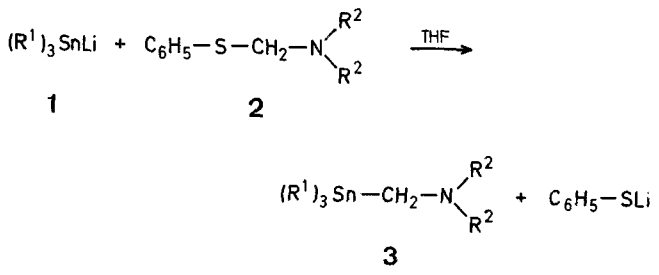
A Convenient Synthesis of *N,N*-Disubstituted Aminomethyltri-*n*-butylstannanes, Precursors of the Corresponding Lithium Reagents

Jean-Paul QUINTARD*, Bernard ELISSONDO, Bernard JOUSSEAUME

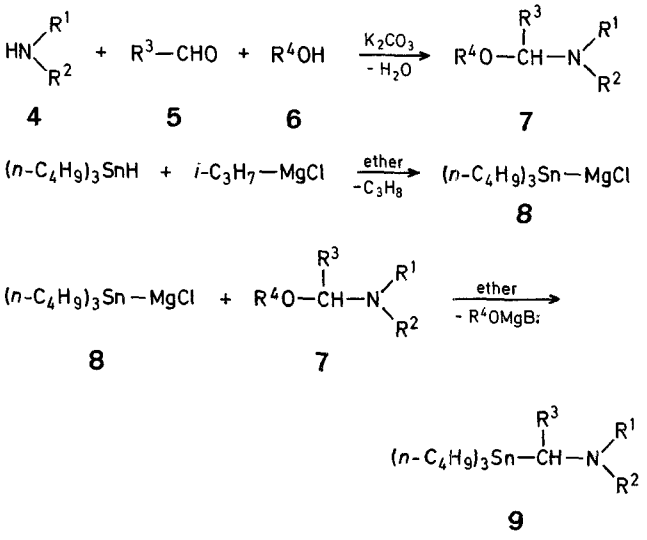
Laboratoire de Chimie Organique du Silicium et de l'Etain, LA 35, Université de Bordeaux I, F-33405 Talence Cédex, France

Aminomethyltrialkylstannanes, despite their potential as precursors for α-aminomethylorganolithium reagents[1,2], remain largely unused. The main reason for this fact probably lies in their synthesis. Methods involving reactions of halomethyltrialkylstannanes with amines or their alkali salts[3,4] can be rejected *a priori* due to the difficult synthesis of the initial halomethyltrialkyltin reagents[5,6]. On the other hand, the reported[7,8,9] preparation of aminomethyltrialkylstannanes **3** from trialkylstannyllithium **1** and aminomethyl phenyl sulfides **2** is comparatively easier.

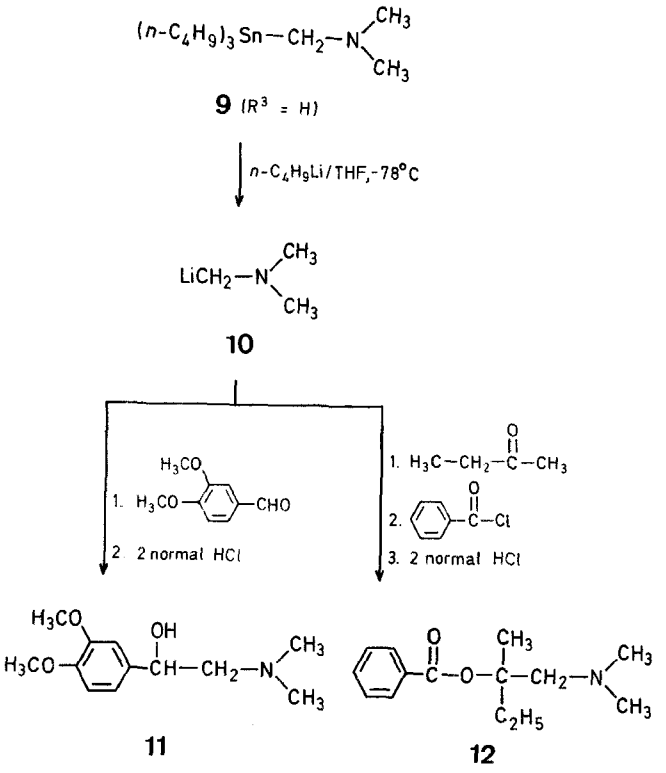


However, the use of thiophenol in the synthesis of aminomethyl phenyl sulfides **2** and tetrahydrofuran solutions of trialkylstannyllithium reagents **1** are not especially attractive, despite subsequent publications of new routes for the synthesis of trialkylstannylalkalis[10,11], which increase the reproducibility of stannylation reactions by limiting side reactions[12].

To achieve an attractive preparation of compounds **3**, one must avoid aminomethyl phenyl sulfides **2** and use, as far as possible, a stannylanion in a more convenient solvent. For these reasons, we used tri-*n*-butyltin magnesium chloride (**8**), easily prepared in ether from tri-*n*-butylstannane and isopropylmagnesium chloride[13,14]. The facile reaction of the Grignard reagent **8** with aminoacetals **7**, easily obtained by conventional methods[15,16] (Table 1), gives the corresponding *N,N*-disubstituted aminomethyltri-*n*-butyltin derivatives **9** in high yields (Table 2).



Transmetallation of compounds **9** gives the corresponding α-aminomethyllithium derivatives **10** which are attractive reagents in organic synthesis, as shown below for the syntheses of the alkaloids macromerine (**11**) and stovaine (**12**) in 95% and 83% yields, respectively.



In conclusion, *N,N*-disubstituted aminomethyltri-*n*-butylstannanes **9** can be synthesized from easily handled starting materials in ether as solvent in high yields. Use of tri-*n*-butylstannyllithium in tetrahydrofuran has given only

Table 1. *N,N*-Disubstituted Aminoacetals **7** prepared

	R^1	R^2	R^3	R^4	Yield [%]	b.p. [°C]/ torr	Molecular formula[a] or Lit. b.p. [°C]/torr	^{1}H-N.M.R. (CCl_4/TMS) δ [ppm]
7a	CH_3	CH_3	H	C_2H_5	83	123°/760	$C_5H_{13}NO$ (103.2)	1.14 (t, 3H, J = 6.7 Hz); 2.28 (s, 6H); 3.32 (q, 2H, J = 6.7 Hz); 4.09 (s, 2H)
7b	C_2H_5	C_2H_5	H	C_2H_5	86	135°/760	132–134°/756[15]	1.04 (t, 6H, J = 7.3 Hz); 1.16 (t, 3H, J = 6.8 Hz); 2.69 (q, 4H, J = 7.3 Hz); 3.37 (q, 2H, J = 6.8 Hz); 4.1 (s, 2H)
7c	i-C_3H_7	i-C_3H_7	H	C_2H_5	87	81°/25	$C_9H_{21}NO$ (159.3)	1.07 (d, 12H, J = 6.7 Hz); 1.12 (t, 3H, J = 6.7 Hz); 3.09 (m, 2H); 3.26 (q, 2H, J = 6.7 Hz); 4.14 (s, 2H)
7d	n-C_4H_9	n-C_4H_9	H	C_2H_5	84	103°/25	84°/6[18]	0.9–1.6 (m, 17H); 2.49 (t, 4H, J = 5.6 Hz); 3.29 (q, 2H, J = 6.7 Hz); 4.08 (s, 2H)
7e	—$(CH_2)_5$—		H	C_2H_5	91	101°/25	52–58°/1[19]	1.11 (t, 3H, J = 6.7 Hz); 1.44 (br.s, 6H); 2.53 (br.s, 4H); 3.38 (q, 2H, J = 6.7 Hz); 3.91 (s, 2H)
7f	CH_3	$C_6H_5CH_2$	H	C_2H_5	93	123°/25	67–70°/0.3[20]	1.11 (t, 3H, J = 6.5 Hz); 2.31 (s, 3H); 3.34 (q, 2H, J = 6.5 Hz); 3.62 (s, 2H); 3.98 (s, 2H); 7.22 (br.s, 5H)
7g	C_2H_5	C_6H_5	H	C_2H_5	83	115°/25	$C_{11}H_{17}NO$ (179.3)	1.06 (t, 3H, J = 6.8 Hz); 1.15 (t, 3H, J = 6.7 Hz); 2.59 (q, 2H, J = 6.8 Hz); 3.36 (q, 2H, J = 6.7 Hz); 4.02 (s, 2H); 6.93 (br.s, 5H)
7h	C_2H_5	C_2H_5	C_6H_5	n-C_4H_9	76	131°/0.5	118–124°/1[16]	0.9–1.6 (m, 13H); 2.62 (q, 4H, J = 6.7 Hz); 3.38 (t, 2H, J = 6.2 Hz); 4.94 (s, 1H); 7.17 (br.s, 5H)
7i	—$(CH_2)_5$—		C_6H_5	n-C_4H_9	84	145°/0.5	153–154°/1[16]	0.9–1.6 (m, 13H); 2.48 (br.s, 4H); 3.4 (t, 2H, J = 6.1 Hz); 4.68 (s, 1H); 7.12 (br.s, 5H)
7j	—$(CH_2)_5$—		2-furyl	n-C_4H_9	64	137°/0.5	$C_{14}H_{23}NO_2$ (237.4)	0.9–1.6 (m, 13H); 2.4 (s, 4H); 3.59 (t, 2H, J = 5.9 Hz); 4.78 (s, 1H); 6.22 (br.s, 2H); 7.38 (br.s, 1H)

[a] Satisfactory microanalyses obtained: C ±0.18, H ±0.07, N ±0.09.

moderate yield; for instance, compound **9f** has been obtained by this route in only 52% yield[9]. By comparison with more conventional syntheses of α-aminoalcohols, our method is especially attractive for the synthesis of unsymetrically substituted β-aminoalcohols. Further work on improvement and generalization of the preparation of α-aminomethyl-substituted organolithium reagents **10** is in progress.

The tri-*n*-butylstannane is prepared according to the literature procedure[17].

Aminoacetals 7; General Procedure[15,16]:
A solution of the secondary amine **4** (0.1 mol), the alcohol **6** (0.3 mol), and potassium carbonate (13.8 g, 0.1 mol) is stirred for 5 min at room temperature. The aldehyde **5** (0.1 mol) is then added in one portion (**7a–g**) or dropwise (**7h–j**) and the mixture is stirred overnight. The mixture is filtered and the filtrate is distilled to give the aminoacetal **7** (Table 1).

N,N-Disubstituted Aminomethyltri-*n*-butylstannanes 9; General Procedure:

Tri-n-*butylstannylmagnesium chloride* (**8**): A 1 molar ether solution of isopropylmagnesium chloride (100 ml, 0.1 mol) is added dropwise under an inert atmosphere and over a period of 1 h to tri-*n*-butylstannane (29.1 g, 0.1 mol) in ether (20 ml) at room temperature. After the addition, the mixture is refluxed for approximately 2 h in the presence of light (tungsten lamp) until no more propane is evolved.

Reaction of aminoacetals **7** *with tri*-n-*butylstannylmagnesium chloride* (**8**): The appropriate aminoacetal **7** (0.1 mol) is added dropwise to the ether solution of **8** (0.1 mol) prepared as above. The reaction is exothermic and stirring is maintained for 2 h after the end of the addition. Then, water is added until aggregation of magnesium salt occurs, the ether layer is separated and dried with magnesium sulfate. After elimination of ether under vacuum, the crude *N,N*-disubstituted aminomethyltri-*n*-butylstannanes are purified by vacuum distillation in the case of **9a–e** or by column chromatography on Florisil in the case of **9f–i** (Table 2). In the latter cases, the by-products, tetra-*n*-butylstannane and hexa-*n*-butyldistannane, are eluted rapidly first using *n*-pentane as eluent. The elution of compounds **9f–i** is achieved using ether.

Macromerine (11):
A 1.6 molar solution of *n*-butyllithium in hexane (18.75 ml, 30 mmol) is added dropwise to dimethylaminomethyltri-*n*-butylstannane (**9a**; 10.4 g) in dry tetrahydrofuran (100 ml) at −78°C under an inert atmosphere, the yellow-brown mixture is stirred for 15 min and treated with 3,4-dimethoxybenzaldehyde (5 g, 30 mmol) in tetrahydrofuran (10 ml). After stirring for 2 h, the temperature is allowed to reach −35°C, the mixture is hydrolyzed with 2 normal hydrochloric acid (80 ml) and extracted with ether (3 × 70 ml) to remove tetra-*n*-butylstannane. The aqueous phase is treated with 2 normal sodium hydroxide solution (100 ml) and extracted with ether (4 × 70 ml). The combined ether extract is washed with water (3 × 10 ml), dried with magnesium sulfate, and the solvent removed under vacuum. Recrystallization of the residue from *n*-hexane gives macromerine (**11**) as white crystals; yield: 6.4 g (95%); m.p. 65°C (Lit.[21], m.p. 66–67.5°C).

Table 2. *N,N*-Disubstituted Aminomethyltri-*n*-butylstannanes **9a–j** prepared

No.	R^1	R^2	R^3	Yield %	b.p.[°C]/ torr	Molecular formula[a] Lit. b.p. [°C]/torr	^{1}H-N.M.R. (CCl_4/TMS_{int}) δ [ppm]	^{119}Sn-N.M.R. (C_6D_6/ $(CH_3)_4Sn_{ext}$) δ [ppm]
9a	CH_3	CH_3	H	81	76°/0.05	75°/0.04[7]	0.7–2.0 (m, 27H); 2.13 (s, 6H); 2.36 (s, 2H, $^2J_{SnH}$ = 22.7 Hz)	−33.6
9b	C_2H_5	C_2H_5	H	83	81°/0.05	$C_{17}H_{39}NSn$ (376.3)	0.7–2.0 (m, 33H); 2.33 (q, 4H, J = 7.3 Hz); 2.58 (s, 2H, $^2J_{SnH}$ = 19 Hz)	−32.2
9c	i-C_3H_7	i-C_3H_7	H	89	96°/0.05	$C_{19}H_{43}NSn$ (404.3)	0.7–2.0 (m, 39H); 2.89 (sept, 2H, J = 6.5 Hz); 2.51 (s, 2H, $^2J_{SnH}$ = 22.3 Hz)	−28.4
9d	n-C_4H_9	n-C_4H_9	H	89	111°/0.05	$C_{21}H_{47}NSn$ (432.4)	0.7–2.0 (m, 41H); 2.23 (t, 4H, J = 6.6 Hz); 2.49 (s, 2H, $^2J_{SnH}$ = 22.9 Hz)	−26.2
9e	—$(CH_2)_5$—		H	86	116°/0.05	119–125°/0.2[8]	0.7–2.0 (m, 33H); 2.22 (m, 4H); 2.33 (s, 2H, $^2J_{SnH}$ = 22.7 Hz)	−31.5
9f	CH_3	$C_6H_5CH_2$	H	95	–[b]	$C_{21}H_{39}NSn$ (424.3)	0.6–2.0 (m, 27H); 2.14 (s, 3H); 3.34 (s, 2H); 7.14 (br.s, 5H); 2.48 (s, 2H, $^2J_{SnH}$ = 21.3 Hz)	−31.7
9g	C_2H_5	C_6H_5	H	65	–[b]	$C_{21}H_{39}NSn$ (424.3)	0.6–2.0 (m, 30H); 2.28 (q, 2H, J = 6.9 Hz); 7.11 (br.s, 5H); 2.5 (s, 2H, $^2J_{SnH}$ = 19.8 Hz)	−31.6
9h	C_2H_5	C_2H_5	C_6H_5	76	–[b]	$C_{23}H_{43}NSn$ (452.4)	0.7–2.0 (m, 33H); 2.56 (q, 4H, J = 6.7 Hz); 7.08 (br.s, 5H); 3.47 (s, 1H, $^2J_{SnH}$ = 26.7 Hz)	−27.8
9i	—$(CH_2)_5$—		C_6H_5	81	–[b]	$C_{24}H_{43}NSn$ (464.4)	0.6–1.9 (m, 33H); 2.33 (m, 4H); 6.8–7.2 (m, 5H); 3.33 (s, 1H, $^2J_{SnH}$ = 24.7 Hz)	−26.6
9j	—$(CH_2)_5$—		2-furyl	73	–[b]	$C_{22}H_{41}NOSn$ (454.3)	0.7–2.0 (m, 33H); 2.21 (m, 4H); 6.26 (m, 2H); 7.29 (m, 1H); 3.29 (s, 1H, $^2J_{SnH}$ = 23.6 Hz)	−27.3

[a] Satisfactory microanalyses obtained: C ±0.14, H ±0.17, N ±0.27, Sn ±0.17. Exceptions: **9f–j**, the C, H, N and Sn values obtained are about 5% lower than the excepted values, which is probably due to the presence of fine particles of Florisil from the chromatographic separation.

[b] Purified by column chromatography on Florisil, eluent: ether.

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): δ = 2.15–2.5 (s, 6H superimposed with m, 2H); 3.88 (s, 3H); 3.93 (s, 3H), 4.1 (s, 1H); 4.58 (dd, 1H, J = 9.1 Hz, 4.2 Hz); 6.86 (br.s, 2H); 6.95 ppm (br.s, 1H).

Stovaine (12):

A 1.6 normal hexane solution of *n*-butyllithium (18.75 ml, 30 mmol) is added dropwise to dimethylaminoaminomethyltri-*n*-butylstannane (**9a**; 10.4 g) in dry tetrahydrofuran (100 ml) at −78 °C under an inert atmosphere. The yellow-brown mixture is stirred for 15 min and 2-butanone (2.2 g, 30 mmol) in tetrahydrofuran (15 ml) is added. The mixture is allowed to reach 0 °C in 2 h and the lithium salt is quenched by the addition of benzoyl chloride (6.3 g, 45 mmol) at −20 °C followed by reflux of the mixture for 1 h. The mixture is cooled to 0 °C, hydrolyzed with 2 normal hydrochloric acid (80 ml), and worked up as given for the isolation of macromerine above. Recrystallization from *n*-hexane gives white-yellow crystals of stovaine (**12**); yield: 5.85 g (83%); m.p. 170 °C (Lit.[22], m.p. 175 °C).

I.R. (CCl_4): ν = 1720, 1280, 1120 cm^{-1}.

^{1}H-N.M.R. (CCl_4/TMS): δ = 0.89 (t, 3H, J = 7 Hz); 1.41 (s, 3H); 1.94 (m, 2H); 2.2 (s, 6H); 2.66 (s, 2H); 7.1–8.2 ppm (m, 5H).

Received: June 27, 1983
(Revised form: October 17, 1983)

[1] D.J. Peterson, *Organomet. Chem. Rev. A* **7**, 295 (1972).
[2] A. Krief, *Tetrahedron* **36**, 2531 (1980).
[3] E.W. Abel, R.J. Rowley, *J. Organomet. Chem.* **97**, 159 (1975).
[4] R.G. Kostyanovskii, A.K. Prokof'ev, *Izv. Akad. Nauk. SSSR* **1965**, 175; *C.A.* **62**, 11843 (1965).
V.V. Khrapov, V.I. Gol'danskii, A.K. Prokof'ev, R.G. Kostyanovskii, *Zh. Obshch. Khim.* **37**, 3 (1967); *C.A.* **66**, 109968 (1967).
A.K. Prokof'ev, V.P. Nechiporenko, R.G. Kostyanovskii, *Izv. Akad. Nauk. SSSR* **1967**, 794; *C.A.* **67**, 73657 (1967).
[5] D. Seyferth, S.B. Andrews, R.L. Lambert, *J. Organomet. Chem.* **37**, 69 (1972).
[6] D. Seyferth, E.G. Rochow, *J. Am. Chem. Soc.* **77**, 1302 (1955).
[7] D.J. Peterson, *J. Organomet. Chem.* **21**, P63 (1970).
[8] D.J. Peterson, *J. Am. Chem. Soc.* **93**, 4027 (1971).
[9] D.J. Peterson, J.F. Ward, *J. Organomet. Chem.* **66**, 209 (1974).
[10] W.C. Still, *J. Am. Chem. Soc.* **100**, 1481 (1978).
[11] R.J.P. Corriu, C. Guerin, *J. Organomet. Chem.* **197**, C19 (1980).
[12] J.P. Quintard, M. Pereyre, *Reviews of Si, Ge, Sn and Pb Compounds* **4**, 151 (1980).
[13] J.C. Lahournere, J. Valade, *J. Organomet. Chem.* **22**, C3 (1970).
J.C. Lahournere, *Ph.D. Thesis*, University of Bordeaux, 1973.
[14] H.J. Albert, W.P. Neumann, *Synthesis* **1980**, 942.
[15] T.D. Stewart, W.E. Bradley, *J. Am. Chem. Soc.* **54**, 4172 (1932).
[16] A.T. Stewart, C.R. Hauser, *J. Am. Chem. Soc.* **77**, 1098 (1955).

[17] K. Hayashi, J. Iyoda, I. Shiihara, *J. Organomet. Chem.* **10**, 81 (1967).
[18] D. Rehn, R. Kowatsch, H. Nolte, *Zbl. Bakt. Hyg. I. Abt. Orig. B* **166**, 408 (1978); *C.A.* **89**, 100795 (1978).
[19] J.E. Fernandez, C. Powell, J.S. Fowler, *J. Chem. Eng. Data* **8**, 600 (1963).
[20] M.A. Ratcliff, J.K. Kochi, *J. Org. Chem.* **36**, 3112 (1971).
[21] S.D. Brown, J.E. Hodgkins, M.G. Reinecke, *J. Org. Chem.* **37**, 773 (1972).
[22] E. Fourneau, I. Ribas, *Bull. Soc. Chim. Fr.* **41**, 989 (1927).