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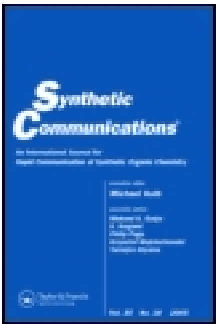

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A Novel Strategy for N-Alkylation of Primary Amines

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SYNTHETIC COMMUNICATIONS, 29(12), 2085-2091 (1999)

A NOVEL STRATEGY FOR N-ALKYLATION OF PRIMARY AMINES[+]

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ABSTRACT : N-alkylation of primary amines has been carried out with alkylbromide using commercial Me_2SO and K_2CO_3 as a base. This process offers a method of selection for obtaining either mono or dialkyl amines.

INTRODUCTION

Alkylation of primary amine continues to be a subject of investigations because in many cases direct N-monoalkylation of primary amines is either unsatisfactory or not possible because subsequent alkylation occurs and cannot be readily prevented[1]. The traditional methods for the synthesis of N-monoalkylamines use costly metals or metal-catalyst combinations[2], metal oxides[3], zeolite[4,5], and phase transfer catalysts[6]. N,N-Dialkylation of primary amines specially

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[+] CDRI Communication No. 5836

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anilines has additional problems. Bunnet and Brotherton[7] proposed a distinct stearic interaction in the preparation of N,N-dibutylaniline which is the important intermediate in fine chemicals, dyes and pigment[8]. In the light of these reports, the need of a convenient method of N-alkylation of primary amine exists which would clearly delineate the course of the reaction. We have observed that N-alkylation of primary amines with alkyl halides in DMSO and in presence of K_2CO_3 offers an opportunity to obtain either N,N-dialkyl or N-alkyl primary amines depending on the nature of alkyl halide used in the reaction. This method also offers an environmentally friendly synthetic strategy for the preparation of N,N-dibutylaniline.

In the present study two primary amines namely aniline and cyclohexylamine were identified as model substrates for studying N-alkylations with alkyl bromides in K_2CO_3 - commercial Me_2SO system.

It was observed that the course of the alkylation reaction had a strong dependency on the number of C-atoms present in the alkyl bromide. As would be evident from the Table 1, anilines reacted with alkyl bromides of smaller chain length (no. of C-atoms < 4) to furnish N,N-dialkylanilines while the reaction of aniline with n-pentyl bromide gave the mixture of N-mono- and N,N-dipentylaniline in the ratio of 44 : 46, determined on the basis of GC analysis. It was interesting to note that for alkyl bromides of longer chain length (no. of C-atoms > 5), only N-mono-alkylanilines were obtained. For example, reactions of aniline with n-hexyl bromide or n-heptyl bromide, yielded either Nhexylaniline or N-heptylaniline in excellent yield. These results suggested a "cut-off limit" for the course of the reaction ; n-butyl bromide was the limit of chain length for obtaining exclusively N,N-dialkyl derivative and n-hexyl bromide offered the first possibility for obtaining N-monoalkyl derivative. The next course of the exploration, therefore, used only two alkyl bromide namely n-butyl and n-hexyl bromides to understand the course of the reaction. Results are presented in table 2. Yet another independent monitoring of the presence or absence of mono or dialkylated products in the reaction mixture was the mass spectral analysis of the products before and after distillation. This method also supported the observation reported here.

On the basis of these results it was concluded that alkylation with alkylhalides in Me_2SO-K_2CO_3 system offered a new strategy and was commercially realistic.

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EXPERIMENTAL SECTION

Generals. IR Spectra were run on a Beckman-Acculab-10-spectrophotometer. ^{13}C and ^{1}H NMR were recorded on using $CDCl_3$ as solvent and trimethylsilane as internal standard. Mass spectra were determined as on jeol JMS-D-300 spectrometer. Chemical analyses were carried out on Carlo-Erba-1108 instrument. GC were recorded on Varian chromatograph.

N-Alkylation Procedure : To the stirred mixture of the amine (20 mmol) in Me_2SO (0.5 ml) and K_2CO_3 (1 g), alkylbromide (20 mmol for

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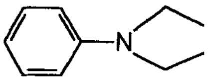
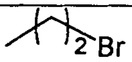
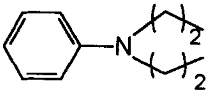
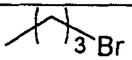
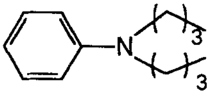
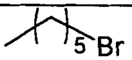
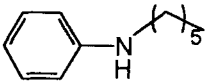
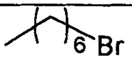
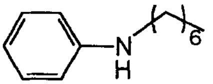
Table 1 : N-alkylation of anilines with alkyl bromides.

Entry	Alkylbromide	Product[a]	Reaction Time/h	Yield[b] (%)	B.P. (°C)	GC and MS analysis
1			6	95	217	c
2			8	92	242	c
3			11	97	269	c
4			13	95	75*	d
5			15	93	85*	d

[a]All products were characterized by their ^{13}C-NMR, ^{1}H-NMR, Mass and IR as well as boiling points[9-10].

* M.P. as HCl salt.

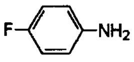
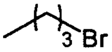
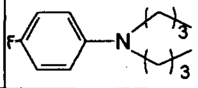
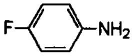
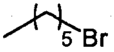
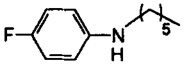
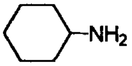
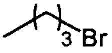
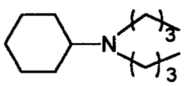
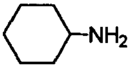
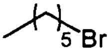
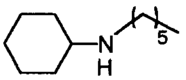
[b]The reported yields are of distilled material.

[c]Single peak and absence of N-monoalkyl derivative.

[d]Single peak and absence of N,N-dialkyl derivative.

N-monoalkylation; 40 mmol for N,N-dialkylation) is added and stirring is continued at 80°C (except in cases of **1** and **2** in table 1 in which stirring is continued at room temperature) until the reaction completion is checked by thin layer silica gel (60-80 mesh) plates and then filtered. The filtrate was poured in water and extracted with chloroform. The combined extract is washed with 10% brine solution,

Table 2 : N-alkylation of substituted anilines and cyclohexylamine with alkylbromides

Entry	Amine	Alkyl bromide	Product[a]	Reaction Time/h	Yield[b] (%)	B.P. (°C)	GC and MS analysis
1.				16	78	125*	c
2.				16	91	162*	d
3.				13	83	116	c
4.				13	95	240*	d

dried over Na_2SO_4 and concentrated to afford the crude product, which was filtered through column. The material thus obtained was distilled to afford the pure product and purity of product was determined by GC.

In the case of reaction of aniline with n-pentyl bromide, we got mixture of two compounds in the ratio of 44:46 and which were characterized by GC of mixture against the authentic samples of N-pentylaniline and N,N-dipentylaniline.

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