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ELECTROSYNTHESIS OF UNSYMMETRICAL BIARYLS USING A $S_{RN}1$ TYPE REACTION

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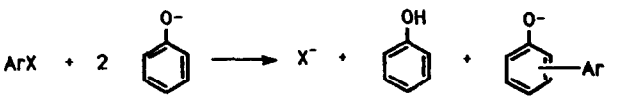
Summary: A new synthetic route to unsymmetrical biaryls is described, involving an electrochemically induced chain reaction of the $S_{RN}1$ type.

The synthesis of unsymmetrical substituted hydroxybiphenyls was recently demonstrated to be possible in liquid ammonia, via a single-step reaction, starting from an aromatic halide ArX and an alkaline phenoxide (1a):



The reaction, the mechanism of which will be further detailed (1b), is electrochemically induced by a monoelectronic transfer to ArX. It gives a mixture of two isomeric hydroxybiphenyls in which the hydroxy group is located either ortho (66%), or para (33%) to the new C-C bond between the two rings.

As this reaction is potentially interesting from a synthetic point of view for the elaboration of hydroxybiphenyls which are intermediates in synthesis of liquids cristals (2), we present an improvement of its selectivity and chemical yield.

It is easy to perform a selective synthesis, giving either the ortho or the para isomer when using phenoxides in which two among the three possible coupling positions are substituted by t-butyl groups. Such protective groups can be easily removed later (3).

We are presenting in this paper the results we obtained in the case of the reaction of 2- ,or 3-,or 4-chlorobenzonitrile (1o,1m and 1p) with 2,6- and 2,4- di-t-butyl phenoxide (2p and 2o).

The reaction is carried out in a reactor containing 80 ml liquid ammonia, equipped with a platinum grid as the cathode and a magnesium soluble anode(4). The electrolyses are performed at a constant current density (i=15 $mA.cm^{-2}$ at the cathode).

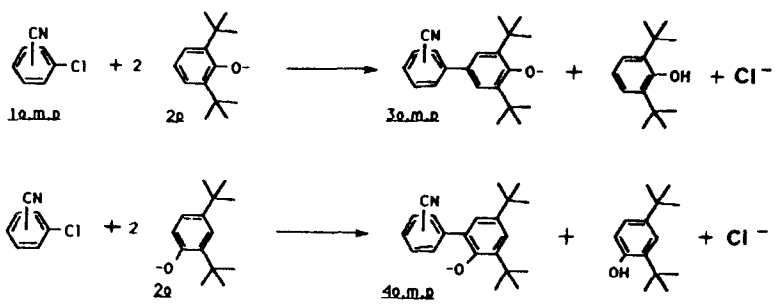
The phenoxide solutions (18 mmol) are prepared *in situ* via phenol(2p,2o) neutralization by potassium t-butoxide. The reaction is generally performed using 3 mmol of substrate (1o,1m,1p) and an equal amount of potassium hydroxide.

Once the reaction is over, the solution is acidified by ammonium bromide; after ammonia evaporation, the solid residue is extracted with dichloromethane; the reaction mixture is analyzed by HPLC. Chromatography yields pure hydroxybiphenyls (see table 1) which are characterized by ^{1}H and ^{13}C NMR (9).

Two techniques are used: the direct reduction, in which the cathode potential is set at the substrate reduction potential(10), and the indirect reduction via a mediator P (2 mmol of 4,4'-bipyridyl) which reduction occurs just before the starting halide, and imposes the cathode potential.

The results are compiled in Table I. It is first noticed that the process is electrocatalytic(1a,1b). Secondly,the coupling product yield is improved when the reaction is indirectly induced by the mediator.

Table I



ArX	Phenoxide (K+)	n1, (n2)a	Reaction product	R1%, (R2%)a	Other products
1o	2p	.15, (.80) .30[e]	3o	89, (54) 87[e]	2-chlorobenzamide
1m	2p	.40, (1.0)	3m	68, (33)	3-chlorobenzamide
1p	2p	.30, (1.5)[b]	3p	78, (22)[b]	4-chlorobenzamide 6%
1o	2o	.60	4o[d]		
1p	2o	.60, (1.9)	4p	47, (6)	4-chlorobenzamide

a n : number of Faraday consumed per mole of ArX; R:coupling product yield relative to the initial ArX ; n_1,R_1:indirect reduction ; (n_2, R_2) : direct reduction.

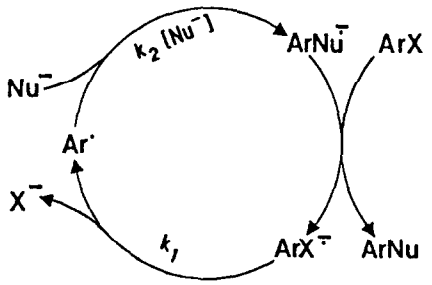
b from ref 1b

c very little reactivity within the cyclic voltammetry scale

d isolated in 20% yield as the lactone derivative obtained by hydrolysis of the cyanophenol during the workup.

e 1o= 20 mmol,2p = 40 mmol , KOH = 20 mmol,4,4'bipyridyl=4 mmol

Such remarks are in good agreement with the predictions that can be made once a chain mechanism of the $S_{RN}1$ type (1a,1b) is assumed. In such conditions the reaction yield is indeed essentially dependant on the competition between the propagation process which is described by the following catalytic cycle and the termination reactions which are mainly due to $Ar^{\bullet}$ reduction.



ArX = 1o, 1m, 1p
Nu⁻ = 2p, 2o

In the present case, because of the cleavage constant rates of $ArX^{\bullet-}$ radical anions(5), the termination step is mainly due to the $Ar^{\bullet}$ reduction at the electrode. In the case of a direct reduction, the reaction yield depends on the ratio $k_2[Nu^-]/k_1$(6), which can be very low when k_1 is large compared to $k_2[Nu^-]$. In the case of an indirect reduction, the situation is quite different because the termination reaction involved corresponds to $Ar^{\bullet}$ reduction by the reduced form of the mediator $P^{\bullet-}$. The reaction yield depends then on the ratio $k_2[Nu^-]/k_d[P^{\bullet-}]$. It can be very large once $k_d[P^{\bullet-}]$ is very small compared to $k_2[Nu^-]$(7,8).

A new synthetic route to unsymmetrical biaryls substituted by a cyano group on one ring and a hydroxy group on the other one in ortho or para to the phenyl-phenyl bond is described. Starting from 2-,or 3-,or 4-chlorobenzonitrile and 2,6-(or 2,4-) di-t-butylphenoxide, 2- (or 3 or 4)-cyano,-3',5'-di-t-butyl-4'(or 2') hydroxybiphenyl is obtained in good yield in liquid ammonia *via* an electrochemically induced synthesis.

References and notes

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9 Product Analysis :

4o m.p.175.5°C. ^{1}H NMR (250MHz-$CDCl_3$) 1.36(s,9H);1.49(s,9H);5.06 (s,1H phenolic); 7.10(d,J=2.5Hz;1H); 7.45(d,J=2.5Hz;1H); 7.68 and 7.85(A_2B_2,Japp=8.5Hz;4H). ^{13}C NMR 29.7($3CH_3$);31.5($3CH_3$);34.3(C); 35.1(C); 111.2(C); 118.4(C); 124.5(CH); 124.8(CH); 126.7(C);130.4 (2CH);132.7(2CH); 136.3(C); 142.8(C); 143.4(C); 148.5(C).

3o m.p.172°C. ^{1}H NMR (250MHz,$CDCl_3$) 1.50(s,18H); 5.44(s,1H phenolic); 7.43 (t,J=8Hz;d,J=1.5Hz;1H); 7.47 (s,2H); 7.59 (d,J=8Hz; d, J=1.5Hz;1H); 7.66(t,J=8Hz;d,J=1.5Hz;1H); 7.81(d,J=8Hz;d, J=1.5Hz; 1H). ^{13}C NMR 30.3 ($6CH_3$;34.5(2C); 111.2(C); 119.1(C);125.7(2CH); 126.6(CH); 129.2(C); 129.8(CH); 132.5(CH); 133.8(CH); 136.3(2C); 146.4(2C);154.5(C).

3m m.p.127°C. ^{1}H NMR (250MHz,$CDCl_3$) 1.51(s,18H); 5.42(s,1H phenolic); 7.42(s,2H); 7.56(t,J=8Hz; d,J=1.5Hz;1H); 7.64(d,J=8Hz; t,J=1.5Hz;1H); 7.84(d,J=8Hz;t,J=1.5Hz;1H); 7.88(br.s,1H). ^{13}C NMR 30.1 ($6CH_3$);34.3(2C); 112.5(C); 118.9(C); 123.7(2CH); 129.3(CH); 129.5 (CH); 130 (C); 130.2(CH); 131(CH); 136.6(2C); 143.2(C); 154.2(C).

3p m.p.155°C. ^{1}H NMR (250MHz,$CDCl_3$) 1.50(s,18H); 5.47(s,1H phenolic);7.47(s,2H);7.70 and 7.77(A_2B_2 Japp=9Hz;4H). ^{13}C NMR ($CDCl_3$) 30.3($6CH_3$); 34.4(2C); 109.8(C); 119(C); 124(2CH);127.3(2CH);130.4 (C); 132.4(2CH); 136.8(2C); 146.6(C); 154.6(C).

Lactone of 4o: m/z:308(mass peak)-293-265-237-57. IR: 2960-1728-1610-1575-1290-780-690. ^{1}H NMR ($CDCl_3$)1.43(s,9H); 1.58(s,9H);7.65 (d,J=2.3Hz;1H);7.66(t,J=8Hz;d,J=1.5Hz;1H);7.92(t,J=8Hz;d,J=1.5Hz; 1H);8.06(d,J=2.3Hz;1H);8.29(br.d,J=8Hz,1H);8.52(br.d,J=8Hz;1H).

10 The reduction potentials of chlorobenzonitriles correspond to -1.45V for 1o, -1.55V for 1m, -1.5V for 1p, in liquid ammonia *versus* Ag/Ag+ ([Ag+] = 10^{-2}M) reference electrode.In the same condition the reduction potential of 4,4' bipyridyl corresponds to -1.33V.

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