# Monoalkylation of Primary Aromatic Amines *via N*-(Alkoxymethyl)aryl Amines. Evidence for the Formation of Stable Monomeric Methyleneamines

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Monomeric methyleneamines (**1**), formed from *N*-(alkoxymethyl)arylamines (**3**), are stable at −60 °C and may be trapped with organometallic reagents to provide the *N*-alkylarylamines (**7**).

The literature on reactions between formaldehyde and aromatic amines goes back at least a century.[1] These processes are the source for di- and oligo-meric amines from which commercially important di- and poly-isocyanates are obtained. However, in most instances the reactions afford mixtures of products containing both carbon–nitrogen and carbon–carbon bonds involving the aromatic ring,[2,3] all of them derived from the hypothetical Schiff's base (**1**).[4] Neither the initial 'aldol' (**2**) nor the Schiff's base (**1**) have ever been isolated.[5,6]

$$\underset{(\mathbf{1})}{ArN{=}CH_2} \qquad \underset{(\mathbf{2})}{ArNHCH_2OH} \qquad \underset{(\mathbf{3})}{ArNHCH_2OR}$$

The methyleneamines (**1**) have eluded preparation probably because the activation energy for the condensation of arylamines and formaldehyde is higher than that required for trimerization leading to *s*-triazines. In fact, when arylamines and paraformaldehyde are mixed below room temperature both reagents are recovered unchanged after normal work-up. For these reasons we felt it would be of interest to synthesize a masked form of the imines (**1**) which could be transformed into the monomeric imine at such a low temperature that the trimerization would not take place. *N*-(Alkoxymethyl)arylamines (**3**) can be envisaged as suitable precursors for methyleneamines through $\beta$-elimination of alkoxide upon treatment with a strong base.

Primary aromatic amines (**4**) react at room temperature with paraformaldehyde and sodium alkoxide (**5**) in the corresponding alcohol as solvent to afford compounds (**3**) in good yield (Scheme 1, Table 1).

**Table 1.** Preparation of the *N*-(alkoxymethyl)arylamines (**3**) from the arylamines (**4**) and the alkoxides (**5**).[a]

| | Ar | R | % Yield |
|---|---|---|---|
| (**3a**) | Ph | Me | 85 |
| (**3b**) | Ph | Et | 65 |
| (**3c**) | Ph | $Pr^n$ | 55 |
| (**3d**) | $o$-$MeC_6H_4$ | Me | 40 |
| (**3e**) | $m$-$MeC_6H_4$ | Me | 90 |
| (**3f**) | $p$-$MeC_6H_4$ | Me | 82 |
| (**3g**) | $p$-$MeOC_6H_4$ | Me | 62 |
| (**3h**) | $o$-$EtOC_6H_4$ | Me | 54 |
| (**3i**) | $p$-$O_2NC_6H_4$ | Me | 87 |

[a] Reactions were carried out at room temperature, and yields are based on the amine (**4**). I.r. and n.m.r. spectra [$CDCl_3$, $Me_4Si$ reference, $\delta(CH_2)$ in the ranges 4.5—4.6 ($^1H$) and 74.9—77.9 ($^{13}C$) p.p.m.] were in good agreement with the proposed structures.

$$\underset{(\mathbf{4})}{ArNH_2} + (CH_2O)_n + \underset{(\mathbf{5})}{NaOR} \xrightarrow[\text{room temp.}]{ROH} (\mathbf{3})$$

**Scheme 1**

Compounds (**3**) are oils which are stable at room temperature for only a few hours but they can be stored at −18 °C without noticeable decomposition.

When *N*-(methoxymethyl)aniline (**3a**) was treated at −60 °C successively with the stoicheiometric amount of

$$\begin{tikzcd}
\underset{(\mathbf{3a})}{PhNHCH_2OMe} \arrow[r, "i"] & \underset{(\mathbf{6})}{[PhNLiCH_2OMe]} \arrow[d, "-LiOMe"] \\
\underset{(\mathbf{7b})}{PhNHCH_2Bu^n} & \underset{(\mathbf{1a})}{PhN{=}CH_2} \arrow[l, "ii"']
\end{tikzcd}$$

**Scheme 2.** *Reagents*: i, MeLi, $Et_2O$, −60 °C; ii, $Bu^nLi$, $Et_2O$, −60 °C, then 1 M KOH.

$$(\mathbf{3}) \xrightarrow[\text{ii, 1 M KOH or } Na_2SO_4.10H_2O]{\text{i, 2 XM, solvent}} \underset{(\mathbf{7})}{ArNHCH_2X}$$

**Scheme 3**

methyl-lithium and then with n-butyl-lithium, *N*-pentylaniline (**7b**) was obtained uncontaminated with *N*-ethylaniline (Scheme 2). This result can be easily rationalized through the formation of the stable (−60 °C) monomeric methyleneamine (**1a**) *via* β-elimination of lithium methoxide from the lithium amide (**6**), and represents the first case in which a methyleneamine is trapped and then allowed to react in a directed way. When *s*-triazines were treated under similar conditions as (**3a**) in Scheme 2, they were recovered unchanged.

Based on this behaviour a new and simple method for the selective monoalkylation of primary arylamines has been developed. *N*-(Methoxymethyl)arylamines are allowed to react with the organometallic (Li or Mg) reagent XM in ether or pentane solution at −60 or 0 °C leading to the corresponding alkylarylamines (**7**), isolated in good yields (Scheme 3, Table 2).

Our method of alkylation affords the alkylamines (**7**) in which the nitrogen is bonded to a primary carbon atom, and has the advantage that the product is uncontaminated with either the corresponding arylamine or the bisalkylated compound. It is noteworthy that most of the existing methods for the alkylation of amines suffer from lack of selectivity for monoalkylation, particularly when primary or benzyl groups are to be introduced, unless alkylations are performed with a large excess of primary amine which finally becomes the main component in the product reaction mixture.

**Table 2.** Synthesis of the *N*-alkylarylamines $ArNHCH_2X$ (**7**) from **3**) and the organometallic reagents XM.[a]

| | | (7) | | | |
|---|---|---|---|---|---|
| (3) | XM | | Ar | X | |
| (**3a**) | MeLi | **a** | Ph | Me | 93[d] |
| (**3a**) | $Bu^nLi$ | **b** | Ph | $Bu^n$ | 87 |
| (**3a**) | PhLi | **c** | Ph | Ph | 92[e] |
| (**3a**) | $Pr^nMgBr$[b] | **d** | Ph | $Pr^n$ | 74 |
| (**3a**) | $c\text{-}C_5H_9Li$[c] | **e** | Ph | $c\text{-}C_5H_9$ | 95 |
| (**3e**) | $Bu^nLi$ | **f** | $m\text{-}MeC_6H_4$ | $Bu^n$ | 94 |
| (**3e**) | $Bu^tLi$[b] | **g** | $m\text{-}MeC_6H_4$ | $Bu^t$ | 88 |

[a] Reactions were carried out in ether at 0 °C unless otherwise noted. Known compounds were identified by comparison with authentic samples. New compounds showed i.r. and n.m.r. spectra and elemental analyses consistent with the assigned structures. [b] At −60 °C. [c] In pentane; $c\text{-}C_5H_9$ = cyclopentyl. [d] Ref. 7(a). [e] Ref. 7(b).

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