Organic Process Research & Development **2005**, *9*, 764–767

Process Development and Pilot Plant Synthesis of Methyl 2-Bromo-6-chlorobenzoate

Matthew R. Hickey,*,† Shawn P. Allwein,† Todd D. Nelson,† Michael H. Kress,† Osama S. Sudah,‡ Aaron J. Moment,‡ Stephen D. Rodgers,‡ Mahmoud Kaba,‡ and Paul Fernandez‡

Merck Research Laboratories, Department of Process Research, 466 Devon Park Drive, Wayne, Pennsylvania 19087, U.S.A., and Chemical Engineering Research and Development, 126 East Lincoln Avenue, Rahway, New Jersey 07654, U.S.A.

Abstract:

A scalable process for a pilot plant synthesis of methyl 2-bromo-6-chlorobenzoate (1) is described. The strategy employed for the synthesis hinged on the esterification of the sterically encumbered parent acid produced through an *o*-lithiation/carboxylation approach. Vigilant temperature control was paramount for the success of this synthetic pathway. Initiation of an exothermic benzyne decomposition pathway during the *o*-lithiation step occurred at −70 °C. In the pilot plant, cooling via the jacket service was suitable to provide batch temperatures of −75 °C. However, control of reaction heat required liquid nitrogen injection into the process vessel simultaneously with the exothermic reagent charges. Esterification of the carboxylic acid was accomplished with potassium carbonate/methyl iodide, and subsequent crystallization resulted in 79% overall yield of the title compound from inexpensive starting materials.

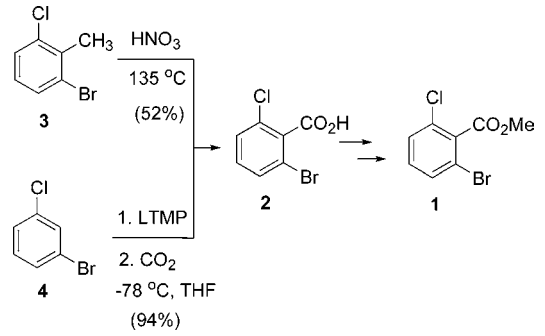
Introduction

A recent program at Merck required kilogram quantities of methyl 2-bromo-6-chlorobenzoate (**1**). To the best of our knowledge, no reported synthesis of this deceptively simple compound has been reported. Initial outsourcing efforts were fruitless. Two vendors were approached for the large scale delivery of **1**; however, both independently defaulted on their respective deliveries. Thus, rapid development of a robust and scalable synthetic sequence was of utmost consequence. We considered esterification of 2-bromo-6-chlorobenzoic acid (**2**) the most direct approach for the synthesis of ester **1**; our strategy hinged on the preparation and esterification of acid **2**.

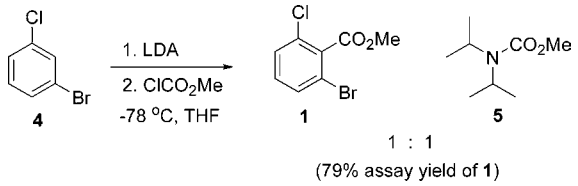
The synthesis of acid **2** has been accomplished via two basic strategies, (i) oxidation of 2-bromo-6-chlorotoluene (**3**)[1] using nitric acid and (ii) *o*-lithiation of 3-bromochlorobenzene (**4**)[2] with lithium 2,2,6,6-tetramethylpiperidide (LTMP), followed by carboxylation with CO_2 (Scheme 1).

We initially envisioned a third strategy, which was founded on the latter *o*-lithiation chemistry. Instead of carboxylation of the anion of **4** with CO_2 to form the acid, carboxymethylation through quench with methyl chloroformate or dimethyl carbonate was the focus (Scheme 2).

Scheme 1. **Reported syntheses of intermediate 2**



Scheme 2. **Carboxymethylation of 3-bromochlorobenzene using LDA and methyl chloroformate**



Results and Discussion

Carboxymethylation of 3-Bromochlorobenzene. Treatment of **4** with LDA at −78 °C, followed by quench of the slurry with methyl chloroformate gave ester **1** in 79% yield.[3] One of the major difficulties with this approach was purification of the product mixture (Scheme 2). Formation of ester **1** was accompanied by stoichiometric formation of the *N*,*N*-diisopropylcarbamate (**5**). Attempts at direct crystallization of ester **1** were unsuccessful. Only column chromatography provided pure product, reinforcing the benefit of having the acid function. The ability to purify acid **2** via an acid base extraction sequence shifted focus to process development of the *o*-lithiation/carboxylation chemistry reported by Schlosser.[2]

Temperature Stability of 2-Bromo-6-chlorophenyllithium (6). An initial perceived drawback to the *o*-lithiation strategy is the use of cryogenics on a large scale. Our initial approach was to determine the thermal stability of the anion of **4** after LDA addition. In a typical experiment on a 5 g scale, a 160 g/L solution of **4** in THF was treated with LDA at −78 °C and aged for 2 h at that temperature. The dry ice acetone bath was removed from the flask, and at an internal temperature of −70 °C, the mixture began to darken. Within 30−45 s the batch temperature was 65 °C and refluxing.

* Corresponding author. E-mail: matthew_hickey@merck.com.
† Department of Process Research.
‡ Chemical Engineering Research and Development.

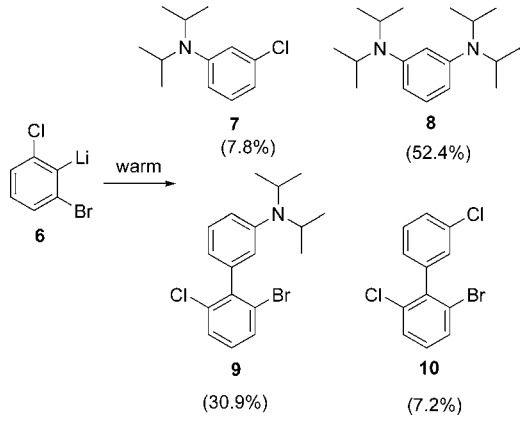
(1) (a) Cohen, J. B.; Raper, H. S. *J. Chem. Soc.* **1904**, *85*, 1262. (b) Cohen, J. B.; Smithells, C. J. *J. Chem. Soc.* **1914**, *105*, 1907.

(2) Mongin, F.; Schlosser, M. *Tetrahedron Lett.* **1997**, *37*, 1559.

(3) Based on analytically pure standard.

Published on Web 10/12/2005
10.1021/op0501444 CCC: $30.25

Scheme 3. **Benzyne type decomposition of 2-bromo-6-chlorophenyllithium (6)**



Assay of the product mixture revealed complete consumption of **4** and generation of four major products. Structural assignments by GC/MS and NMR (Scheme 3) corresponded to products generated via benzyne type decomposition analogous to observations from decomposition of 2,6-dichloro- or 2,6-dibromophenyllithium.[4]

This insight into the mechanism of the decomposition allowed for a rational solution. By diluting the reaction concentration 4-fold to 40 g/L (based on **4**), the increased heat capacity of the system better absorbed heat generation during benzyne formation. Additionally, the more dilute conditions slowed the trapping of the benzyne intermediate by possible nucleophiles (LDA, DIPA, or **6**; Scheme 3). The decomposition still occurred under the revised conditions; however, the temperature did not rise above 0 °C (ice bath). This eased our safety concerns for this exothermic pathway, but temperature was still a parameter that was controlled and monitored with vigilance.

In Situ Reaction Monitoring. A carboxylation reaction using standard conditions was monitored by an in situ IR probe. The results are plotted as Figure 1.

Bromochlorobenzene **4** was added to a solution of LDA at −78 °C over 5 min. The formation of aryllithium **6** was indicated by an increase in red signal, which coincided well with the consumption of **4** (black signal). Decrease in the red signal corresponded nicely with the visually observed precipitation (equilibirum concentration ca. 0.11 M). The internal temperature of the stirred slurry was maintained between −70 and −76 °C for 5 h. Gaseous CO_2 (purple signal) was added subsurface. Essentially no buildup of CO_2 in the solution was evident, until most of the aryllithium was consumed, suggesting a fast reaction as anticipated. Pause in CO_2 addition was visible in the plot as a slight plateau in both the red and blue lines. A sharp drop in the blue line during the CO_2 addition coincided with a visually observed precipitation of the lithium carboxylate **11**. A large exotherm resulting from the carbon dioxide addition (32−34 kcal/mol)[5] suggested a fast reaction rate. Unfortunately, precipitation of various key intermediates clouded detailed kinetic measurements.

Extractive workup of the reaction mixture removed lithium salt **11** from the organic waste into 0.1 N NaOH, with an aqueous back extraction to ensure complete removal of the desired product from the organic waste phase (<3% loss). The organic waste was discarded, and the aqueous pH was adjusted to 1 with 6 N HCl. The resultant oil (bottom phase) was collected, and the aqueous waste phase was salted with solid NaCl and back extracted with THF, further reducing the product loss below 3%. The combined organic extracts contained product in typical assay yields of 88−90% as a solution in THF.

Esterification. The initial discovery of the esterification of acid **2** was not straightforward. Traditional Fisher type esterification conditions using methanol failed to provide suitable yield of the ester **1**. The large size of the bromine and chloride substituents flanking the acid prohibits passage through a tetrahedral intermediate.[6] Attempts at activation with DCC and 1-ethyl-3-[3-(dimethylamino)propyl] carbodiimide (EDC) also provided low levels of conversion. Alternative methylation conditions using methyl iodide and DBU gave 63% assay yield of ester **1**.[7] This reaction was scalable and was carried out in similar yield to prepare 10 kg of ester **1** as a stream in toluene.

To minimize raw material cost for this process, a screen of suitable bases was performed to replace the expensive DBU in this transformation. This approach identified aqueous potassium carbonate as a viable solution. Heating a mixture of acid **2** with 1.3 equiv of methyl iodide and 1.5 equiv of potassium carbonate (as a 50 wt % aqueous solution) to 65 °C under reflux routinely gave the ester in >95% assay yield. After an extractive workup with MTBE and THF, the solvents in the organic stream were switched to 2-propanol. This solution was concentrated to a final ester concentration of 350 g/L. Addition of two volumes of water (relative to total batch volume) gave crystalline ester **1** in 93% isolated yield (Scheme 4).

Pilot Plant Synthesis of 1. The foremost concern in planning the pilot plant campaign was temperature control of the *o*-lithiation/carboxylation procedure. The jacket service was sufficient to reduce batch temperature to −75 °C. However, jacket service alone could not control the heat of reaction during the exothermic bromochlorobenzene **4** (37 kcal/mol) and CO_2 (32 kcal/mol) charge. Temperatures below −70 °C were ensured by equipping the vessel with a direct liquid nitrogen injection assembly. A flow meter would monitor both flow rate and amount of liquid nitrogen used. Care had to be exercised, however, since cooling the batch below −100 °C exceeded the rating of the vessel. Thus, a temperature window of −85 to −70 °C was established to protect both the batch and the vessel.

(4) (a) 2,6-Dichlorophenyllithium: Kress, T. H.; Leanna, M. R. *Synthesis* **1988**, 803. (b) 2,6-Dibromophenyllithium: Luliński, S.; Serwatowski, J. *J. Org. Chem.* **2003**, *68*, 5384. (c) Halophenyl triflates: Wickham, P. P.; Reuter, K. H.; Senanayake, H. G.; Zalesky, M.; Scott, W. J. *Tetrahedron Lett.* **1993**, *34*, 7521.

(5) Determined by reaction calorimetry.

(6) (a) Thomas, J.; Canty, J. *J. Pharm. Pharmacol.* **1962**, *14*, 587. (b) A survey of the literature suggests dominance of esterification of 2,6-dihalobenozic acids by alkylative procedures. An instance of Fisher esterification of difluoro-iodo benzoic acids has been reported in poor yields: Rausis, T.; Schlosser, M. *Eur. J. Org. Chem.* **2002**, 3351.

(7) Ono, N.; Yamada, T.; Saito, T.; Tanaka, K.; Kaji, A. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 2401.

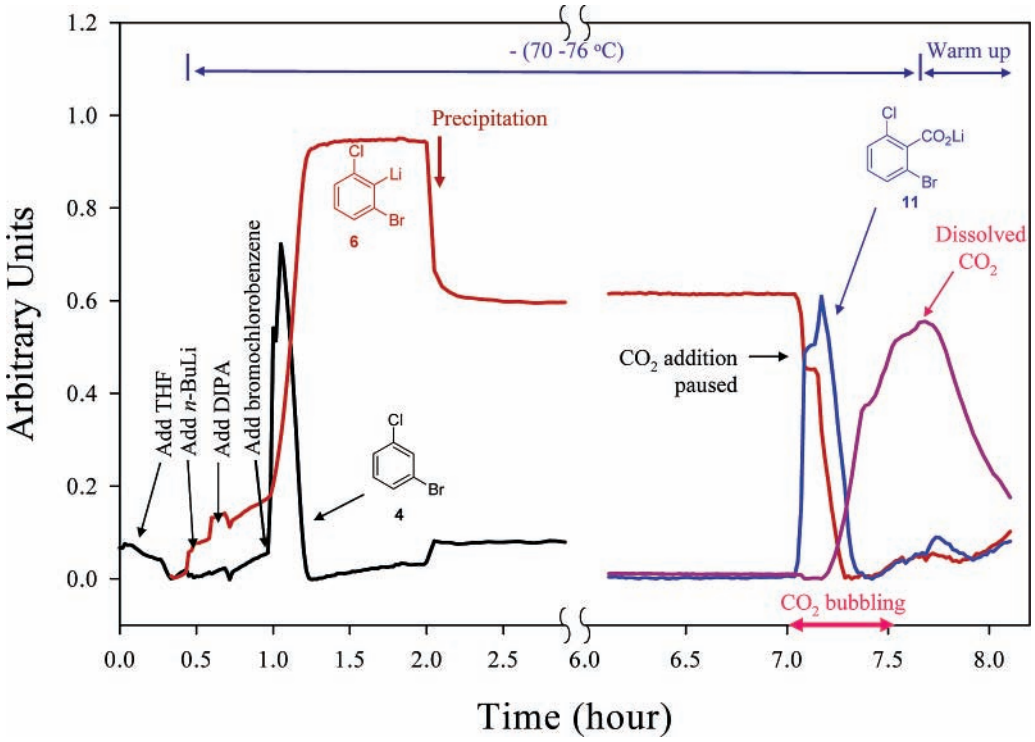
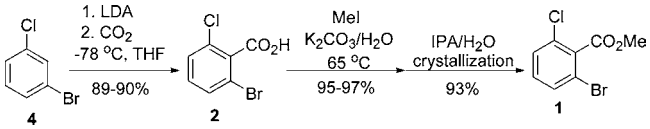


Figure 1. **FTIR data for a typical carboxylation experiment.**

Scheme 4. **Through process to synthesize 1**



As above, LDA (0.2 M) was generated in THF at −50 °C and cooled to −76 °C. 3-Bromochlorobenzene (**4**) was added over 30 min, with concomitant liquid nitrogen charge (2 kg/min) to minimize potential heating of the batch. The thin slurry was aged at −75 °C for 4 h. Control of the subsurface[7] addition of gaseous CO_2 was ensured by using a needle valve from manifolded cylinders on a scale. After 1.2 equiv of CO_2 were added, the exotherm subsided and the batch was prepared for workup. The batch temperature was slowly raised to 20 °C over 5.5 h to control offgassing of dissolved CO_2, which was then degassed for 15 min at 600 mmHg. Degassing minimized formation of Na_2CO_3 upon transfer of the batch to aqueous NaOH and, hence, minimized effervescence upon pH adjustment. After transfer of the batch to the workup vessel, a similar workup protocol (vide supra) was utilized to afford a final THF stream of the acid in 89% assay yield.[9]

With the acid stream obtained above, 50 wt % aqueous K_2CO_3 and methyl iodide were charged to a vessel. The vessel was sealed, and the batch was heated to 80 °C for 7 h and then cooled to room temperature for an end of reaction assay. Assay confirmed >95% assay yield. The aqueous waste was separated, and the organics were diluted with MTBE and washed with water to remove any residual inorganic salts. Both the aqueous phase and the water wash contained <1% ester **1**. The organics from the first batch were stored and then combined with the second batch[10] during solvent switch to 2-propanol. It was imperative that all THF was removed during the solvent switch, as the solubility of ester **1** in THF was very high (≫100 g/L) and greatly affected solubility during the crystallization.

Once the solvent switch was complete, two volumes of water were added giving crystalline ester **1** in 93% isolated yield. The single batch crystallization produced 120 kg of ester **1** (>99 LCAP, >99 LCWP[11]). This represents a 79% overall yield from 3-bromochlorobenzene and is directly in accordance with the results obtained on a 2 kg scale.

In summary, we have developed a robust two-step process to synthesize methyl 2-bromo-6-chlorobenzoate (**1**). Our strategy relied on *o*-lithiation/carboxylation chemistry to produce acid **2**. Exploiting the acid function of this intermediate allowed for consistent interbatch purity. Success of this transformation was ensured through direct liquid nitrogen injected cryogenic reaction conditions in the pilot plant. This route has provided crystalline material consistent in yield and purity on multiple 50 kg batches in 79−80% overall isolated yield.

Experimental Section

General. All reagents and solvents were obtained from commercial sources and used without purification.

(8) To control the exotherm on a 2 kg scale, the CO_2 was added into the headspace of the reaction at −70 °C. The addition rate was maintained such that CO_2 bubbling through oil was kept constant. The exotherm under these conditions is much less pronounced in comparison to subsurface addition. The yields are identical regardless of the mode of exposure of the batch to CO_2.

(9) The batch was drummed at this point to obtain an accurate assay yield, for basis of the charges for the subsequent esterification.

(10) Batch 2 gave the acid in 90% assay yield followed by a 95% assay yield of the esterification.

(11) LCAP represents LC area percent; LCWP represents LC weight percent.

HPLC Conditions: Zorbax Eclipse XBD C8 column, 5 micron, 4.6 mm × 150 mm; mobile phase gradient 0.1% aqueous H_3PO_4/acetonitrile 85/15 for 5 min, then to 5/95 over 15 min, then to 85/15 over 2 min; 1.5 mL/min; 40 °C; detector 220 nm.

Retention times:

2-Bromo-6-chlorobenzoic acid 9.20 min

Methyl 2-bromo-6-chlorobenzoate 14.28 min

3-Bromochlorobenzene 15.74 min

Synthesis of 1 Using Methyl Chloroformate. A 50 mL round-bottomed flask containing 5 mL of THF was cooled to −70 °C in an ice−water bath. To the solvent *n*-butyllithium (2.5 M in hexanes, 2.3 mL, 5.75 mmol) and diisopropylamine (0.81 mL, 5.78 mmol) were added. The mixture was cooled to −78 °C, and 3-bromochlorobenzene (0.52 mL, 4.43 mmol) was added. After stirring the white suspension for 3 h, a solution of methyl chloroformate (1.7 mL, 22.0 mmol) in THF (5 mL) was added over 15 min such that the internal temperature did not exceed −70 °C. The resulting yellow suspension was stirred at −78 °C for 1 h, and then the cooling bath was removed. Once at room temperature, the reaction was treated with 10 mL of water and the phases were separated. The aqueous was extracted once with 10 mL of isopropyl acetate. Assay of the combined organic extracts revealed a 79% assay yield of the product, with little starting material remaining. Crude NMR of the concentrated organic stream confirmed the major products of the reaction to be **1** and **5** in 1:1 ratio. Other impurities were present in lesser amounts and were uncharacterized.

Pilot Plant Process for the Synthesis of Methyl 2-Bromo-6-chlorobenzoate (1). Tetrahydrofuran (1000 L) was charged to a 500 gal glass lined (cryo-rated) vessel, and cooling was started. Once the solvent was at an internal temperature of −40 °C, 1.6 M *n*-butyllithium (169 kg, 398 mol) in hexanes was charged over 25 min maintaining the batch temperature below −34 °C. The batch was cooled further during the 15 min charge of diisopropylamine (43 kg, 429 mol) to a final temperature of −77 °C, using liquid nitrogen injections into the batch to supplement jacket cooling. 3-Bromochlorobenzene (58.6 kg, 306 mol) was charged over 30 min, with a constant liquid nitrogen flow of 2 kg/min into the batch. This simultaneous liquid nitrogen charge ensured the batch to remain below −75 °C. During the 4 h age, a quench vessel was prepared by charging 560 L of 0.1 M NaOH(aq) to a 1000 gal glass lined vessel. After a 4 h age at −75 °C, carbon dioxide (35 kg, 795 mol) was charged subsurface, again with a concomitant liquid nitrogen flow of 6 kg/min, maintaining a batch temperature below −70 °C. To maintain control of offgassing of dissolved carbon dioxide, the batch was slowly warmed to 20 °C over 5.5 h and then degassed at 600 mmHg for 10 min. The batch was transferred to the quench vessel, agitated for 40 min, and then settled for 1 h. Phase separation completed in 1 h, and the aqueous product was transferred to a third glass lined 500 gal vessel. An additional 280 L of 0.1 N NaOH(aq) was charged into the organic waste phase still in the quench vessel, and the mixture was agitated for 30 min and then settled for 1 h. The phases were separated, and the second aqueous product stream was combined with the first. To the aqueous product stream, 6 N HCl (143 L) was added over 1 h to minimize offgassing and foaming. An oily second phase formed, and the biphasic mixture at pH 0.5 was allowed to settle for 1 h. The oily product phase was drummed off (241.5 kg total), and the aqueous phase in the vessel was treated with solid sodium chloride (48 kg) and THF (286 L) for the back extraction. After agitation and settling, the phases were separated and the aqueous phase was sent to waste. The second organic phase (246.8 kg) was drummed separately to get an accurate weight for assay calculations. The combined assay yield was 63.9 kg of **1**, which represents an 88% yield.

The product streams were combined in a clean 500 gal glass lined vessel, and 50% w/w solution of potassium carbonate (90 kg) added, followed by addition of methyl iodide (50 kg, 353 mol). After sealing the vessel, the biphasic reaction mixture was heated to 80 °C for 7 h. Upon cooling the reaction mixture, MTBE (86 kg) and water (115 kg) were added and the phases separated. A 115 kg water wash of the organic product phase was conducted to remove any remaining inorganic salts, and the organic phase was drummed.

A second batch of carboxylation and esterification was conducted in the same manner on a similar scale in 90% and 95% assay yields, respectively. The first batch product stream was transferred to a 500 gal glass lined vessel, and distillation started. During the distillation of the first batch product stream, the second batch was fed in. Once both batches were combined in a single vessel, the solvent switch to 2-propanol was performed. When the target concentration of ester **1** in 2-propanol (246 g/L) was achieved, and the quantity of residual THF (<1% v/v[12]), 2 volumes (based on the total batch volume) of water were added, resulting in formation of crystalline ester **1**. The slurry was filtered in two drops to give a total physical yield of 120 kg (481 mol) of **1** as large crystals: ^{1}H NMR δ 7.49 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.21 (t, J = 8.0 Hz, 1H), 3.98 (s, 3H); ^{13}C NMR δ 166.0, 135.7, 131.8, 131.3, 131.0, 128.4, 119.9, 23.1.

(12) Determined by quantitative GC analysis.

Acknowledgment

We thank Li Pan, Claire Lee, and Lili Zhou for analytical support during the pilot plant campaign, Doug Frantz and Damian Weaver for the Fisher esterification investigation, and Peter Dormer for NMR structure analysis of the decomposition products.

Received for review August 10, 2005.

OP0501444