Notes

Preparation of Primary Amines via N-Diisobutylaluminum Imines

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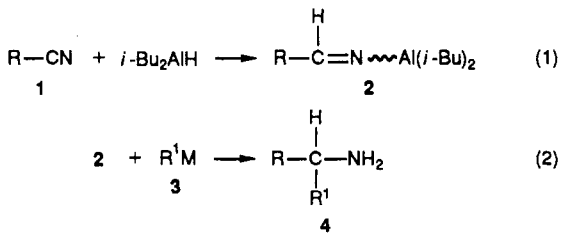
The importance of the azomethine group in organic synthesis is well documented[1]. Davis and Mancinelli[2] have demonstrated the usefulness of "masked" imine derivatives of ammonia in the synthesis of secondary and tertiary carbinamines from enolizable and nonenolizable sulfenimines. More recently metalloimines have found application in the synthesis of β-lactams through the reaction with ester enolates.[3] *N*-Trimethylsilyl imines have been also utilized by Hart in the synthesis of primary amines.[4a] The use of *N*-trimethylsilyl imines, however, is generally restricted to nonenolizable aldimines since it has been reported[4a] that the enolizable ones, upon reaction with alkyllithium or Grignard reagents, give poor yields of the expected amines due to a competitive enolization reaction of the starting material.

N-Diisobutylaluminum imines **2**, easily obtained from nitriles **1** and diisobutylaluminum hydride (DIBAH)[5] (eq 1), under mild conditions, may potentially act as alternative "masked" imine derivatives of ammonia.[6] We wish to report a convenient "one-step" synthesis of primary amines **4** from **1** and alkyllithium, aryllithium or Grignard reagents **3** using the reaction sequence described in eqs 1 and 2. All the diisobutylaluminum imines used in this

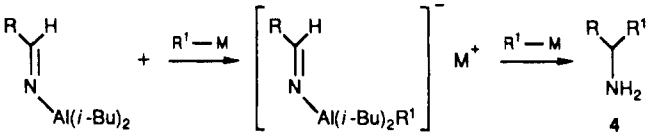


study were prepared by treatment of a pentane solution of nitrile with neat diisobutylaluminum hydride (1 equiv) at −78 °C. Most of the imines prepared were utilized as such. However, pure diisobutylaluminum imines could be characterized by their IR and NMR spectra.[7]

The *N*-diisobutylaluminum imines thus generated were allowed to react with a variety of alkyl and aryl Grignard or lithium reagents by simply adding a solution of the organometallic species **3** in THF at −78 °C and then allowing the reaction mixture to stand at room temperature for 48 h.

The results of these studies are shown in Table I. Maximum yields of amine **4** were obtained when 2 equiv of the nucleophile **3** were added. Higher reaction temperatures resulted in lower yields. Using this procedure a variety of primary amines were synthesized (Table I).

Table I. Synthesis of Amines from *N*-Diisobutylaluminum Imines



entry	R	R^1	M	yield,[a] %	method[b]	ref
a	phenyl	benzyl	MgCl	46	A	*c*
b	phenyl	allyl	MgCl	98, 95	A, B	*d*
c	phenyl	butyl	Li	92	B	*e*
d	phenyl	*sec*-butyl	Li	80	B	*f*
e	phenyl	*tert*-butyl	Li	65	B	*g*
f	2-furyl	allyl	MgCl	70	A	*h*
g	2-furyl	*n*-butyl	Li	72	B	*i*
h	2-thienyl	*n*-butyl	Li	80	A	
i	2-thienyl	allyl	MgCl	98	B	
j	2-thienyl	benzyl	MgCl	52	A	*j*
k	*p*-methoxyphenyl	butyl	Li	70	A	*k*
l	*n*-octyl	allyl	MgCl	96	A	
m	5-(trityl-amino)-pentyl	allyl	MgCl	89	A	
n	*n*-butyl	allyl	MgCl	50	A	

[a] Isolated yields. [b] A = method A. B = method B. [c] Fox, H.H.; Wenner, W. *J. Org. Chem.* **1951**, *16*, 225. [d] Horowitz, R. M.; Geissman, T. A. *J. Am. Chem. Soc.* **1950**, *72*, 1518. [e] de Roocher, A.; de Radzitsky, *Bull. Soc. Chim. Belg.* **1963**, *82*, 195. [f] Patel Shailendra, B. *J. Inst. Chem. (India)* **1981**, *53*, 274; *Chem. Abstr.* **1982**, *97*, 5878. [g] Cristol, H.; Lavrent, A.; Mousseron, M. *Bull. Chem. Soc. Fr.* **1961**, 2319. [h] See ref 4a. [i] *Chem. Abstr.* **1937**, *52*, 19967. [j] Mrongovius, R. I.; Ghosh, P.; Bolt, A. G.; Ternai, B. *Arzneim.-Forsch./Drug Res.* **1981**, *31*, 1718. [k] See ref 4a.

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(3) (a) Andreoli, P.; Cainelli, G.; Contento, M.; Giacomini, D.; Martelli, G.; Panunzio, M. *Tetrahedron Lett.* **1986**, *27*, 1695. (b) Andreoli, P.; Cainelli, G.; Contento, M.; Giacomini, D.; Martelli, G.; Panunzio, M. *J. Chem. Soc. Perkin Trans. 1* **1988**, 945. (c) Ha, D. C.; Hart, D. J.; Yang, T. K. *J. Am. Chem. Soc.* **1984**, *106*, 4819. (d) Uyehara, T.; Suzuki, I.; Yamamoto, Y. *Tetrahedron Lett.* **1989**, *30*, 4275. (e) Chiba, T.; Nakai, T. *Chem. Lett.* **1984**, 1927. (f) Chiba, T.; Nakai, T. *Ibid.* **1985**, 651. (g) Chiba, T.; Nakai, T.; Nagatasuma, M. *Ibid.* **1985**, 1343. Chiba, T. Nakai, T. *Tetrahedron Lett.* **1985**, *26*, 5493. (h) Oguni, N.; Onkawa, Y. *J. Chem. Soc., Chem Commun.* **1988**, 1376. (i) Guillemin, J.-C.; Ammi, L.; Denis, J.-M. *Tetrahedron Lett.* **1986**, *29*, 1287.

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(6) Diisobutylaluminum aldimines have been recently utilized for the preparation of α-alkylated aldehydes [Goering, L. H.; Tsung, C. C. *J. Org. Chem.* **1981**, *46*, 5252] and cyclic imines from haloalkyl nitriles [Overman, L. E.; Burk, R. M. *Tetrahedron Lett.* **1984**, *25* 5737]

Amines obtained by this method were essentially pure, as indicated by NMR spectroscopy, GLC, and TLC and were identified by comparison of their properties with literature values.

From these results, it is clear that enolizable as well as nonenolizable *N*-diisobutylaluminum imines react with a variety of organometallic reagents to afford good to excellent yields of primary amines after aqueous workup. The stoichiometry of the reaction generally required the use of 2 equiv of organometallic reagents against 1 equiv of imine due to the competitive attack of the organometallic reagent on the aluminum atom.

The method presented herein provides rapid access to primary amines from nitriles. The foundation is now established for a future study of an asymmetric variant of this chemistry as well as its applications to α-heterosubstituted aluminum imines. We are actively investigating these matters and will report on additional developments in due course.

Experimental Section

^{1}H NMR spectra were recorded at 90 or 300 MHz. All reactions were carried out under a blanket of argon. Column flash chromatography was performed on Merck silica gel (70–230 mesh). Butyllithium and *sec*-butyllithium were purchased from Aldrich as 15% hexane solutions. *tert*-Butyllithium was purchased from Ric-Roc. i-Bu_2AlH was purchased from Fluka. The purity of all title compounds was judged to be >95% by GC, GC-mass spectra, and ^{1}H NMR determinations.

Procedures for the preparation of selected primary amines are provided below. Known compounds gave spectral data according to those reported in literature and to the assigned structure.

Preparation of *N*-Diisobutylaluminum Imines. *N*-(Diisobutylaluminio)benzaldimine (2a). In a 50-mL, two-necked flask equipped with magnetic stirring bar and with nitrogen and syringe inlets was placed 5 mmol (0.516 g) of benzonitrile **2** in 10 mL of dry pentane. *i*-Bu_2AlH (5 mmol, 0.781 g) was added via syringe at −78 °C. The solution was maintained at the same temperature for 3 h, and the pentane removed under vacuum.[8] A sample of this material was subjected to spectral identification: IR ($CHCl_3$) 1635 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 8.97 (s, 1 H), 7.76–7.50 (m, 5 H), 1.77 (m, 2 H), 1.5–0.8 (m, 16 H).

One-Pot Preparation of Primary Amines from Nitriles. 1-Phenyl-3-butenamine (4b). Method A. From the *N*-(diisobutylaluminio)benzaldimine solution prepared as described above, the pentane was completely removed under vacuum, 8 mL of anhydrous THF and 2 mL of an ethereal 2 M solution of allylmagnesium chloride[9] were added at −78 °C. This solution was allowed to reach room temperature (overnight) and stirred for a further 48 h. The reaction mixture was then cautiously hydrolyzed with 50 mL of water and extracted with ethyl acetate. After drying over $MgSO_4$, removal of the solvent gave 0.720 g (98%) of an oil essentially constituted by the amine as indicated by its NMR and GLC-MS.

Method B. To the reaction mixture of the amine, obtained as described in the method A, was added saturated NH_4Cl (10 mL), followed by concentrated ammonium hydroxide (10 mL) at 0 °C. After being stirred for 1 h, the mixture was extracted with diethyl ether (3 × 30 mL). The combined organic phases were washed with 1 M NaOH, dried over $MgSO_4$, and evaporated. The residue was dissolved in anhydrous diethyl ether (10 mL) and a saturated ethereal HCl solution was added to precipitate the amine hydrochloride. The product was filtered off and washed with anhydrous diethyl ether and acetone to give the amine hydrochloride as a white solid (mp 222 °C; lit.[10] mp 224–226 °C) (95%). The free amine was quantitatively obtained upon treatment with NaOH (1 N) and extraction with ether: IR (film) 3370, 3290, 3080, 1640, 1600, 1490 cm^{-1}; ^{1}H NMR ($CDCl_3$, 90 MHz) 7.3 (m, 5 H), 5.6 (m, 1 H), 5.1 (m, 2 H), 4.0 (dd, J_1 = 6 Hz, J_2 = 7.5 Hz, 1 H), 2.4 (m, 2 H), 1.9 (s, 2 H, NH_2); GC/MS 147, 146 (100) (M^+ − 1). Anal. Calcd for $C_{10}H_{13}N$:C, 81.59; H, 8.9. Found: C, 81.67; H, 8.92.

1-(2-Thienyl)pentanamine (4h): IR (film) 3360, 3280, 3100, 3060 cm^{-1}; ^{1}H NMR ($CDCl_3$) 7.0 (m, 1 H), 6.8 (m, 2 H), 4.1 (t, 1 H, J = 6 Hz), 2.0 (bs, 2 H, NH_2), 1.7–0.7 (m, 9 H); GC/MS 169 (M^+), 112 (M^+ − butyl) (100). Anal. Calcd for $C_9H_{15}NS$: C, 63.86, H, 8.93. Found: C, 63.97; H, 8.92.

1-(2-Thienyl)-3-butenamine (4i): IR (film) 3360, 3280, 3100, 3060, 1650, 1630 cm^{-1}; ^{1}H NMR ($CDCl_3$, 90 MHz) 7.2 (m, 1 H), 6.9 (m, 2 H), 5.7 (m, 1 H), 5.1 (m, 2 H), 4.3 (dd, J_1 = 7.5 Hz, J_2 = 6 Hz, 1 H), 2.5 (m, 2 H), 1.7 (bs, 2 H, NH_2); GC/MS 152 (M^+ − 1), 112 (M^+ − allyl) (100). Anal. Calcd for $C_8H_{11}NS$: C, 62.7; H, 7.24. Found: C, 62.56; H, 7.25.

1-Dodecen-4-amine (4l): IR (film) 3360, 3280, 3070 cm^{-1}; ^{1}H NMR ($CDCl_3$, 90 MHz) 5.7 (m, 1 H), 5.1 (m, 2 H), 2.8 (m, 1 H), 2.2 (m, 2 H), 2.0–0.7 (m, 17 H, and NH_2); GC/MS 142 (100) (M^+ − allyl). Anal. Calcd for $C_{12}H_{25}N$: C: 78.62; H, 13.74. Found: C, 78.43; H, 13.67.

***N*^{1}-(Triphenylmethyl)-8-nonene-1,6-diamine (4m):** IR (film) 3380, 3320, 3280, 1650, 1630, 1590 cm^{-1}; ^{1}H NMR ($CDCl_3$) 7.3 (m, 15 H), 5.7 (m, 1 H), 5.1 (m, 2 H), 3.4 (m, 1 H), 2.2 (m, 4 H), 1.4 (m, 8 H, NH_2, NH). The crude amine was converted to the benzamide for the purpose of identification. Spectra are as follows.

***N*^{1}-(Triphenylmethyl)-*N*^{6}-(benzyloxycarbonyl)-8-nonene-1,6-diamine (4m'):** mp 112–114 °C; IR ($CHCl_3$) 3440, 3080, 3060, 3000, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) 7.7 (m, 1 H); 7.5–7.1 (m, 19 H), 5.8 (m, 1 H, N*H*CO), 5.1 (m, 2 H), 4.2 (m, 1 H), 2.3 (m, 2 H), 2.1 (m, 2 H), 1.7–1.2 (m, 8 H, Ph_3NH); exact mass calcd for $C_{35}H_{38}N_2O$ m/e 502.29841, found 502.29852. Anal. Calcd for $C_{35}H_{38}N_2O$: C, 83.63; H, 7.62; Found: C, 83.35; H, 7.71.

1-Octen-4-amine (4n): IR (film) 3360, 3280, 3080; ^{1}H NMR ($CDCl_3$) 5.7 (m, 1 H), 5.1 (m, 2 H), 2.8 (m, 1 H), 2.1 (m, 2 H), 1.8–0.7 (m, 9 H, NH_2); GC/MS 126 (M^+ − 1); 86 (M^+ − allyl) (100). Anal. Calcd. for $C_8H_{17}N$: C, 75.51; H, 13.48. Found: C, 75.43; H, 13.44.

Acknowledgment. This investigation was supported by Ministero Pubblica Istruzione (Fondi 60%) and Progetto Finalizzato Chimica Fine e Secondaria II.

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(8) Generally speaking, after addition of *i*-Bu_2AlH the reactions were monitored by GC and further processed after complete disappearance of the starting nitrile (2–3 h).

(9) Allylmagnesium chloride was purchased from Aldrich. No difference could be noted with freshly prepared reagent.

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Thioaldehydes and Thioketones from 1,3-Dithiolane *S*-Oxides

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Thiocarbonyl compounds such as thioaldehydes or thioketones are highly reactive and, consequently, interesting synthetic intermediates. However, unless sterically or electronically stabilized, they show a pronounced tendency to di-, oligo-, or even polymerize.[1] Therefore, a prerequisite for synthetic uses of reactive thiocarbonyl compounds is their generation under conditions that avoid oligo- or polymerization and, preferably, also minimize

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