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MODIFICATION OF THE NICKL REACTION. A GENERAL SYNTHETIC APPROACH TO 2-VINYL-2,3-DIHYDROBENZOFURANS

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Abstract—The annelation reaction of metal phenolates **1** with 1,4-dibromo-2-butenes **2** to give 2-vinyl-2,3-dihydrobenzofuran derivatives **3** (Nickl reaction) was critically examined and markedly improved. Use of lithium phenolates, instead of sodium phenolates, as substrates and toluene, instead of methanol, as reaction medium, caused the yield of annelated compounds to rise dramatically. The relevance of this modified route to the synthesis of Euparinoid 2,3-dihydrobenzofurans and their synthetic analogues was emphasized.

2,3-Dihydrobenzofurans occur widely in nature and many 2-isopropenyl derivatives have high toxic activities which render them of considerable interest.[1]

Among the synthetic approaches to these compounds, the one-step heteroannelation of sodium phenolates (**1a**, M = Na) with 1,4-dibromo-2-butenes **2**, initially developed by Nickl, represents in principle the most straightforward route. This procedure, however, in spite of its simplicity, often fails to offer very much in the way of yield and selectivity, a consequence of competitive oxygen alkylation processes. Therefore, only scant isolated examples of synthetic application are reported.[3,4]

As part of our continuing programme in the selective alkylation and heteroannelation processes of metal phenolates with electrophilic reagent[5] we have been engaged in reinvestigating the condensation of metal phenolates **1** with 1,4-dibromo-2-butenes **2** with a view to obtaining a practically viable route of large applicability to 2-vinyl-2,3-dihydrobenzofurans **3**.

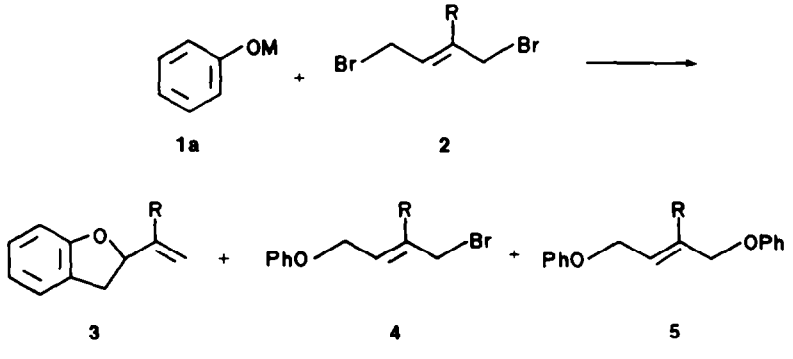
This paper deals, in particular, with a substantial modification of the Nickl procedure and its application to the synthesis of a variety of synthetic and naturally occurring 2-vinyl- and 2-isopropenyl-2,3-dihydrobenzofuran derivatives.

Modification experiments

We first investigated the reaction between sodium phenolate (**1a**, M = Na) in methanol with *trans*-1,4-dibromo-2-butene (**2a**) according to the original Nickl procedure (see Table 1, run 1). Accurate gas chromatographic analyses (SE 52 pyrex capillary column) of compounds produced showed no traces of the expected 2-vinyl-2,3-dihydrobenzofuran **3a**, 1-bromo-4-phenoxy-2-butene **4a** and 1,4-diphenoxy-2-butene **5a** being solely produced in 36 and 52% yield, respectively. Similarly, the reaction of sodium phenolate (**1a**, M = Na) in methanol with *trans*-1,4-dibromo-2-methyl-2-butene **2b** only gave rise to the oxygen alkylated compounds **4b** and **5b** (37 and 52% yield respectively), although a 43% yield of the benzofuran **3b** was recently reported by this method.[4,6]

Since the role of both solvent and phenolate metal counter-ion is well known to be crucial in directing the alkylation processes of ambident phenolate anions,[7] a study on the influence of these parameters on the course of the reaction between metal phenolates **1a** and *trans*-1,4-dibromo-2-butene **2a** was undertaken.

Table 1 summarizes some significant experiments under varied conditions. After some abortive attempts, our goal was reached when a slurry of lithium phenolate (**1a**, M = Li) in toluene (run 4) was refluxed for 22 h with an



2, 3, 4, 5a: R = H
b: R = CH_3

Scheme 1.

Table 1. Reactions of metal phenolates **1a** with *trans* 1, 4 - dibromo - 2 - butene **2a** under varied conditions

Run	Phenolate counter-ion	Solvent	Additive[a]	Conditions[b]	Appearance	Conversion[c] (%)	Product yield (%)[c] 3	4	5
1	Na	methanol	none	20°	homogeneous	90		36	52
2	Li	methanol	none	20°	homogeneous	86		33	46
3	Li	toluene	none	20°	heterogeneous		no reaction		
4	Li	toluene	none	reflux	heterogeneous	55	52	2	
5	Na	toluene	none	reflux	heterogeneous	52	34	8	8
6	K	toluene	none	reflux	heterogeneous	50	38	6	4
7	H	toluene	none	reflux	heterogeneous		no reaction		
8	Zn	toluene	none	reflux	heterogeneous	60[d]			
9	Al	toluene	none	reflux	heterogeneous		no reaction		
10	Li	decalin	none	110	heterogeneous	51	39		
11	Li	dioxane	none	reflux	homogeneous	83[d]			
12	Li	dimethyl-formamide	none	110	homogeneous	80[d]			
13	Li	toluene	Bu^tOLi	reflux	heterogeneous	73	45	10	14
14	Li	toluene	Li_2CO_3	reflux	heterogeneous	58	49	3	
15	Li	toluene	$(C_6H_{11})_2NLi$	reflux	heterogeneous	62	38	6	4

[a] 1.0 mol equiv.

[b] Reaction time = 22 h.

[c] Determined by GLC analyses (SE 52 Pyrex capillary column), based on total amounts of phenol charged.

[d] Very complex reaction mixture.

equimolar amount of *trans*-1,4-dibromo-2-butene **2a** yielding 2-vinyl-2,3-dihydrobenzofuran **3a** in 52% yield with a selectivity of about 95%. Also, using a heterogeneous slurry of potassium phenolate (**1a**, M = K) in toluene (run 6), **3a** was the predominant product (38% yield) accompanied by minor amounts of **4a** and **5a**.

Since, for 1 mol of **3a** produced 1 mol of hydrogen bromide is formally liberated, the overall phenol conversion was not higher than 50–55%, the remaining metal phenolate being transformed into unreactive phenol by the acid liberated.

So, in searching for an improved yield of **3a**, we examined some hydrogen bromide scavengers (runs 13–15), but our attempts, while often resulting in improved phenol conversion, failed with respect to selectivity.

These results suggested that at least two modifications could be essential in formulating an efficient procedure for the selective heteroannelation of metal phenolates with 1,4-dibromo-2-butenes, minimizing the competition of oxygen alkylation side-processes: (a) the use of a coordinating metal counter-ion on the phenolic substrate and (b) the use of an aprotic poorly donor reaction medium in heterogeneous conditions.

These objectives have been met by a method which utilizes lithium or potassium phenolates as substrates and toluene as reaction medium.

Synthetic scope

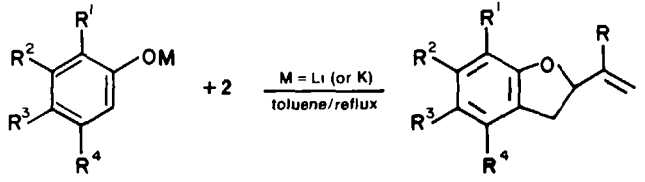
The synthetic potential of our modified procedure was evaluated using a variety of mono- and polyhydric lithium phenolates (**1**, M = Li) in reactions with *trans*-1,4-dibromo-2-butene **2a** and *trans*-1,4-dibromo-2-methyl-2-butene **2b**.

Lithium phenolates were generated quantitatively *in situ* by addition of 1.0 equiv. of *n*-butyllithium to a toluene solution of the appropriate phenol at room temperature or, in the case of phenols bearing butyllithium-sensitive substituents (*i.e.* acetyl or formyl-groups), by exchange with lithium *tert.* butoxide in toluene under azeotropic removal of the *tert.* butanol formed. Subsequent treatment of the lithium salts with 1.0 molar equiv. of the dibromide **2** produced a heterogeneous slurry which, after 20–30 h at 110°C, was quenched by addition of an excess of aqueous ammonium chloride solution. Conventional work-up and purification procedures (see Experimental section) afforded pure products **3a–p** in moderate-good yields as summarized in Table 2. In some instances, however, where polyhydric phenols are involved, potassium derivatives (**1**, M = K) could be the salts of choice as illustrated in Table 2, run 13.

Although the yield of pure isolated products ranged from 36–64%, the yield based on converted phenolic precursor are higher than 75% in all the reported examples, demonstrating the good substrate and positional selectivity of the present modified procedure.

Also, the reaction tolerates a wide variety of phenol substituents ranging from those which are electron-donating to those which are electron-withdrawing such as formyl- and acetyl-groups. Thus, for example, racemic tremetone **3k**,[4,8] fomannoxin **3l**,[9] hydroxytremetone **3m**,[10] and demethylremirol **3o** were readily synthesized in a single step reaction starting from the corresponding commercially available hydroxyacetophenone or hydroxybenzaldehyde precursors.

The structures **3a–p** were established by the elemental analyses and spectral data (Table 3), particularly by the characteristic resonances at about δ 2.9 and 3.3 in chloroform-*d* assignable to H-3 protons. Some of them (**3a**, **3b**, **3k** and **3l**) were also substantiated by comparison of ^{1}H-NMR and UV data with those reported.



1 3

With	R	R¹	R²	R³	R⁴
3a	H	H	H	H	H
3b	CH_3	H	H	H	H
3c	H	CH_3	H	CH_3	H
3d	H	H	$-OCH_2O-$		H
3e	H	H	OCH_3	H	H
3f	H	H	H	H	OCH_3
3g	H	H	H	OCH_3	H
3g	H	H	Cl	H	H

With	R	R¹	R²	R³	R⁴
3i	H	H	H	$-(CH=CH)_2-$	
3j	H	H	H	$COCH_3$	H
3k	CH_3	H	H	$COCH_3$	H
3l	CH_3	H	H	CHO	H
3m	CH_3	H	OH	$COCH_3$	H
3n	CH_3	H	H	$COCH_3$	OH
3o	CH_3	$COCH_3$	OH	H	OH
3p	CH_3	H	OH	$COCH_3$	OH

Scheme 2.

Table 2. Preparation of 2 - vinyl - 2,3 - dihydrobenzofurans 3a–p

Entry	Substrate[a]	Reagent	Product	Yield[b] (%)	B.p. [°C]/torr (n_D/°C)	Molecular formula (M.w.)[c] or Lit. Reference
1	phenol	2a	3a	48 (95)	116/20 (1.5493/18)	15, 16, 17
2	phenol	2b	3b	46 (90)	128/18 (1.5408/16)	4, 17
3	2,4-dimethyl-phenol	2a	3c	45 (90)	148-149/18 (1.5383/16)	$C_{12}H_{14}O$ (174.2)
4	2,3-methylene-dioxyphenol	2a	3d	50 (92)	m.p. 43°	$C_{11}H_{10}O_3$ (190.2)
5	3-methoxyphenol	2a	3e	30 (58)	149-152/18 (1.5486/16)	$C_{11}H_{12}O_2$ (176.2)
			3f	19 (36)	(1.5470/16)	$C_{11}H_{12}O_2$ (176.2)
6	4-methoxyphenol	2a	3g	50 (94)	142-144/18 (1.5483/15)	$C_{11}H_{12}O_2$ (176.2)
7	3-chlorophenol	2a	3h[d]	47 (91)	118/18 (1.5562/16)	$C_{10}H_9ClO$ (180.6)
8	2-naphthol	2a	3i	55 (96)	153-155/18 (1.6280/15)	$C_{14}H_{12}O$ (196.2)
9	4-acetylphenol	2a	3l	42 (87)	155/18 (1.5704/15)	$C_{12}H_{12}O_2$ (188.2)
10	4-acetylphenol	2b	3k	36 (82)	196/22 (1.5660/16)	4, 8
11	4-hydroxy-benzaldehyde	2b	3l	40 (77)	166/19 (1.5777/16)	9
12	resacetophenone	2b	3m	15 (36)	m.p. 45-48°	10
			3n	21 (50)	oil (1.5773/16)	$C_{13}H_{14}O_3$ (218.2)
13	phloroacetophenone[e]	2b	3o	21 (36)	m.p. 178-182°	2
			3p	23 (39)	m.p. 125-126°	$C_{13}H_{14}O_4$ (234.2)

[a] Lithium salts were used unless otherwise stated.
[b] Isolated yields based on total amount of starting phenol. Values in parentheses refer to yields based upon unrecovered starting phenol, not optimized.
[c] Correct elemental analyses obtained for all new compounds prepared.
[d] 10% of 2-vinyl-4-chloro-2,3-dihydrobenzofuran also formed (by GC-Ms analisis).
[e] The bis.potassium salt was used.

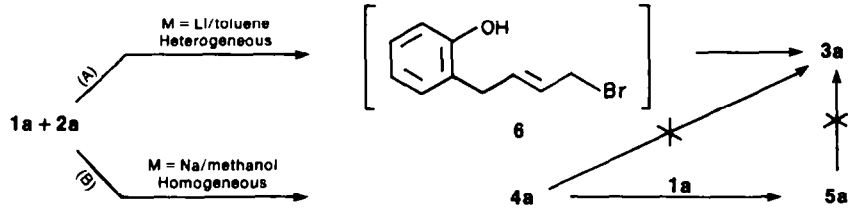
Mechanistic consideration

With regard to the mechanism of this annelation we propose a path such as the one outlined in Scheme 3 (path A), for the reaction of metal phenolates **1a** with *trans*-1,4-dibromo-2-butene **2a**. Instead, we have ruled out the intermediacy of the oxygen alkylated derivatives **4a** and **5a** (Path A) since all the attempts to convert them, under our reaction conditions, into benzofuran derivative **3a** were unsuccessfull.

The solvent and cation effect as well as the homogeneity-heterogeneity problems in the alkylation and allylation of ambident metal phenolates are well studied.[7] According to the fundamental works of Kornblum[11,12] it can be stated, *inter alia*, that: (a) "when the salts of phenols are alkylated in solution, only oxygen alkylation occurs" and (b) "the truly heterogeneous reaction gives exclusively carbon alkylation and the carbon alkylation thus achieved takes place solely at the *ortho* position". Thus, likely, using the Nickl experimental conditions (homogeneous solutions of sodium phenolates in methanol) the reaction enters almost exclusively into route B, yielding the oxygen alkylated compound **4a** and then **5a**, while conversely, using the heterogeneous lithium phenolate/toluene system of this study, predominant C-*ortho* alkylation occurs affording to the *ortho*-allylphenol intermediate **6** which under the reaction conditions is converted into **3a** easily and quantitatively presumably *via* a metal phenolate-promoted 5-Exo-Trig heteroannelation process.[13]

CONCLUSION

In summary, the results presented here, described a substantial modification of the Nickl heteroannelation of metal phenolates with 1,4-dibromo-2-butene derivatives



Scheme 3.

Table 3. Significant IR, UV, ^{1}H NMR and mass spectral data of compounds **3a–o**

Compound	IR [cm^{-1}]	UV (95% ethanol) ν_{max} [nm] (log ε)	^{1}H NMR ($CDCl_3$) δ [ppm]	Mass m/e (% relative abundance)
3a	1602,1488,1468, 1233,755	216(3.69), 278(3.41), 286(3.33)	2.89 (1H,dd,H-3, J=16.0 and 8.5 Hz); 3.28 (1H,dd,H-3, J=16.0 and 9.0 Hz); 4.7-5.5 (3H,m,H-2 and $C=CH_2$); 5.6-6.3(1H,m,CH=C); 6.4-7.3(4H,m,H_{arom})	146(100), 145(95), 131(58), 117(24), 115(19), 91(15)
3b	1593,1477,1460, 1228,900,745	216(3.72), 226(3.69), 279(3.40), 287(3.39)	1.70 (3H,d,CH_3, J=1.0 Hz); 2.85 (1H,dd,H-3, J=16.0 and 8.5 Hz); 3.20 (1H,dd,H-3, J=16.0 and 9.0 Hz); 4.5-6.3 (3H,m,H-2 and $C=CH_2$); 6.3-7.2 (4H,m,H_{arom})	160(32), 145(100),117(25), 115(28), 91(14)
3c	1500,1250,1220, 1130,798	216(3.71), 272(3.40), 284(3.38)	2.15(3H,s,CH_3); 2.20 (3H,s,CH_3); 2.82 (1H,dd,H-3, J=16.0 and 8.0 Hz); 3.30 (1H, dd,H-3, J=16.0 and 8.0 Hz); 4.7-5.53 (3H, m,H-2 and $C=CH_2$); 5.6-6.3 (1H,m,CH=C); 6.7 (2H,bs,H_{arom})	174(58), 159(100), 132(15), 91(14)
3d	1640,1490,1152, 1045,944[b]	238(3.39), 300(3.63), 310(3.57)	2.78 (1H,dd,H-3, J=16.0 and 8.5 Hz); 3.20 (1H,dd,H-3, J=16.0 and 9.0 Hz); 4.8-5.5 (3H,m,H-2 and $C=CH_2$); 5.5-6.3 (1H,m, CH=C); 5.80 (2H,s,O-CH_2O); 6.30 (1H,s,H-4); 6.52 (1H,s,H-7)	190(100), 175(90), 131(31), 119(23),115(19), 103(23)
3e	1628,1603,1504, 1200,1150	225(3.69), 288(3.61), 292(3.57)	2.60 (1H,dd,H-3, J=16.0 and 8.5 Hz); 3.28 (1H,dd,H-3, J=16.0 and 9.0 Hz); 3.68 (3H,s,OCH_3); 4.8-5.5(3H,m,H-2 and $C=CH_2$); 5.6-6.2 (1H,m,CH=C); 6.2-7.3 (3H,m,H_{arom})	176(100), 175(90), 161(48), 145(19), 115(26), 105(18), 91(19)
3f	1613,1500,1472, 1238,1095,767	225(3.96), 230(3.89), 275(3.13), 281(3.13)	2.80 (1H,dd,H-3, J=16.0 and 8.0 Hz); 3.28 (1H,dd,H-3, J=16.0 and 8.5 Hz); 3.73 (3H,s,OCH_3); 4.8-5.5 (3H,m,H-2 and $C=CH_2$); 5.6-6.2 (1H,m,CH=C); 6.29 and 6.34 (2H,2d,H-5 and H-7, J= 8.0 Hz); 7.00 (1H,t,H-6, J=8.0 Hz)	176(76), 161(100), 145(29), 115(25), 105(16), 91(20)
3g	1495,1210,1040, 816	218(3.68), 229(3.78), 300(3.59)	2.85 (1H,dd,H-3, J=16.0 and 8.5 Hz); 3.29 (1H,dd,H-3, J=16.0 and 9.0 Hz); 3.68 (3H,s,OCH_3); 4.8-5.5 (3H,m,H-2 and $C=CH_2$); 5.6-6.3 (1H,m,CH=C); 6.4-6.9 (3H,m,H_{arom})	176(100), 161(99), 145(33), 115(33), 105(28), 91(17)
3h	1600,1489,1460, 1240,930,773	219(3.83), 283(3.42), 287(3.40)	2.80 (1H,dd,H-3, J=16.0 and 8.0 Hz); 3.28 (1H,dd,H-3, J=16.0 and 9.0 Hz); 4.8-5.5 (3H,m,H-2 and $C=CH_2$); 5.6-6.3 (1H,m, CH=C); 6.4-7.3 (3H,m,H_{arom})	182(23), 180(62), 167(19), 165(55), 145(100), 127(77), 117(52), 115(55)
3i	1640,1470,1247, 962,812,750	211(4.40), 232(4.65), 271(3.62), 281(3.70), 293(3.57)	2.80 (1H,dd,H-3,J=16.0 and 8.5 Hz); 3.30 (1H,dd,H-3, J=16.0 and 8.5 Hz); 4.7-5.5 (3H,m,H-2 and $C=CH_2$); 5.5-6.3 (1H,m, CH=C); 6.8-7.9 (6H,m,H_{arom})	196(100), 181(85), 167(15), 165(19), 152(23), 139(15), 115(10)
3j	1685,1614,1496, 1367,1274,960, 830	226(4.05), 278(4.13), 295(4.05)	2.50 (3H,s,$COCH_3$); 2.91 (1H,dd,H-3,J=16.0 and 8.0 Hz); 3.41 (1H,dd,H-3,J=16.0 and 8.5 Hz); 4.9-5.5 (3H,m,H-2 and $C=CH_2$), 5.6-6.4 (1H,m,CH=C); 6.5-7.9 (3H,m,H_{arom})	188(72), 173(100), 145(64), 127(34), 115(31), 91(16)
3k	1680,1610,1490, 1270,910,825	226(4.06), 282(4.08), 287(4.08)	1.75 (3H,d,CH_3, J=1.0 Hz); 2.52 (3H,s,$COCH_3$); 2.95 (1H,dd, H-3, J=16.0 and 8.5 Hz); 3.40 (1H,dd,H-3, J=16.0 and 9.0 Hz), 4.8-5.1 (2H,m,C=CH_2); 5.20 (1H,t, H-2, J=9.0 Hz); 6.73 (1H, d,H-7, J=9.0 Hz); 7.5-7.9 (2H,m,H-4 and H-6)	202(70), 187(100), 159(52), 144(50), 131(34), 115(31)
3l	1685,1610,1490, 1448,1250,1110, 828	229(4.21), 284(4.25), 293(4.26)	1.76 (3H,d,CH_3, J=1.0 Hz); 2.98 (1H,dd,H-3, J=16.0 and 8.5 Hz); 3.37 (1H,dd,H-3, J=16.0 and 9.5 Hz); 4.8-5.2 (2H,m, C=CH_2); 5.22 (1H,t,H-2, J=9.0 Hz); 6.79 (1H,d,H-7, J=9.0 Hz); 7.4-7.7 (2H,m,H-4 and H-6); 9.74 (1H,s, CHO)	118(100), 173(95), 159(65), 91(46)
3m	3300,1645,1488, 1260,1048	214(4.22), 237(4.05), 280(4.07), 327(3.89)	1.73(3H,d,CH_3, J=1.0 Hz); 2.50(3H,s,$COCH_3$); 2.88 (1H,dd,H-3, J=15.0 and 8.0 Hz); 3.30 (1H,dd,H-3, J=15.5 and 9.0 Hz); 4.8-5.1 (2H,m,C=CH_2); 5.18 (1H,t,H-2, J=9.0 Hz); 6.26 (1H,s,H-7); 7.38 (1H,bs,H-4); 12.88 (1H,s,OH)	218(100), 203(90), 175(51), 165(18), 161(10), 160(17), 147(13), 105(12)
3n	3090,2930,1625, 1442,1275,1073, 804	214(4.26), 235(3.93), 241(3.92), 289(4.17)	1.75 (3H,d,CH_3, J=1.0 Hz); 2.52 (3H,s,$COCH_3$); 2.90 (1H,dd,H-3, J=15.5 and 8.5 Hz); 3.30 (1H,dd,H-3, J=16.0 and 9.5 Hz); 4.8-5.1 (2H,m,C=CH_2); 5.22 (1H,t,H-2, J=9.0 Hz); 6.28 (1H,d,H-7, J=9.0 Hz); 7.48 (1H, d,H-6, J=9.0 Hz); 12.62 (1H,s,OH)	218(89), 203(100), 175(33), 161(22), 147(37), 91(26)
3o	3260,1645,1442, 1278,1062,810[b]	216(4.01), 228(4.02), 288(4.18), 331(3.42)	1.79 (3H,d,CH_3, J=1.0 Hz); 2.65 (3H,s,$COCH_3$); 2.7-3.5 (2H,m, H-3); 4.8-5.5 (3H,m,H-2 and $C=CH_2$); 5.90 (1H,s,H-5); 13.2 (1H, s,OH)	234(69), 220(55), 219(48), 201(20), 149(28), 108(32), 57(50), 43(100)
3p	3220,1645,1448, 1280,1098,812[b]	213(4.14), 222(4.08), 292(4.19), 321(3.53)	1.73 (3H,bs,CH_3); 2.70 (3H,s,$COCH_3$); 2.8-3.4 (2H,m,H-3); 4.8-5.1 (2H,m,C=CH_2); 5.23 (1H,t,H-2, J=8.5 Hz); 5.92 (1H,s,H-7); 12.0 (1H,bs,OH)	234(100), 219(89), 202(34), 177(20), 149(24), 108(25), 69(39), 43(96)

[a] Film unless otherwise stated.
[b] KBr disc.

which affords in straightforward operation and in preparatively useful yield a variety of 2-vinyl- and 2-isopropenyl-2,3-dihydrobenzofurans. This procedure may have considerable value in the synthesis of naturally occurring Euparinoid 2,3-dihydrobenzofurans as well as their synthetic analogues, since only relatively simple experimental procedures and readily available reagents are involved.

EXPERIMENTAL

General. All b.ps were measured in a Büchi apparatus and are uncorrected. UV spectra were recorded on a Jasco UVIDEC 505 instrument and were run in 95% ethanol soln; IR spectra on a Perkin–Elmer 298 spectrophotometer; Mass spectra on a Varian MAT CH-5 spectrometer using direct insertion probe (70 eV). ^{1}H NMR spectra were taken at 60 MHz on a Varian EM-360 instrument and were run as solns in chloroform-*d*, using TMS as internal standard; the chemical shifts are expressed in ppm. TLC experiments were carried out on Merck silica gel GF_{254} plates. Column chromatography was conducted with Merck silica gel 60–230 mesh ASTM. Preparative TLC were carried out on 1 mm thick layers. *Trans* 1,4-dibromo-2-butene **2a** and *trans* 1,4-dibromo-2-methyl-2-butene **2b** were prepared by bromination of 1,3-butadiene and isoprene, respectively, according to literature.[14] All reactions were run in dry conditions under pure nitrogen. Microanalyses were performed by Istituto di Chimica Farmaceutica dell'Università di Parma, Italy.

Representative examples of preparation of 2,3-dihydrobenzofuran derivatives from simple phenols and hydroxyacetophenone derivatives as well as polyhydric phenols are given here.

2-Vinyl-2,3-dihydrobenzofuran **3a**. [*Typical procedure for simple phenols*]

To a solution of phenol (0.94 g, 10 mmol) in anhydrous toluene (40 ml), *n*-butyllithium (6.25 ml of 1.6 *M* hexane solution) was added and the mixture was stirred for 15 min at room temperature while a stream of dry nitrogen was passing. Then a solution of 1,4-dibromo-2-butene **2a** (2.14 g, 10 mmol) in toluene (10 ml) was added and the resulting slurry was heated under reflux for 22 h. After cooling to room temperature, the reaction mixture was quenched with an excess of an aqueous ammonium chloride solution and extracted with diethyl ether (3 × 50 ml). After drying (Na_2SO_4) the ether was evaporated and **1a** was separated from the residue by chromatography on silica gel using hexane as eluant: yield 0.70 g (48%; 95% based on unrecovered

phenol); colourless liquid, b.p. 115°C/20 torr; n_D^{18} 1.5498 (Lit.[15] b.p. 218–220°C; n_D^{20} 1.5408).

Compounds **3b–i** were prepared in similar way.

2 - Isopropenyl - 5 - acetyl - 2,3 - dihydrobenzofuran (tremetone) **3k**. *Typical procedure for hydroxyacetophenone and hydroxybenzaldehyde derivatives*

To a solution of 10 mmol of lithium *tert.* butoxide [generated *in situ* by reaction of *tert.* butanol (0.741 g) and *n*-butyllithium (6.25 ml of 1.6 *M* hexane solution)] in toluene (40 ml), 4-hydroxyacetophenone (1.36 g, 10 mmol) was added at room temperature, and the resulting mixture was heated with stirring under azeotropic removal of the *tert.* butanol formed until the temperature rose to 110°C (*ca.* 1 h). After cooling to room temperature, *trans* 1,4-dibromo-2-methyl-2-butene **2b** (2.28 g, 10 mmol) in toluene (10 ml) was added and, after the volume was adjusted to 50 ml with toluene, the slurry was refluxed with stirring for 22 h. After conventional work up procedure (aqueous quenching, extraction with ether, drying, removal of the solvent) racemic tremetone **3k** was isolated by chromatography on silica gel using hexane/ethyle acetate 85:15 (v/v): yield 0.73 g (36%; 82% based on unrecovered 4-hydroxyacetophenone); colourless liquid, b.p. 196°C/22 torr; n_D^{16} 1.5660 (Lit.[4] b.p. 120–127°C/2 torr).

Compounds **3j** to **3n** were prepared in a similar way.

2 - Isopropenyl - 5 - acetyl - 4,6 - dihydroxy - 2,3 - dihydrobenzofuran **3p** *and 2 - isopropenyl - 7 - acetyl - 4, 6 - dihydroxy - 2, 3 - dihydrobenzofuran* **3o**. [*Useful procedure for polyhydric phenols*]

To a solution of 2, 4, 6-trihydroxyacetophenone (phloracetophenone, 1.86 g, 10 mmol) in anhydrous toluene (50 ml), potassium *tert.* butoxide (2.24 g, 20 mmol) was added at room temperature and the resulting mixture was heated with stirring under azeotropic removal of the *tert.* butanol formed, until the temperature rose to 110°C (*ca.* 1 h). After cooling to room temperature, *trans* 1,4-dibromo-2-methyl-2-butene **2b** (2.28 g, 10 mmol) in toluene (10 ml) was added and, after the volume was adjusted to 50 ml with toluene, the slurry was refluxed with stirring for 22 h. After conventional work up procedure (aqueous quenching, extraction with ether, drying, removal of the solvent), racemic products **3p** and **3o** were isolated by chromatography on silica gel using hexane/ethyl acetate 8:2 (v/v). Yield: **3p**, 0.54 g (23%; 39% based on unrecovered starting phloracetophenone), pale yellow crystals, m.p. 125–126°C; **3o**, 0.49 g (21%; 36% based on unrecovered starting phloracetophenone), pale yellow crystals, m.p. 178–182°C (Lit.[2] m.p. 186–188°C).

Preparative data and physical properties for all synthesized 2-vinyl-2,3-dihydrobenzofurans **3a–p** are shown in Table 2. Significant spectroscopic data are reported in Table 3.

Reaction of sodium phenolate (**1a**, *M* = Na) *with 1,4 - dibromo - 2 - butene* **2a** *in methanol (Nickl procedure): 1 - bromo - 4 - phenoxy - 2 - butene* **4a** *and 1,4 - diphenoxy - 2 - butene* **5a**

To a solution of sodium (0.23 g, 10 mmol) in methanol (40 ml), phenol (0.94 g, 10 mmol) in methanol (10 ml) was added at room temperature. To the resulting solution 1,4-dibromo-2-butene **2a** (2.14 g, 10 mmol) in methanol (10 ml) was added and the colourless solution was stirred for 22 h at room temperature (*ca.* 20°C). After conventional work up procedure (aqueous quenching, extraction, drying, removal of the solvent) the oily residue was chromatographed on a silica gel column using hexane/ethyl acetate 9:1 (v/v) solvent system to give 1-bromo-4-phenoxy-2-butene **4a** (yield 0.80 g, 35%) and then 1,4-diphenoxy-2-butene **3a** (yield 0.60 g, 50%).

4a: colourless oil; δ ($CDCl_3$) 3.86 (2H, m, $-CH_2Br$), 4.42 (2H, m, $O-CH_2$), 5.8–6.1 (2H, m, CH=CH), 6.6–7.4 (5H, m, H_{arom}); *m/e* 228 (1%), 226 (1), 145 (22), 133 (9), 131 (10), 94 (100), 77 (15).

5a: colourless plates, m.p. 88°C; δ ($CDCl_3$), 4.46 (4H, m, CH_2), 6.00 (2H, m, CH=CH), 6.6–7.5 (10H, m, H_{arom}); *m/e* 240 (12%), 147 (100), 146 (74), 107 (31), 91 (46), 77 (62).

Reaction of sodium phenolate (**1a**, *M* = Na) *with 1,4 - dibromo - 2 - methyl - 2 - butene* **2b** *in methanol*: *1 - bromo - 2 - methyl - 4 - phenoxy - 2 - butene* **4b** *and 1,4 - diphenoxy - 2 - methyl - 2 - butene* **5b**

The procedure described above, using phenol, sodium, and 1,4-dibromo-2-methyl-2-butene **2b** in methanol, gave:

4b: yield 0.89 g (37%); colourless oil; ν_{max} (film) 1605, 1500, 1242, 758, 695 cm^{-1}; λ_{max} (log ε) (95% EtOH) 220 (4.21), 264 (3.18), 271 (3.28), 277 nm (3.19); δ ($CDCl_3$) 1.80 (3H, s, CH_3), 3.85 (2H, s, CH_2Br), 4.45 (2H, d, CH_2O, J = 6.0 Hz), 5.75 (1H, t, CH, J = 6.0 Hz), 6.6–7.4 (5H, m, H_{arom}); *m/e* 242 (1%), 240 (1), 161 (12), 149 (3), 147 (3), 94 (100).

5b: yield 0.66 g (52%); colourless plates, m.p. 57–58°C; ν_{max} (KBr) 1603, 1495, 1255, 1010, 750, 700 cm^{-1}; λ_{max} (log. ε) (95% EtOH) 221 (4.30), 267 (3.75), 271 (3.82), 278 (376); δ ($CDCl_3$) 1.76 (3H, s, CH_3), 4.33 (2H, s, CH_2C=), 4.50 (2H, d, CH_2-CH=, J = 6.0 Hz), 5.80 (1H, t, CH_2-CH=, J = 6.0 Hz), 6.6–7.4 (10H, m, H_{arom}); *m/e* 254 (4%), 161 (97), 160 (100), 145 (23), 133 (19), 119 (19), 107 (22), 77 (44).

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