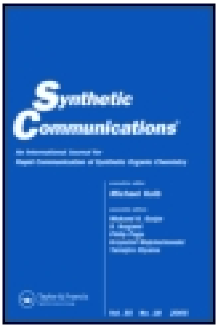

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A New Phase Transfer Catalyst (PTC) for N-Alkylation Reactions

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A NEW PHASE TRANSFER CATALYST (PTC) FOR N-ALKYLATION REACTIONS

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Abstract : Hexamethylene tetramine bromide $HMTA^+ Br^-$ - a new phase transfer catalyst is reported for N-Alkylation reactions of industrially important anilides.

From the various available phase transfer catalysts, choice is often made from highly expensive and potentially carcinogenic simple crown ethers[1] having a general structure (1) to highly elaborate cryptates[2] (having two different electro-negative heteroatoms eg. N & O) (2) or from quaternary salts of elements of the Group V A of the periodic table[3] having a general structure (3) (where R_1, R_2, R_3 and R_4 could be same or different alkyl or aryl groups; M could be nitrogen, phosphorus, arsenic, antimony or bismuth and X could be halide or sulfate, however, in this series more predominant are quaternary ammonium or phosphonium salts.

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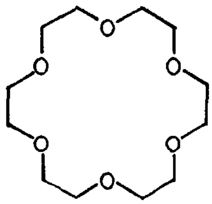
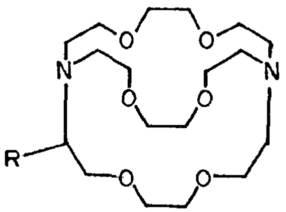
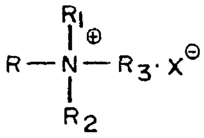
On close comparison of the structures (1-2) with hexamethylene tetramine (HMTA) (4) which has symmetrical Adamantane like structure[4] having all the four Nitrogen atoms chemically and sterically equivalent[5 & 6], it discerns that both crown ether (1) and HMTA (4) are cyclic molecules having heteroatoms i.e.six oxygen atoms in (1) and four Nitrogen atoms in (4). Further, each heteroatom is bound to two other heteroatoms through a methylene bridge, (eg. a dimethylene bridge in (1 or 2) and mono methylene bridge in (4)). HMTA (4) structurally resembling the simple crown ether, as such, does not act as PTC. However, in the present paper, through its monoquaternization, Hexamethylene tetramine Hydrobromide ($HMTA^+ Br^-$) (5) has been demonstrated, for the first time, to act as PTC, catalysing N-alkylation reactions



(1)

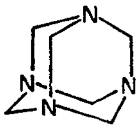


(2)

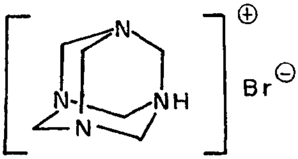


$R-\overset{R_1}{\underset{R_2}{N^{\oplus}}}-R_3 \cdot X^{\ominus}$

(3)



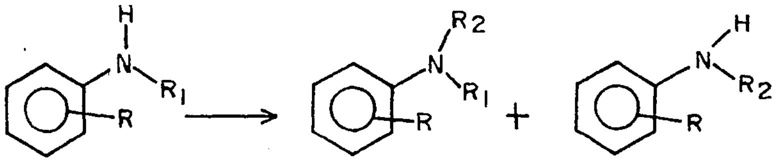
(4)



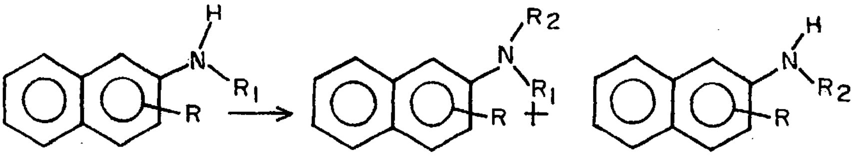
(5)

in high yields, of industrially important intermediates eg. N-Acyl, N-Formyl, N-Tosyl, N-aryl anilides, and certain Naphthyl amides, useful for preparing mono N-alkyl anilines. HMTA$^+$ Br$^-$ may be considered to belong to a class of PTC, in between crown ethers or its analogues, and aliphatic/aromatic quaternised salts, but still different from Host Guest compounds[7] of simple crown ethers where guest is positively charged metal ion of group I A or II A of periodic Table.

The results obtained using this new PTC (HMTA$^+$ Br$^-$) for N-alkylation of protected primary aromatic amines (6a-6f;9a-9b) compare well (Table-1) with the results obtained with Tetrabutyl Ammonium bromide (TBA$^+$ Br$^-$) a more commonly used PTC.



(6a – 6f) (7a – 7i) (8a-8b;8d-8h)



(9a – 9b) (10a –10b) (11a – 11b)

TABLE 1 : Comparision of N-alkylations using HMTA+Br- and TBA+ Br-

	Substrate Substituents		Product Substituents		% Yield using $HMTA^+Br^-$	% Yield using TBA^+Br^-	MP or BP^o C/mm		Ref
No.	R	R_1	No.	R_2			Observed	Reported	
6a	$2CH_3$	CHO	7a	C_2H_5	93	94	84-87/1.5	255-265	8
6b	$2CH_3$	$COCH_3$	7b	C_2H_5	95	95	85-89/1	*	
6c	$2CH_3$	Tos	7c	C_2H_5	97	96	76	75	9
6a	$2CH_3$	CHO	7d	CH_3	93	92	87-90/1	85-90/1	10
6b	$2CH_3$	$COCH_3$	7e	CH_3	90	90	57-58	58	11
6d	$4CH_3$	$COCH_3$	7f	C_2H_5	93	93	148-50/1.5	*	
6e	H	$COCH_3$	7g	C_2H_5	93	93	55	55	12
6e	H	$COCH_3$	7h	CH_3	93	84[13]	101-102	102	14
6f	H	$CH_2C_6H_5$	7i	C_2H_5	90	90	132-35/1	170-80/14	15
9a	H	CHO	10a	C_2H_5	93	96	115-20/1.5	*	
9b	H	$COCH_3$	10b	C_2H_5	95	95	68-69	68	14

* These compounds were characterized by ^1HNMR

It was observed that under the experimental conditions, with both PTC, besides the products (7a-i) and 10(a-b) in isolated yields, reported above, a minor product (8) or (11), arising from the hydrolysis[16-17] of (7) and (10) (except 7c & 7i) is also formed to the extent of 1.5-3% which was readily characterized by comparing with authentic samples of mono N-alkyl amines

The conclusions derived from the results presented in Table 1 may be summarized as follows :

1. HMTA$^+$Br$^-$ when used as PTC in N-alkylation reaction, as shown in Table 1, behaves almost identically with the commonly used PTC TBA$^+$Br$^-$, in terms of ease of reaction, reaction time, product selectivity and yield.

2. Simple substitution like methyl group in *o*- or *p*- position does not affect the course of reaction.

3. The nature of protecting group varying from formyl, acetyl, to more bulkier tosyl or benzyl group does not alter the rate of reaction, however, in case of bulkier groups, product selectivity increases from 97:3 to > 99% as no deprotected N-alkyl amine is formed in the reaction (eg. 8c and 8i).

4. Even with less bulkier protecting groups as studied here, during N-alkylation, in the presence of aqueous alkali, deprotection does not occur to a significant extent (1-3%).

5. Wherever hydrolysis occurs it is essentially N-alkylation which precedes the deprotection step, as the product obtained was always deprotected N-alkylated amine and not an unalkylated amine.

EXPERIMENTAL

All the melting points and boiling points are uncorrected. Infra-red spectra were recorded on Perkin Elmer 137 B in Nujol mull. ^{1}HNMR Spectra were recorded on Brucker WH-90 FT spectrometer using TMS as internal standard. UV Spectra were recorded on UV/VIS Spectrophotometer model GBC 911A. All the new compounds gave satisfactory elemental analysis which was carried out on CHNS-O elemental Analyser model ES 1108 Carlo Erbo. Reaction monitoring and the purity of the compounds were checked on TLC (Silica gel coated plates) or on GC (on SE-30 column).

Except acetanilide (6e), which was commercially available, all other substrates eg. Substituted N-Formo anilides (6a, mp 62°; 9a, mp 139-141°); Substituted N-acetoanilides (6b, mp 110°; 6d, mp 146°; 9b, mp 159-160°); N-para toluene sulfoanilide (6c, mp 110°) and N-Benzyl anilide (6f, bp 80-81/21mm), were prepared following the established procedures.

GENERAL PROCEDURE FOR N-ETHYLATION :

N-ETHYLATION OF ACETO-PARA-TOLUIDIDE

(a) **Using HMTA$^+$ Br$^-$:** In a three necked RB flask, mixture of substrate (6d) (14.9g, 0.1 mole), in benzene (50ml), HMTA$^+$Br$^-$ (0.7g, .003 mole), anhydrous potassium carbonate (2g, 0.14 mole) and diethyl sulfate (17g, 0.11 moles) was stirred (at 8-10°) for 0.75 hr. An aqueous solution of

NaOH (20g, 0.5 moles, dissolved in 20ml water) was gradually added under vigorous stirring during 0.25 hr; reaction temperature rose to 15^{o}. Stirring was continued at 30-35^{o} till the completion of the reaction, 3hr. (monitored by TLC on silica gel plate; solvent system Pet. ether, Ethyl acetate 80:20). The reaction was diluted with water (50ml), the organic phase was separated and the aq. phase was extracted with benzene (2 x 40ml). The combination of organic phase and extracts was washed with water (2 x 30ml), dried over anhydrous sodium sulfate and solvent was stripped off to yield yellowish orange crude product which was fractionated to furnish a fraction bp 148-150^{o}/1.5mm (16.46g, yield 93%). This major product, N-Ethyl aceto p-toluidide (7f) showed in its ^{1}HNMR ($CDCl_3$) a N-ethyl group (at δ 1.12 (t) 3H and δ 3.72 (q) 2H), amido methyl group (at δ 1.82 (t) 3H), aromatic methyl group (at 2.4 (S) 3H) and aromatic ring protons (at δ 6.44 - 6.66, (m) 4H).

The low boiling fraction (bp 45-46^{o}/1.5 mm; 0.5g, yield 3%) was readily identified as N-Ethyl-p-toluidine by co-injecting with authentic sample, in GC, on 20% SE-30 on chromosorb W, ss column (180 cm x 0.318 cm) at 220^{o} with H_2 flow:50ml/minute when the peak with RT of 2.75 or RRT of 0.659 (with respect to N-Ethyl-paratoluidine) corresponding to (8f) got accentuated.

(b) **Using TBA$^+$ Br$^-$** : Experiments were carried out in same manner as in (a) except TBA$^+$Br$^-$ (0.966g; .003 mole) was used in place of HMTA $^+$ Br$^-$.

GENERAL PROCEDURE FOR N-METHYLATION

A general procedure for N-Methylation is the same as that for N-ethylation except that in place of diethyl sulfate, dimethyl sulfate (13.86g, 0.11 moles) was used.

Compounds (6a-6f and 9a-9b) were N-ethylated and/or N-methylated using both the Phase Transfer Catalysts, under the conditions given above for N-ethylation or N-methylation, and the results are given in Table 1.

The PTC HMTA$^+$ Br$^-$: had mp 201-203^0 (Lit[19] 202-204^{0}C), showed in its UV spectrum . λ max = 220nm; ϵ , 9113 (conc. 2 x 10^{-4} M in H_2O)[20] and analysed for $C_6H_{13}N_4Br$.

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20. $^{cf}TBA^+Br^-$ in its UV shows λ max = 196nm, ϵ 6398 (conc. $3x10^{-4}$ M in H_2O)

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