Allylamine Functionalization through β-Nitrogen-Functionalized Organolithium Compounds

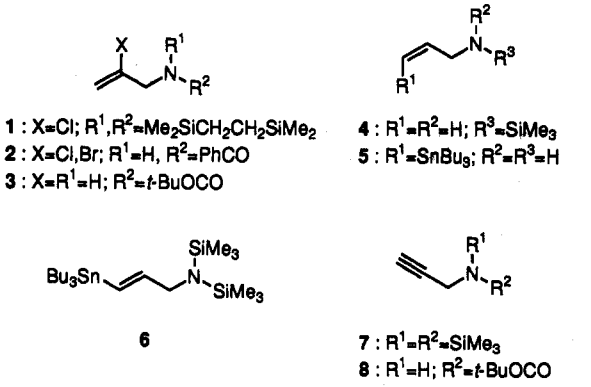
José Barluenga,* Rosa-María Canteli, and Josefa Flórez

Departamento de Química Organometálica, Facultad de Química, Universidad de Oviedo, 33071 Oviedo, Spain

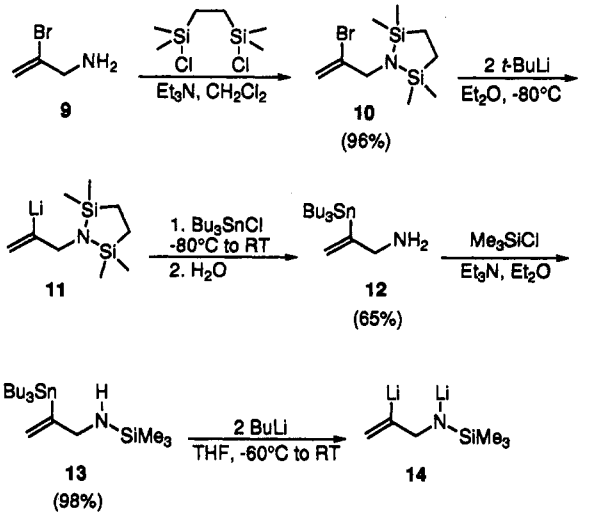
Received August 9, 1993

Primary allylic amines functionalities are present in many naturally occurring compounds[1] and biologically active molecules.[2] A straightforward entry to the synthesis[1,3] of these structural units is the functionalization of allylamine itself. In this way, primary 2-substituted allylamines have been prepared from compound 1 (Scheme 1) by means of nickel-catalyzed cross-coupling with Grignard reagents[4] and from benzoyl derivative 2 by successive reaction with phenyllithium and lithium naphthalenide and subsequent treatment with various electrophiles.[5] 1-Substituted allylamines have been formed by α-lithiation of *N*-Boc-allylamine (3) followed by reaction with $ZnCl_2$ and aldehydes or ketones.[6] Syntheses of primary 3-substituted (*Z*)-allylamines have been reported via dimetalation of *N*-(trimethylsilyl)allylamine (4)[7] and by palladium-catalyzed cross-coupling of stannyl compound 5 with aryl bromides.[8] The preparation of (*E*)-allylamines from tin reagent 6, either by using the mentioned palladium-catalyzed reaction or by tin–lithium transmetalation and further reaction with electrophiles, has also been described.[9] In this context, the synthesis of primary 2,3-disubstituted allylamines from propargylamine, an equivalent atom skeleton to allylamine must be mentioned. This has been carried out by silylcupration[10] or carbocupration[11] of 7, and by stannylcupration[12] of 8,

Scheme 1



Scheme 2



followed by reaction with electrophiles. Herein we report a new approach to the synthesis of primary 2-substituted allylamines, products of interest as enzyme inhibitors,[13] from the parent allylamine unit, via β-nitrogen-functionalized organolithium compounds.

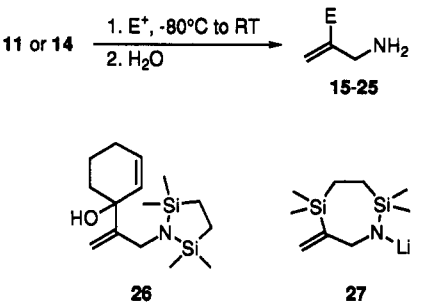
Results and Discussion

Two new β-nitrogen-functionalized organolithium compounds 11 and 14 have been prepared using the same methodology described in a previous report,[14] summarized in Scheme 2. 2-Bromoallylamine (9) was protected as its stabase adduct 10 following the literature procedure.[15] Reaction of 10 with *t*-BuLi in Et_2O at −80 °C led to the monoanionic compound 11, which upon reaction with tributyltin chloride and after hydrolysis gave stannylamine 12. Monosilylated amine 13 was obtained by reaction of 12 with 1 equiv of Me_3SiCl in the presence of Et_3N. Treatment of 13 with BuLi in THF with warming from

(1) Cheikh, R. B.; Chaabouni, R.; Laurent, A.; Mison, P.; Nafti, A. *Synthesis* **1983**, 685.
(2) (a) Rando, R. R. *Acc. Chem. Res.* **1975**, *8*, 281. (b) Stütz, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 320.
(3) (a) Kresze, G.; Münsterer, H. *J. Org. Chem.* **1983**, *48*, 3561. (b) Germon, C.; Alexakis, A.; Normant, J. F. *Synthesis* **1984**, 40. (c) Laurent, A.; Mison, P.; Nafti, A.; Cheikh, R. B.; Chaabouni, R. *J. Chem. Res.* (*S*) **1984**, 354; (*M*) **1984**, 3164. (d) Murahashi, S.-I.; Tanigawa, Y.; Imada, Y.; Taniguchi, Y. *Tetrahedron Lett.* **1986**, *27*, 227. (e) Shea, R. G.; Fitzner, J. N.; Fankhauser, J. E.; Spaltenstein, A.; Carpino, P. A.; Peevey, R. M.; Pratt, D. V.; Tenge, B. J.; Hopkins, P. B. *J. Org. Chem.* **1986**, *51*, 5243. (f) Connell, R. D.; Rein, T.; Akermark, B.; Helquist, P. *J. Org. Chem.* **1988**, *53*, 3845. (g) Deleris, G.; Dunogues, J.; Gadras, A. *Tetrahedron* **1988**, *44*, 4243. (h) Barluenga, J.; Aguilar, E.; Joglar, J.; Olano, B.; Fustero, S. *J. Chem. Soc., Chem. Commun.* **1989**, 1132. (i) Buchwald, S. L.; Watson, B. T.; Wannamaker, M. W.; Dewan, J. C. *J. Am. Chem. Soc.* **1989**, *111*, 4486. (j) Coles, N.; Whitby, R. J.; Blagg, J. *Synlett* **1992**, 143.
(4) Bargar, T. M.; McCowan, J. R.; McCarthy, J. R.; Wagner, E. R. *J. Org. Chem.* **1987**, *52*, 678.
(5) Barluenga, J.; Foubelo, F.; Fañanás, F. J.; Yus, M. *J. Chem. Soc., Perkin Trans. 1* **1989**, *553*.
(6) Resek, J. E.; Beak, P. *Tetrahedron Lett.* **1993**, *34*, 3043.
(7) (a) Burns, S. A.; Corriu, R. J. P.; Huynh, V.; Moreau, J. J. E. *J. Organomet. Chem.* **1987**, *333*, 281. For a related method of selective lithiation of secondary allylamines see: (b) Barluenga, J.; Fañanás, F. J.; Foubelo, F.; Yus, M. *J. Chem. Soc., Chem. Commun.* **1988**, 1135. (c) Barluenga, J.; Foubelo, F.; Fañanás, F. J.; Yus, M. *J. Chem. Res.* (*S*) **1989**, 200; (*M*) **1989**, 1524.
(8) Corriu, R. J. P.; Geng, B.; Moreau, J. J. E. *J. Org. Chem.* **1993**, *58*, 1443.
(9) Corriu, R. J. P.; Bolin, G.; Moreau, J. J. E. *Tetrahedron Lett.* **1991**, *32*, 4121.
(10) Capella, L.; Degl'Innocenti, A.; Reginato, G.; Ricci, A.; Taddei, M.; Seconi, G. *J. Org. Chem.* **1989**, *54*, 1473.
(11) (a) Corriu, R. J. P.; Huynh, V.; Iqbal, J.; Moreau, J. J. E. *J. Organomet. Chem.* **1984**, *276*, C61. (b) Corriu, R. J. P.; Moreau, J. J. E.; Vernhet, C. *Tetrahedron Lett.* **1987**, *28*, 2963. (c) Corriu, R. J. P.; Huynh, V.; Iqbal, J.; Moreau, J. J. E.; Vernhet, C. *Tetrahedron* **1992**, *48*, 6231.
(12) Capella, L.; Degl'Innocenti, A.; Mordini, A.; Reginato, G.; Ricci, A.; Seconi, G. *Synthesis* **1991**, *1201*.
(13) (a) Walsh, C. *Tetrahedron* **1982**, *38*, 871. (b) Burkhart, J. P.; Holbert, G. W.; Metcalf, B. W. *Tetrahedron Lett.* **1984**, *25*, 5267. (c) McDonald, I. A.; Palfreyman, M. G.; Jung, M.; Bey, P. *Tetrahedron Lett.* **1985**, *26*, 4091. (d) Silverman, R. B.; Hiebert, C. K.; Vazquez, M. L. *J. Biol. Chem.* **1985**, *260*, 14648. (e) McDonald, I. A.; LaCoste, J. M.; Bey, P.; Palfreyman, M. G.; Zreika, M. *J. Med. Chem.* **1985**, *28*, 186. (f) Padgette, S. R.; Wimalasena, K.; Herman, H. H.; Sirimanne, S. R.; May, S. W. *Biochemistry* **1985**, *24*, 5826. (g) Bargar, T. M.; Broersma, R. J.; Creemer, L. C.; McCarthy, J. R.; Hornsperger, J. M.; Palfreyman, M. G.; Wagner, J.; Jung, M. J. *J. Med. Chem.* **1986**, *29*, 315.
(14) Barluenga, J.; Canteli, R. M.; Flórez, J. *J. Org. Chem.*, in press.
(15) (a) Djuric, S.; Venit, J.; Magnus, P. *Tetrahedron Lett.* **1981**, *22*, 1787. (b) Cavelier-Frontin, F.; Jacquier, R.; Paladino, J.; Verducci, J. *Tetrahedron* **1991**, *47*, 9807.

0022-3263/94/1959-1586$04.50/0

Scheme 3



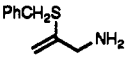
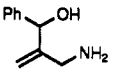
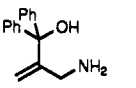
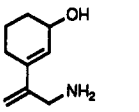
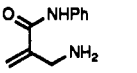
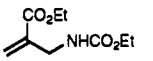
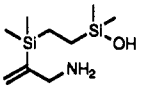
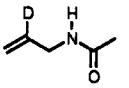
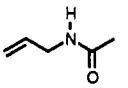
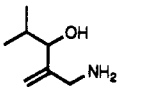
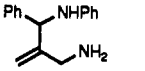
−60 °C to room temperature afforded the dianionic derivative **14**. Organolithium compounds **11** and **14** reacted with various electrophiles, at between −80 °C and rt, to give functionalized allylamines **15–25** (Scheme 3). The results are presented in Table 1.

The reaction of lithiated compound **11** with dibenzyl disulfide, carbonyl compounds, and phenyl isocyanate furnished the expected products **15–17** and **19** (entries 1–3 and 5). Addition of 2-cyclohexenone to **11** gave, regioselectively after aqueous hydrolysis, the stabase adduct of the 1,2-addition product **26** (Scheme 3). Desilylation to the primary amine was accomplished by acidic hydrolysis (2 N H_2SO_4) and took place with simultaneous allylic rearrangement of the hydroxy group, yielding functionalized 1,3-diene **18** (entry 4). Unexpectedly, the reaction of **11** with 1 equiv of ethyl chloroformate occurred to nearly the same extent at the carbanionic center and on the bis-silylated nitrogen atom, providing carbamate **20** (48%; entry 6). A higher yield (78%) was obtained using 2 equiv of $ClCO_2Et$. Organolithium compound **11** is not stable at room temperature. Thus, when a solution of **11** was quenched with D_2O at rt, C-silylated amine **21** was isolated (entry 7). This product seems to arise from hydrolysis of cyclic lithium amide **27** (Scheme 3) initially generated by a probable intramolecular 1,3-migration of the silicon atom from nitrogen to carbon,[14,16] when the temperature of compound **11** is raised.[17]

On the other hand, dilithiated derivative **14** is stable up to room temperature. Quenching a solution of **14** with D_2O at rt, followed by addition of acetyl chloride in order to simplify product isolation, afforded deuterated compound **22** (entry 8). This same treatment at 65 °C, after heating for 2 h, led to non-deuterated product **23** (entry 9), indicating a decomposition of organolithium **14** by abstraction of a proton, probably from the solvent.[14] The reaction of dilithiated intermediate **14** with dibenzyl disulfide, aldehydes, and *N*-benzylideneaniline also proceeded smoothly to give functionalized products **15**, **16**, **24**, **25** (entries 10–13).

In summary, we have shown that two novel organolithium compounds **11** and **14** are convenient precursors to a wide range of primary 2-substituted allylamines, by reaction with electrophiles. This new method complements former methodologies. The main difference between the monoanionic intermediate **11** and the dianionic **14** is their thermal stabilities. Thus, although **11** (stable at −80 °C) is more accessible, **14** (stable at rt) could be best used in reactions with less-reactive electrophiles that require higher reaction temperatures.

Table I. Reaction of Intermediates 11 and 14 with Electrophiles

entry	intermediate	electrophile	product	yield (%)[a]
1	11	$(PhCH_2S)_2$	 **15**	67
2	11	PhCHO	 **16**	90
3	11	Ph_2CO	 **17**	65
4	11		 **18**	80
5	11	PhNCO	 **19**	82
6	11	$ClCO_2Et$[b]	 **20**	78
7	11	D_2O[c]	 **21**	53
8	14	D_2O[c]/CH_3COCl	 **22**[d]	55
9	14	D_2O[e]/CH_3COCl	 **23**[f]	66
10	14	$(PhCH_2S)_2$	**15**	60
11	14	*i*-PrCHO	 **24**	78
12	14	PhCHO	**16**	47
13	14	PhCH=NPh	 **25**	65

[a] Isolated yields based on the corresponding starting material **10** or **13**. [b] Two equivalents; when 1 equiv of $ClCO_2Et$ was used, compound **20** was isolated in 48% yield. [c] Added at room temperature. [d] Degree of incorporation of deuterium 91%. [e] Added at 65 °C. [f] See ref 18.

Experimental Section

General. General experimental information have been reported.[14] 2-Bromoallylamine was prepared according to the

(16) (a) Brook, A. G.; Bassindale, A. R. *Molecular Rearrangements of Organosilicon Compounds*, in *Rearrangements in Ground and Excited States*; De Mayo, P., Ed.; Academic Press: New York, 1980; Vol. 2, p 149–227. (b) Colvin, E. *Silicon in Organic Synthesis*, Butterworths, London, 1981. (c) For a closely related 1,4-silyl migration from N to C see: Degl'Innocenti, A.; Mordini, A.; Pinzani, D.; Reginato, G.; Ricci, A. *Synlett* **1991**, 712 and ref 8.

(17) The related anionic 1,4-N to C silyl migration occurs through an intramolecular process (ref 8). Nevertheless, in this case the possibility that product **21** formed after hydrolysis of the species resulting from intermolecular reaction of vinyllithium unit on silicon cannot be ruled out as suggested by a referee.

(18) Beilstein **1922**, *4*, 208.

literature.[19] 1,2-Bis(chlorodimethylsilyl)ethane was commercially available. $\Delta\nu$ Values are given in hertz. The ^{29}Si NMR spectrum was recorded in $CDCl_3$ at 59.63 MHz and δ values are relative to external hexamethyldisiloxane ($Me_3SiOSiMe_3$, 0 ppm). The degree of deuteration was determined by ^1H NMR.

The following general experimental procedures are selected as typical for use of this methodology. Data for compounds not described here are provided as supplementary material.[20]

General Procedure for the Preparation of Organolithium Compound 11 and Reaction with Electrophiles. A solution of **10** (4 mmol) in Et_2O (20 mL) was cooled to −80 °C and treated with *t*-BuLi (1.7 M in pentane, 8 mmol) dropwise. The solution was stirred for 3 h at −80 °C and then the corresponding electrophile (4.4 mmol) was added. The mixture was slowly warmed to rt overnight and then hydrolyzed with 2 N H_2SO_4 for 10–15 min, neutralized with 2 N NaOH, and extracted with ether. When Bu_3SnCl was used as electrophile, the reaction mixture was hydrolyzed with water with some drops of 2 N H_2SO_4 solution for 2 d and then neutralized. The organic phase was dried (Na_2SO_4) and concentrated in vacuo and the resulting crude material was submitted to a flash chromatographic purification on silica gel or crystallization to give products **12** or **15–21**. Yields are reported in Scheme 2 and Table 1.

2-(Tributylstannyl)allylamine (12): R_f 0.3 (AcOEt); ^1H NMR δ 0.85 (m, 15H), 1.2–1.6 (m, 14H), 3.4 (m, 2H), 5.15, 5.75 (2m, 2H); ^{13}C NMR δ 9.3, 13.5, 27.2, 28.9, 50.5, 122.0, 156.2.

2-(Benzylthio)allylamine (15): R_f 0.28 (AcOEt); ^1H NMR δ 1.5 (br s, 2H), 3.2 (s, 2H), 3.8 (s, 2H), 4.7, 5.1 (2s, 2H), 7.1–7.3 (m, 5H); ^{13}C NMR δ 35.2, 46.9, 105.7, 126.3, 127.6, 127.9, 135.8, 147.0; MS *m/e* 179 (M^+, 3), 91 (100), 65 (37), 39 (26).

General Procedure for the Preparation of Organolithium Compound 14 and Reaction with Electrophiles. A solution of **13** (4 mmol) in THF (20 mL) was cooled to −60 °C and treated with BuLi (2.5 M in hexane, 8 mmol) dropwise. The mixture was stirred for 4 h between −60 °C and rt. Then, it was cooled again to −80 °C and treated with the appropriate electrophile (4.4 mmol). The resulting mixture was stirred and slowly warmed to rt overnight and then quenched with 2 N H_2SO_4 and treated with ether to remove Bu_4Sn side product. The aqueous layer was neutralized with 2 N NaOH and extracted with ether. The organic phase was dried (Na_2SO_4) and concentrated in vacuo and the resulting crude material purified by crystallization or flash column chromatography on silica gel to give products **15**, **16**, or **22–25**. In the case of using D_2O as electrophile the reaction mixture was quenched with acetyl chloride (6 mmol) added at rt and stirring was continued for 1 h at this same temperature. Then it was hydrolyzed with water and extracted with ether and the organic phase worked up as above. In the thermal stability test the reaction mixture, obtained after stirring for 4 h between −60 °C and rt, was refluxed for 2 h before adding the electrophile (an excess of D_2O). Yields are listed in Table 1.

***N*-(2-Deuterioallyl)acetamide (22):** R_f 0.3 (hexane:AcOEt, 1:1); ^1H NMR δ 1.75 (s, 3H), 3.55 (s, 2H), 4.85, 4.9 (2s, 2H), 7.5 (br s, 1H); ^{13}C NMR δ 22.1, 41.1, 114.9, 136.3 (t, J = 23.9), 170.2; MS *m/e* 100 (M^+, 3), 58 (100), 57 (90), 43 (50).

2-(Aminomethyl)-4-methyl-1-penten-3-ol (24): mp 85–87 °C (hexane/THF); ^1H NMR δ 0.8 (d, J = 6.7, 3H), 1.0 (d, J = 6.7, 3H), 1.8 (m, 1H), 2.1–2.7 (br s, 3H), 3.45 (AB q, $\Delta\nu$ = 14.8, J = 14, 2H), 3.75 (d, J = 8, 1H), 4.95, 5.0 (2s, 2H); ^{13}C NMR δ 18.4, 19.3, 32.3, 44.5, 81.9, 112.8, 149.6; MS *m/e* 111 (M^+ − 18, 16), 96 (40), 86 (100), 56 (25), 30 (25).

Acknowledgment. Financial support from DGICYT (PB89-0538) is gratefully acknowledged. R. M. Canteli thanks the Ministerio de Educación y Ciencia for a predoctoral fellowship. We also like to thank Dr. P. Bernad for MS measurements and helpful discussions.

Supplementary Material Available: Experimental procedures for **10** and **13**; physical and spectral data for **10**, **13**, **16–21**, **23**, and **25**; and copies of ^1H and ^{13}C NMR spectra of **10**, **12**, **13**, and **15–25** (16 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.

(19) Bottini, A. T.; Dev, V.; Klinck, J. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 121.

(20) The level of purity of compounds is indicated by the inclusion of copies of NMR spectra presented in the supplementary material.