SYNTHESIS OF PHENOXYPYRIDINES UNDER PHASE TRANSFER CATALYSIS CONDITIONS

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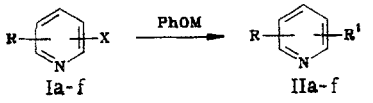
Reactions of halopyridines with alkali metal phenoxides in a two phase liquid–solid catalytic system, rather than in a liquid–liquid phase transfer catalytic system, make it possible to prepare 2-, 3-, and 4-phenoxypyridines from unactivated bromo- or chloropyridines and 2-chloropicolines. In polyhalogenated pyridines only α- and γ-halogen atoms undergo substitution. 7, 8-Dibromo-6-azaphenoxane has been prepared by the reaction of 2,3,5,6-tetrabromopyridine with the dipotassium salt of pyrocatechol.

Nucleophilic substitution of halogen atoms in alkyl-, allyl-, benzyl-, and aryl halides by alkoxide anions under phase transfer catalysis conditions represents a convenient preparative method for the synthesis of the corresponding ethers, among them phenyl ethers [1]. This reaction also takes place in the halopyridine series. 2-Chloropyridines containing an electron withdrawing substituent in the 3- or 5-position (such as NO_2 or Cl) react with phenols, either ring-substituted or unsubstituted, in a two-phase benzene (or toluene)–50% aqueous NaOH in the presence of a phase transfer catalyst ($Bu_4\overset{+}{N}\overset{-}{Cl}$ or $Bu_3\overset{+}{P}C_{16}H_{33}\overset{-}{Br}$) at 25-100°C to give the corresponding 2-phenoxypyridines in satisfactory yields [2]. It is not possible to prepare 2-phenoxypyridine from 2-chloropyridine under these conditions, however [2].

We have examined the reactions in the series of halopyridines with alkali metal phenoxides under conditions of liquid–solid phase transfer catalysis. This variation has broader possibilities in terms of varying the reaction temperature than traditional liquid–liquid phase transfer catalysis. Based on the data in the previous paper [2], we assumed that a reaction temperature greater than 100°C would be required for the reactions of halopyridines with phenoxides. For this reason, o-xylene was selected as the reaction solvent and crown ethers, quaternary phosphonium salts, and tributylphosphine oxide as catalysts, since these compounds are significantly more thermally stable [3] than quaternary ammonium salts, which generally are used at temperatures below 100°C.

In the absence of a phase transfer catalyst the reaction of 2-bromopyridine Ia with sodium or potassium phenoxide in o-xylene at the boiling point of the mixture occurs very slowly and generates only a very low yield (1-6%) of 2-phenoxypyridine IIa. The introduction of 10% catalyst markedly accelerates the reaction, although potassium phenoxide is substantially more effective in the reaction than sodium phenoxide (see Table 1).



Ia-f IIa-f

I, II a,e,f R=H; b R=3-CH_3; c R=4-CH_3; d R=6-CH_3; a-d R^1=2-PhO; e R^1=4-PhO, f R^1=3-PhO; Ia X=2-Br; b–d X=2-Cl; e X=4-Cl; f X=3-Br

In both cases crown ethers are the most active catalysts. In the case of PhONa the best catalyst was found to be 15-crown-5, which has a pore diameter size (0.17-0.22 nm) that is more favorable for complex formation with Na ion (ionic diameter 0.194 nm) than K (ionic diameter 0.266 nm) [4]. Tetrabutylphosphonium chloride is somewhat less active than crown ethers, whereas tributylphosphine oxide catalyzes the reaction of 2-bromopyridine Ia with potassium or sodium phenoxide only to an insignificant extent. The reaction of compound Ia with alkali

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TABLE 1. Reaction Conditions for the Reaction of 2-Bromopyridine with Sodium and Potassium Phenoxides under Liquid–Solid Phase Transfer Catalysis Conditions (145°C, 10% catalyst)

Catalyst	Yield of 2-phenoxypyridine, % (based on GLC data)					
	sodium phenoxide			potassium phenoxide		
	4 h	10 h	24 h	3 h	8 h	10 h
18-Crown-6	6,8	10,7	16,1	24,5	26,8	48,9
Dibenzo-18-crown-6	1,1	2,8	8,6	44,4	64,7	72,1
15-Crown-5	5,0	7,8	26,1	9,2	—	33,6
$Bu_4\overset{+}{P}\overset{-}{Cl}$	1,9	4,3	11,7	7,9	36,3	38,5
$Bu_3P\rightarrow O$	1,6	5,6	15,4	3,7	10,6	9,6
$P-CH_2\overset{+}{P}Bu_3\overset{-}{Cl}$*	2,4	2,8	6,9	6,1	16,8	—
$P-(CH_2)_6\overset{+}{P}Bu_3\overset{-}{Br}$**	1,1	5,4	12,8	7,0	24,0	33,5
In the absence of catalyst	0,2	0,4	0,7	0,2	3,6	6,4

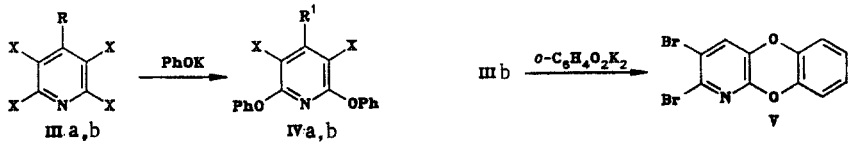
*Tributylmethylphosphonium chloride on a polymeric support (0.78 mmole Cl/g).
**Tributylhexylphosphonium bromide on a polymeric support (83 mmole Br/g).

metal phenoxides also occurs under the conditions of "triphase catalysis" [5] in the presence of phosphonium salts which have been affixed to a polymeric support material which is insoluble in the reaction medium. These catalysts, although inferior to the soluble $Bu_4\overset{+}{P}\overset{-}{Cl}$ phosphonium salt in terms of its activity, are nevertheless capable of being regenerated and can thus be used repeatedly in the reaction. As was demonstrated in the case of other nucleophilic substitution reactions [5], a polymer-supported catalyst in which the onium salt is separated from the polymer matrix by a longer methylene chain is more active (Table 1). The activities of various phase transfer catalysts (see Table 1) were compared using semi-micro amounts of reagents (2 mmole). When the reaction of Ia with PhOK in the presence of 18-crown-6 was carried out on a preparative scale (based on 5 g of starting material Ia), compound IIa was isolated in 40% yield (based on GLC analysis the yield when working with small amounts of reagents was 49%; the reaction time was increased from 10 h to 22 h).

Potassium phenoxide was used for the synthesis of other phenoxypyridine derivatives. For instance, reaction of 4-chloropyridine Id (in the form of its hydrochloride, since the free base is unstable) under conditions analogous to those used for the preparation of compound IIa (refluxing xylene, dibenzo-18-crown-6 catalyst) gave 4-phenoxypyridine IIe in ~30% yield. We have also verified the suitability of this reaction for the synthesis of phenoxypyridines containing electron donating methyl groups (IIb-d), starting with 2-chloropicolines Ib-d. Phenoxypicolines are formed in extremely low yields (~4%) upon extended reflux of solutions of Ib-d in xylene with PhOK in the presence of 18-crown-6; for this reason, we examined the feasibility of preparing these compounds in the absence of solvent. This variation of the two-phase catalytic method [6] has been successfully applied to a variety of other nucleophilic reactions (cf., for example, [7] and references therein). This method has been found to be effective for the synthesis of compounds IIb-d. The 2-pyridyl phenyl ethers IIb-d were obtained in 54-67% yields by heating compounds Ib-d with PhOK in the presence of 18-crown-6 (150-160°C, 7-9 h).

Phase transfer catalysis in the absence of solvent is also suitable for the preparation of 3-phenoxypyridine (IIf). A halogen atom in a β-position is substantially more stable with respect to nucleophilic substitution reactions than halogen atoms in α- and γ-positions. Upon reflux of a solution of 3-bromopyridine If in xylene in the presence of PhOK and 18-crown-6 compound IIf was formed practically not at all. In the absence of the solvent, however, compound IIf was obtained in 44% yield (170°C, 35 h).

We have also investigated the reactions of polyhalopyridines IIIa,b with PhOK in a two-phase liquid–solid catalytic system. As might be expected, the reaction of 2,3,5,6-tetrabromopyridine IIIa with PhOK in refluxing xylene in the presence of 18-crown-6 gave 3,5-dibromo-2,6-diphenoxypyridine IVa in 70% yield. Pentachloropyridine IIIb is converted in 67% yield to 3,5-dichloro-2,4,6-triphenoxypyridine IVb under similar conditions.



III, IVa X=Br, R=R¹=H; b X=R=Cl, R¹=PhO

Tetrabromopyridine IIIa was also allowed to react with the dipotassium salt of pyrocatechol. Since the bromine atom in the β-position of the ring is significantly less active in nucleophilic substitution reactions than a bromine in the α-position, and since it is not possible to carry out the latter reaction in the absence of solvent, mesitylene (bp 165°C) was chosen as the solvent for the reaction. The reaction of compound IIIa with potassium pyrocatecholate under phase transfer catalysis conditions gave 7,8-dibromo-6-azaphenoxane V, which was isolated in 11% yield. It was not possible to substitute another two bromine atoms and prepare a pentacyclic compound under these reaction conditions, even when using an excess of the nucleophilic reagent.

EXPERIMENTAL

^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker WH-90/DS spectrometer (at 90 and 22.63 MHz, respectively) using $CDCl_3$ solutions versus TMS as internal standard. Mass spectra were recorded on Kratos MS-25 and AEI MS-50 spectrometers at an ionizing electron energy of 70 eV.

GLC analyses were carried out on a Chrom-5 chromatograph with a flame ionization detector and a glass column (1.2 m × 3 mm), which was filled with 5% OV-17 on W-HP chromosorb (80-100 mesh). Helium (60 cm^3/min) was used as the carrier gas. The analysis temperature was varied between 170-250°C depending on the composition of the reaction mixture. Melting point temperatures were determined using a Boetius block and are reported without correction.

2- and 3-Bromopyridines were distilled under vacuum prior to their use. 4-Chloropyridine hydrochloride, tributylphosphine oxide (Aldrich), 18-crown-6, dibenzo-18-crown-6, tetrabutylphosphonium chloride, and polymerbound tributylmethylphosphonium chloride (0.78 mmole Cl/g) and tributylhexylphosphonium bromide (0.83 mmole Br/g) (Fluka) were used without further purification. 2-Chloropicolines (Ib-d) were synthesized from the corresponding 2-aminopicolines (Fluka) according to [8].

Reaction of 2-Bromopyridine (Ia) with Sodium and Potassium Phenoxides in the Presence of Different Catalysts. A 5 ml Pierce reaction vessel was charged with 0.3 g (1.9 mmole) of compound Ia, 0.27 g (2 mmole) sodium or potassium phenoxide, 3 ml o-xylene, and 0.19 mmole (10%) catalyst (see Table 1). The reaction was stirred at reflux, and the course of the reaction was followed by GLC. The concentration of compound IIa in solution was determined by an absolute calibration method. The results obtained under these conditions are reported in Table 1.

2-Phenoxypyridine (IIa). To a solution of 5 g (31.4 mmole) of compound Ia and 0.83 g (3.14 mmole) 18-crown-6 in 50 ml o-xylene was added 5.28 g (40 mmole) potassium phenoxide and the mixture was stirred 22 h at 145°C. The reaction mixture was diluted with benzene twice, washed with 20% aqueous NaOH (30 ml), and the organic layer was separated and dried ($CaCl_2$). The solvents were removed at reduced pressure, and the residue was distilled under vacuum. Yield 2.15 g (40%), bp 85°C (0.05 mm Hg), mp 36°C [according to [9], bp 134-135°C (11 mm Hg); according to [10], mp 41-42°C]. PMR spectrum: 6.7-7.7 (8H, m); 8.1-8.2 ppm (1H, m); M^+ 171.

3-Methyl-2-phenoxypyridine (IIb). A mixture of 6 g (47 mmole) compound Ib, 4.62 g (35 mmole) PhOK, and 1.26 g (3.5 mmole) dibenzo-18-crown-6 was stirred for 7 h at 160°C. The reaction mixture was diluted with benzene fivefold, washed with 5% aqueous NaOH (20 ml), and the organic layer was separated and dried ($CaCl_2$); the benzene was evaporated and the residue fractionally distilled under vacuum. Yield 4.4 g (68% based on PhOK), bp 100°C (2 mm Hg) [according to [10], bp 101-102°C (1 mm Hg)]. PMR spectrum: 2.33 (3H, s); 6.8-7.6 (7H, m); 7.9-8.0 ppm. (1H, m); M^+ 185.

4-Methyl-2-phenoxypyridine (IIc). This was prepared analogously to compound IIb from 12.7 g (100 mmole) compound Ic and 9.24 g (70 mmole) PhOK in the presence of 1.85 g (7 mmole) 18-crown-6 at 150°C for 6 h. Yield 7 g (54% based on the amount of PhOK); bp 120°C (3 mm Hg). PMR spectrum: 2.40 (3H, s); 6.74 (1H, br. s); 6.86 (1H, d, J = 5 Hz); 7.0-7.6 (5H, m); 8.09 ppm. (1H, d, J = 5 Hz); M^+ 185.

6-Methyl-2-phenoxypyridine (IId). As described above for compound IIb, reaction of 20 g (160 mmole) compound Id and 13.2 g (100 mmole) PhOK in the presence of 2.64 g (10 mmole) 18-crown-6 at 150°C for 9 h gave a yield of 10 g (54% based on PhOK), bp 93°C (1.5 mm Hg) [according to the data in [8], bp 140°C (15 mm Hg)]. PMR spectrum: 2.40 (3H, s); 6.3-7.5 ppm (8H, m); M^+ 185.

4-Phenoxypyridine (IIe). A suspension of 10 g (67 mmole) Ie and 8.8 g (67 mmole) PhOK in 60 ml o-xylene, containing 2.16 g (6 mmole) dibenzo-18-crown-6, was refluxed with stirring for 6 h. The reaction mixture was diluted twofold with benzene and washed with 10% aqueous NaOH (50 ml). The organic layer was separated, dried over $CaCl_2$, and the solvent was evaporated; the residue was distilled under vacuum. Yield 3.15 g (28%), bp 90°C (2.5 mm Hg) [according to [9], bp 157-158°C (21 mm Hg)]. PMR spectrum: 6.7-7.6 (7H, m); 8.42 ppm (2H, dd, J_1 = 6, J_2 = 1.8 Hz); M^+ 171.

3-Phenoxypyridine (IIf). This was prepared as described above for compound IIb, starting with 23.8 g (150 mmole) of 3-bromopyridine If and 13.2 g (100 mmole) PhOK in the presence of 2.64 g (10 mmole) 18-crown-6 at 170°C for 35 h. Yield 6 g (44% based on PhOK), bp 100-103°C (4 mm Hg) [according to the data in [9], bp 147-149°C (17 mm Hg)]. PMR spectrum: 6.8-7.4 (7H, m); 8.1-8.4 ppm (2H, m); M^+ 171.

2,3,5,6-Tetrabromopyridine (IIIa). Prepared by diazotization of 2,6-diaminopyridine with sodium nitrite in a mixture of 48% HBr with bromine under the conditions reported by Craig [11] for the preparation of 2-bromopyridine from 2-aminopyridine. To 315 ml 48% HBr was added 16.37 g (150 mmole) of 2,6-diaminopyridine (Fluka) over a 10 min period; the resulting solution was cooled to ~0°C and stirred vigorously as 75.2 ml (940 mmole) $NaNO_2$ in a minimum amount of water was added over 1 h, at such a rate that temperature remained below 0°C. After $NaNO_2$ addition was complete the reaction mixture was stirred an additional 1 h at 0°C, then diluted with 20% aqueous NaOH to give a pH value of ~8; the mixture was allowed to stand at 20°C for 18 h. The mixture was extracted with ether (6 × 100 ml), and the organic layer was separated and dried over Na_2SO_4; the ether was evaporated and the orange crystalline precipitate was recrystallized from hexane. Yield 24 g (40.5%), mp 103°C (according to the data in [12], mp 103.5-104°C). PMR spectrum, δ: 8.04 ppm (s) [according to [13], τ 1.91 (s)]; ^{13}C-NMR spectrum: 122.8, 140.4, 145.1 ppm (d, J = 40 Hz, 4-H); M^+ 391 (^{79}Br).

This method for the synthesis of compound IIIa is substantially more convenient and simpler than other known methods for its preparation (such as high temperature bromination of 2,6-dibromopyridine [14], bromination of 1-methyl-6-bromo-2-pyridone to give 1-methyl-3,5,6-tribromo-2-pyridone and reaction of the latter with PBr_5/PBr_3 in a sealed tube [12], or electrolytic reduction of pentabromopyridine [15]).

3,5-Dibromo-2,6-diphenoxypyridine (IVa). To a solution of 3.94 g (10 mmole) compound IIIa was added 3 g (23 mmole) PhOK and 0.53 g (2 mmole) 18-crown-6 in 25 ml o-xylene, and the mixture was refluxed for 6 h. The reaction mixture was diluted twofold with benzene, washed with 20% aqueous NaOH (50 ml), and the organic layer was separated and dried over $CaCl_2$; the solvent was removed under vacuum and the residue was recrystallized from hexane. Yield 3.0 g (71%), mp 74°C. PMR spectrum: 6.8-7.3 (10H, m, C_6H_5); 8.02 ppm (1H, s, 4-H); M^+ 419 (^{79}Br). Found, %: C 48.8, H 2.4, N 3.0. $C_{17}H_{11}Br_2NO_2$. Calculated, %: C 48.5, H 2.6, N 3.3.

3,5-Dichloro-2,4,6-triphenoxypyridine (IVb). To a solution of 4.27 g (17 mmole) pentachloropyridine (Fluka) and 0.62 g (1.7 mmole) dibenzo-18-crown-6 in 50 ml o-xylene was added 8 g (60 mmole) potassium phenoxide and the mixture was stirred 2 h at 140°C. The reaction mixture was diluted twofold with benzene and washed with 20% aqueous NaOH (50 ml); the organic layer was separated and dried ($CaCl_2$) and the solvents were removed under vacuum and the residue recrystallized from hexane. Yield 4.82 g (67%), mp 106°C (according to the data in [16], mp 105-107°C). PMR spectrum: 6.8-7.4 ppm (m); M^+ 423 (^{35}Cl).

7,8-Dibromo-6-azaphenoxane (V). A mixture of 4 g (10 mmole) compound IIIa, 3.77 g (20 mmole) potassium pyrocatecholate, and 0.36 g (1 mmole) dibenzo-18-crown-6 in 15 ml mesitylene was refluxed for 2 h; an additional 1 g of potassium pyrocatecholate was added and the mixture was refluxed with stirring another 1 h 30 min. The mixture was cooled to 20°C, diluted twofold with benzene, and washed with 10% aqueous NaOH (30 ml); the organic layer was separated and dried ($CaCl_2$), and the solvents were removed under vacuum and the residue recrystallized from hexane. Yield 0.37 g (11%) of colorless crystals, mp 172-174°C. PMR spectrum: 6.8-7.1 (4H, m); 7.33 ppm (1H, s); M^+ 341 (^{79}Br). Found, %: C 38.8, H 1.5, N 4.0. $C_{11}H_5Br_2NO_2$. Calculated, %: C 38.5, H 1.5, N 4.1.

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PHYSICOCHEMICAL PROPERTIES AND STRUCTURES OF 4-AZAFLUORENONES AND 2,3-BENZO-4-AZAFLUORENONES

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The quantum-chemical characteristics and the results of a comparative analysis of the IR and electronic absorption spectra and the polarographic reduction of methyl-containing 4-azafluorenones (structural analogs of the alkaloid onychine – 1-methyl-4-azafluorenone) and condensed benzo-4-azafluorenones are presented.

Some physicochemical properties of azafluorenones (ketoindenopyridines), which are isoelectronic analogs of fluorenones, were examined in [1]; however, detailed studies of these compounds have not yet been made. In the present communication we present the results of a comparative study of the IR and electronic absorption spectra and polarography of 4-azafluorenones (5H-indeno[1,2-b]pyridin-5-ones) and 2,3-benzo-4-azafluorenones (6H-indeno[3,2-b]-quinolin-6-ones) and give an analysis of them with the use of the calculated quantum-chemical characteristics of the molecules of the investigated compounds (see middle of following page).

IR Absorption Spectra. It is known [10] that a change in the $\nu_{C=O}$ frequency and the integral intensity $A_{(C=O)}$ of molecules that do not participate in hydrogen and donor-acceptor bonds is determined primarily by conjugation and the inductive effect; the intensity of the absorption band is a more sensitive parameter. It has been shown [10, pp. 168, 327; 11] that conjugation of the carbonyl group with a multiple bond and phenyl rings decreases $\nu_{(C=O)}$ by 25-30 cm^{-1}, while the intensity of the band increases by ~30%.

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