A New and Specific Method for the Monomethylation of Primary Amines

José Barluenga, Ana M. Bayón, and Gregorio Asensio

Departamento de Química Orgánica, Facultad de Química, Universidad de Oviedo, Oviedo, Spain

The reduction of monomeric methyleneamines, representing a convenient and highly specific procedure for the title reaction, is studied.

In recent communications we reported the synthesis of *N*-(alkoxymethyl)-*N*-arylamines (**1**) and the use of these compounds and their sulphur analogues, *N*-alkyl-*N*-(alkylthiomethyl)ammonium chlorides (**2**), for the first preparation of stable monomeric (−60 °C) aryl-(**3**)[1] and alkylmethyleneamines (**4**).[2]

$$\underset{(\mathbf{1})}{\mathrm{ArNHCH_2OR}} \quad \underset{(\mathbf{2})}{(\mathrm{R^1\overset{+}{N}H_2CH_2SR^2})\mathrm{Cl^-}} \quad \underset{(\mathbf{3})}{\mathrm{ArN{=}CH_2}} \quad \underset{(\mathbf{4})}{\mathrm{RN{=}CH_2}}$$

$$\underset{(\mathbf{5})}{(\mathrm{ArNCH_2})_3}$$

We have observed that compounds (**1**) when allowed to stand at room temperature decompose slowly to afford the corresponding triazinane (**5**) and alcohol. The decomposition is greatly accelerated by heating under reduced pressure. Based on these findings we now report a convenient and specific general method for the monomethylation of amines, which is a key functional group transformation in organic synthesis.[3]

Table 1. Synthesis of *N*-substituted methylamines[a] ArNHMe (**6**) (Scheme 2) and R[1]NHMe (**8**) (Scheme 3).

	Ar	R^1	R^2	Product	Yield%
(**7a**)	Ph			(**6a**)	82
(**7b**)	*o*-MeC_6H_4			(**6b**)	75
(**7c**)	*m*-MeC_6H_4			(**6c**)	89
(**7d**)	*p*-MeC_6H_4			(**6d**)	85
(**7e**)	*o*-$MeOC_6H_4$			(**6e**)	65
(**7f**)	*p*-$MeOC_6H_4$			(**6f**)	65
(**7g**)	*o*-$EtOC_6H_4$			(**6g**)	65
(**2a**)		CH_2Ph	CH_2Ph	(**8a**)	75
(**2b**)		c-C_6H_{11}[b]	Ph	(**8b**)	67
(**2c**)		Bu^t	CH_2Ph	(**8c**)	54
(**2d**)		n-$C_{12}H_{25}$	CH_2Ph	(**8d**)	79

[a] Known compounds were identified by comparison with authentic samples. New compounds showed i.r. and n.m.r. spectra (^1H and ^{13}C) and elemental analyses consistent with the assigned structures. [b] c-C_6H_{11} = cyclohexyl.

$$(\mathbf{1}) \xrightarrow{\text{i}} (\mathbf{3}) \xrightarrow{\text{ii}} \underset{(\mathbf{6})}{\text{ArNHMe}}$$

Scheme 1. *Reagents:* i, MeOH, heat; ii, $NaBH_4$.

When compounds (**1**) are treated with $NaBH_4$ in MeOH solution under reflux, *N*-methyl-*N*-arylamines (**6**) are obtained in high yield. Their formation can be easily rationalized as a reduction of the imine (**3**) which is an intermediate in the formation of triazinanes (**5**) from compounds (**1**) (Scheme 1). From the synthetic point of view the method can be greatly improved by carrying out the direct methylation of the amine (Table 1) in a single reaction vessel without isolation of the intermediate (**1**) (see Scheme 2).[†]

$$\underset{(\mathbf{7})}{\text{ArNH}_2} \xrightarrow[\text{ii}]{\text{i}} (\mathbf{6})$$

Scheme 2. *Reagents:* i, $[CH_2O]_n$, NaOMe, MeOH, room temp., 5h; ii, $NaBH_4$, reflux, then 1 M KOH.

$$(\mathbf{2}) \xrightarrow[\text{ii}]{\text{i}} \underset{(\mathbf{8})}{\text{R}^1\text{NHMe}}$$

Scheme 3. *Reagents:* i, $LiAlH_4$, Et_2O, −60 °C; ii, $Na_2SO_4{\cdot}10H_2O$.

The treatment of compounds (**2**) under similar conditions does not yield the expected monomethylated alkylamines (**8**) but other compounds whose structures have not yet been determined. However, when compounds (**2**) were slowly added to a diethyl ether solution of $LiAlH_4$ cooled to −60 °C, monomethylated amines (**8**) were obtained in good yields (Scheme 3, Table 1).

The methods for the monomethylation of amines reported herein avoid the usual problems[3] found in most of the known procedures for this transformation. Among the advantages it is noteworthy that the product is not contaminated with either the corresponding primary or dimethylated amine and also that the reagents used are all convenient, readily available, and easy to handle.

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References

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[†] *Typical experimental procedure* for *N*-methylaniline (**6a**): Na (2.3 g, 100 mmol) was slowly added to MeOH (30 ml). Once the evolution of hydrogen had ceased, aniline (1.8 g, 20 mmol) was added and the resulting hot solution poured into a suspension of paraformaldehyde (0.84 g, 28 mmol) in MeOH (20 ml). The mixture was stirred at room temp. for 5 h and then $NaBH_4$ (0.7 g, 20 mmol) added. The solution was heated under reflux and hydrolysed with 1 M KOH. After usual work-up procedures (**6a**) (1.8 g, 82%) was isolated as the reaction residue. For *N*-methylbenzylamine (**8a**): *N*-benzyl-*N*-(benzylthiomethyl)ammonium chloride (**2a**)[4] (1.4 g, 5 mmol) was slowly added to $LiAlH_4$ (0.38 g, 10 mmol) in dry Et_2O (15 ml) under Ar at −60 °C. The mixture was allowed to reach room temp. and then hydrolysed with $Na_2SO_4{\cdot}10H_2O$. Solids were filtered out and the resulting clear solution washed with 3 M KOH three times. After usual work-up procedures (**8a**) (0.45 g, 75%) was isolated as the reaction residue.

N.B. Water soluble amines, *i.e.* (**8c**) were recovered as hydrochlorides from the reaction mixture after filtration of inorganic solids, by bubbling HCl through the Et_2O solution.