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N-ALKYL-4-(N',N'-DIALKYLAMINO)PYRIDINIUM SALTS: THERMALLY STABLE PHASE TRANSFER CATALYSTS FOR NUCLEOPHILIC AROMATIC DISPLACEMENT

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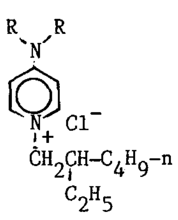
Abstract: N-Alkyl salts of 4-dialkylaminopyridines are effective phase transfer catalysts which are up to 100 times more stable than tetrabutylammonium bromide to conditions encountered in nucleophilic aromatic substitution reactions. These salts are thermally stable to over 300°C, and promote reactions in non-polar solvents (or in the absence of solvent) at temperatures as high as 200°C.

The art and practice of phase transfer catalysis (PTC) in organic chemistry has grown extensively in the past several years.[1] The technique has proved to be important industrially, in cases where the alternative use of polar aprotic solvents would be prohibitively expensive.[2] Although substantial efforts in the synthesis of new catalysts have been made in the areas of crown ether chemistry[3] and polymer-supported catalysts,[4] relatively few examples of new ammonium salt PTC's have appeared.[5] Ammonium salts are attractive since they are generally prepared more conveniently and inexpensively than crown ethers. During a general investigation of PTC catalyzed nucleophilic aromatic substitution reactions,[6] we became aware of the limitations of ammonium and phosphonium salts in reactions under severe conditions. Tetrabutylammonium bromide, for example, is attacked by alkyl mercaptans at ambient temperature, and is totally consumed by sodium phenoxide in 1 hr in refluxing toluene. We now wish to report that N-alkyl-4-(N',N'-dialkylamino)pyridinium salts (**1-4**) are effective phase transfer catalysts which are up to 100 times more stable than Bu_4NBr to phenoxide.



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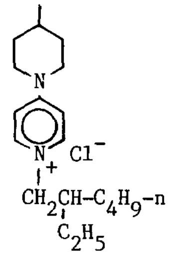

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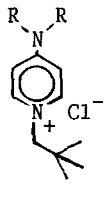

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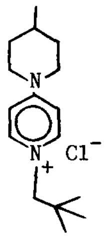

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a R = CH_3
b R = n-Bu
c R = n-Hexyl

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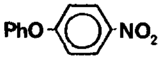
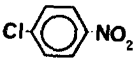
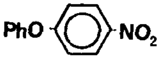
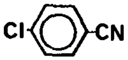
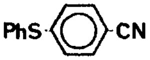
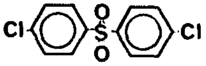
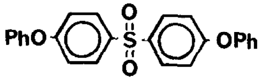
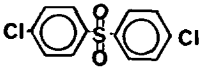
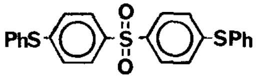
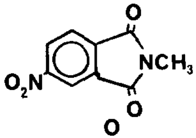
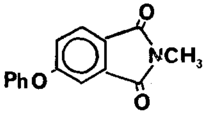
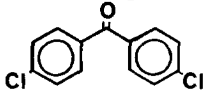
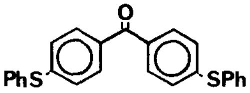
b R = n-Hexyl

Table 1. Phase Transfer Catalyzed Nucleophilic Aromatic Displacement Reactions[a]

Substrate	Nucleophile	Catalyst (%)[b]	time/temp	Product (yield)[c]	
	PhONa	2(0.5)	15 min/110[d]		(97)
	PhONa	**3a**(5)	30 min/125[e]		(95)
	PhONa	Bu_4NBr(10)	8 hr/125[e]		(12)
	PhSNa	**1a**(5)	4 hr/150[f]		(86)
	PhONa	2(5)	2 hr/180[f]		(87)
	PhSNa	**1a**(5)	2 hr/150[f]		(90)
	PhONa	3(2)	1 hr/110[d]		(99)
	PhSNa	**1b**(5)	2 hr/110[d]		(90)

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[a] All reactions were carried out under N_2, using anhydrous conditions, with 5% excess nucleophile. [b] Mole % relative to substrate. [c] Isolated yields. [d] Toluene solvent. [e] Chlorobenzene solvent. [f] o-Dichlorobenzene solvent. [g] Vpc yield.

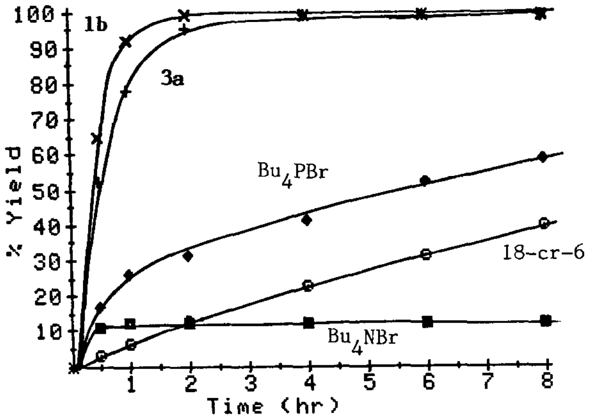


Figure 1. Preparation of nitrophenyl phenyl ether from sodium phenoxide and p-chloronitrobenzene using 5% catalyst in chlorobenzene at reflux.

Pyridinium salts **1** and **2**[7] are readily prepared in quantitative yield by refluxing the parent p-dialkylaminopyridine and 2-ethylhexyl mesylate in toluene for 3 hr, or by refluxing in CH_3CN for one hour. Metathesis to the chloride or bromide may be carried out via ion exchange or simply by washing methylene chloride solutions of the mesylate salts with satd. NaCl or NaBr. Salts **3** and **4** are prepared in 60-80% yield via reaction of the dialkylaminopyridines with neopentyl mesylate neat at 130° for 72 hr (higher temperatures fragment neopentyl mesylate). The chloride salts are recrystallized from CH_3CN/EtOAc mixtures, and are slightly hygroscopic. Salts **1** and **2** are thermally stable to 250°; salts **3** and **4** are stable to over 300°.

The utility of salts **1–4** as phase transfer catalysts is summarized in Table 1. In many cases, reactions have been carried out under conditions which totally consume Bu_4NBr. For example, sodium thiophenolate reacts with bis-(4-chlorophenyl)sulfone, at 150°, using catalyst **1a**, to form the bis-sulfide sulfone in 90% isolated yield; use of Bu_4NBr affords less than a 10% yield. Salts **1a–c** were the most efficient catalysts, generally providing complete reaction at 5% catalyst level. None of the reactions in Table 1 provide more than 1% product in the absence of catalyst.

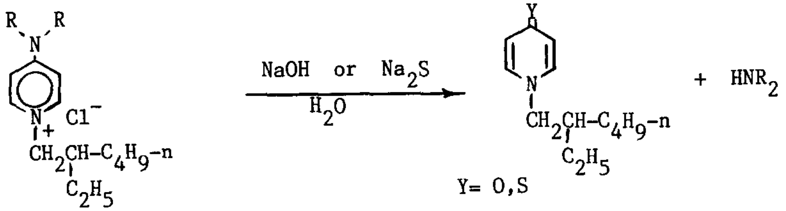
Figure 1 is a graphic representation of the reaction of 4-chloronitrobenzene and sodium phenoxide, using various catalysts at the 5% level. Salts **1b** and **3a** provide quantitative yields in 2 hr in refluxing chlorobenzene; Bu_4NBr is effective at first, but is destroyed in less than one hour, with the yield of nitrophenyl phenyl ether reaching only 12%. Results using 18-crown-6 and Bu_4PBr are included for comparison.

We have obtained a measure of relative catalyst stabilities to displacement conditions by reacting a two-fold excess of sodium phenoxide with the catalysts in the absence of electrophiles. The amount of catalyst remaining at various times was determined by nmr, using tetrachloroethane as an internal standard. Assuming pseudo-first order kinetics, one can calculate half-lives for catalyst destruction at various temperatures. The results are shown in Table 2. All of our catalysts are significantly more stable than Bu_4NBr.

Table 2. Catalyst Half-lives in presence of Sodium Phenoxide

Catalyst	Solvent	Temp	Half-life
Bu_4NBr	toluene	110°	7 min
1a	toluene	110°	8 hr
2	toluene	110°	11 hr
2	PhCl	125°	9 hr
3a	toluene	110°	12 hr

Unfortunately, these catalysts have very limited utility in the presence of NaOH or Na_2S at high temperatures. Displacement of dialkylamine and formation of N-alkylpyridone or thiopyridone occurs rapidly at 100°.



We are continuing to explore the utility of these catalysts in PTC rections involving other nucleophiles and electrophiles. Preliminary results indicate that salts **1** and **3** are effective catalysts for displacement by NaCN and NaF.[8]

Acknowledgement. We thank Reilly Tar and Chemical Corp for a generous sample of 4-(4-methylpiperidinyl)pyridine, and Steven B. Dorn for providing high resolution mass spectral data.

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8. Preliminary results indicate that catalyst **3a** transfers KCN with an efficiency comparable to 18-cr-6; Chloride/fluoride exchange of activated aromatic systems has been achieved in neat reactions at 200-220° using catalysts **1** and **2** (J. A. Cella, personal communication).

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