Monoalkylation of Primary Aliphatic Amines *via* *N*-Alkyl-*N*-(alkylthiomethyl)ammonium Chlorides. Evidence for the Formation of Stable *N*-Methylenealkylamines

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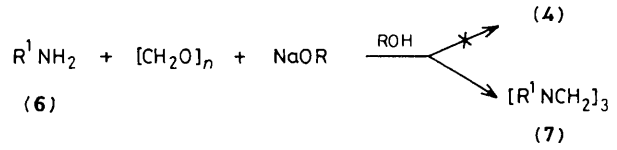
Monomeric *N*-methylenealkylamines (**3**), formed from *N*-alkyl-*N*-(alkylthiomethyl)ammonium chlorides (**5**) are stable at −60 °C and may be trapped with organometallic reagents to provide the *N,N*-dialkylamines (**8**).

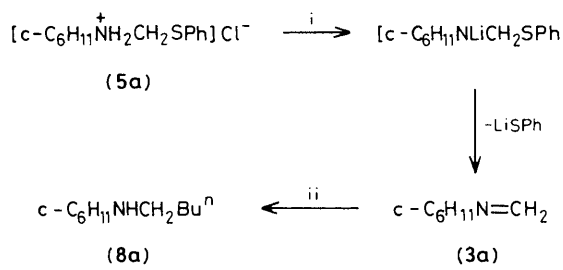
In a recent communication[1] we reported the first synthesis of stable monomeric methylenearylamines (**1**) *via* β-elimination of alcohol from *N*-(alkoxymethyl)arylamines (**2**). However, our attempts to generalize this process for the synthesis of methylenealkylamines (**3**) were unsuccessful since we could not prepare the corresponding aliphatic precursor (**4**). The aliphatic amines (**6**) form 1,3,5-trialkylhexahydro-1,3,5-triazines (**7**) (Scheme 1) when treated with paraformaldehyde under the conditions used to obtain compounds (**2**) from aromatic amines.[1]

$ArN{=}CH_2$ (**1**) $ArNHCH_2OR$ (**2**) $R^1N{=}CH_2$ (**3**)

R^1NHCH_2OR (**4**) $(R^1\overset{+}{N}H_2CH_2SR^2)Cl^-$ (**5**)



Scheme 1



Scheme 2. *Reagents:* i, 2MeLi, Et_2O, −60 °C; ii, Bu^nLi, Et_2O, −60 °C, then 1 M KOH at room temp. c-C_6H_{11} = cyclohexyl.

Table 1. Synthesis of the *N,N*-dialkylamines $R^1NHCH_2R^3$ (**8**) from (**5**) and the organometallic reagent R^3M.[a]

	(5)				
	R^1	R^2	R^3M	(**8**)	Yield, %
(**a**)	c-C_6H_{11}	Ph	Bu^nLi	**a**	90[b]
(**a**)			MeLi	**b**	88[c]
(**a**)			PhLi	**c**	68
(**a**)			AllylMgBr	**d**	82
(**b**)	Bu^n	Ph	MeLi	**e**	76[d]
(**b**)			PhLi	**f**	70[e]
(**c**)	CH_2Ph	CH_2Ph	MeLi	**g**	85[f]
(**c**)			Bu^nLi	**h**	83

[a] Reactions were carried out in diethyl ether at −60 °C and the temperature was allowed to rise to room temp. prior to hydrolysis. 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. [c] Ref. 3(a). [d] Ref. 3(b). [e] Ref. 3(c). [f] Ref. 3(d).

$$(6) \xrightarrow{i} (5) \xrightarrow[iii]{ii} R^1NHCH_2R^3 \quad (8)$$

Scheme 3. *Reagents:* i, (a) $[CH_2O]_n$, (b) 3HCl in dry diethyl ether, −20 °C, (c) R^2SH; ii, $3R^3M$, diethyl ether; iii, 1 M KOH.

Some years ago, Reynolds and Cossar[2] reported the preparation of *N*-alkyl-*N*-(alkylthiomethyl)ammonium chlorides (**5**) which should be suitable precursors for the preparation of the methylenealkylamines (**3**) using the strategy described by us in the synthesis of (**1**). The reaction of (**5a**) with two equivalents of methyl-lithium in diethyl ether at −60 °C followed by addition of one equivalent of n-butyl-lithium afforded *N,N*-cyclohexyl-n-pentylamine (**8a**) uncontaminated with *N,N*-cyclohexylethylamine (**8b**) (Scheme 2). This result is clear evidence for the monomeric methyleneamine (**3a**) which is stable at −60 °C (or higher temperatures) and is trapped by n-butyl-lithium to afford the alkylation product (**8a**).

Based on this sequence we have developed a simple general method for the monoalkylation of primary aliphatic amines as shown in Table 1 (Scheme 3).

The secondary aliphatic amines (**8**) in which the nitrogen is bonded to at least one primary carbon atom are obtained in good yields by this method for the monoalkylation of primary amines. Among its advantages it should be mentioned that the product is not contaminated with either the corresponding primary or dialkylated amine. Work is in progress to explore the reactivity and synthetic applications of the monomeric methyleneamines which are important alkylating agents in biological systems.

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References

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