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A Simple Preparation of O-Substituted o-Aminophenols

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A SIMPLE PREPARATION OF O-SUBSTITUTED *o*-AMINOPHENOLS.

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Abstract

A simple and not protective method, phase transfer catalysis (PTC) in solvent-free conditions, to prepare the title compounds is described.

Introduction

Alkoxyanilines are ussually prepared by alkylation of nitrophenol[1-3] and subsequent hydrogenation or from hydroxyacetamides[4-6] following by hydrolysis. Also anisidines have been prepared from aminophenol and methyl chloride[7,8] or carbonate[9] in dimethylacetamide as solvent. Bis(*o*-aminophenoxy)alkanes have been also prepared from nitrophenol and ditosylates[10,11] or dichlorides,[12] by nucleophilic aromatic substitution of fluoronitrobenzenes with oxyethyleneglycols[13,14] or from hydroxyacetamides.[15,16] Previously we have reported[17] the selective alkylation of *p*-aminophenol by PTC in the absence of solvent with

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satisfactory results. Now we have tested the O- and N-alkylation of *o*-aminophenol using alkyl halides and α,ω-dihaloderivatives in order to prepare, in one step, starting materials for azacrown ethers.

Results and Discussion

Reactions are performed stirring at 60°C during 8 hours a mixture of *o*-aminophenol **1**, n-butyl or n-octyl chloride, sodium hydroxyde (mole ratio, 1:1:4) and the phase transfer agent (tetra n-butylammonium bromide, TBAB, 5% w/w from **1**) in the absence of any kind of solvent. In these conditions an 86 and 95% of *o*-butoxy **2** and *o*-octyloxyaniline **3**, respectively, have been isolated. In both cases a 3% of O,N-dialkylated derivatives **4** have been obtained. The steric hindrance and the minor reactivity of the octyl chloride must explain the better selectivity observed in this case. Longer reaction time than 8 hours do not provide better results. Using alkyl bromides or potassium hydroxide as base major amounts of O,N-dialkylated compounds have been obtained. Minor proportions of base not guarantee an eficient deprotonation of **1** and, consequently, N-alkylation is more effective.

N-alkylation of *o*-aminophenol in the absence of base was unsuccesfully tried. However from *o*-alkoxyanilines, N-alkylation was performed in the absence or in the presence of base (sodium hydroxyde). In this case n-butyl and n-octyl bromides are used in a 1:1 mole ratio. Working in the presence of base (mole ratio 1:1:1) better yield are obtained (92 *vs* 80%, butyl, 80°C, 16 h). This fact suggest the existence of an efective phase transfer catalysis process.

Bis(*o*-aminophenoxy)derivatives **5** have been prepared in satisfactory yields (49-84%) using α,ω-dihaloderivatives and the appropriate conditions for (**1**:NaOH: chloro derivatives mole ratio, 1:4:0.5; TBAB, 5%; 60°C, 24 h). In the preparation of **5b** and **5c** lower yields were obtained because elimination in the alkyl halide is favoured by the oxygen atom in the β-position. In order to minimize the elimination reaction potassium carbonate was used as base, but in this case N-(*o*-hydroxyphenyl) morpholine **6** is formed by double N-alkylation. Attemps to N-alkylate the bis(*o*-aminophenoxy)derivatives

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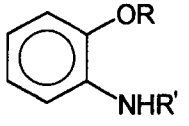
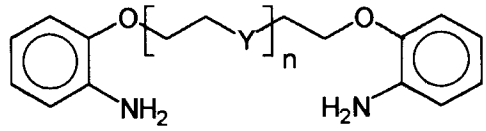
allow to polymeric mixtures. In our reactions conditions polymerization is favoured with regard to cyclization, that requires high dilution techniques.





2; R= Bu, R'= H
3; R= Oct, R'= H
4a; R= R'= Bu
4b; R= R'= Oct

5a; Y= CH_2, n=1
5b; Y= O, n= 1
5c; Y= O, n= 2

Table. Selected conditions for O- and N-alkylations.

product	mole ratio[a)]	T (°C)	t (h)	yield
2	1 / 4 / 1	60	8	86
3	1 / 4 / 1	60	8	95
4a	1 / 1 / 1	80	16	88
4b	1 / 1 / 1	80	16	90
5a	1 / 4 / 0.5	60	24	84
5b	1 / 4 / 0.5	60	24	63
5c	1 / 4 / 0.5	60	24	49

a) **1** / base / alkylating agent.

In conclusion, phase transfer catalysis in solvent-free conditions provides a simple and non protective method to prepare *o*-alkoxyanilines and bis(*o*-aminophenoxy) derivatives.

Experimental

General procedure. Phenol derivative (10 mmol), sodium hydroxide and TBAB (5%) were mixed at room temperature and stirred for 10 min. Alkylating agent was added at once and the mixture was heated

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during the time and at the required temperature (see table). Products were isolated by flash chromatography.

o-butoxyaniline, 2. b.p.(°C/mmHg) 115/2 (lit.[18] 129/11). Eluent: light petroleum/ ethyl acetate (9:1). IR(neat) $\nu_{max}(cm^{-1})$: 3465, 3373, 2870, 1218. ^{1}H-NMR ($CDCl_3$) δ(ppm): 0.9 (t, J= 7.5, 3H, CH_3), 1.5 (m, 2H, CH_2CH_3), 1.8 (m, 2H, O-CH_2CH_2), 3.7 (s, 2H, NH_2), 3.9 (t, J= 6.1, 2H, O-CH_2), 6.7 (m, 4H, H arom.)

o-octyloxyaniline, 3. b.p.(°C/mmHg) 120/0.05 (lit.[18] 147-8/4). Eluent: light petroleum/ ethyl acetate (99:1). IR(neat) $\nu_{max}(cm^{-1})$: 3472, 3377, 2853, 1219. ^{1}H-NMR ($CDCl_3$) δ(ppm): 0.9 (t, J= 6.3, 3H, CH_3), 1.2-1.5 (m, 10H, $(CH_2)_5CH_3$), 1.8 (m, 2H, O-CH_2CH_2), 3.7 (s, 2H, NH_2), 4.0 (t, J= 6.2, 2H, O-CH_2), 6.7-6.8 (m, 4H, H arom.)

N-butyl-o-butoxyaniline, 4a. b.p.(°C/mmHg) 125/0.1. IR(neat) ν_{max} (cm^{-1}): 3425, 2869, 1210. ^{1}H-NMR ($CDCl_3$) δ(ppm): 0.9 (m, 6H, CH_3), 1.4-1.8 (m, 8H, $CH_2CH_2CH_3$), 3.1 (t, J= 5.9, 2H, N-CH_2), 3.9 (t, J= 6.0, 2H, O-CH_2), 4.2 (bs, 1H, NH), 6.6-6.9 (m, 4H, H arom.). Calculated for $C_{14}H_{23}NO$, C 75.97, H 10.47, N 6.33. Found C 75.58, H 10.12, N 6.69.

N-octyl-o-octyloxyaniline, 4b. b.p.(°C/mmHg) 185/0.05. IR(neat) ν_{max} (cm^{-1}): 3425, 2853. ^{1}H-NMR ($CDCl_3$) δ(ppm): 0.9 (t, J= 6.1, 6H, CH_3), 1.2-1.8 (m, 24H, $(CH_2)_6CH_3$), 3.1 (t, J= 7.0, 2H, N-CH_2), 3.9 (t, J= 6.4, 2H, O-CH_2), 4.2 (bs, 1H, NH), 6.6-6.8 (m, 4H, H arom.). Calculated for $C_{22}H_{39}NO$, C 79.22, H 11.79, N 4.20. Found C 78.89, H 11.57, N 4.68.

1,5-bis(o-aminophenoxy)pentane, 5a. m.p.(°C) 59-60 (ethyl ether/hexane) (lit.[19] 61-62). Eluent: light petroleum/ ethyl acetate (7:3). IR(KBr) ν_{max} (cm^{-1}): 3445, 3366, 2866. ^{1}H-NMR ($CDCl_3$) δ(ppm): 1.6-1.7 (m, 2H, O-$CH_2CH_2CH_2$-), 1.8-1.9 (m, 4H, O-$CH_2CH_2CH_2$-), 3.7 (s, 4H, NH_2), 4.0 (t, J= 6.3, 4H, O-CH_2), 6.7-6.8 (m, 8H, H arom.).

bis(2-(o-aminophenoxy)ethyl)ether, 5b. m.p.(°C) 62-63 (ethyl ether/hexane) (lit.[10] 63-65). Eluent: light petroleum/ ethyl acetate (1:1). IR(KBr) ν_{max} (cm^{-1}): 3466, 3376, 2868. ^{1}H-NMR ($CDCl_3$)

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δ(ppm): 3.8 (s, 4H, NH_2), 3.9 (m, 4H, CH_2-O-CH_2), 4.15 (m, 4H, Ar-O-CH_2), 6.6-6.8 (m, 8H, H arom.).

1,2-bis(2-(o-aminophenoxy)ethoxy)ethane, 5c. m.p.(°C) 53-55 (ethyl ether/hexane). Eluent: ethyl acetate. IR(KBr) ν_{max} (cm^{-1}): 3396, 3304, 3198. ^{1}H-NMR ($CDCl_3$) δ(ppm): 3.7 (s, 4H, NH_2), 3.8-3.9 (m, 8H, CH_2-O-CH_2), 4.1 (t, J= 4.8, 4H, Ar-O-CH_2), 6.6-6.8 (m, 8H, H arom.). Calculated for $C_{18}H_{24}N_2O_2$, C 65.04, H 7.28, N 8.43. Found C 64.89, H 7.14, N 8.39.

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