Synthesis of Amines via Carbon-Sulfur Bond Cleavages of Substituted Aminomethyl Sulfides with Organolithium Reagents: Aminocarbene Route to Enamines and Sterically Hindered Amines[1]

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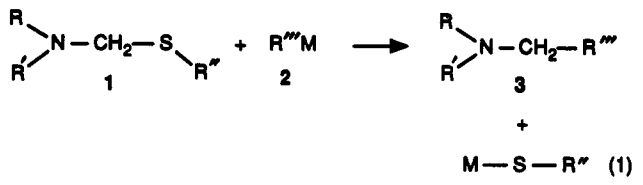
Summary: N-Substituted and N,N-disubstituted aminomethyl sulfides can be converted into secondary and tertiary amines, respectively, by organolithium reagents in high yields, regardless of whether the N-substituent is alkyl or aryl; for the former case, imines, and for the latter case, aminocarbenes, are the most likely intermediates.

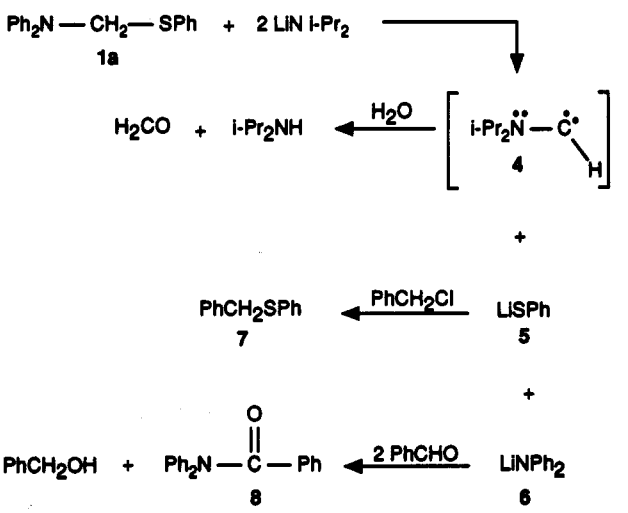
Although the reactions of substituted aminomethyl sulfides 1 with Grignard reagents have previously shown considerable scope for the preparation of some substituted amines,[2,3] the method fails with bulky Grignard reagents, such as *t*-BuMgCl,[2] and with (*N*,*N*-diarylamino)methyl sulfides **1a**.[4] In a study designed to evaluate the suitability of a variety of organolithium reagents for the synthesis of amines from 1, we have found not only that RLi reagents have greater scope than the corresponding RMgX reactants but also that novel mechanistic pathways account for their greater utility (eq 1, M = MgX, Li). In exploring the scope



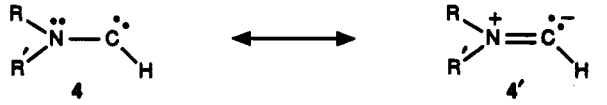
(1)

of organolithium reagents in this process, we have examined as substrates aminomethyl sulfides where R″ = Ph or *t*-Bu and R,R′ = Ph, Ph (**1a**), Ph, H (**1b**), Ph, Me (**1c**), and $PhCH_2$, $PhCH_2$ (**1d**) and those R‴Li reagents where R‴ = Me, *n*-Bu, *t*-Bu, and Ph. All such substrates are readily accessible through the interaction of the appropriate amine with formaldehyde and the mercaptan.[5] In obtaining feasible conversions of 1 into 3, it was found that the nature of the solvent and the presence of a basic catalyst exerted a marked influence, positive or negative, whose cause was not immediately obvious. For example, THF promoted the reaction of t-BuLi with **1a** (runs 2 vs 3) but retarded its reaction with **1d** (run 19); LDA accelerated the reaction of **1a** with *n*-BuLi in THF (runs 4 vs 5) but did not significantly change its rate with **1d**. However, by a systematic variation of solvent between THF and hexane and by use of 1 or more equiv of RLi, as well as basic catalysts such as LDA or KO-*t*-Bu, high yields of the desired amine could be obtained from 1, regardless of whether R and R′ were aryl, alkyl, or H. The yields and the products obtained under various experimental conditions are summarized in Table 1.

Scheme 1



It should be noted that both electron-donating ($PhCH_2$, Me, H) and electron-withdrawing substituents on N (Ph) in 1 give high yields of 3 with 1 or 2 equiv of R‴Li, regardless of whether R‴ is bulky (*t*-Bu) or not (CH_3). Hence, this method of preparing amines from 1 is superior to the Grignard method. Moreover, the superior reactivity of Ph_2NCH_2SR toward R‴Li in THF and with catalysis by LDA indicates the occurrence of a novel reaction pathway from **1a** to **3a**, namely an elimination-readdition route via an aminocarbene **4**, which would be stabilized through its iminium methylenide character **4′**.



Evidence for the immediacy of aminocarbenes was adduced from the stoichiometric reaction of **1a** in THF with exactly 2 equiv of LDA, from which reaction 1 equiv each of lithium thiophenolate (**5**) and lithium diphenylamide (**6**) was produced (Scheme 1). The presence of **5** and **6** in the reaction mixture follows from (a) the isolating of thiophenol and diphenylamine upon hydrolysis, (b) the isolation of benzyl phenyl sulfide (**7**) upon addition of 1 equiv of benzyl chloride, and (c) the isolation of *N*-benzoyldiphenylamine (**8**) and benzyl alcohol upon addition of 2 equiv of benzaldehyde.[6] The presumed aminocarbene

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(1) Functionalized Organolithium Reagents. 10. Part 9: Eisch, J. J.; Shah, J. H. *J. Org. Chem.* **1991**, *56*, 2955.

(2) Pollak, I. E.; Trifunac, A. D.; Grillot, G. F. *J. Org. Chem.* **1967**, *32*, 272.

(3) Pollak, I. E.; Grillot, G. F. *J. Org. Chem.* **1967**, *32*, 2892.

(4) Compound **1a** fails to react with EtMgBr under conditions which were found to be successful in refs 2 and 3.

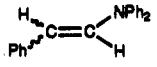
(5) Grillot, G. F.; Schaffrath, R. E. *J. Org. Chem.* **1959**, *24*, 1035.

(6) In a separate experiment we showed that preformed $LiNPh_2$ reacts with PhCHO to give these cross Cannizzaro-like products: ^1H NMR of **8** ($CDCl_3$) δ 7.47-7.14 (m); ^{13}C NMR δ 170.59, 143.90, 136.10, 130.13, 129.14, 129.07, 127.83, 127.47, 126.30.

(7) Since all evidence points to the persistence and relative stability of **4** in THF, we are attempting to isolate it or its complex with a transition metal center. From our failure to find any *i*-Pr_2NCH_2N-*i*-Pr_2 upon hydrolytic workup of this reaction mixture, it is clear that **4** does not add to the *i*-Pr_2NH present in the solution. For the isolation and complete structural characterization of cyclic aminocarbenes of the imidazol-2-ylidene type, *cf.*, Arduengo, A. J., III; Rasika Dias, H. V.; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1992**, *114*, 5530.

0022-3263/94/1959-0007$04.50/0

Table 1. Reactions of N-Substituted Aminomethyl Sulfides with Organolithium Reagents[a]

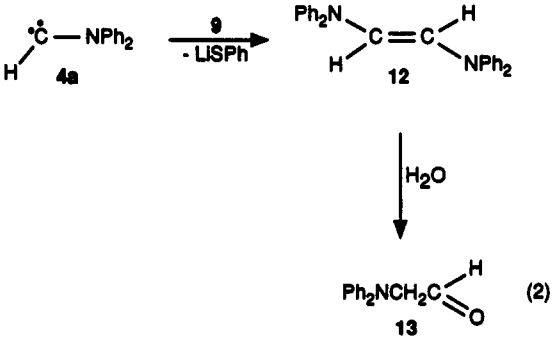
run	RR'NCH$_2$SR'' 1 R	R'	R''	R'''Li (equiv) 2[b]	solvent (cat.)[c]	temp[d] (°C)	product 3	yield[e] (%)
1	Ph	Ph	*t*-Bu	*t*-BuLi (2)	THF	0 → 25	*t*-BuCH$_2$NPh$_2$	80
2	Ph	Ph	Ph	*t*-BuLi (1)	THF		*t*-BuCH$_2$NPh$_2$	75
3				*t*-BuLi (2)	hexane	25		0
						70	*t*-BuCH$_2$NPh$_2$	85
4				*n*-BuLi (1)	THF (LDA)	0 → 25	*n*-BuCH$_2$NPh$_2$	90
5				*n*-BuLi (1)	THF	−10 → 0	n-BuCH$_2$NPh$_2$	20
6				*n*-BuLi (2)	hexane	70	*n*-BuCH$_2$NPh$_2$	86
7				PhLi (2)	THF (LDA)	25		0
8				PhLi (2)	hexane	70	PhCH$_2$NPh$_2$	96
9				MeLi (2)	hexane	70	MeCH$_2$NPh$_2$	82
10				PhSO$_2$CHLi$_2$ (1)	THF (LDA)	25	H$_2$C=CHNPh$_2$	78
11				PhSO$_2$CPhLi$_2$ (1)	THF (LDA)	25		92[f]
12	Ph	H	Ph	MeLi (2)	Et$_2$O	25	MeCH$_2$NHPh	85
13				PhLi (2)	Et$_2$O	25	PhCH$_2$NHPh	88
14				*n*-BuLi (2)	Et$_2$O	25	*n*-BuCH$_2$NHPh	82
15				*t*-BuLi (2)	Et$_2$O	25	*t*-BuCH$_2$NHPh	90
16	Ph	Me	Ph	*n*-BuLi (1)	THF (LDA)	25	*n*-BuCH$_2$NMePh	85
17				*n*-BuLi (2)	hexane	70	*n*-BuCH$_2$NMePh	73
18	PhCH$_2$	PhCH$_2$	Ph	*n*-BuLi (2)	hexane	70	*n*-BuCH$_2$N(CH$_2$Ph)$_2$	86
19				*t*-BuLi (2)	THF	0		0
					hexane	25	*t*-BuCH$_2$N(CH$_2$Ph)$_2$	86[g]
20				PhLi (2)	hexane	25	PhCH$_2$N(CH$_2$Ph)$_2$	95

[a] Typical procedures employed for these reactions are as follows. (1) Run 4: under a nitrogen atmosphere 40 mmol of *n*-butyllithium in 75 mL of THF at −78 °C was treated with 2 mmol of *i*-Pr$_2$NH, and the solution was brought to −10 °C. Then a solution of 10 g (34 mmol) of **1a** dissolved in 50 mL of THF was slowly introduced and the mixture stirred between 0 and 25 °C for 4 h. Hydrolytic workup and column chromatographic separation gave 90% of CH$_3$CH$_2$CH$_2$CH$_2$CH$_2$NPh$_2$ and 2% of Ph$_2$NH. (2) Run 6: under a nitrogen atmosphere 5.0 g (17 mmol) of **1a** dissolved in 60 mL of hexane was treated with 38 mmol of *n*-butyllithium in hexane to produce a creamy yellow suspension. After being stirred at reflux for 8 h the mixture was hydrolyzed and the organic layer separated. The product was separated as an oil in 86% yield by column chromatography on alumina with a 1:4 (v/v) mixture of CH$_2$Cl$_2$ and CCl$_4$: ^{1}H NMR (CDCl$_3$) 0.7–1.8 (9H, m), 3.6 (2H, t), 7.0–7.6 (10H, t). (3) Run 12: similarly, 5.0 g (23 mmol) of **1c** dissolved in 30 mL of anhydrous Et$_2$O was treated at 25 °C with 50 mmol of methyllithium in Et$_2$O and the mixture stirred for 4 h. Hydrolytic workup and column chromatographic separation of the product, as above, yielded 85% of an oil: ^{1}H NMR (CDCl$_3$) 1.0 (3H, t), 2.9 (2H, q), 3.2 (1H, s), 6.4–7.2 (5H, m). (4) Run 19: similarly, 6.4 g (20 mmol) of **1d** dissolved in 100 mL of hexane was treated at −78 °C with 44 mmol of *tert*-butyllithium in pentane. The mixture was warmed to 25 °C and stirred for 8 h, as the LiSPh precipitated. Hydrolytic workup and flash column chromatography gave 86% of the product as an oil: ^{1}H NMR (CDCl$_3$) 0.80 (9H, s), 2.32 (2H, s), 3.58 (4H, s), 7.2–7.4 (10H, m). [b] At least a 10% excess of the organolithium reagent (over the 1 or 2 equiv specified) was employed. [c] Anhydrous, deoxygenated solvent was prepared just before use. The LDA was prepared *in situ* from the RLi and *i*-Pr$_2$NH. That no LDA catalyst was required for *t*-BuLi in THF (runs 1 and 2) is most likely due to attack of *t*-BuLi on THF, which would generate LiOCH=CH$_2$, a most satisfactory basic catalyst. [d] The duration of the reaction at this temperature varied from 2 to 10 h in THF or hexane. In hexane the progress of the reaction could be monitored by the precipitation of the LiSPh. [e] This is the unoptimized yield of product isolated by flash column chromatography. By ^{1}H NMR spectral analysis of the crude, hydrolyzed reaction product it was concluded that **1** was essentially consumed in most runs and **3** formed quantitatively. [f] The cis:trans ratio of this enamine was 30:70. [g] A small amount of CH$_3$N(CH$_2$Ph)$_2$ was formed in this reaction; this observation has a bearing on the prevailing reaction mechanism.[14]

4 (R, R' = *i*-Pr) would revert to the secondary amine and formaldehyde upon hydrolysis.[7]

Accordingly, the LDA-catalyzed reaction of *n*-BuLi with **1a** can be most reasonably explained by the following steps: (*1*) lithiation at the methylene carbene;[8] (2) a precedented α-elimination to a carbene intermediate;[9] (3) the rapid addition of an anionic nucleophile to such a carbene;[10] and (4) the proton–lithiation exchange between this adduct and **1a** to form the final product (Scheme 2). In step 3 the nucleophile RLi would be the organolithium reagent; alternatively, RLi would be LDA for the stoichiometric reaction depicted in Scheme 1.[11]

Furthermore, there is evidence that **4a** can also be captured by **9** (eq 2). When **1a** is slowly added to LDA in



(2)

THF at 25 °C, small amounts of **13** can be obtained upon hydrolytic workup.[12] The origin of **13** can best be viewed as arising from the hydrolysis of enamine **12**, which in turn could be pictured as being generated from **4a**, either by dimerization or, more likely, from the addition of **9** to **4a** and the β-elimination of LiSPh. The failure of any RLi nucleophile to add to **4'**, in the manner they do to **4a**, can be ascribed to the bulky, electron-donating *i*-Pr$_2$N

(8) The methylene carbon in Ph$_2$NCH$_2$CH=CH$_2$ and Ph(Me)NCH$_2$-CH=CH$_2$ is readily lithiated by *n*-BuLi in THF: Eisch, J. J.; Shah, J. H. *J. Org. Chem.* **1991**, *56*, 2955.

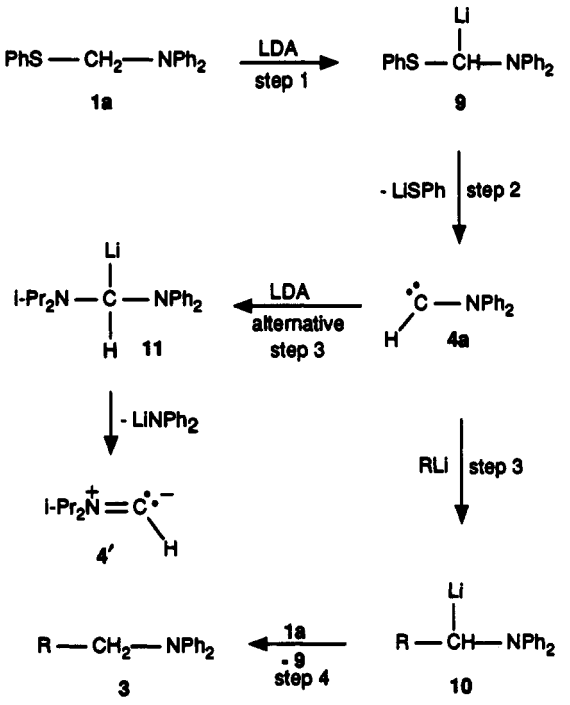
(9) *Cf.* the behavior of dilithio derivatives of thioacetals: Ritter, R. H.; Cohen, T. *J. Am. Chem. Soc.* **1986**, *108*, 3718.

(10) *Cf.* the facile addition of RLi to the carbene-like isonitriles: Walborsky, H. M.; Niznik, G. E. *J. Am. Chem. Soc.* **1969**, *91*, 7778.

(11) Although the role assigned to LDA in generating an aminocarbene from **1a** is congruent with the experimental facts, other explanations involving RLi–LDA aggregates could also be proposed for the reactions depicted in Schemes 2 and 3. For an overview of the complexity attending lithium amide-promoted RLi reactions, consult the insightful treatment: Collum, D. B. *Acc. Chem. Res.* **1992**, *25*, 448.

(12) This and all other new compounds have been fully characterized by analytical and spectral data: ^{1}H NMR of **13** (CDCl$_3$) δ 9.84 (t, J = 1.4 Hz, 1H), 7.31–6.96 (m, 10H), 4.41 (d, J = 1.4 Hz, 2H); ^{13}C NMR δ 201.88, 147.50, 129.58, 122.34, 120.74, 62.20.

Scheme 2



group, which increases electron density at the carbene center, thereby impeding nucleophilic attack, and sterically blocks ready access to the carbenoid carbon.

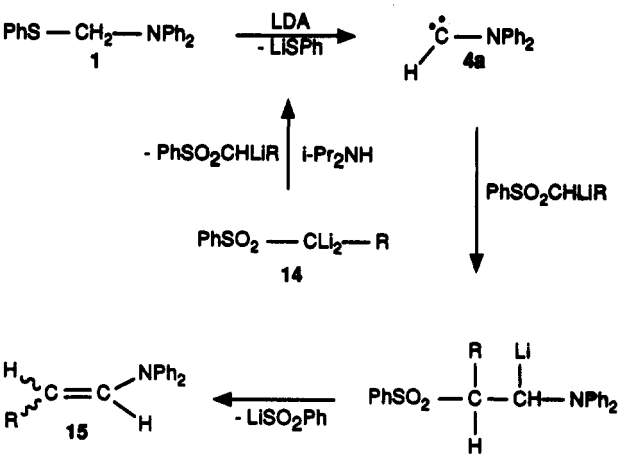
The intermediacy of such aminocarbenes explains why bulky organometallics like *tert*-butyllithium can react readily with **1a** to give such high yields of tertiary amines. A further indirect proof that carbene intermediates are essential for these reactions in THF is the behavior of **1a** toward dilithiated sulfones of the type $PhSO_2CLi_2R$ (**14**): [13] in the absence of catalytic LDA, they do not react with **1a**; with LDA high yields of the corresponding enamine (**15**) are obtained. These observations are readily accommodated by Scheme 3.

Thus, because of the intermediacy of aminocarbenes these (*N*,*N*-diarylamino)methyl sulfides (**1**: R, R′ = aryl) represent most useful substrates for preparing bulky tertiary amines or enamines, which would be difficult to prepare in any other way. The resulting enamines can be readily hydrolyzed to the aldehyde,[8] so this method offers a novel way of transforming alkyl sulfones into versatile nitrogen- and oxygen-functionalized reagents.

Although it is likely that a similar aminocarbene pathway is operative for the reactions of *N*-alkyl-*N*-aryl analogs of **1** in THF,[8] another pathway not involving aminocarbenes would seem to prevail for the reactions of the *N*,*N*-diaryl, the *N*-alkyl-*N*-aryl, and the *N*,*N*-dialkyl analogs of **1** in *hexane* (**1a**, **1c**, and **1d**). In this solvent, for example, essentially no reaction occurs between **1a** and RLi at

(13) *Cf.* Eisch, J. J.; Dua, S. K.; Behrooz, M. *J. Org. Chem.* **1985**, *50*, 3674. Eisch, J. J.; Behrooz, M.; Dua, S. K. *J. Organomet. Chem.* **1985**, *285*, 121 for the facile preparation of **14** from the sulfone and 2 equiv of *n*-BuLi in THF.

Scheme 3



room temperature; only upon reflux does cleavage of the C–S bond take place with the consumption of 2 equiv of RLi. Furthermore, even when $PhSCH_2N(CH_2Ph)_2$ (**1d**) is treated with *n*-BuLi in THF with LDA as a catalyst, no promotion but rather retardation of the C–S bond cleavage is observed. This supports the conclusion that *N*,*N*-dialkyl analogs of **1**, such as **1d**, are unable to pursue an aminocarbene pathway, regardless of whether the solvent is THF or hexane. The nature of the cleavage mechanism for the reactions of **1a**, **1c**, and **1d** with RLi in hexane is under investigation.[14] Finally, yet a third mechanistic pathway is most likely followed for the reaction of *N*-aryl analogs **1** with RLi. From prior studies of these systems with Grignard reagents, we suggest that 1 equiv of RLi induces a β-elimination of LiSPh to produce the reactive imine, CH_2=NPh, which promptly adds RLi.[3,15]

Brief illustrative experimental details given in Table 1 for preparing amines from RLi and *N*,*N*-diaryl, *N*-aryl, and *N*,*N*-dialkyl derivatives of **1** serve to highlight the utility of this method.

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Supplementary Material Available: General experimental procedures and characterization data for all new compounds (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.

(14) Preliminary indications are that in hexane **1d** forms a complex with RLi, thereby inducing a heterolysis in the C–S bond. But whether the new C–C bond is formed in a polar manner or by way of SET processes is as yet unclear.

(15) For similar interpretations of reactions of RLi with *N*-(alkoxymethyl)arylamines and with *N*-alkyl-*N*-((alkylthio)methyl)ammonium chlorides, *cf.* Barluenga, J.; Bayón, A. M.; Asensio, G. *J. Chem. Soc., Chem. Commun.* **1983**, 1109. Barluenga, J.; Bayón, A. M.; Asensio, G. *J. Chem. Soc., Chem. Commun.* **1984**, 427.