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Reductive Lithiation of a Trimethyl Benzo-1,3-thiazoline: Generation of an α-Amino Tertiary Carbanion and Reactions with Electrophiles.

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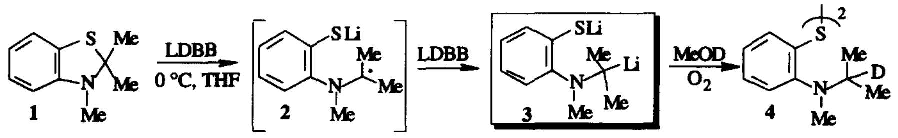
Abstract: Trimethylbenzothiazoline **1** has been reductively lithiated by lithium 4,4'- di-*t*-butylbiphenylide (LDBB) leading to dianion **3**, that has been trapped with electrophiles to give aminodisulfides **4**, aminosulfide **8** and aminoalcohols **9**.

α–Heterosubstituted carbanions represent a category of reactive intermediates of great utility in synthetic organic chemistry.[1] "Stabilized" α–aminocarbanions, in which an appropriate electron withdrawing substituent is attached to the nitrogen atom, as in amides, N-BOC amines, nitroso compounds, isocyanides, formamidines, imines, nitroalkanes, are well known and have been extensively employed in synthetic organic chemistry.[2] "Non-stabilized" α–aminocarbanions, instead, have received little attention. Some α-amino primary and secondary carbanions have been produced by transmetallation of α–aminoorganotin compounds.[3] α-Amino primary carbanions can be generated by the removal of a methyl proton by a powerful base.[4] Some primary and benzylic secondary carbanions can be produced by deprotonation of tertiary amines which are complexed to a Lewis acid.[5] Some secondary α-amino anions with rather specific structures can be prepared by generating an α-amino radical by hydrogen atom transfer and capturing the radical with SmI_2.[6] Two reductive methods have also been used to produce α-aminocarbanions. One of these utilizes reductive lithiation by radical anions of α-(phenylthio) tertiary amines.[7] The other reports the reductive lithiation of α-cyano tertiary amines.[8]

The only α-amino tertiary anions which have thus far been prepared have enjoyed benzylic or allylic stabilization.[9] Reductive lithiation of aryl sulfides by radical anions has been used recently to prepare a variety of tertiary carbanions.[10] In this and the preceding paper we report for the first time reductive lithiation of systems in which the arylthio group is part of a ring fused system so that the resulting arenethiolate and alkyllithium groups are both in the product of reductive ring cleavage. In the present paper, we report the use of this ring cleavage protocol to generate the first example of an unstabilized α-amino tertiary carbanion.

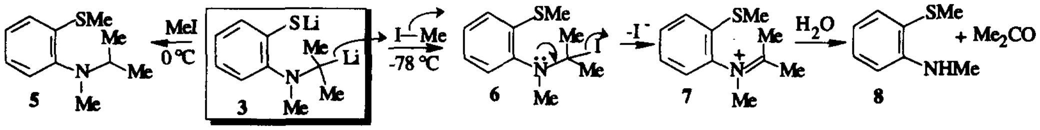
When 1 molar equiv. of trimethylbenzothiazoline **1**[11] in THF was added dropwise to 3 molar equiv. of lithium 4,4'- di-*t*-butylbiphenylide (LDBB)[12] at 0 °C under an argon atmosphere, the greenish-blue color of LDBB changed to the dark red color of dianion **3**. The formation of **3**, which probably results from electron transfer to the putative radical anion **2**, was proved by its trapping after 1 h with MeOD to give deuterated *N*-methyl-*N*-isopropyl-*o*-aminophenyl disulfide **4** in 57% yield (Scheme 1). Disulfide **4** very likely results from the oxidation (O_2) of the corresponding thiophenol.

Scheme 1

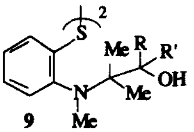


When the dark red solution of 3, generated as above at 0 °C, was treated with MeI at 0 °C *N*-methyl-*N*-isopropyl-*o*-aminophenyl methyl sulfide 5 formed in satisfactory yield.[13] In contrast, *N*-methyl-*o*-aminophenyl methyl sulfide 8 was obtained as the main product when LDBB, generated at 0 °C as above, was cooled to -78 °C, treated with benzothiazoline 1 and subsequently quenched with excess MeI after 30 min. To rationalize these results,we suggest that dianion 3, generated at 0 °C, reacts with MeI undergoing methylation at the arenethiolate group and protonation by THF at the tertiary carbanionic site to give 5. When generated at -78 °C, instead, dianion 3 survives long enough to cause deiodination of MeI, through a metal-halogen exchange process, a common type of reaction largely used to produce primary organolithiums from primary alkyl halides and *t*-BuLi.[14] The resulting iodide 6 would then undergo halogen displacement to give iminium ion 7. Quenching with aqueous NH_4Cl would finally lead to 8 and acetone (Scheme 2).

Scheme 2



Treatment of dianion 3 with *p*-chlorobenzaldehyde gave a satisfactory yield of the aminoalcohol **9a**. Comparable results were obtained when 3 was treated with other aromatic aldehydes to give aminoalcohols **9b-e** (See Table).



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9a: R' = H; R = 4-Cl-C_6H_4-

9b: R' = H; R = 3-NO_2-C_6H_4-

9c: R' = H; R = -C_6H_5

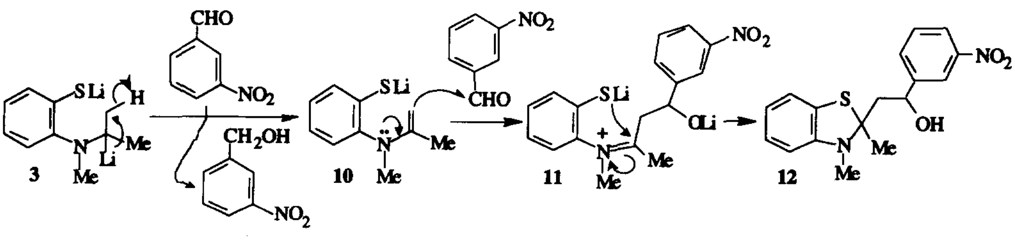
9d: R' = H; R = 2-MeO-C_6H_4-

9e: R' = H; R = -CH=CH-C_6H_5

9f: R' = H; R = -CH$(CH_3)_2$

In the reaction with *m*-nitrobenzaldehyde the formation of the aminoalcohol **12** was also observed. A possible explanation for this is that dianion 3 transfers a hydride ion to the very electrophilic *m*-nitrobenzaldehyde to give the enamine **10**.[15] Nucleophilic attack on the aldehyde, followed by the ring-closure, would furnish thiazoline **12** (Scheme 3).

Scheme 3



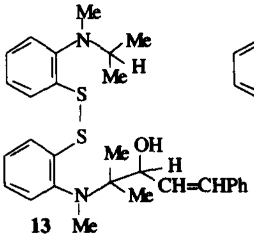
In the reaction of **3** with cinnamaldehyde the formation of compound **13** was also observed.

Dianion **3** adds also to aliphatic carbonyl compounds. Indeed, when **3** was treated with isobutyraldehyde the expected alcohol **9f** formed along with *N*-methyl-*N*-isopropyl-*o*-aminophenyl disulfide **14**, likely derived from deprotonation of the aldehyde.

Table Reaction of dianion **3** with electrophiles in THF.

Electrophile	Temp. (°C)	Reaction products (% yield) [a, b, c]
MeOD	0	**4** (57)
MeI	"	**5** (57)
"	-78	**5** (8) + **8** (53)
4-Cl-C_6H_4CHO	0	**9a** (56)
3-NO_2-C_6H_4CHO	"	**9b** (50) + **12** (17)
C_6H_5CHO	"	**9c** (52)
2-MeO-C_6H_4CHO	"	**9d** (72)
PhCH=CHCHO	"	**9e** (60) + **14** (22)
$(CH_3)_2$CHCHO	"	**9f** (35) + **14** (20)

a) Unoptimized yields were calculated on isolated, purified compounds.
b) Compounds characterized by IR; ^{1}H, ^{13}CNMR and GC-MS.
c) All the new compounds showed satisfactory microanalytical data.



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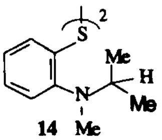

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In conclusion, we have shown here how the tertiary α–amino tertiary carbanion **3** can be generated and trapped with electrophiles leading to aminoalcohols **9**,[16] which may be synthetically useful for cyclisation to benzothiazine derivatives. More work is in progress in our laboratory to this end.

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11. Trimethylbenzothiazoline **1** was prepared by methylation of commercial 2-methylbenzothiazole and subsequent reaction with MeMgI.
12. For detailed directions on the preparation of LDBB, see: Freeman, P.; Hutchinson, L. *J. Org. Chem.* **1980**, *45*, 1924; Mudryk, B.; Cohen, T. *Organic Synthesis* **1995**, *72*, 173.
13. The methylation of the carbanionic site of **3** did not take place: protonation by the solvent (THF) apparently occurred faster. This is reasonable considering that tertiary carbanions usually deprotonate THF very rapidly.
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15. It is not surprising that an intermediate such as **3** behaves as a hydride ion donor, since organometallics bearing β-hydrogen atoms frequently transfer hydride ions to carbonyl groups: Cohen, T.; Jeong, In-H.; Mudryk, B.; Bhupathy, M.; Awad, M. M. A. *J. Org. Chem.* **1990**, *55*, 1528 and citations therein.
16. **Typical Procedure. Reductive Lithiation of 1 and capture of the carbanion 3 with electrophiles**. The reaction with *p*-chlorobenzaldehyde is here described as an example. To a preformed solution of LDBB[12] (3.0 mmol) at 0 °C a THF (1.5 ml) solution of benzothiazoline **1** (1.21 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 15 min and then the THF (1.5 ml) solution of *p*-chlorobenzaldehyde (1.57 mmol) was added dropwise. After 30 min, the reaction mixture was allowed to warm to RT, quenched with aqueous NH_4Cl, extracted with ether and dried over Na_2SO_4. The solvent was removed by rotary evaporation. Column chromatography (petroleum ether/ether: 7/3) gave **9a** as a yellow solid, m.p. 95-97 °C. IR (KBr) ν: 3420 (OH) cm^{-1}. ^{1}HNMR ($CDCl_3$) δ: 0.72 (s, 3H), 1.24 (s, 3H), 2.80 (s, 3H), 4.81 (s, 1H, exchange with D_2O), 4.94 (s, 1H), 7.14-7.50 (m, 8H). Anal. Calcd for $C_{34}H_{38}Cl_2N_2O_2S_2$: C, 63.64; H, 5.97; N, 4.37. Found: C, 63.85; H, 6.01; N, 4.15.

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