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A CONVENIENT SYNTHESIS OF UNSYMMETRICAL SECONDARY AMINES. *IN SITU* FORMATION OF UNSTABLE FORMALDEHYDE IMINES.

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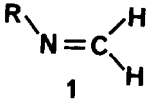
Summary: The monoalkylation of aliphatic and aromatic primary amines can be accomplished by the reaction of organolithium or Grignard reagents with N-(cyanomethyl) or N-(aminomethyl) derivatives.

Although monomeric formaldehyde imines (N-methyleneamines, 1) are well known in the gas phase,[1] they are rarely isolated or detected in the condensed state since they rapidly trimerize to hexahydro-1,3,5-triazines 2.[2,3] We required a method for generating formaldehyde imines in solution and discovered that they could be produced from the reaction of secondary N-(cyanomethyl)amines (3) with strong bases.[4] In this Letter we report that the reaction of 3, or secondary N-(aminomethyl)amines, with organolithium or Grignard reagents at low temperatures affords unsymmetrical secondary amines in synthetically useful yields. Since secondary N-(cyanomethyl)amines can be prepared from virtually any aliphatic or aromatic primary amine,[5] the two-step sequence illustrated in eq 1 provides a very convenient method for the monoalkylation of primary amines. This method is obviously related to the classical synthesis of tertiary amines from the reaction of Grignard reagents with tertiary N-(cyanomethyl)amines.[6,7] Barluenga[8] has also recently reported a conceptually related procedure for alkylation of primary amines *via* N-(alkoxymethyl) intermediates



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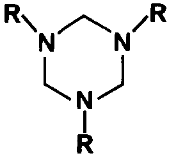

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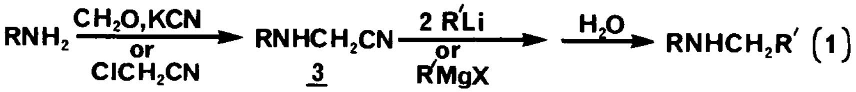
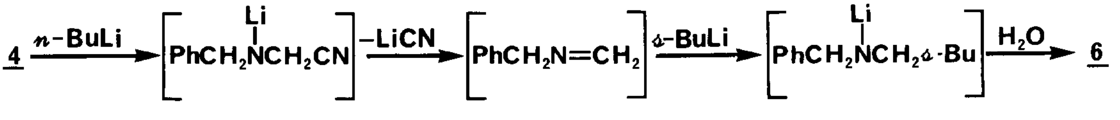


$$RNH_2 \xrightarrow[ClCH_2CN]{CH_2O,KCN \text{ or}} \underset{\underline{3}}{RNHCH_2CN} \xrightarrow[R'MgX]{2R'Li \text{ or}} \xrightarrow{H_2O} RNHCH_2R' \quad (1)$$

Primary amines were converted to their N-(cyanomethyl) derivatives 3 (R=CH_2Ph, 80%;[5b] R=C_6H_{11}, 75%;[5d] R=Ph, 77%[5b]) using standard conditions. Results obtained from the reaction of these intermediates with 2.0 equiv of a lithium or Grignard reagent are summarized in the Table.[9] Primary, secondary, and tertiary alkyllithiums, alkenyllithiums, and aryl Grignard reagents all reacted in good yields. Of particular note is the convenient preparation of 7 and 8, which are masked forms of an α-secondary amino ketone and an α-secondary amino aldehyde, respectively Product yields appear to be relatively insensitive to reaction temperature, since the yield of 5 was unchanged whether n-BuLi was added at -70 or -25°C. Allowing the reaction to warm to 0°C was also not essential, since 5 was obtained in 55% yield when the reaction of 4 with n-BuLi was quenched after 1 h at -45°C. This method is apparently not useful for the preparation of homoallylic amines, since both allylmagnesium bromide and 3-(trimethylsilyl)allyllithium failed to react with 4 in useful yields.

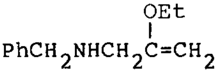
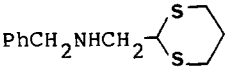
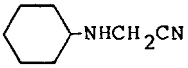
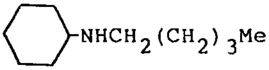
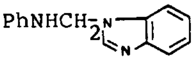
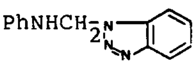
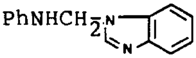
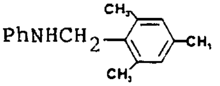
Since the use of cyanide as the leaving group in this sequence is potentially complicated by competing addition of the organometallic to the nitrile group,[10] we briefly investigated the known[11] benzimidazole and benzotriazole derivatives 9 and 10. A 67% yield of N-pentylaniline was obtained from the reaction of 9 with 2.0 equiv of n-BuLi, which was somewhat higher than that realized with the N-(cyanomethyl) or N-(benzotriazolmethyl) derivatives under identical conditions.

To obtain evidence for an intermediate in these reactions, we investigated the sequential reaction of 4 with two different organometallic reagents. Treatment of 4 with 1.0 equiv of n-BuLi at -70°C for 30 min, followed by the addition of 1.0 equiv of s-BuLi at -70°C and subsequent workup at 0°C provided (in 55% yield) a 4:1 mixture of the s-butyl and n-butyl adducts 6 and 5. This result requires the formation of an intermediate, which is most likely the monomeric formaldehyde imine (see eq 2). Unfortunately, under none of the conditions[12,13] we examined could the two steps be completely separated and in all cases some secondary amine arising from addition of the first organometallic reagent was obtained. We could conclusively demonstrate that this secondary amine synthesis did not involve the reaction of the organometallic reagent with a s-triazine.[14] Thus, reaction of hexahydro-1,3,5-tribenzyl-1,3,5-triazine[15] with 3.0 equiv of n-BuLi or s-BuLi at -70 → 0°C afforded no detectable 5 or 6 and resulted in nearly complete recovery of the s-triazine.



$$\underline{4}\xrightarrow{\textit{n}\text{-BuLi}}\left[\mathrm{PhCH_2\overset{Li}{N}CH_2CN}\right]\xrightarrow{-\mathrm{LiCN}}\left[\mathrm{PhCH_2N{=}CH_2}\right]\xrightarrow{\textit{s}\text{-BuLi}}\left[\mathrm{PhCH_2\overset{Li}{N}CH_2}\textit{s}\text{-Bu}\right]\xrightarrow{\mathrm{H_2O}}\underline{6}\qquad(2)$$

Table. Unsymmetrical Secondary Amines From the Reaction of Organometallics with Primary Amine Derivatives.[a]

Entry	$RNHCH_2X$	R'M,Equiv	$RNHCH_2R'$	Yield,%
1	$PhCH_2NHCH_2CN$ (4)	R'Li, 2.0	$PhCH_2NHCH_2(CH_2)_3Me$ (5)	81
2	$PhCH_2NHCH_2CN$	R'Li, 2.0	$PhCH_2NHCH_2CHMeCH_2Me$ (6)	71
3	$PhCH_2NHCH_2CN$	R'Li, 2.0	$PhCH_2NHCH_2CMe_3$	79
4	$PhCH_2NHCH_2CN$	R'MgBr, 2.5	$PhCH_2NHCH_2Ph$	69[b]
5	$PhCH_2NHCH_2CN$	R'Li, 2.0	 $PhCH_2NHCH_2C(OEt)=CH_2$ (7)	63
6	$PhCH_2NHCH_2CN$	R'Li, 2.0	 (8)	58
7		R'Li, 2.0		65
8	$PhNHCH_2CN$	R'Li, 2.0	$PhNHCH_2(CH_2)_3Me$	50
9	$PhNHCH_2CN$	R'MgBr, 2.0	$PhNHCH_2Me$	54[c]
10	 (9)	R'Li, 2.0	$PhNHCH_2(CH_2)_3Me$	67
11	 (10)	R'Li, 2.0	$PhNHCH_2(CH_2)_3Me$	59
12		R'Li, 2.0		65

[a] In THF at -70° → 0°C for ~ 1 h, unless otherwise noted. [b] THF-Et_2O (1:1). [c] In refluxing Et_2O for 2-15 h.

Considering the large number of functionalized organolithium reagents which are currently available, we anticipate that this method will be attractive for the preparation of a variety of functionalized secondary amines. Although N-(alkoxymethyl)[8] and N-(aminomethyl) derivatives of aromatic amines appear to give higher yields of secondary amines upon reaction with organometallics than the corresponding N-(cyanomethyl) derivatives, the latter will still be the intermediates of choice for monoalkylation of aliphatic amines, since secondary N-(cyanomethyl) amines are much more readily available.

We are actively investigating[4] numerous other applications of formaldehyde imine intermediates.

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References and Notes

1. Cf. Braillon, B.; Lasne, M.C.; Ripoll, J.L.; Denis, J.M. *Nouveau J. Chem.* 1982, 6, 121-122; and references cited therein.

2. A few formaldehyde imines of *highly hindered* aromatic[3a] and tertiary aliphatic amines[3b] have been isolated and well characterized.

3. Cf. (a) Harff, G.A.; Sinnema, A.; Wepster, B.M. *Recl. Trav. Chim. Pays-Bas* 1979, 98, 71-74. (b) Möhrle, H.; Scharf, U.; Rühmann, E.; Schmid, R. *Arch. Pharm. (Weinheim)* 1983, 316, 222-229.

4. The generation of formaldehyde imines in this way and their subsequent participation in [3,3]-sigmatropic rearrangements was first reported (by L.E.O.) at the RSC Eighth International Symposium on "Synthesis in Organic Chemistry," Cambridge, England, July 19, 1983.

5. Cf. (a) Bucherer, H.; Schwalbe, A. *Chem. Ber.* 1906, 39, 2796-2804. (b) Baker, W.; Ollis, W.D.; Poole, V.D. *J. Chem. Soc.* 1949, 307-313. (c) Okawara, T.; Harada, K. *J. Org. Chem.* 1972, 37, 3286-3289.

6. These reactions are believed to proceed *via* the intermediacy of formaldehyde iminium ions.[7a] We are aware of *only* one report[7b] of the reaction of a secondary N-(cyanomethyl)amine with an organometallic reagent.

7. (a) Hellman, H.; Opitz, G. "α-Aminoalkylierung"; Verlag Chemie: Weinheim, 1960; pp 230-243; (b) Stevens, T.S.; Cowan, J.M.; MacKinnon, J. *J. Chem. Soc.* 1931, 2568-2572. We obtained N-ethylaniline in 57% yield (Table entry 9) using their conditions.

8. Barluenga, J.; Bayon, A.M.; Asensio, G. *J. Chem. Soc. Chem. Commun.* 1983, 1109-1110.

9. Yields refer to pure material isolated after chromatography. New compounds showed IR, 250 MHz ^{1}H NMR and mass spectra consistent with their assigned structures.

10. Cf. Wasserman, H.H.; Dion, R.P. *Tetrahedron Lett.* 1982, 23, 1413-1416.

11. Bachman, G.B.; Heisey, L.V. *J. Am. Chem. Soc.* 1946, 68, 2496-2499. Licari, J.J.; Hartzel, L.W.; Doughert, G.; Benson, F.R. *Ibid.* 1955, 77, 5386-5387.

12. n-BuLi, s-BuLi, t-BuLi, MeLi, MeMgBr, LDA, Ph_3CLi and mesityllithium, among other bases, were all investigated as the initial base. Reaction temperatures were varied from -100 to -20 ^{o}C and THF, Et_2O and hexane were examined as reaction solvents.

13. In contrast, N-pentylaniline is cleanly formed by sequential treatment of N-(methoxymethyl)aniline with MeLi and BuLi.[8]

14. The reaction of s-triazines with acids is commonly employed for the *in situ* generation of formaldehyde iminium ions. Cf. McDonagh, A.F.; Smith, H.E. *J. Org. Chem.* 1968, 33, 8-12.

15. Pine, S.H.; Sanchez, B.L. *J. Org. Chem.* 1971, 36, 829-832.

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