Generation and Reactions of Nonstabilized Bis(α-amino carbanions)

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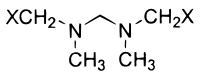
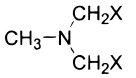
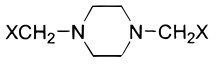
The development of new strategies for the single-step achievement of multiple reactions can allow the efficient construction of complex molecules. Among available strategies, the utility of dicarbanions has recently emerged.[1] Bis(α-amino carbanions) lacking stabilizing groups are rare because there are only a few methodologies available for the preparation of nonstabilized α-amino carbanions in general.[2−4] Previously, successful preparations of such bis-derivatives have been limited to (i) direct double lithiation of bis(dimethylamino)methane (**1a**) by *t*-BuLi to give 1,5-dicarbanion **1b**,[5] (ii) lithium-



1a X = H
1b X = Li



2a X = $SnBu_3$
2b X = Li

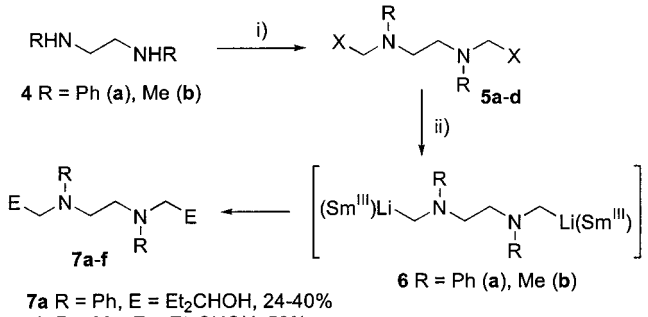


3a X = SPh
3b X = Li

metal exchange of organotin compound **2a** to form 1,3-dicarbanions **2b**,[6] and (iii) reductive C−S bond cleavage of α-thioamine **3a** to prepare 1,6-dicarbanion **3b**.[7] Moreover, only silyl chlorides[5−7] and deuterium oxide[5] were employed as electrophiles in the reported reactions of bis(α-amino carbanions) **1b**, **2b**, and **3b**.

We recently demonstrated that readily available *N*-(α-aminoalkyl)benzotriazoles[8] and tosylmethylamines[9a] are advantageous and versatile precursors of nonstabilized α-amino carbanions. We have now found that our previous and other methods[7,9b,10] can be extended to the generation of various nonstabilized bis(α-amino carbanions) which can be trapped with a variety of electrophiles.

Scheme 1. Formation of 1,6-Bis(α-amino carbanions)



7a R = Ph, E = Et_2CHOH, 24-40%
7b R = Me, E = Et_2CHOH, 53%
7c R = Me, E = $(CH_2)_5OH$, 60%
7d R = Me, E = *i*-PrCHOH, 57%
7e R = Me, E = PhCHOH, 69%
7f R = Me, E = PhC(OH)Me, 62%

5a X = Bt, R = Ph, 94%
5b X = SO_2Tol, R = Ph, 90%
5c X = SPh, R = Ph, 63%
5d X = SPh, R = Me, 86%

Key: i) for **5a**, $BtCH_2OH$, toluene, reflux; for **5b**, $TolSO_2H$, HCHO, MeOH, 0 °C; for **5c**,**d**, PhSH, HCHO, EtOH, reflux; ii) Method A: **5a**, 3-pentanone, SmI_2/THF-HMPA, 0 °C; B: **5a**, 3-pentanone, LiNap, THF, -78 °C; C: **5b**, 3-pentanone, SmI_2/THF-HMPA, 0 °C; D: **5b**, 3-pentanone, SmI_2/THP-HMPA, 0 °C; E: **5c**, 3-pentanone, Li/LiBr, THF, -78 °C to rt; F: **5d**, Li/LiBr, THF, 3-pentanone, -78 °C; or G: **5d**, Li/LiBr, THF, -78 °C, 2 h, then E^+, -78 °C.

Results and Discussion

The bis(α-aminobenzotriazole) **5a** was prepared from 1,2-anilinoethane (**4a**), and 1-(hydroxymethyl)benzotriazole ($BtCH_2OH$) in refluxing toluene in 94% yield. The utilization of **5a** as a formal dicarbanion synthon equivalent and its subsequent reaction with electrophile 2-pentanone was attempted under two different conditions: using (i) SmI_2[8] and (ii) lithium naphthalene (LiNap) as reducing reagents (Scheme 1).[7] The first reaction gave product **7a**, expected from a dicarbanion intermediate (**6a**), together with a byproduct deriving from a C−N(Ph) bond cleavage of the starting **5a** due to the presence of two C−N bonds.[8] The use of LiNap as reducing reagent for **5a** resulted in a complex mixture.

To avoid the low C−N bond selectivity in the above reaction, the bis(α-sulfonylamine) **5b** was prepared from **4a**, toluenesulfonic acid, and formaldehyde in 90% yield (Scheme 1) by using a modified version of a previously published method.[11] However, reaction of **5b** with 3-pentanone in the presence of SmI_2/THP (tetrahydropyran)−HMPA[9a] gave only 31% bis(α-amino alcohol) **7a** (24% of **7a** was isolated when SmI_2/THF−HMPA was used). A somewhat higher yield (40%) of **7a** was afforded when bis(α-phenylthioamine) **5c** was treated with lithium/lithium bromide[12] and 3-pentanone. Compound **5c** was synthesized from **4a** in a fashion similar to the literature methods.[13] In all the reactions of **5b**,**c**, 1,3-diphenylimi-

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(1) (a) Thompson, C. M. *Dianion Chemistry in Organic Synthesis*; CRC Press: Boca Raton, FL, 1994. (b) Marek, I.; Normant, J.-F. *Chem. Rev.* **1996**, *96*, 3241.

(2) For recent reviews of the generation of nonstabilized α-aminocarbanions, see: (a) Katritzky, A. R.; Qi, M. *Tetrahedron* **1998**, *54*, 2647. (b) Kessar, S. V.; Singh, P. *Chem. Rev.* **1997**, *97*, 721.

(3) Representative reviews on stabilized α-amino carbanions: (a) Beak, P.; Zajdel, W. J.; Reitz, D. B. *Chem. Rev.* **1984**, *84*, 471. (b) Seebach, D.; Enders, D. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 15.

(4) Representative reviews on lithium/element exchange: (a) Kauffmann, T. *Top. Cur. Chem.* **1980**, *92*, 109. (b) Cohen, T.; Bhupathy, M. *Acc. Chem. Res.* **1989**, *22*, 152.

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(7) Strohmann, C.; Abele, B. C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2378.

(8) Katritzky, A. R.; Qi, M.; Feng, D.; Nichols, D. A. *J. Org. Chem.* **1997**, *62*, 4121.

(9) (a) Katritzky, A. R.; Feng, D.; Qi, M. *J. Org. Chem.* **1997**, *62*, 6222. (b) Alonso, D. A.; Alonso, E.; Nájera, C.; Ramón, D. J.; Yus, M. *Tetrahedron* **1997**, *53*, 4835.

(10) (a) Broka, C. A.; Shen, T. *J. Am. Chem. Soc.* **1989**, *111*, 2981. (b) Tsunoda, T.; Fujiwara, K.; Yamamoto, Y.-i.; Itô, S. *Tetrahedron Lett.* **1991**, *32*, 1975.

(11) Bäder, E.; Hermann, H. D. *Chem. Ber.* **1955**, *88*, 41.

(12) It is noteworthy to point out that the use of Li/LiBr[8] instead of LiNap[7, 10a] or lithium di-*tert*-butylbiphenyl (LiDBB)[10b] avoids the introduction of equivalent amount of aromatic hydrocarbons, which have to be removed by chromatography, into the reaction system.

(13) (a) Grillot, G. F.; Felton, H. R.; Garrett, B. R.; Greenberg, H.; Green, R.; Clementi, R.; Moskowitz, M. *J. Am. Chem. Soc.* **1954**, *76*, 3969. (b) Pollard, C. B.; Butler, D. E. *J. Org. Chem.* **1961**, *26*, 600.

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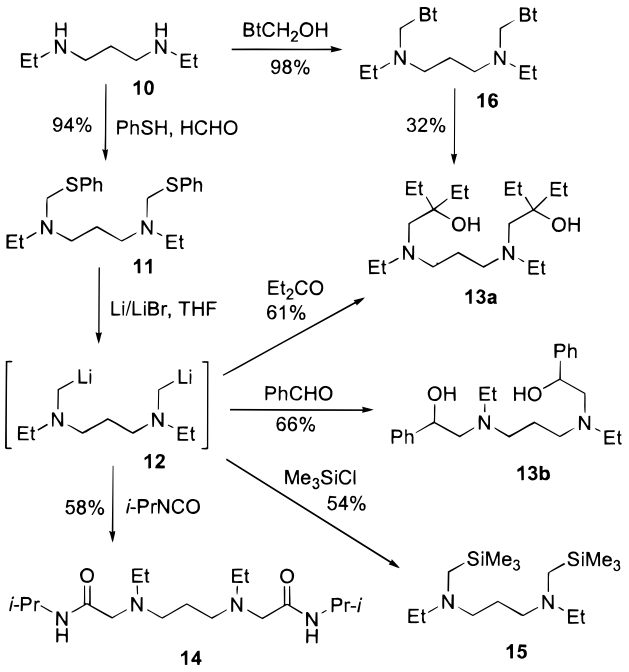
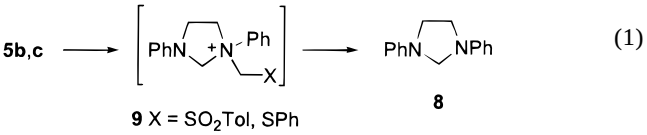
Scheme 2. Formation of 1,7-Bis(α-amino carbanions)



dazolidine (**8**) was a major byproduct. The formation of compound **8** probably involved an intramolecular cyclization of **5b**,**c** to form an ammonium salt **9**, which was hydrolyzed to give imidazolidine **8** (eq 1).



(1)

We believe that the low yields of the above reactions are due to the low stability of the expected dicarbanion intermediate **6a**. As alkyl-substituted α-amino carbanions are more stable than their aryl-substituted counterparts,[14] we prepared bis(α-thioamine) **5d**. We found that **5d** reacted easily with electrophiles, either in the presence of Li/LiBr or using a two-step procedure, to give **7b**−**f** in good yields (Scheme 1, method G).

We successfully extended this reaction to the generation of nonstabilized α-amino 1,7-dicarbanion **12** from bis(α-thioamine) **11** (Scheme 2). Preformation of the nonstabilized α-amino dicarbanion **12** significantly expanded the scope of the electrophiles that could be utilized in this reaction to include carbonyl compounds, isocyanates, and chlorotrimethylsilane. Thus, bis(*β*-hydroxyamines) **13**, bis(*β*-aminoamide) **14**, and bis(*β*-aminosilane) **15** were synthesized in 54−66% yields. For the *N*-alkyl-substituted α-amino dicarbanion, bis(α-aminobenzotriazole) **16** can also be used as the precursor; compound **13a** was prepared from **16** in 32% yield.

We previously found that *N*-(α-aminoalkyl)benzotriazoles, due to their ready availability, moderate reaction conditions, and easy workup, are better precursors for the nonstabilized α-amino carbanions[8] than either α-thioamines, for which stronger reducing reagents (e.g. LiNap) have to be used,[7,10] or α-sulfonylamines, for which only *N*-phenyl-substituted α-amino carbanions can be prepared.[9] However, for the bifunctional nonstabilized bis(α-amino carbanions) now studied it transpires that bis(α-thioamines) are the best precursors. The two-step approach now reported gives access to various multifunctionalized organic compounds in one-pot reactions.

(14) Peterson, D. J. *J. Am. Chem. Soc.* **1971**, *93*, 4027.

Experimental Section

For general information, see our previous papers.[8,9a]

***N,N′*-Bis(benzotriazolylmethyl)-*N,N′*-diphenylethylenediamine (5a).** A solution of 1-(hydroxymethyl)benzotriazole (2.98 g, 20 mmol) and 1,2-dianilinoethane (2.12 g, 10 mmol) in toluene (50 mL) was heated to reflux for 6 h, using a Dean-Stark trap to remove the produced water. After evaporation of the solvent, the crude product was dried under vacuum to give the title compound in 94% yield: white solid; mp 151−154 °C; ^{1}H NMR (benzotriazol-1-yl (Bt^1) and benzotriazol-2-yl (Bt^2) isomers, peaks corresponding to the major (90%) Bt^{1}Bt^1 isomer reported here) *δ* 3.71 (s, 4H), 6.02 (s, 4H), 6.80−7.15 (m, 7H), 7.16−7.50 (m, 9H), 7.90−8.10 (m, 2H); ^{13}C NMR *δ* 47.3, 66.0, 109.8, 116.7, 119.9, 121.0, 123.9, 127.5, 129.8, 132.6, 146.1, 146.4. Anal. Calcd for $C_{28}H_{26}N_8$: C, 70.87; H, 5.52; N, 23.61. Found: C, 70.97; H, 5.55; N, 23.40.

***N,N′*-Di(tosylmethyl)-1,2-dianilinoethane (5b).** Aqueous formaldehyde (37%, 1.5 g, 18 mmol) and a solution of the 1,2-dianilinoethane (1.6 g, 7.5 mmol) in methanol (20 mL) were added, in turn, to a solution of *p*-toluenesulfinic acid (2.52 g 16 mmol) in methanol (15 mL) at 0 °C and stirred for 3 h. The precipitate was filtered with suction and dried in a vacuum system to give **5b** in 90% yield: white solid, mp 139−141 °C; ^{1}H NMR *δ* 2.38 (s, 6H), 3.66 (s, 4H), 4.65 (s, 4H), 6.68 (d, 4H, *J* = 8.1 Hz), 6.79 (t, 2H, *J* = 7.1 Hz), 7.12 (t, 4H, *J* = 8.0 Hz), 7.22 (d, 4H, *J* = 8.0 Hz), 7.66 (d, 4H, *J* = 8.2 Hz); ^{13}C NMR *δ* 21.6, 48.4, 75.4, 114.2, 119.7, 128.7, 129.3, 129.9, 135.5, 145.0, 145.3. Anal. Calcd for $C_{30}H_{32}N_2O_4S_2$: C, 65.67; H, 5.88; N, 5.11. Found: C, 66.00; H, 5.99; N, 5.18.

***N,N′*-Dimethyl-*N,N′*-bis[(thiophenyl)methyl]ethylenediamine (5d).** Aqueous formaldehyde (37%, 4.87 g, 60 mmol) and thiophenol (4.45 g, 40 mmol) were added, in turn, to a solution of the *N,N′*-dimethylethylenediamine (1.78 g, 20 mmol) in methanol (35 mL) at 0 °C and stirred for 1 h and then heated to reflux for 5 h. The precipitate was filtered off with suction, washed with cold EtOH, and dried under vacuum to give **5d** in 86% yield: mp 48−50 °C; ^{1}H NMR *δ* 2.28 (s, 6H), 2.52 (s, 4H), 4.48 (s, 4H), 7.13−7.29 (m, 6H), 7.74 (d, 4H, *J* = 7.2 Hz); ^{13}C NMR *δ* 40.8, 51.4, 67.5, 126.4, 128.8, 132.0, 137.7. Anal. Calcd for $C_{18}H_{24}N_2S_2$: C, 65.02; H, 7.27; N, 8.42. Found: C, 64.90; H, 7.34; N, 8.35.

***N,N′*-Bis(2-ethyl-2-hydroxybutyl)-1,2-dianilinoethane (7a). Method A or C.** A solution of compound **5a** or **5b** (1.0 mmol) and 3-pentanone (0.22 g, 2.5 mmol) was added to SmI_2 (0.1 N, 5 mmol) in THF/HMPA (20:1) at 0 °C under nitrogen and stirred for 6 h. The reaction was quenched with water and extracted with ether. The organic phase was dried and concentrated to give a residue, which was purified by column chromatography (eluent: hexane/EtOAc/Et_3N) to afford **7a**: white solid, mp 89−90 °C; ^{1}H NMR *δ* 0.76 (t, 12H, *J* = 7.2 Hz), 1.30−1.53 (m, 8H), 1.65 (s, 2H), 3.12 (s, 4H), 3.52 (s, 4H), 6.66 (t, 2H, *J* = 7.1 Hz), 6.83 (d, 4H, *J* = 8.3 Hz), 7.15 (t, 4H, *J* = 7.3 Hz); ^{13}C NMR *δ* 7.8, 29.1, 48.3, 58.6, 76.4, 113.9, 117.4, 129.2, 149.5. Anal. Calcd for $C_{26}H_{40}N_2O_2$: C, 75.68; H, 9.77; N, 6.79. Found: C, 76.13; H, 9.57; N, 7.13.

General Procedure for the Preparation of 7b−f, 13−15. Method G. Lithium (30% in mineral oil, 0.46 g, 20 mmol) was washed twice with THF under argon and treated with 1,2-dibromoethane (2.3 mmol) in THF (30 mL) for 30 min to form the Li/LiBr suspension. The mixture was cooled to −78 °C, and a THF solution of the diamine derivative (**5d** or **11**, 2 mmol) was added. The reaction mixture was stirred for 2 h, and then an electrophile was added. After 1 h, the mixture was quenched with water at the same temperature and extracted with ethyl acetate. The solvent was removed to give a residue, which was purified by column chromatography on silica gel (eluent: hexane/EtOAc/Et_3N) to afford the desired product.

***N,N′*-Dimethyl-*N,N′*-bis(2-ethyl-2-hydroxybutyl)ethylenediamine (7b).** 53% yield; colorless oil; ^{1}H NMR *δ* 0.86 (t,

12H, $J = 7.4$ Hz), 1.33−1.62 (m, 8H), 2.37 (s, 6H), 2.39 (s, 4H), 2.54 (s, 4H), 4.97 (br s, 2H); ^{13}C NMR δ 7.8, 28.9, 47.1, 57.7, 63.2, 74.0. Anal. Calcd for $C_{16}H_{36}N_2O_2$: C, 66.62; H, 12.58; N, 9.71. Found: C, 66.53; H, 13.04; N, 9.88.

***N,N′*-Diethyl-*N,N′*-bis(2-ethyl-2-hydroxybutyl)-1,3-propylenediamine (13a).** 61% yield; colorless oil; ^{1}H NMR δ 0.85 (t, 12H, $J = 7.5$ Hz), 1.01 (t, 6H, $J = 7.1$ Hz), 1.32−1.52 (m, 8H), 1.53−1.68 (m, 2H), 2.36 (s, 4H), 2.45−2.66 (m, 8H), 3.53 (br s, 2H); ^{13}C NMR δ 7.9, 11.8, 25.5, 29.8, 49.5, 53.7, 61.0, 72.5. Anal. Calcd for $C_{19}H_{42}N_2O_2$: C, 69.04; H, 12.81; N, 8.47. Found: C, 69.27; H, 13.29; N, 8.70.

***N,N′*-Diethyl-*N,N′*-bis((isopropylcarbamoyl)methyl)-1,3-propylenediamine (14):** 58% yield; colorless oil; ^{1}H NMR δ 1.03 (t, $J = 7.1$ Hz) and 1.20 (t, $J = 6.6$ Hz) (total 6H), 1.02 (d, $J = 6.4$ Hz) and 1.37 (d, $J = 6.5$ Hz) (total 12H), 1.50−1.67 (m, 2H), 2.36−2.70 (m, 8H), 2.99 (s) and 3.36 (s) (total 4H), 3.90−4.17 (m) and 4.40−4.55 (m) (total 2H), 7.10 (d, $J = 7.8$ Hz) and 8.19 (d, $J = 6.0$ Hz) (total 2H); ^{13}C NMR δ 12.0 (11.0), 22.6 (22.2), 25.2 (24.1), 40.4 (42.5), 49.0 (47.6), 48.9 (47.2), 52.9 (50.4), 57.9 (58.4), 170.3 (153.8). Anal. Calcd for $C_{17}H_{36}N_4O_2$: C, 62.16; H, 11.05; N, 17.06. Found: C, 61.61; H, 11.08; N, 16.80.

***N,N′*-Diethyl-*N,N′*-bis((trimethylsilyl)methyl)-1,3-propylenediamine (15):** 54% yield; colorless oil; ^{1}H NMR δ −0.09 (s, 18H), 0.84 (t, 6H, $J = 7.1$ Hz), 1.41 (m, 2H), 1.78 (s, 4H), 2.22 (t, 4H, $J = 7.3$ Hz), 2.31 (q, 4H, $J = 6.9$ Hz); ^{13}C NMR δ −1.2, 11.5, 24.2, 45.4, 50.7, 55.1; HRMS (FAB) (*m/e*) calcd for $C_{15}H_{38}N_2Si_2$ + H 303.2652, found 303.2653.

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Supporting Information Available: Text providing fully detailed analytical data (^{1}H and ^{13}C NMR and microanalysis) for compounds **5c**, **7c**−**f**, **8**, **11**, **13b**, and **16** (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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