A Practical Ortholithiation-Based Synthesis of 2-Chloro-6-methylaniline

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As part of the synthesis of a new pharmaceutical agent, we required an efficient, multikilogram preparation of 2-chloro-6-methylaniline (4). Subsequent steps in the synthesis required that 4 have high purity and low levels of positional isomers. These purity requirements led us away from classical electrophilic aromatic substitution methods, which are often limited to specific substrate substitution patterns and can give undesirable mixtures of isomeric and multiple substitution products.[1] Instead, we developed an ortholithiation approach (Scheme I) because reactions of this type are known to give clean monosubstitution in the ortho position.[2]

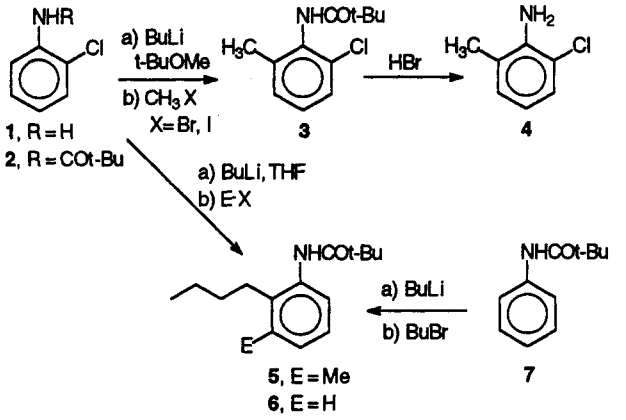
Direct ortholithiation of unprotected anilines is generally not synthetically useful.[3] However, N-functionalized aniline derivatives including the *t*-BOC,[4] trimethylacetyl-(pivaloyl),[5] and lithium carbamate analogs[6] (prepared *in situ*) are known to undergo efficient ortholithiation/alkylation. We chose the pivalamide directing group because ortholithiation is effected under mild conditions conducive to large-scale production (BuLi, THF, 0 °C).[7] In addition, 4-chloro-2-methylpivalanilide (isomeric to 3) was previously synthesized via ortholithiation of 4-chloropivalanilide.[5a]

Results and Discussion

Preparation of 2-chloropivalanilide 2 was accomplished by acylation of 2-chloroaniline (1) in high yield using two-phase (Schotten–Baumann) conditions (pivaloyl chloride, 25% NaOH, either EtOAc or *t*-BuOMe).

Lithiation. Contrary to our expectations, the lithiation step was not straightforward and gave multiple products depending on the reaction conditions, particularly the choice of solvent. Application of the ortholithiation conditions used for 4-chloropivalanilide[5a] (BuLi, THF; MeI) to substrate 2 gave little of the desired alkylated product 3. The major product was ring-butylated anilide 5, which was isolated as a mixture with starting material (2) and small amounts of biaryls. The use of excess BuLi

Scheme I



(3 equiv) and ambient temperature increased the conversion to the butylated products 5 (CH_3I quench; 60%) or 6[8] (H_2O quench; 98%). The structure of 6 was verified by independent synthesis (ortholithiation of 7 followed by alkylation with BuBr).

The butylated products are probably formed via a benzyne[8,9] intermediate (8) which undergoes regioselective nucleophilic addition of BuLi at the ortho position. Electrophilic quenching of the resulting aryl anion would give the observed butylated product (5 or 6). Aryl chlorides are known to react with alkyllithium reagents to give benzynes via ortholithiation followed by elimination of LiCl (at temperatures above −100 °C).[10,11]

Benzyne 8 could theoretically undergo attack of BuLi at either terminus of the benzyne triple bond; however, only products of ortho attack (5 and 6) were observed. This regioselectivity can be rationalized by prior coordination of BuLi to the pivalamide group followed by directed nucleophilic addition to the ortho position. Meyers' observation of a regioselective (ortho) addition of BuLi to an oxazolinobenzyne intermediate was rationalized by a similar mechanism.[12,13]

By changing to less polar solvents for the lithiation/alkylation sequence, the desired product (3) could be obtained as a major product, and the butyl products (5 and 6) could be minimized (although not completely eliminated). The choice of solvent was critical (Table I): Et_2O and *t*-BuOMe gave the highest yield of the desired product 3. Hexane also gave good selectivity but with low conversion (unreacted starting material), probably due to insolubility of the intermediate dianion. THF gave predominantly the undesired product 5.

Temperature. In general, lower temperatures gave more of the desired ortholithiation product 3 at the expense

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(1) For example, direct chlorination of *o*-toluidine gives a mixture of products including 4-chloro-2-methylaniline (major) and 2-chloro-6-methylaniline (very minor). (a) Crocker, H. P. US3754034, 1973, example 3. (b) Nishihara, I.; Kato, H.; Jimbo, Y.; Tomada, Y.; Omi, J. US3916014, 1975, examples 1, 6, and 7.

(2) For a review of ortholithiation see: Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1.

(3) Reference 2, p 45.

(4) Muchowski, J. M.; Venuti, M. C. *J. Org. Chem.* **1980**, *45*, 4798.

(5) (a) Fuhrer, W.; Gschwend, H. W. *J. Org. Chem.* **1979**, *44*, 1133. (b) Hillis, L. R.; Gould, S. J. *J. Org. Chem.* **1985**, *50*, 718.

(6) Katritzky, A. R.; Fan, W.-Q.; Kunichiko, A. *Tetrahedron* **1986**, *42*, 4027.

(7) Alternative directing groups were less practical in that *s*- or *t*-BuLi are needed for the lithiation.[4,6] In contrast, BuLi (used with the pivalanilide directing group) is practical and commonly used in bulk quantities with standard airless handling techniques.

(8) During preparation of this manuscript a synthesis of 6 from 2 using similar conditions was reported. An aryne intermediate was postulated. Guijarro, A.; Ramon, D. J.; Yus, M. *Tetrahedron* **1993**, *49*, 469.

(9) Attempts to trap 9 by [4 + 2] cycloaddition (a common test for these intermediates) with furan, *N*-methylpyrrole, or 1,3-diphenylisobenzofuran failed to give cycloadducts.[9,12] This may be due to the anionic nature of 9. Evidence for the existence of 9 is nonetheless supported by the formation of 5, having been substituted in both the ortho and meta positions with the loss of the chlorine substituent.

(10) (a) Iwao, M. *J. Org. Chem.* **1990**, *55*, 3622. (b) Kress, T. H.; Leanna, M. R. *Synthesis* **1988**, 803.

(11) Reference 2, pp 17, 74.

(12) (a) Meyers, A. I.; Pansegrau, P. D. *Tetrahedron Lett.* **1983**, *24*, 4935. (b) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356. (c) Pansegrau, P. D.; Riecker, W. F.; Meyers, A. I. *J. Am. Chem. Soc.* **1988**, *110*, 7178. (d) Sielecki, T. M.; Meyers, A. I. *J. Org. Chem.* **1992**, *57*, 3673.

(13) For a recent discussion of regioselectivity in nucleophilic addition to arynes see: Khanapure, S. P.; Crenshaw, A. W.; Reddy, R. T.; Biehl, E. R. *J. Org. Chem.* **1988**, *53*, 4915.

0022-3263/93/1958-5537$04.00/0

Table I. Effect of Solvent and Temperature on Ortholithiation Product Distribution[a]

variable	product ratio[b] (%) 2	3	5	6
Solvent (TMEDA Equiv)				
THF (0.0)	69	0	31	0
t-BuOMe (0.0)	58	42	0	0
t-BuOMe (0.2)[c]	31	66	3	0
t-BuOMe (0.2 + 0.2)[c,d]	15	81	4	0
t-BuOMe (0.5)	4	90	3	3
t-BuOMe (0.7)	2	92	6	0
Et_2O (0.7)	3	84	14	0
hexane (0.7)	45	50	4	0
Temperature				
−23	2	92	6	0
−10	2	87	11	0
0	3	23	61	13

[a] Run under standard conditions (BuLi, −23 °C, MeI, *t*-BuOMe/TMEDA (0.7 equiv)) with the exception of the given variable. [b] VPC (area %) ratios normalized to 100%; minor impurities not included. [c] In-process results. Aliquots were removed, quenched with MeI/*t*-BuOMe (rt, 1 h), and assayed. [d] Continuation of the above experiment (0.2 equiv). Once conversion reached a plateau, another 0.2 equiv of TMEDA was added.

of the butylated product **5** (Table I). Careful temperature control was required during the exothermic BuLi addition to maximize the **3**/**5** product ratio.

The dependence of the product distribution on solvent and temperature may be explained as follows. Deprotonation of the incipient monoanion can occur either at the 3-position (path A) followed by elimination of LiCl to give benzyne (**8**) or at the 6-position (path B) to give the desired ortholithiation intermediate.

Path A is thermodynamically favored and predominates at higher temperatures and in more polar solvents (THF) in which BuLi exists as a more reactive, less aggregated species.[14] Under these conditions, the solvated BuLi species is sufficiently reactive to deprotonate the 3-position without prior coordination to a directing group.

Path B is kinetically favored and predominates at lower temperatures and in less polar solvents (e.g., *t*-BuOMe)[14] where BuLi exists as a less reactive, more highly aggregated species. Under these conditions ortholithiation is favored because the $(BuLi)_n$ is not very reactive until it is solvated by coordination to the pivalamide directing group, which is then followed by proximal deprotonation at the 6-position.[15] This competitive reaction model offered an understanding of the chemoselectivity of the reaction.

We next examined several additional variables in order to increase the yield of **3** and to facilitate scale-up.

Chelating Agent. The use of *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) as a chelating agent[16] improved the conversion of **2** to **3** (Table I) without altering the product selectivity (**3** vs **5**). The addition of at least 0.5 equiv of TMEDA prior to alkylation led to nearly complete conversion. The TMEDA stoichiometry was important: the conversion improved steadily in a linear fashion from no added TMEDA (ca. 50% conversion) to 0.5 equiv of TMEDA (>90% conversion). Additional TMEDA gave no further increase in conversion.

Scheme II

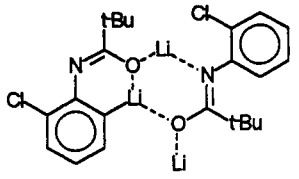

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Table II. Effect of MeX and Concentration on Ortholithiation Product Distribution[a]

variable	product ratio[b] (%) 2	3	5	6
Methylating Agent				
MeI	2	92	6	0
MeBr	3	94	3	0
Concentration ([2/*t*-BuOMe] M)				
0.3	2	92	6	0
0.5	3	90	7	0
1.0	5	92	6	0
2.0	5	91	4	0

[a] Run under standard conditions (BuLi, −23 °C, MeI, *t*-BuOMe/TMEDA (0.7 equiv)) with the exception of the given variable. [b] VPC (area %) ratios normalized to 100%; minor impurities not included.

This can be explained by the formation of a 1:1 aggregate of monoanion/dianion species (e.g., **9**) in the absence of TMEDA (Scheme II). The monoanion portion of **9** is occupied with intermolecular chelation and cannot readily coordinate $(BuLi)_n$. This prevents ortholithiation to generate the dianion and leads ultimately to the isolation of starting material. This would limit the theoretical maximum yield to about 50%, in close agreement with observed results. TMEDA presumably disrupts the intermolecular chelation, liberates the monoanion to participate in ortholithiation, and increases conversion.

Methylating Agent. Both methyl iodide and methyl bromide gave good results in the methylation (Table II). Dimethyl sulfate gave substantially lower yields and produced numerous impurities including N-methylated products (based on NMR). Methyl bromide was chosen for scale-up due to easier handling and lower cost.

Concentration. The reaction concentration (Table II) was increased from 0.3 M (a typical literature level[5a]) to 2.0 M with little change in selectivity or yield. This seemingly minor alteration has several advantages on a larger scale: (1) throughput is increased (more product from a given reactor volume), (2) the quantity of waste solvent is reduced, (3) solvent charging, distillation, and waste treatment cycle times are reduced, and (4) overall costs are reduced.

Under the optimized reaction conditions, compound **3** was obtained in 81% yield (>95% VPC purity) in one step from **2**. Subsequent removal of the amide directing group required strongly acidic conditions (50% H_2SO_4 or 48% HBr). Concentrated HCl, HCl/HOAc mixtures, and 25% NaOH failed to give significant hydrolysis within a 24-h period.

Process Scale-up. As part of development for scale-up, the acylation and lithiation/methylation steps were combined. Thus, the crude amide **2** in *t*-BuOMe was

(14) (a) Reference 2, pp 7–10. (b) Comparison of THF vs *t*-BuOMe (Table I) in the absence of TMEDA suggests a relationship between solvent polarity and chemoselectivity. This argument can be indirectly extended to Et_2O/TMEDA and hexane/TMEDA examples since the TMEDA is used catalytically and is believed to act primarily as a chelating agent for intermediate species such as **9**.[16]

(15) (a) Gribble, G. W.; Keavy, J. K.; Branz, S. E.; Kelly, W. J.; Pals, M. A. *Tetrahedron Lett.* **1988**, *29*, 6227. (b) Shakespeare, W. C.; Johnson, R. P. *J. Am. Chem. Soc.* **1990**, *112*, 8758.

(16) In the *t*-BuOMe series (Table I) incorporation of TMEDA did not alter the chemoselectivity, but dramatically increased the conversion to **3**. Conversion is increased regardless of whether the TMEDA is added before or after BuLi (Table I, footnote *d*). Thus, TMEDA is presumed to be acting primarily as a chelating agent for intermediate anionic species, rather than as an agent for the solvation/activation of $(BuLi)_n$.

azeotropically dried *in situ* and carried directly to the lithiation step without isolation. After lithiation/methylation, the crude **3** was isolated, dried, and deprotected to give 2-chloro-6-methylaniline (**4**) in 65% overall yield (98.7% purity) from **1**.

Conclusion

The described process was practical for multigram preparations in the laboratory. With minor modifications, the process was successfully scaled up to pilot plant equipment for the production of multikilogram lots.

Experimental Section

General. All reactions were carried out under an inert (nitrogen or argon) atmosphere. All commercial materials were used as received. ^{1}H NMR spectra were obtained at 200 MHz using TMS as a reference. ^{13}C NMR spectra were obtained at 50 MHz with the solvent as reference using attached proton test (APT) experiments (quaternary carbons and CH_2's designated +; CH's and CH_3's designated −). All melting points are uncorrected.

General Procedure for Preparation of Pivalanilides. A three-necked flask with a mechanical agitator was charged with 25% NaOH, the desired aniline, and *t*-BuOMe. The mixture was treated dropwise with pivaloyl chloride (ice bath cooling as needed). The mixture was stirred until complete (VPC or TLC). Isolation is described for individual compounds below.

2-Chloropivalanilide (2). Prepared from 2-chloroaniline (**1**, 12.74 g, 99.9 mmol), 25% NaOH (25.2 g, 157.5 mmol), pivaloyl chloride (12.80 g, 106.2 mmol), and *t*-BuOMe (50 mL). The reaction mixture was diluted with ether and water. The organic phase was washed sequentially with 1 M NaOH, H_2O, 5% HCl, H_2O, and saturated NaCl and then dried ($MgSO_4$) and concentrated in vacuo to give **2** (20.01 g, 95.0 mmol, 95.1%; 99.5% VPC purity) as a white solid suitable for further use. Recrystallization (hexanes) gave an analytical sample as a white crystalline solid: mp 74.9–76.1 °C; IR (KBr) 3340, 2966, 1666, 1520, 1471, 1439, 1294, 1167 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.32 (s, 9 H), 6.97 (t, J = 7.7 Hz, 1 H), 7.18–7.33 (m, 2 H), 8.01 (br s, 1 H), 8.38 (d, J = 8.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 27.3 (−), 39.8 (+), 121.3 (−), 122.8 (+), 124.1 (−), 127.4 (−), 128.5 (−), 134.6 (+), 176.1 (+); MS *m/e* (rel intensity) 213 (2, M + 2), 211 (6, M$^+$), 176 (27), 129 (11), 127 (37), 99 (7), 57 (100), 41 (35), 39 (17), 32 (13). Anal. Calcd for $C_{11}H_{14}NOCl$: C, 62.41; H, 6.67; N, 6.61. Found: C, 62.60; H, 6.71; N, 6.54.

Pivalanilide (7). Prepared from aniline (19.63 g, 0.21 mol), 25% NaOH (48 g, 0.30 mol), pivaloyl chloride (25.68 g, 0.21 mol), and *t*-BuOMe (180 mL). The organic phase was separated and washed with H_2O (200 mL), 1 M NaOH (2 × 200 mL), 18% NaCl (200 mL), and dried ($MgSO_4$). The filtrate was concentrated to a solid which was recrystallized from hexane/ethyl acetate to give **7** (19.4 g, 51.9%, not optimized) as a white solid: mp 133.8–135.0 °C; IR (KBr) 3315, 2986, 2968, 1653, 1595, 1538, 1504, 1492, 1476, 1440, 1317 cm^{-1}; MS *m/e* (rel intensity) 178 (4, M + 1), 177 (34, M$^+$), 93 (56), 57 (100), 41 (29).

2-Butylpivalanilide (6) from 2. A solution of **2** (2.15 g, 10.2 mmol) in THF (30 mL) was cooled to 0–5 °C (ice bath) and treated with BuLi (14 mL of a 2.5 M solution in hexane, 35 mmol) over the course of 15 min (T_{max} = 12 °C). The mixture was then warmed to 20–30 °C (1 h 40 min), cooled to 0–5 °C, and quenched by careful addition of 25 mL of H_2O. The layers were separated and the aqueous phase washed with *t*-BuOMe (3 × 25 mL). The organic layers were combined and washed with saturated NaCl, dried ($MgSO_4$) and concentrated to give **6** (2.33 g, 98.5%) as a cream-colored solid (91.4% by VPC). Recrystallization (heptane) gave an analytical sample as a cream-colored solid: mp 69.1–70.7 °C; IR (KBr) 3313, 2965, 2932, 2860, 1651, 1510 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.93 (t, J = 7.0 Hz, 3 H), 1.28 (s, 9 H), 1.28–1.54 (m, 4 H), 2.52 (t, J = 7.7 Hz, 2 H), 7.04–7.18 (m, 3H), 7.46 (br s, 1 H), 7.72 (d, J = 7.8 Hz, 1 H); ^{13}C NMR δ 13.9 (−), 22.5 (+), 27.4 (−), 31.2 (+), 31.9 (+), 39.4 (+), 123.8 (−), 124.8 (−), 126.2 (−), 129.1 (−), 133.8 (+), 135.1 (+), 176.2 (+); MS *m/e* (rel intensity) 234 (3, M + 1), 233 (15, M$^+$), 204 (12), 176 (20), 106 (33), 57 (100). Anal. Calcd for $C_{15}H_{23}NO$: C, 77.21; H, 9.93; N, 6.00. Found: C, 77.32; H, 10.06; N, 5.98.

6 by Ortholithiation of 7. Using the general method of Gschwend,[5a] a solution of **7** (1.80 g, 10.2 mmol) in THF (30 mL) was cooled to 0–5 °C (ice bath) and treated with BuLi (10 mL of a 2.5 M solution in hexane, 25 mmol) over the course of 5 min (T_{max} = 20 °C). The mixture was stirred at 0–10 °C (2 h) and treated with *n*-BuBr (1.6 mL, 14.9 mmol). The mixture was stirred at 20–30 °C (28 h), quenched with H_2O, and isolated as described above for **7** to give 1.94 g of colorless solid (not optimized) as a ca. 1:1 mixture (VPC) of starting material **7** and **6**. Radial-layer chromatography (3:1 heptane/*t*-BuOMe) gave pure **6** as a colorless solid identical by NMR (^{1}H and ^{13}C), GC/MS, and VPC (coinjection) to material prepared from **2**.

2-Butyl-3-methylpivalanilide (5). A solution of **2** (2.13 g, 10.1 mmol) in THF (30 mL) was cooled to 0–5 °C (ice bath) and treated with BuLi (13 mL of a 2.5 M solution in hexane, 33 mmol) over the course of 15 min (T_{max} = 12 °C). The mixture was warmed to 20–25 °C (1 h 15 min), cooled to 0–5 °C, and treated with a solution of MeI (0.71 mL, 11.4 mmol) in THF (5 mL) over 20–30 min (T_{max} = 12 °C). The mixture was allowed to warm gradually to 20–25 °C overnight and was quenched by addition of 25 mL of H_2O. Workup as described for **6** followed by recrystallization (heptane) gave **5** (1.48 g, 59.6%, not optimized, 97.80% VPC purity) as a tan solid. A second recrystallization (heptane) gave an analytical sample as a tan solid: mp 174.1–175.7 °C; IR (KBr) 3303, 3023, 2958, 1649, 1510 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.90 (t, J = 7.0 Hz, 3 H), 1.28 (s, 9 H), 1.28–1.49 (m, 4 H), 2.12 (s, 3 H), 2.47 (t, J = 7.7 Hz, 2 H), 7.01–7.13 (m, 4H); ^{13}C NMR δ 13.9 (−), 18.2 (−), 22.8 (+), 27.7 (−), 31.8 (+), 32.6 (+), 39.1 (+), 127.0 (−), 128.0 (−), 133.6 (+), 136.0 (+), 176.4 (+); MS *m/e* (rel intensity) 247 (17, M$^+$), 218 (16), 190 (48), 120 (29), 57 (100). Anal. Calcd for $C_{16}H_{25}NO$: C, 77.68; H, 10.19; N, 5.66. Found: C, 77.23; H, 10.12; N, 5.77.

2-Chloro-6-methylpivalanilide (3). One-Step Procedure from 2 and CH_3I. A cooled (−23 °C bath) mixture of 2-chloropivalanilide (**2**; 10.58 g, 50 mmol), TMEDA (5.7 mL, 37.8 mmol), and *t*-BuOMe (100 mL) was treated with BuLi (50.0 mL of a 2.5 M solution in hexane, 125 mmol) over 20 min (T_{max} = −5 °C). After 65 min a solution of CH_3I (6.0 mL, 96.4 mmol) in *t*-BuOMe (9 mL) was added slowly. The cooling bath was removed, and the mixture was stirred for 1 h. The reaction was quenched by addition of water. The aqueous phase was separated and washed with Et_2O. The combined organic layers were washed with water and saturated NaCl and dried ($MgSO_4$). The solvent was removed *in vacuo* to give crude **3** (11.31 g of an off-white solid, 86.2% VPC purity). Recrystallization (hexane/EtOAc; two crops) gave **3** (9.15 g, 81.1%, >95% VPC purity). A second recrystallization (hexane/EtOAc) gave an analytical sample as a white solid: mp 166.3–167.3 °C; IR (KBr) 3292, 2962, 1655, 1506, 1456, 1173 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.25 (s, 9 H), 2.12 (s, 3 H), 7.02–7.19 (m, 3 H), 7.44 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 18.4 (−), 27.4 (−), 39.1 (+), 126.6 (−), 127.2 (−), 128.8 (−), 131.4 (+), 133.0 (+), 138.1 (+), 176.6 (+); MS *m/e* (rel intensity) 225 (1, M$^+$), 190 (47), 143 (7), 142 (5), 141 (22), 140 (9), 106 (17), 77 (17), 57 (100), 41 (31), 39 (13), 32 (13). Anal. Calcd for $C_{12}H_{16}NOCl$: C, 63.86; H, 7.14; N, 6.20. Found: C, 64.09; H, 7.18; N, 6.20.

Combined Process for Preparation of 2-Chloro-6-Methylaniline (4) from 1. A 3-L flask with a mechanical agitator was charged with NaOH (176 g of a 25% aqueous solution, 1.10 mol), **1** (127.6 g, 1.00 mol), and *t*-BuOMe (950 mL). The mixture was treated dropwise with pivaloyl chloride (124.2 g, 1.03 mol) over 15 min (16–27 °C, ice bath cooling as needed). The mixture was stirred for 3.5 h. The phases were separated, and the organic phase was washed with 6% NaOH (500 mL), 5% HCl (2 × 500 mL), and H_2O (500 mL). TMEDA (87.2 g, 0.75 mol) was added, and the mixture was heated to reflux, removing water with a Dean-Stark trap. The solution was cooled to below −20 °C under argon and treated with BuLi (1.5 L of a 1.6 M solution in hexane, 2.4 mol) over 45 min, controlling the temperature as follows: T_{max} = 10 °C during addition of the first 600 mL (approximately 1 equiv); T_{max} = −12 °C during the remainder of the addition. The mixture was stirred at −12 to −20 °C (50 min) and, using a cold finger condenser (−78 °C), was treated with gaseous MeBr (135 g, 1.42 mol) over 30 min (T_{max} = −3 °C). The mixture was

cooled to −20 °C, stirred for 2 h, quenched by addition of NH_4OH (300 mL 28% solution), and warmed gradually to room temperature overnight. The mixture was diluted with 300 mL of water. A minimum quantity of toluene was added to dissolve solids. The organic phase was washed 5% HCl (2 × 500 mL), concentrated to a volume of about 1 L (50 min), diluted with hexane (1 L), and cooled to 0–5 °C. The white precipitate was collected by filtration, rinsed with hexane, and dried *in vacuo* to give 162.7 g (72.1%) of **3**, suitable for further use.

The crude product (161.0 g, 0.71 mol) was refluxed with concentrated HBr (540 mL of a 48% aqueous solution) for 4.5 h. The mixture was cooled to 0–5 °C overnight, and the precipitated HBr salt was collected by filtration. The damp solid was dissolved in water (450 mL), cooled (ice bath), and treated with NaOH (183.6 g of 50% NaOH solution) maintaining the temperature below 30 °C. The mixture was extracted with hexane (500 mL). The hexane layer was washed with water (200 mL) and concentrated *in vacuo* to give **4** (verified by comparison to authentic samples including a commercial sample obtained from Aldrich) as an oil (93.3 g, 65.9% overall from **1**) with 98.7% VPC purity.

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