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USE OF HEXAMETHYLPHOSPHORAMIDE (HMPA) IN THE ALKYLATION OF AROMATIC AMINES.[1]

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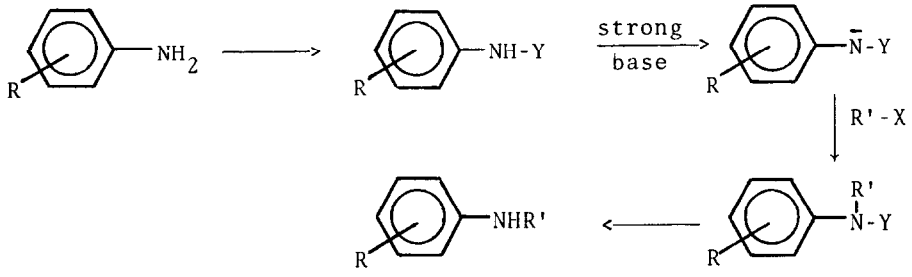
Abstract. The convenience of using HMPA as solvent in the mono and dialkylation of anilines was demonstrated through the study of the reaction of p-toluidine with alkyl halides, tosylates and epoxides.

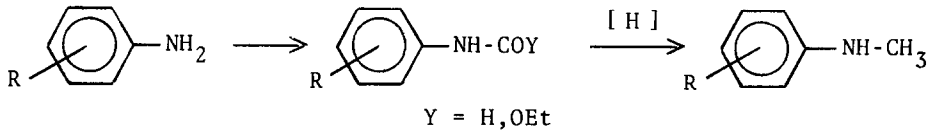
Introduction. The alkylation of amines plays an important role in synthetic organic chemistry partly because of the ubiquitous presence of nitrogen derivatives in nature. In contrast to the relative ease of aliphatic amine alkylations, the delocalyzed nature of the nitrogen lone pair of electrons in aromatic amines causes their decreased reactivity toward alkylating agents. As a consequence, drastic conditions are usually required for the direct alkylation of anilines.[2-6]

More generally, the monoalkylation of aromatic amines is accomplished through the sequence shown in Scheme 1, where Y is a labile group which increases the acidity of N-H.[7]



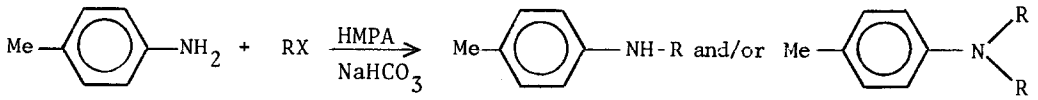
Scheme 1

Alternative indirect methods for the methylation of anilines have also been developed.[8] (Scheme 2).



Scheme 2

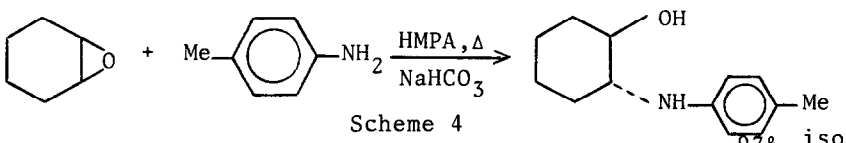
Since HMPA is well known for its ability to increase the nucleophilicity of carbanions and other electron-rich species,[9] we decided to carry out the reaction between p-toluidine (as a model for aromatic amines) and alkyl halides in HMPA as solvent. Sodium bicarbonate was used to neutralize the ammonium salt when generated. Scheme 3. It was then expected that direct alkylation would take place under smooth conditions.[10]



Scheme 3

Results and Discussion. The results are summarized in Table 1. Good to excellent yields of the monoalkylated product are observed with one equivalent of primary or secondary chlorides, bromides and iodides. Dialkylation is observed when an excess of primary halide is used (no dialkylated product results from secondary halides).

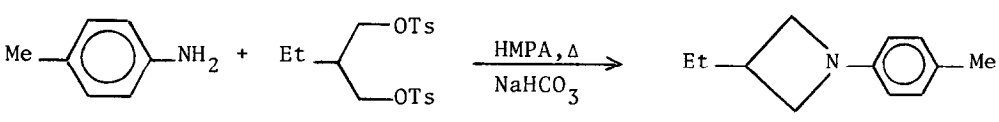
The reaction appears to proceed by a normal S_N2 displacement as suggested by the observed halide reactivity order: benzylic > methylic > primary > secondary >> cyclohexylic >>>> tertiary (no reaction). Also, p-toluidine reacted with cyclohexene oxide in HMPA to afford trans-2-p-toluidin-cyclohexanol as the sole product (Scheme 4).



Scheme 4

97% isolated

The usefulness of HMPA in the alkylation of anilines with tosylates is being evaluated presently.[14] We would like to advance the finding of a high-yield preparation of azetidines from the reaction of p-toluidine and 1,3-ditosylates (Scheme 5).



99.6% isolated

Scheme 5

Table 1. Reaction of p-Toluidine with Alkyl Halides in HMPA as Solvent.[12]

RX	Equivalents of RX	T(°C)	Reaction Time (h)	Product[a]	Isolated Yield (%)
CH_3I	1	-10	5	ArNHR	47.3
CH_3I	3	25	8	$ArNR_2$	71.9
EtI	1	25	40	ArNHR	91.1
EtI	3	25	4	$ArNR_2$	98.2
EtBr	1	-10→25	1+47	ArNHR	58.8
EtBr	3	25	30	$ArNR_2$	92.1
n-PrBr	1	25	24	ArNHR	70.1
n-PrBr	3	reflux	4	$ArNR_2$	96.1
n-BuI	1	25	16	ArNHR	93.4
n-BuI	3	25	16	$ArNR_2$	93.0
n-BuBr	1	25	24	ArNHR	94.7
n-BuBr	3	reflux	2.5	$ArNR_2$	96.8
n-BuCl	10	reflux	6	ArNHR	51.0
n-BuCl	10	reflux	48	$ArNR_2$	97.0
i-PrBr	1	25	48	ArNHR	68.0
i-PrBr	3	reflux	2	ArNHR	94.2
sec-BuBr	3	reflux	3	ArNHR	98.0
t-BuBr	3	reflux	20	ArNHR	0
BzBr	3	25	1	$ArNR_2$	82.2
BzBr	3	reflux	0.5	$ArNR_2$	100.0
c-$C_6H_{11}I$	3	25	72	ArNHR	84.8
c-$C_6H_{11}Br$	3	reflux	40	ArNHR	10.6

[a] Ar = p-MeC_6H_4.

References and Notes.

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10. While this work was still in progress, Hutchins and Taffer reported the conversion of alkyl halides into alcohols in wet HMPA:[11]

$$RX \xrightarrow{\text{HMPA-}H_2O} ROH$$

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12. The amine (p-toluidine, 1.0 g, 9.34 mmol) was placed in a 100 mL round-bottomed flask and dissolved in 10 mL of dry HMPA. An excess of sodium bicarbonate was added and then the reaction mixture was stirred under nitrogen at the required temperature (see Table 1). The reaction was monitored by tlc [hexane-ethyl acetate (70:30)] and the product extracted with ether and concentrated. Purification of the product was attained by flash chromatography[13] followed by distillation in a kugelrohr apparatus or recrystallization.

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