal standard TMS, and IR spectra in films on an IKS-22 instrument. GC-MS analyses were carried out on a Finnigan MAT 112S, ionizing energy 80 eV, with a glass capillary column (l = 25 m, d = 0.25 mm), OV-101, temperature 120-180°C.

Deuterium—hydrogen exchange was carried out as described in [5], by treatment with a solution of sodium methoxide in deuterated methanol CH_3OD and CD_3OD (0.25-0.3 mole/liter), in sealed ampuls under argon. The solutions of sodium methoxide in deuterated methanol were prepared by adding freshly-cut sodium to the deuterated alcohol under argon, and standardized by titration with hydrochloric acid (0.1 mole/liter). The reaction mixtures were prepared using a ratio of substrate—internal standard (toluene)—sodium methoxide of 1:1:0.06. The deuterium exchange products were analyzed by PMR using a Tesla instrument. The percentage deuterium (or protium) content in various positions of the molecule were calculated by comparing the values of the integral intensities of the appropriate resonance signals with those of standard mixtures in which H = 100% and D = 0%. The rate constants for deuterium exchange in the different positions of the molecules were calculated by a first-order equation [6].

2-Allyloxymethylfuran (I) was obtained by reacting equimolar amounts of allyl bromide and sodium furfuryl oxide in an excess of furfuryl alcohol at 100°C. Yield 75%, bp 168-169°C,

n_D^{20} 1.4749. PMR spectrum 4.0 (2H, d, CH_2), 4.5 ($_2$H, s, CH_2), 5.5 (3H, m, $-CH=CH_2$), 6.3 (2H, m, fur.), 7.3 ppm (1H, d, fur.). Calculated: C 62.1, H 6.4%. $C_8H_{10}O_2$. Found: C 62.3, H 6.5%.

2-Allyloxymethyl-5-methylfuran (VIII) was obtained by the Kishner reduction of the intermediate 2-allyloxymethyl-5-formylfuran, synthesized by formylation of the ether (I) [yield 62%, bp 190-192°C (120 mm), n_D^{20} 1.5190, IR spectrum: 1700 (C=O), 1640 cm^{-1} (C=C)], yield 65%, bp 118-119°C (140 mm), n_D^{20} 1.4720. PMR spectrum: 2.3 (3H, s, CH_3), 3.9 (2H, d, CH_2), 4.3 (2H, s, CH_2), 4.9-5.8 (3H, m, $CH=CH_2$), 6.0 ppm (2H, d, fur.). Mass spectrum, m/z: 152 (M^+).

2-Allylthiomethylfuran (II) was obtained as described in [7] by the reaction of furfuryl mercaptan with allyl bromide in aqueous solution. Yield 74%, bp 196-198°C, n_D^{20} 1.5354. PMR spectrum: 3.0 (2H, d, CH_2), 3.5 (2H, s, CH_2), 5.3 (3H, m, $CH=CH_2$), 6.1 (2H, m, thiophen), 7.2 ppm (1H, m, thiophen). Mass spectrum, m/z: 154 (M^+). Calculated: C 62.4, H 6,5, S 20.8. $C_8H_{10}OS$. Found: C 62.3, H 6.5, S 20.8.

2-Allylthiomethylthiophen (XI) was obtained as for 2-allylthiomethylfuran, from 2-chloromethylthiophen. Yield 52%, bp 118-119°C (13 mm), n_D^{20} 1.5237. PMR spectrum: 3.0 (2H, d, CH_2), 3.8 (2H, s, CH_2), 4.8-5.8 (3H, m, $CH=CH_2$), 6.7-7.2 ppm (3H, m, thiophen). Mass spectrum m/z: 170 (M^+). Calculated: C 56.7, H 5.9, S 38.0%. $C_8H_{10}S_2$. Found: C 56.5, H 5.9, S 37.6%.

2-Allylthiomethylbenzofuran (XV) was synthesized by the reaction between potassium allylmercaptide and 2-chloromethylbenzofuran as described in [7], in aqueous solution at 20°C. Yield 32%, mp 40-42°C. PMR spectrum: 3.0 (2H, d, CH_2), 3.6 (2H, s, CH_2), 5.2 (3H, m, $CH=CH_2$), 6.4 (1H, s, 3-H), 7.3 ppm (4H, m, arom.). Mass spectrum, m/z: 204 (M^+).

2-Allylthiomethyl-3-methylbenzothiophen (XVI) was obtained as for 2-allylthiomethylbenzofuran, from 2-chloromethyl-3-methylbenzothiophen. Yield 40%, mp 47-48°C. PMR spectrum: 2.3 (3H, s, CH_3), 3.1 (2H, d, CH_2), 3.8 (2H, s, CH_2), 4.8-5.8 (3H, m, $-CH=CH_2$), 7.0-7.8 ppm (4H, m, arom.). Mass spectrum, m/z: 234 (M^+).

2-(1-Methyl-2-butenyloxymethyl)benzofuran (XIX) was prepared from 2-chloromethylbenzofuran and pent-2-en-4-ol. Yield 30%, bp 90-93°C (2 mm), n_D^{20} 1.5385. PMR spectrum: 1.3 (3H, d, CH_3), 1.8 (3H, d, CH_3), 4.5 (1H, m, CH), 4.7 (2H, s, CH_2), 5.2-5.8 (2H, m, $CH=CH_2$), 6.6 (1H, s, 3-H), 7.0-7.5 ppm (4H, m, arom.). Mass spectrum, m/z: 216 (M^+).

The reactions between the ethers or sulfides and butyllithium were carried out under argon in dry ether. The ratio of substrate—butyllithium varied from 1:2 to 1:1.2. In a flask cooled to −60°C was placed the calculated amount of a titrated solution of butyllithium in dry ether (0.5-0.6 N), and a solution of 0.01 mole of the substrate in 5 ml of dry ether was added with stirring. The mixture was kept at the required temperature, followed by the addition of trimethylchlorosilane or methyl iodide as required, and the mixture stirred for a further 30 min with continued cooling. A saturated solution of sodium chloride was then added, and the ether solution separated, dried, and analyzed.

The purities of the starting materials and the course of the reactions were followed by TLC on Silufol UV-254 plates, and the isolation and purification of the products on plates with an unbound layer of silica gel 40/100 μm, the eluents used being a mixture of hexane, carbon tetrachloride and ether (47:43:10) and benzene—chloroform (7:3).

The following compounds were isolated from the reaction mixtures:

4-(2-Furyl)but-2-en-4-ol (IV). PMR spectrum: 2.5-2.7 (2H, m, CH_2), 3.0 (1H, s, OH), 4.5 (1H, t, CH), 5.3-5.7 (3H, m, $CH=CH_2$), 6.2 (2H, m, fur.), 7.2 ppm (1H, m, fur.). IR spectrum: 3400 (OH), 1650 cm^{-1} (C=C). Mass spectrum, m/z: 138 (M^+).

5-Trimethylsilyl-2-allyloxymethylfuran (III). PMR spectrum: 0.3 [9H, s, $(CH_3)_3Si$], 4.1 (2H, d, CH_2), 4.5 (2H, s, CH_2), 5.3 (2H, d, $=CH_2$), 5.8 (1H, m, $=CH-$), 6.2 (1H, d, fur.), 6.6 ppm (1H, d, fur.). IR spectrum: 1640 (C=C), 755 cm^{-1} (SiOOC). Mass spectrum, m/z: 210 (M^+).

4-(5-Trimethylsilyl-2-furyl)but-2-en-4-ol (V). PMR spectrum: 0.5 [9H, s, $(CH_3)_3Si$], 2.5 (2H, m, CH_2), 3.2 (1H, s, OH), 4.7 (1H, m, CH), 5.0-5.7 (3H, m, $CH=CH_2$), 6.2 ppm (2H, d, fur.). IR spectrum: 3400 (OH), 1650 (C=C), 785 cm^{-1} (Si—C). Mass spectrum, m/z: 210 (M^+).

5-Trimethylsilyl-2-allylthiomethylfuran (VII). PMR spectrum: 0.3 [9H, s, $(CH_3)_3Si$], 4.4-4.5 (2H, s, CH_2), 6.2 (1H, d, fur.), 6.4 (1H, d, fur.). IR spectrum: 1645 (C=C), 780 cm^{-1} (Si—C). Mass spectrum, m/z: 255 (M^+).

3-Trimethylsilyl-5-(2-methyl-5-furyl)-4-oxapent-1-ene (IX). PMR spectrum: 0.4 [9H, s, $(CH_3)_3Si$], 1.8 (3H, s, CH_3), 3.9 (1H, d, CH), 4.5 (2H, s, CH_2), 5.8 ppm (2H, m, fur.). IR spectrum: 1645 (C=C), 780 cm^{-1} (Si–C). Mass spectrum, m/z: 233 (M^+).

4-(2-Methyl-5-furyl)but-2-en-4-ol (X). PMR spectrum: 1.7 (3H, s, CH_3), 2.7 (2H, m, CH_2), 3.0 (1H, s, OH), 4.6 (1H, t, CH), 5.2-5.8 (3H, m, $CH=CH_2$), 6.3 ppm (2H, m, fur.). IR spectrum: 3200 (OH), 1640 cm^{-1} (C=C). Mass spectrum, m/z: 152 (M^+).

2-Allylthiomethyl-5-methylthiophen (XII). PMR spectrum: 1.2 (3H, s, CH_3), 2.8 (2H, d, CH_2), 3.8 (2H, s, CH_2), 5.0-6.0 (3H, m, $CH=CH_2$), 6.9-7.2 ppm (3H, m, thiophen). IR spectrum: 1645 cm^{-1} (C=C). Mass spectrum, m/z: 184 (M^+).

4-Methylthio-4-(2-thienyl)but-1-ene (XIII). PMR spectrum: 2.0 (3H, s, CH_3S), 3.0 (2H, m, CH_2), 4.0 (1H, t, CH), 4.7-5.5 (3H, m, $CH=CH_2$), 6.7-7.3 ppm (3H, m, thiophen). IR spectrum: 1645 cm^{-1} (C=C). Mass spectrum, m/z: 184 (M^+).

4-Methylthio-4-(2-methyl-5-thienyl)but-1-ene (XIV). PMR spectrum: 1.3 (3H, s, CH_3), 2.0 (3H, s, CH_3S), 3.0 (2H, m, CH_2), 3.8 (1H, t, CH), 4.8-5.8 (3H, m, $CH=CH_2$), 6.8 ppm (2H, m, thiophen). IR spectrum: 1640 cm^{-1} (C=C). Mass spectrum, m/z: 198 (M^+).

4-Methylthio-4-(2-benzofuryl)but-1-ene (XVII). PMR spectrum: 1.2 (3H, s, CH_3), 3.0 (2H, m, CH_2), 3.8 (1H, d, CH), 4.8-5.2 (3H, m, $CH=CH_2$), 6.7 (1H, s, fur.), 7.2-7.6 ppm (4H, m, arom.). IR spectrum: 1645 cm^{-1} (C=C). Mass spectrum, m/z: 218 (M^+).

4-Methylthio-4-(3-methyl-2-benzothienyl)but-1-ene (XVIII). PMR spectrum: 2.8 (3H, s, CH_3), 2.9 (2H, m, CH_2), 3.4 (3H, s, CH_3), 3.5 (1H, m, CH), 4.6-5.0 (3H, m, $CH=CH_2$), 7.0-7.5 ppm (4H, m, arom.). IR spectrum: 1645 cm^{-1} (C=C).

4-(2-Benzofuryl-3-methylpent-2-en-4-ol (XX). PMR spectrum: 1.5 (3H, d, CH_3), 1.8 (3H, d, CH_3), 3.1 (1H, s, OH), 3.9 (1H, m, CH), 4.6 (1H, m, CH), 5.0-5.8 (2H, m, J = 12 Hz, $CH=CH_2$), 6.5 (1H, s, fur.), 7.0-7.5 ppm (4H, m, arom.). IR spectrum: 3400-3440 (OH), 1670 cm^{-1} (C=C).

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