United States National Institutes of Health (Grant No. AM 17989) and the Canadian National Science and Engineering Research Council. This work was performed while R.K.D. was a traveling scholar of the Department of Biological Chemistry, Harvard Medical School.

Registry No. 2 (R = H), 553-12-8; 2 (R = $(CH_3)_3C$), 75112-37-7; 5 (R = $(CH_3)_3C$), 75125-16-5; **7** (isomer 1), 75112-38-8; **7** (isomer 2), 75112-39-9; **10** (isomer 1), 75112-40-2; **10** (isomer 2), 75112-41-3; **13** (isomer 1), 75112-42-4; **13** (isomer 2), 75125-17-6; **14** (isomer 1), 75112-43-5; **14** (isomer 2), 75125-18-7; **15**, 75112-44-6; **16**, 75112-45-7; **17**, 75112-46-8; **18**, 75112-47-9; **19**, 75112-48-0; **20**, 75112-49-1; **21**, 75112-50-4; 2-formyl-4-vinyldeuteroporphryrin di-*tert*-butyl ester, 75112-51-5; 2-vinyl-4-formyldeuteroporphryrin di-*tert*-butyl ester, 75125-19-8; TCNE, 670-54-2; *tert*-butyl alcohol, 75-65-0.

Notes

Metalation–Carboxylation of *p*- and *m*-(Trimethylsilyl)toluenes as a Convenient Route to [*p*- and *m*-(Trimethylsilyl)phenyl]acetic Acids[1a]

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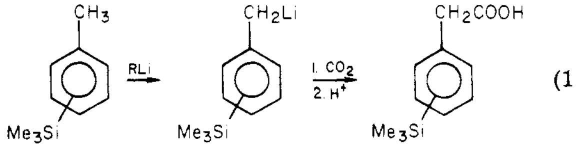
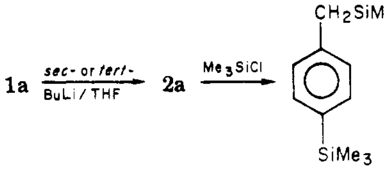
Received February 25, 1980

In connection with the synthesis of new anticonvulsant agents, we required moderate quantities of [*p*- and *m*-(trimethylsilyl)phenyl]acetic acids (**3a**) and (**3b**), respectively. Both of these acids have been prepared from (trimethylsilyl)toluenes **1a**,**b** by a classical, but circuitous, route involving benzylic bromination, displacement of bromide by cyanide, and hydrolysis of the resulting [(trimethylsilyl)phenyl]acetonitriles.[2] It occurred to us that metalation of **1a**,**b** to form (trimethylsilyl)benzyllithiums **2a**,**b**, followed by carboxylation could afford the desired acids in essentially one step (eq 1). It is well-documented that toluene can be converted to benzyllithium by means of alkyllithium reagents, provided the metalation is conducted in the presence of Lewis bases such as TMEDA, DABCO, certain ethers, or potassium *tert*-butoxide.[3] However, examination of these studies reveals that yields of benzyllithium are highly dependent on the ratio of toluene–alkyllithium–complexing agent, as well as the nature of the complexing agent. The most satisfactory conversions involve the use of excess toluene, while reactions of various alkyllithium–Lewis base complexes with stoichiometric or substoichiometric quantities of toluene tend to give mixtures of mono-, di-, and trilithiated derivatives. In an earlier study directly related to the present work, West and Jones[4,5] found that metalation of **1a** and **1b** with a twofold excess of 4:1 *n*-butyllithium–TMEDA complex gave only 13 and 28% of **2a** and **2b**, respectively.



1ab **2ab** **3ab** (1)

On the basis of the foregoing observations, it was evident that in order to use the desired metalation–carboxylation sequence for the synthesis of **3a**,**b**, it would be necessary to control the metalation of **1a**,**b** to give predominately the benzylic lithium derivatives **2a**,**b**, without having to employ an excess of **1a**,**b**. Attention was therefore focused on a study of the metalation of **1a** employing *sec*- or *tert*-butyllithium with THF as the complexing agent. The extent of metalation was determined from the ratio of [*p*-(trimethylsilyl)benzyl]trimethylsilane (**4**) to unreacted **1a** produced on quenching the reaction mixture with excess trimethylchlorosilane (eq 2).[4] Results of these experiments are shown in Table I.



(2)

4

Several conclusions can be drawn from the data in Table I. Highest yields of **4** were produced in reactions employing considerably greater than stoichiometric quantities of alkyllithium. This is apparently due to consumption of alkyllithium by the competing decomposition of THF, since those experiments employing lesser amounts of THF were most successful (expt 2 vs. 4 or expt 6 vs. 7). Some indication as to the sensitivity of metalation to the mole ratios of reactants may be gained by comparing the results of expt 5 and 8. Both experiments afforded approximately 50% of **4** based on **1a**. However, the yields of **4** based on *sec*-butyllithium consumed are quite different. In expt 5, a twofold excess of *sec*-butyllithium relative to **1a** was employed with THF as a cosolvent (method A). Under these conditions only 25% *sec*-butyllithium was converted to **2a** and eventually to **4** on quenching. In expt 8 a slight excess of **1a** relative to *sec*-butyllithium was used with a limited amount of THF (method B). In this case, about 62% of the *sec*-butyllithium was converted to **2a**. These results suggest that the rates of reaction of *sec*-butyllithium with **1a** and with THF are of similar magnitude and that

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(1) (a) Supported by Grant No. NS 10197 from the National Institute of Neurological and Communicative Disorders and Stroke. (b) From the Ph.D. dissertation of M. P. Sleevi, Virginia Polytechnic Institute and State University, June 1979.

(2) Frankel, M.; Broze, M.; Gertner, D.; Zilka, A. *J. Chem. Soc. C* **1966**, 379 and references cited therein.

(3) (a) For a comprehensive discussion, see: "Polyamine-Chelated Alkali Metal Compounds"; Langer, A. W., Ed.; American Chemical Society: Washington, DC, 1974. (b) Broaddus, C. D. *J. Org. Chem.* **1970**, *35*, 10. (c) Mitteilungen, K. *Chimia* **1970**, *24*, 109. (d) Schlosser, M.; Hartman, J. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 508.

(4) West, R.; Jones, P. C. *J. Am. Chem. Soc.* **1968**, *90*, 2656.

(5) Chalk, A. J.; Hoogeboom, T. J. *J. Organometl. Chem.* **1968**, *11*, 615.

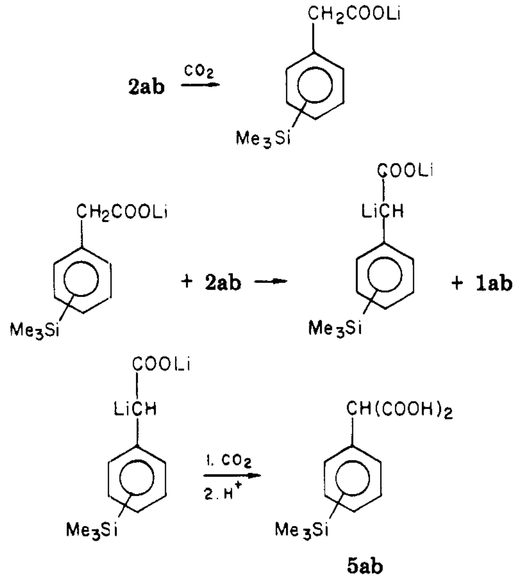
0022-3263/80/1945-5204$01.00/0

Table I. Metalation of *p*-(Trimethylsilyl)toluene (1a) by Alkyllithiums

expt	RLi	mol ratio,[a] RLi/1a	mol ratio, THF/RLi	method	reaction temp, °C	reaction time, h	mol ratio,[b] 4/1a	% yield[b,c] of 4
1	*t*-BuLi	1.1	18	A	−25	1	0.79	44
2	*t*-BuLi	1.1	18	A	−20	3.5	0.79	44
3	*t*-BuLi	2.0	10	A	−25	1	3.96	80
4	*t*-BuLi	1.2	3.7	B	−25	1	1.88	65
5	*sec*-BuLi	2.0	10	A	−8-10	1	1.02	50
6	*sec*-BuLi	2.0	10	A	−6-10	4	1.04	51
7	*sec*-BuLi	2.0	2	B	−9-10	4	7.89	89
8	*sec*-BuLi	0.74	2	B	−8-10	2	1.00	50

[a] All reactions were performed on 6.08 mmol of 1a. [b] Determined by GC analysis. [c] Based on 1a.

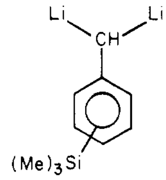
Scheme I



lower ratios of **1a**–THF favor unproductive solvent decomposition.

From the experiments described in Table I, it appeared that acids **3a,b** could best be obtained by mixing **1a,b** with a twofold excess of alkyllithium, slowly adding about 4 equiv (based on **1a**) of THF, and then carboxylating the resulting lithio derivatives **2a,b**. A solution of **2a** prepared in this manner from **1a** and *sec*-butyllithium afforded **3a** in 67% isolated yield upon carboxylation. In similar experiments, solutions of **2b** were prepared from **1b** with *sec*- or *tert*-butyllithium and carboxylated to afford **3b** in isolated yields of 59 and 55%, respectively.

The lower yields obtained in the carboxylation reactions compared with the silylation experiments are due in part to formation of malonic acids **5a,b** by proton transfer during the dry ice quenching procedure (Scheme I). Although malonic acids **5a,b** were not isolated, a pressure rise during distillation of the acidified carboxylation suggested decarboxylation. Further evidence for formation of **5a,b** was obtained from the ^{1}H NMR spectra of the crude acid products, which exhibited methine proton resonances at 4.60 and 5.63 ppm, respectively.[6] These peaks accounted for as much as 25% of the crude acid mixtures, depending on the method of quenching. For small-scale reactions, where it was feasible to spray the reaction solution over a large surface of crushed dry ice, only small (<10%) amounts of **5a,b** were formed. This observation, coupled with the fact that the corresponding disilylated derivatives were not detected in the experiments described in Table I, suggests that **5a,b** do indeed arise during the quenching process (Scheme I) rather than from a dianion intermediate such as **6**.[3b,4]



6

Similar results have been reported for carboxylation of solutions of benzyllithium.[3c] Even though **5a,b** decarboxylate smoothly during distillation, consumption of lithio derivatives **2a,b** to form the dianions of the [(trimethylsilyl)phenyl]acetic acids shown in Scheme I reduces the yields of **3a,b** somewhat. In spite of this, the present procedure offers obvious advantages of convenience over previous preparations of **3a,b**. Moreover, the selective monolithiation procedure developed for **1a,b** may be useful for related systems where the use of excess substrate is not practical.

Experimental Section

General. Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. Boiling points are also uncorrected. Elemental analyses were performed under the direction of Thomas E. Glass in this laboratory, using a Perkin-Elmer 240 C, H, and N analyzer, or by Galbraith Laboratories of Knoxville, TN.

Infrared spectra were obtained on samples as dilute solutions in deuteriochloroform or as a neat film on sodium chloride plates, using a Beckman IR-20 AX spectrometer. ^{1}H NMR spectra were recorded on either a JEOL JMN-PS-100 or Varian EM-390 spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane as internal standard. The splitting patterns are reported as m = multiplet, q = quartet, t = triplet, d = doublet, and s = singlet. Tetrahydrofuran (THF) was distilled from lithium aluminum hydride and stored prior to use over 4-Å molecular sieves under a positive pressure of argon. Solutions of alkyllithium reagents were obtained from Aldrich Chemical Company, Milwaukee, WI, or Ventron Corporation, Inc., Beverly, MA, and were periodically standardized against diphenylacetic acid.[7] Unless otherwise specified all other chemicals were commercial reagent grade and were used without further purification. Gas chromatographic (GC) analyses and separations were accomplished on a Varian Associates 90-P instrument using columns and conditions described below.

Preparation of *p*-(Trimethylsilyl)toluene (1a) and *m*-(Trimethylsilyl)toluene (1b). In our hands, attempts to reproduce earlier syntheses[4,8] of **1a** from *p*-bromotoluene consistently gave significant amounts of unreacted *p*-bromotoluene, which was difficult to separate from **1a** by distillation. The following procedures using the cheaper and more volatile *p*- and *m*-chlorotoluenes circumvented this problem.

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[6] The methine proton of dimethyl phenylmalonate appears at δ 4.55.[3b]

[7] Kofron, N. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.

[8] Clark, H. A.; Gordon, A. F.; Young, C. W.; Hunter, M. J. *J. Am. Chem. Soc.* **1951**, *73*, 3798.

A mixture of 38.00 g (0.30 mol) of *p*-chlorotoluene, 80 mL (0.63 mol) of trimethylchlorosilane, and 8.00 g (0.33 mol) of magnesium metal in 500 mL of dry THF was heated to reflux under nitrogen in a round-bottomed flask equipped with a condenser and a magnetic stirrer. The reaction mixture was stirred at reflux for 18 h, at the end of which most of the magnesium had been consumed and a thick gray precipitate had formed. The reaction mixture was cooled to room temperature and poured into 300 mL of water. After the magnesium salts had dissolved, 200 mL of ether was added and the layers were separated. The organic layer was washed with water and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The resulting crude yellow liquid was distilled to yield 37.21 g (75%) of *p*-(trimethylsilyl)toluene (**1a**) as a colorless liquid: bp 92–94 °C (33 mm) [lit.[8] bp 192 °C (748 mm)]; ^1H NMR ($CDCl_3$) δ 7.30 (d, J = 8 Hz, 2 H, aromatic), 7.19 (d, J = 8 Hz, 2 M aromatic), 2.32 (s, 3 H, CH_3), 0.22 (s, 9 H, $Si(CH_3)_3$).

Under conditions identical with those above, 38.00 g (0.30 mmol) of *m*-chlorotoluene was converted to 38.16 g (77%) of *m*-(trimethylsilyl)toluene (**1b**) as a colorless liquid: bp 92–94 °C (33 mm) [lit.[8] bp 188 °C (748 mm)]; ^1H NMR ($CDCl_3$) δ 7.16 (m, 4 H, aromatic), 2.36 (s, 3 H, CH_3), 0.28 (s, 9 H, $Si(CH_3)_3$).

Preparation of *p*-(Trimethylsilyl)benzyllithium (2a) with Alkyllithiums/THF. Method A. In a typical experiment, 1.00 g (6.08 mmol) of **1a** was dissolved in 10 mL of dry THF under nitrogen and cooled to −30 °C. Then 2.9 mL (6.67 mmol) of 2.3 M *tert*-butyllithium in pentane was added slowly over 5 min. The solution was allowed to warm to −20 °C and was stirred at this temperature for 1 h. The bright orange solution was then allowed to come to room temperature and was quenched with excess trimethylchlorosilane (1.55 mL, 12.2 mmol). The volume of the solution was doubled with ether, the mixture was transferred to a separatory funnel, washed with water (3 × 20 mL), and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The mixture was analyzed by gas chromatography on a 7 ft × 0.25 in. column of 5% Carbowax 20M on 80/100 mesh Chromosorb G at a temperature of 107 °C. The mole ratio of [*p*-(trimethylsilyl)benzyl]trimethylsilane (4) to **1a** was determined (after correction for the relative detector response) to be 0.79:1. This corresponded to a 44% yield of *p*-(trimethylsilyl)benzyllithium (**2a**) based on the amount of **1a** used. No derivatives resulting from polylithiation[4] were detected by either GC or ^1H NMR analysis of the crude mixture. Samples of **1a** and **4** were obtained by preparative gas chromatography and identified by their ^1H NMR spectra. The spectrum of **4** was identical with that reported by West.[4]

In a similar manner, several experiments were conducted, varying the reaction time, quantity of THF used, or employing 1.18 M *sec*-butyllithium in hexane in place of *tert*-butyllithium. Experimental conditions and results are summarized in Table I.

Method B. In a typical experiment, 10.5 mL (12.4 mmol) of 1.18 *sec*-butyllithium in hexane was added to 1.00 g (6.08 mmol) of **1a** stirred at −8 °C under nitrogen, followed by 2.0 mL (24 mmol) of THF added dropwise over 1 min. The bright orange reaction mixture was allowed to warm up to 8 °C over a period of 4 h and then was quenched with excess trimethylchlorosilane (2.5 mL, 20 mmol). The color of the reaction mixture faded immediately on addition of the trimethylchlorosilane. Workup was identical with that in method A. By gas chromatographic analysis of the resulting reaction mixture, the ratio of **4** to **1a** was determined to be 7.89:1, corresponding to an 89% yield of lithio salt **2a** based on the amount of **1a** used. Conditions and results for similar experiments using method B are summarized in Table I.

Preparation of [*p*-(Trimethylsilyl)phenyl]acetic Acid (3a). To a solution of 51.5 mL (60 mmol) of 1.18 M *sec*-butyllithium in hexane and 5.00 g (30 mmol) of **1a** at −10 °C under nitrogen was added 10 mL (123 mmol) of dry THF over a period of 5 min. The rate of addition was controlled to maintain the temperature of the reaction mixture below −5 °C. After addition was completed, the reaction mixture was allowed to warm slowly to room temperature over 1.5 h, stirred for an additional 2 h, and then quenched by pouring over crushed dry ice with vigorous stirring. After the excess dry ice had sublimed, the residual solid was dissolved in 250 mL of 10% KOH. The aqueous solution was washed with ether (1 × 100 mL), acidified with concentrated HCl, and then extracted with ether (3 × 100 mL). The combined ethereal extracts were dried over $MgSO_4$ and evaporated under reduced pressure. The resulting crude yellow oil was distilled and, after a small forerun, yielded 4.18 g (67%) of **3a** as a pale yellow oil which rapidly solidified on cooling: bp 116 °C (0.10 mm); mp 52–54 °C (lit.[2] mp 40 °C); ^1H NMR ($CDCl_3$) δ 11.90 (s, 1 H, OH), 7.34 (d, J = 8, Hz, 2 H, aromatic), 7.10 (d, J = 8 Hz, 2 H, aromatic), 3.50 (s, 2 H, CH_2), 0.22 (s, 9 H, $Si(CH_3)_3$); IR ($CDCl_3$) 3000 (OH), 1710 cm^{-1} (C=O). Anal. Calcd for $C_{11}H_{16}O_2Si$: C, 63.41; H, 7.74. Found: C, 63.45; H, 7.56.

Preparation of [*m*-(Trimethylsilyl)phenyl]acetic Acid (3b). To a solution of 74.7 mL (85.4 mmol) of 1.14 M *sec*-butyllithium in hexane and 7.00 g (42.6 mmol) of *m*-(trimethylsilyl)toluene (**1b**) at −10 °C under nitrogen was added 14 mL (172 mmol) of dry THF over a period of 5 min. After the addition was completed, the reaction mixture was allowed to warm slowly to room temperature over 1 h, stirred for an additional 15 min, and then quenched by pouring over crushed dry ice with vigorous stirring. The reaction was processed as above. The resulting yellow oil was distilled to yield 5.27 g (59%) of **3b** as a pale yellow oil which solidified slowly on standing: bp 122–125 °C (0.25 mm); mp 33–34 °C (lit.[2] mp 33 °C); ^1H NMR ($CDCl_3$) δ 11.88 (s, 1 H, OH), 7.32 (m, 4 H, aromatic), 3.58 (s, 2 H, CH_2), 0.25 (s, 9 H, $Si(CH_3)_3$); IR (NaCl) 2950 (OH), 1700 cm^{-1} (C=O).

In a similar experiment 18 mL (221 mmol) of dry THF was added to a solution of 165 mL (110 mmol) of 1.5 M *tert*-butyllithium in pentane and 9.00 g (55 mmol) of **1b** over 10 min at −30 °C. The resulting solution was allowed to warm to room temperature and then quenched by pouring over dry ice. Workup as before afforded 6.34 g (55%) of **3b** identical with that obtained above.

Registry No. 1a, 3728-43-6; **1b**, 3728-44-7; **2a**, 74542-26-0; **3a**, 5112-65-2; **3b**, 5112-64-1; **4**, 2415-91-0; *p*-chlorotoluene, 106-43-4; *m*-chlorotoluene, 108-41-8.

Halogenations of Conjugated Dienes. Bromination and Chlorination of *cis*- and *trans*-3-Methyl-1,3-pentadienes

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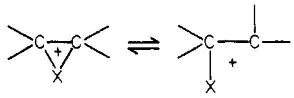
It is well-known that halogen additions to many alkenes are stereospecific and form only anti products.[1] The preference for anti addition is rationalized on the basis of the involvement of cyclic halonium ion intermediates in the reactions. Thus, the study of electrophilic addition becomes a tool for observing the behavior of halonium ions and their ion pairs, with the added interest that these can be generated in aprotic solvents of widely varying polarities. Previous studies[2] have revealed that halonium ions are marginally stable in comparison to open carbocations.



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[1] For a recent review of electrophilic addition, see G. H. Schmid and D. G. Garrett, "The Chemistry of the Double Bonded Functional Groups", Supplement A, S. Patai, Ed., Wiley, London, 1977.

[2] See, e.g., S. P. McManus and P. E. Peterson, *Tetrahedron Lett.*, 2753 (1975), and F. Freeman, *Chem. Rev.*, **75**, 452 (1975), and references contained in these articles.

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