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Synthesis of 4-(3,5-dialkyl-4-hydroxyphenyl)pyridines.

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Key Words: 2,6-dipentylphenol; $S_{RN}1$; hydroxyphenylpyridine; pyridinio-phenoxide zwitterions.

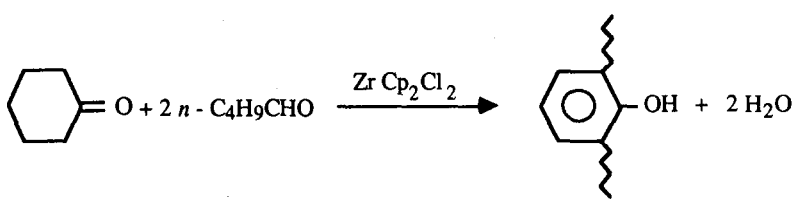
Abstract: *Starting from 4-chloropyridine and 2,6-dialkylphenoxides, 4-(3,5-dialkyl-4-hydroxyphenyl)pyridines are obtained via an electrochemically induced $S_{RN}1$ reaction using 2,4'-bipyridine as a mediator (alkyl= pentyl, isopropyl, methyl) . Quaternization of 4-(3,5-dipentyl-4-hydroxyphenyl)pyridine by linear alkyl halides, followed by deprotonation, gives (pyridinio-phenoxide) zwitterions.*

The electrosynthesis of unsymmetrical biaryls by a $S_{RN}1$ reaction starting from an aromatic halide and a phenoxide is a well documented process.[1,3] Starting from phenoxide itself, the reaction leads to a mixture of two coupling products (ortho coupling:2/3, para coupling: 1/3)[1,2],whilst it is regioselective with 2,6-di-tert-butylphenoxide .[3] We have tried to increase the range of application of the reaction by using phenoxides *ortho* substituted by other groups (pentyl, isopropyl, methyl and methoxy). We have used 4-chloropyridine as starting aromatic halide because the obtained hydroxyphenylpyridine could be transformed into a zwitterion, which is interesting for applications in nonlinear optics.[4,5]

We are describing the synthesis of 2,6-dipentylphenol, which is not commercially available, the coupling reaction with the different nucleophiles and the synthesis of zwitterionic derivatives.

I. Synthesis of 2,6-dipentylphenol

We have used a procedure proposed by Nakako *et al.*[6] It consisted in mixing cyclohexanone, pentanal and a crossed aldolisation and isomerization catalyst, such as zirconocene dichloride or titanocene dichloride:

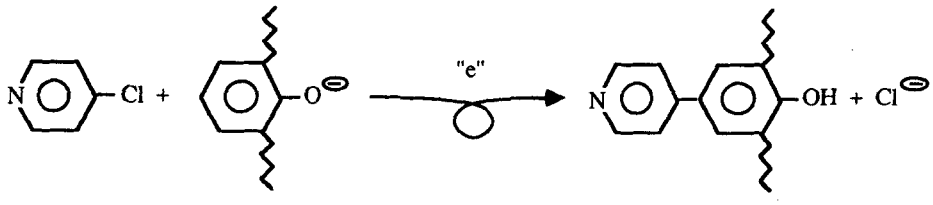


$ZrCp_2Cl_2$ (1.5 mmol, 0.44 g), cyclohexanone (15 mmol, 1.47 g) and pentanal (30 mmol, 2.58 g) were successively introduced into an autoclave and heated for 8 hours at 150°C. After cooling, the remaining catalyst was filtrated. 10 mL dichloromethane and about 30 mL chlorhydric acid were added to the filtrate (pH=1). The product was obtained from the organic phase by flash chromatography (silica gel, pentane/dichloromethane, 80/20 then 70/30, V/V).

The yield of isolated product was 35%, which was lower than that obtained by Nakako (80%), although same experimental conditions were used.

II. Electrosynthesis of 4-(3,5-dipentyl-4-hydroxyphenyl)pyridine (**1**)

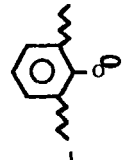
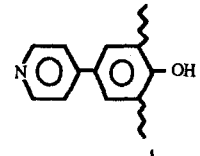
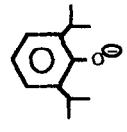
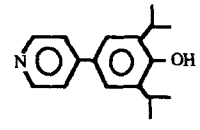
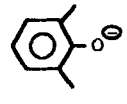
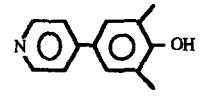
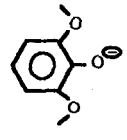
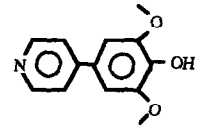
The mechanism involved was an electrochemically induced $S_{RN}1$ reaction using a previously described method.[1,3] The overall reaction was the following in the case of 2,6-dipentylphenoxide:



Because of the low solubility of phenoxides *ortho* substituted by linear alkyl groups in liquid ammonia, the reaction was performed in a mixture of ammonia and tetrahydrofuran. 2,4'-bipyridine (2 mmol, 0.31 g), 4-chloropyridine hydrochloride (4 mmol, 0.60 g), 2,6-dialkylphenol (10 mmol), water (4 mmol, 0.07 g) and potassium *tert*-butoxide (18 mmol, 2.02 g) were successively introduced into an electrochemical cell containing a mixture of 80 mL liquid ammonia, 20 mL tetrahydrofuran and potassium bromide (10^{-1}M, 1.20 g) as supporting electrolyte. The temperature was maintained at -40°C with a cryocooler (Bioblock scientific). A constant current density of 0.25 A.dm^{-2} was imposed between a platinum grid (10 cm^2, 1024 mesh per cm^2) and a cylindrical magnesium rod (h=8cm,Φ=1cm), till the disappearance of the starting chloropyridine. About 0.5 Faraday per mole of starting aromatic halide was then passed through the circuit. After ammonia evaporation, compound (**1**) was extracted by dichloromethane, separated from the other organic products by flash chromatography (silica gel, dichloromethane/ethyl acetate, 70/30) and recrystallized from a mixture of acetonitrile and diethyl oxide (90/10, V/V).

No coupling product was obtained with 2,6-dimethoxyphenoxide. The results obtained with the other nucleophiles are gathered in Table 1.

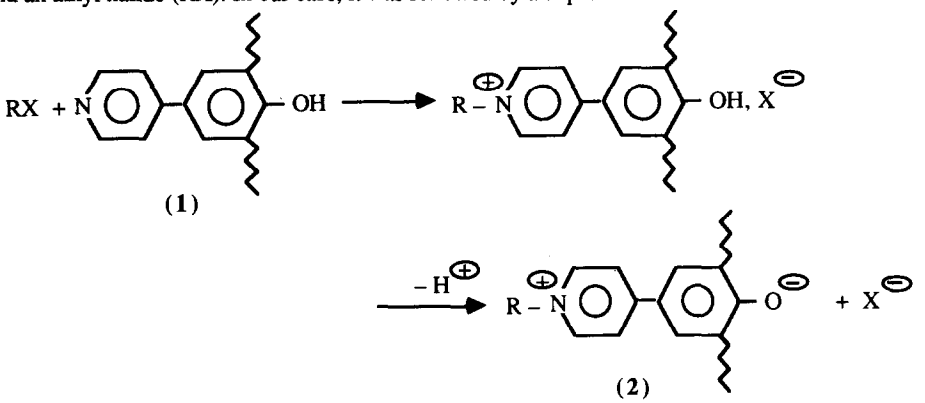
Table I.
Results of the Electrolyses with Phenoxides Ortho Substituted by Different Groups.

Nucleophile	Product	Isolated Product Yield
		30%
		21%
		6%
		0

The yields of isolated product were lower than that obtained with 2,6–di–*tert*–butylphenoxide as a nucleophile (75%).[3] They decreased when the steric hindrance of the substituents decreased and when the.electron-withdrawing character of the substituents increased. Research about the reactivity of phenoxides *ortho* substituted by different substituents is going on at present.

III. Quaternization and deprotonation of 4-(3,5-dipentyl-4-hydroxyphenyl)pyridine.

The quaternization of tertiary amines included in a ring is a well-known process, referred to as the Menschutkin reaction.[7-11] The Menschutkin reaction consists of a nucleophilic substitution between a pyridine.and an alkyl halide (RX). In our case, it was followed by a deprotonation reaction:



Because iodides are more reactive than bromides[8,9], we have used iodide derivatives whenever possible. We have performed the reaction with 4-(3,5-dipentyl-4-hydroxyphenyl)pyridine (**1**) and methyl iodide (**a**), *n*-octyl iodide (**b**) and *n*-tetradecyl bromide (**c**).

As the reactants do not bear any charge, whilst the product is a salt, the kinetics of the Menschutkin reaction depends largely on the solvent polarity.[8-11] The more polar the solvent, the fastest the reaction. From the results obtained by Auriel[8] about the reaction of ethylbenzene halides with diazabicyclooctane, DMSO was found to be the solvent in which the reaction was the fastest. It was 5 times slower in acetonitrile and 10 times slower in acetone . We have not used DMSO because of difficulties to eliminate it. In the case of (**a**) and (**b**), the reaction could be performed in acetonitrile, whilst it was performed in acetone in the case of (**c**).

Compound (**1**) (0.225 mmol, 70 mg) was dissolved in an excess of RX (2 equivalents for **a** and **b**, 5 equivalents for **c**) and 4 mL of solvent (acetonitrile or acetone). The mixture was heated at 100°C for 4 hours (**a**), 8 hours (**b**), 24 hours (**c**). In the case of (**c**), when the reaction was stopped, some starting product remained. The organic solvent was then evaporated. The pyridinium salt was precipitated in diethyl oxide. It was then deprotonated with NaOH 1M (0.5 mL) and the obtained zwitterion was extracted with diethyloxide. After decantation, washing of the organic phase with water, drying over $MgSO_4$ and evaporation of the solvent, compound (**2**) was obtained. Compounds (**2a,b**) , which were solid were recrystallized in acetone. Compound (**2c**), which was liquid was not further purified. The yields of isolated products were about 60% for (**2a,b**) and 45% for (**2c**).

Quaternization of (**1**) by other groups is going on at present.

References and notes

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(12) Product analyses:

1:4-(3,5-dipentyl-4-hydroxyphenyl)pyridine. m.p.: 144°C. UV (THF), λ(nm): 265, 292. ^{1}H NMR (90 MHz, $CDCl_3$), δ (ppm): 0.9 (t, 6H), 1.1-1.9 (m, 12H), 2.7 (t, 4H), 7.3 (s, 2H), 7.5 and 8.6 (AA'BB', J_{app}=9 Hz, 4H). MS (EI, m/z): 311(M), 255, 254. Anal. Calcd. for $C_{21}H_{29}ON$: C, 80.98; H, 9.38; N, 4.49; Found: C, 80.42; H, 9.37; N, 4.28.

2a:4-(N-methylpyridinio)-3,5-dipentylphenoxide. m.p.: 260-263°C. UV (THF), λ(nm): 491, 522. ^{1}H NMR (250 MHz, acetone D6), δ (ppm): 0.9 (t, J=6Hz, 6H), 1.2-1.9 (m, 12H), 2.7_5 (t, J=8Hz, 4H), 4.5 (s, 3H), 7.8 (s, 2H), 8.4 and 9.0 (AA'BB', J_{app}=9 Hz, 4H). ^{13}C NMR (250 MHz, acetone D6), δ (ppm): 14.3 ($2CH_3$), 23.2 ($2CH_2$), 30.4 ($2CH_2$), 31.2 ($2CH_2$), 32.5 ($2CH_2$), 47.5 (N-CH_3), 123.2 (2CH), 124.1 (C), 126.2 (C), 128.7 (2CH), 132.0 (2C), 145.6 (2CH), 156.2 (C), MS (EI, m/z): 325 (M), 311, 268, 254, 184.

2b:4-(N-octylpyridinio)-3,5-dipentylphenoxide. m.p.: 98°C. UV (THF), λ(nm): 492, 524. ^{1}H NMR (90 MHz, $CDCl_3$), δ (ppm): 0.9 (br. t, 9H), 1.1-1.9 (m, 24H), 2.5 (t, J=8Hz, 4H), 3.9 (t, J=8Hz, 2H), 7.2 (s, 2H), 7.2_5 and 7.5 (AA'BB', J_{app}=9 Hz, 4H). ^{13}C NMR (250 MHz, acetone D6), δ (ppm): 14.22 (CH_3), 14.38 ($2CH_3$), 23.03 (CH_2), 23.19 ($2CH_2$), 26.62 (CH_2), 29.50 ($2CH_2$), 30.12 ($2CH_2$), 31.62 ($2CH_2$), 31.75 (CH_2), 32.22 (CH_2), 32.59 ($2CH_2$), 59.47 (N-CH_2), 117.54 (C), 120.08 (2CH), 127.96 (2CH), 133.17 (C), 142.90 (2CH), 154.48 (C), 169.34 (C), MS (EI, m/z): 423 (M), 394, 380, 367, 339, 338, 326, 325, 324, 312, 311, 282, 268, 254, 224, 211, 210, 198, 184, 179, 168, 167, 155, 150, 137, 135, 129, 128, 123, 122, 115, 113, 105.

2c:4-(N-tetradecylpyridinio)-3,5-dipentylphenoxide. Liquid at room temperature. ^{1}H NMR (90 MHz, acetone D6), δ (ppm): 0.8 (br. t, 9H), 1.0-2.0 (m, 36H), 2.6 (t, J=8Hz, 4H), 4.1_5 (m, 2H), 7.5 (s, 2H), 7.8 and 8.5 (non resolved AA'BB', 4H).

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