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PHASE TRANSFER CATALYSIS WITHOUT SOLVENT. ALKYLATION OF PHENOL AND DERIVATIVES.

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ABSTRACT: The alkylation of phenol, hydroquinone and p-aminophenol is performed by phase transfer catalysis without solvent. High yields of α,ω-diphenoxyalkanes, hydroquinone diethers and high selective mono O-alkylation of p-aminophenol are obtained in very mild conditions.

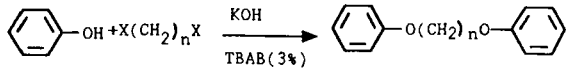
The alkylation of sodium or potassium phenoxide with alkyl halides (Williamson's synthesis) is the best method to prepare alkylarylethers[1]. The use of α,ω-dihaloalkanes does not give good results[2,3] (yields:54-74%) which are even limited to 80% using 1,4-dibromobutane and KOH/Aliquat in PTC without solvent[1]. Only treatment of polymer supported phenoxide ions with dichloromethane gives diaryloxymethanes in good yields[4].

The alkylation of hydroquinone 1 has been performed in several ways: i) mixtures of mono-, di- and non alkylated products are obtained by heating 1 with alkyl halides in the presence of $NaHCO_3$ and triethanolamine in toluene[5]; ii) by heating 1 with alkyl p-toluenesulfonate[6] or bromides[7] in alkaline media under nitrogen; iii) or by using polyethyleneglycol chlorides or tosylates to obtain host compounds[8].

In the other hand, p-alkoxyanilines 2 have considerable interest as starting material for the synthesis of compounds with specific properties. They are precursors of Schiff bases leading to numerous compounds possesing mesomorphic properties as nematic

TABLE 1

Preparation of α,ω-diphenoxyalkanes 5.



3 4 5

n	X	3/4/KOH ratio	t(h)	T(°C)	Yield(%)[a]
1	Cl	1/0.5/1	24	25	20
	Cl	1/0.5/1.5	24	25	83
	Br	1/0.5/1.5	24	25	90
5	Br	1/0.5/1.5	24	80	98
10	Br	1/0.5/1.5	14	85	92
	Br	1/0.5/1.5	7	85	80

a) isolated product.

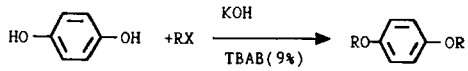
and/or smectic liquid crystals[9-13]. They can also lead to derivatives of alkoxyphenyl carbamic acids with interesting anesthetic activity[14] or to hydantoins possesing anticonvulsant activity[15]. Compounds 2, themselves present antipyretic action in animals[16] or, furthermore they are synergistic antioxidants[17].

Classical synthesis of these compounds involved indirect pathways: i) alkylation of nitrophenol followed by reduction or hydrogenation of the nitro group[18-20], ii) previous protection of the amino group, for instance by acetylation (paracetamol), followed by alkylation of hydroxy group, and acidic or basic hydrolysis of the alkoxyacetanilides thus obtained[21]. Yields are consequently limited and treatments rather tedious.

A selective esterification of aminophenols was reported[22] in a very specific case, but there isn't yet any method for the selective etherification of p-aminophenol. Selective monoalkylation has been described by us[1] in the case of ortho-catechol by an appropiate choice of the basic system in PTC conditions without solvent.

TABLE 2

Preparation of hydroquinone diethers 6.



1 6

RX	1/RX/KOH ratio	t(h)	T(°C)	Yield(%)[a]
MeI	1/3/2.5	24	40	96
	1/2.5/2.5	24	40	73
EtI	1/3/2.5	24	60	90
	1/2.5/2.5	24	60	76
n-BuBr	1/2.5/2	4	80	75
	1/2.5/2.5	4	80	99
	1/2.5/2.5	2	80	54
	1/2.5/2.5	12	60	92
	1/2/2.5	4	80	91
n-OctBr	1/2.5/2.5	4	80	55
	1/2.5/2.5	12	80	99
	1/2.5/2.5	24	60	86

a) isolated product.

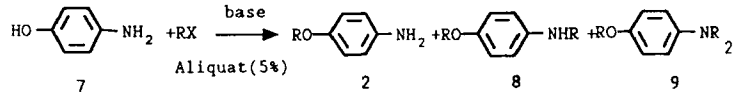
The alkylation of phenol 3 with $Br(CH_2)Br$ 4 (n=1,5,10) has been performed under PTC without solvent conditions using TBAB(3%)/KOH as basic system. Selected results are summarized in table 1.

It can be appreciated that it is possible to obtain α,ω-diphenoxyalkanes 5 (n=1 to n=10) in high yield (90-98%). These results constitute an appreciable enhacement in the obtention of these products when compared to published ones[4].

The alkylation of hydroquinone has been performed in the same way (TBAB(9%)/KOH). Several factors have been considered to determinate the best conditions in the formation of hydroquinone diethers 6. Selected results are given in table 2.

TABLE 3

Alkylation of p-aminophenol.



7 2 8 9

RX	Base	7/base/RX	t(h)	Yields(%) 2/8/9/[a]
n-BuBr	KOH	1/1/1	0.5	29/28/7
		1/1/1	2	15/47/30
n-BuCl	KOH	1/1/1	2	28/3/0
		1/1/1	24	59/32/0
	NaOH	1/1/1	15	30/18/0
		1/2/1	15	70/12/0
				(67)/(11)
n-OctCl	NaOH	1/2/1	15	72/25/0
				(65)/(22)
n-BuBr	KOH	1/3/3	5	5/25/50
		1/4/4	7	2/6/88
				(82)
n-OctBr	KOH	1/4/4	24	0/0/87
				(81)

a) glc yields with internal standard; isolated yields in brackets.

With MeI and EtI major amount of alkyl halide was used due to their high volatility.

Yields less than 15% have been obtained when reactions are carried out at room temperature, even after two days.

This method provides several advantages when compared to the previously reported[4-7]. Obtained yields are excellents. No monoalkylated products have been detected. When 4% of TBAB, usual percentaje in this kind of reaction, was used yields decrease to 50%. When a 1:1 hydroquinone:RX ratio is used hydroquinone diethers are obtained in a 40%. These results would be explained considering that the transfer to the organic phase is only possible when both hydroxy groups are deprotonated.

The main results on the alkylation of p-aminophenol 7 are collected in table 3. Reactions have been performed at 60ºC. O-alkylated 2, O,N-dialkylated 8 and trialkylated 9 compounds can be obtained.

From this results, it is obvious that we succeed in the obtention of highly selective mono O-alkylation by an adequate choice of reactants: NaOH/Aliquat as base and RCl as electrophile. These conditions are not the generally best ones as KOH and RBr are always advocated[23] in such conditions. When applied here, they led to a mixture of all three products without selectivity.

The trialkylated product can be obtained from p-aminophenol in very mild conditions and with good yields simply using KOH/Aliquat and RBr and the appropiate ratio of reactants (1:4:4).

The method proposed permits therefore the preparation of several p-alkoxyanilines, with rather long alkyl chain, in one step from aminophenol. Good yields and selectivities are observed without need for indirect pathways and avoiding amine protection.

EXPERIMENTAL

General procedures

Phenol and hydroquinone. The adequate amounts of phenol or hydroquinone, TBAB and base were mixed and stirred for 15 minutes at room temperature. The alkyl halide (see tables) was then added and the mixture was heated in an oil bath for the required time at the indicate temperature. The crude mixture was extracted with

diethylether (50 ml). Filtration and evaporation of the solvent afforded the pure products. Characterization have been made by ^{1}H-NMR. 5a(n=1): 5.6 (s,2H), CH_2; 6.8-7.4 (m,10H), arom. 5b(n=5): 1.8-2.2 (m,6H), $OCH_2(CH_2)_3$; 3.8-4.1 (t,4H), OCH_2; 6.8-7.4 (m,10H), arom. 5c(n=10): 1.5-2.0 (m,16H), $OCH_2(CH_2)_8$; 3.8-4.1 (t,4H), OCH_2; 6.8-7.4 (m,10H), arom. 6a(Me): 3.8 (s,6H), CH_3; 6.8 (s,4H), arom. 6b(Et): 1.2-1.5 (t,6H), CH_3; 3.8-4.1 (q,4H), CH_2; 6.9 (s,4H), arom. 6c(Bu^n): 1-1.8 (m,14H), $CH_2CH_2CH_3$; 3.8-4.1 (t,4H), CH_2O; 6.9 (s,4H), arom. 6d(Oct^n): 0.8-1.8 (m,30H), $(CH_2)_6CH_3$; 3.8-4.1 (t,4H), CH_2O; 6.9 (s,4H), arom.

p-aminophenol. Finely ground commercial KOH (containing roughly 15% water) or NaOH is mixed with 5% mol Aliquat 336 and the adequate amount of p-aminophenol. After shaking for 5 minutes at room temperature, alkyl halide (see table) is added to the mixture which is consequently heated in an oil bath at 60ºC for the required time. Organic compounds are removed by addition of 50 ml methylene chloride and subsequent filtration on Florisil (which retains mineral salts and the catalyst). They are analyzed by glc and characterized by ms-glc and ^{1}H-NMR after isolation on silica column (pentane-ether 10 to 30%). 2a(Bu^n): 0.8-1.9 (m,7H), $CH_2CH_2CH_3$;; 3.35 (2H), NH_2; 3.8 (t,2H), OCH_2; 6.5-6.85 (m,4H), arom. 2b(Oct^n): 0.75-2.0 (m,15H), $(CH_2)_6CH_3$; 3.3 (2H), NH_2; 3.85 (t,2H), OCH_2; 6.5-6.85 (m,4H), arom. 9a(Bu^n): 0.8-1.9 (m,21H), $(CH_2CH_2CH_3)_3$; 3.15 (t,4H), $N(CH_2)_2$; 3.85 (t,2H), OCH_2; 6.5-6.9 (m,4H), arom. 9b(Oct^n): 0.75-2.0 (m,45H), $((CH_2)_6CH_3)_3$; 3.15 (t,4H), $N(CH_2)_2$; 3.88 (t,2H), OCH_2; 6.55-6.9 (m,4H), arom.

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