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Development of a Safe and Robust Process for the Large-Scale Preparation of a Vinyl Bromide from a Ketone Using a $(PhO)_3P/Br_2$-Derived Reagent

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ABSTRACT: The large-scale synthesis of ethyl 4-bromocyclohex-3-enecarboxyalate, using a mild brominating reagent derived from triphenyl phosphite and bromine, is reported. The development and comparison of both continuous and batch processes are described. A modified addition sequence was developed based on the knowledge garnered from flow-processing, resulting in a safe and efficient process for the in situ generation of the unstable active reagent and its immediate reaction with the ketone in a batch mode process.

■ INTRODUCTION

The increasing structural complexity of active pharmaceutical ingredients and intermediates presents unprecedented challenges during their synthesis, especially on a large scale. Metal-mediated cross-coupling reactions have emerged as powerful tools in the synthetic chemist's arsenal, enabling the rapid and selective formation of complex structural motifs in a relatively straightforward manner.[1] As these technologies (i.e., Suzuki, Suzuki−Miyaura, Buchwald−Hartwig, Sonogashira, Heck coupling, etc.) continue to evolve, so too must the chemistry to prepare the desired electrophilic cross coupling partners, such as enol triflates and vinyl halides. While both of these electrophiles are competent in cross-coupling transformations, the vinyl bromides are generally far superior with respect to chemical stability—a key attribute often required in large-scale multistep syntheses.

Traditional methods for the direct preparation of vinyl halides from carbonyl compounds often involve the use of halogenating agents under harsh conditions.[2] Multistep processes have also been reported involving the isolation of synthetic intermediates which require further modification.[3] Recently, Prati and co-workers reported a mild protocol for the synthesis of vinyl halides and *gem*-dihalides using triphenyl phosphite/halogen-based reagents.[4] This method exhibits good functional group compatibility and is amenable to the synthesis of structurally diverse halides from their corresponding carbonyl precursors. To the best of our knowledge, there are no reports documenting the application of this method for the large-scale synthesis of vinyl halides.

In this report, we describe the successful development and application of the Prati method for the large-scale synthesis of an important vinyl bromide intermediate. An initial batch process highlighted some issues with the protocol, especially around stability of the active reagent; thus a continuous flow process was developed for reagent preparation. The lessons learned during the course of developing the flow protocol paved the way for the development of an efficient second-generation batch process, vide infra.

■ RESULTS AND DISCUSSION

Vinyl bromide **5** (Scheme 1) is a key building block for the synthesis of a new drug candidate currently under evaluation. We envisioned that **5** could be synthesized from ketone **3** using an appropriate brominating reagent. Based on literature precedent, we explored the possibility of effecting this transformation using Prati's triphenyl phosphite-bromine-derived reagent, presumed to be active in its ionic form **2a** (Scheme 1).[4]

The first step in the original protocol was to prepare the active brominating reagent (**2a**) by the addition of molecular bromine to a solution of triphenyl phosphite **1** in dichloromethane, maintaining the temperature below −60 °C. Further addition of triethylamine and starting material (ethyl cyclohexanone-4-carboxylate, **3**) led to the formation of the *gem*-dibromo intermediate **4**. Subsequent warming of the reaction mixture to ambient temperature and elimination of HBr furnished **5** upon workup. Our preliminary experiments suggested that the reaction mixture had to be warmed to ambient temperature and maintained for 24 h in order to effect the desired elimination reaction (Scheme 1, **4** → **5**).[5]

This first-generation batch mode process was adopted for supporting early scale-up activities and delivered ~70% yield of **5** (Figure 1).[6] However, we encountered several challenges during the execution of this process in the pilot plant, especially while charging bromine, triethylamine, and starting material within the stipulated times, controlling the reaction temperature below −60 °C. Addition of molecular bromine to a solution of triphenyl phosphite in dichloromethane was exothermic, such that

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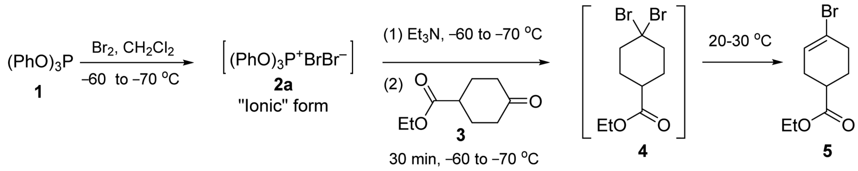
Scheme 1



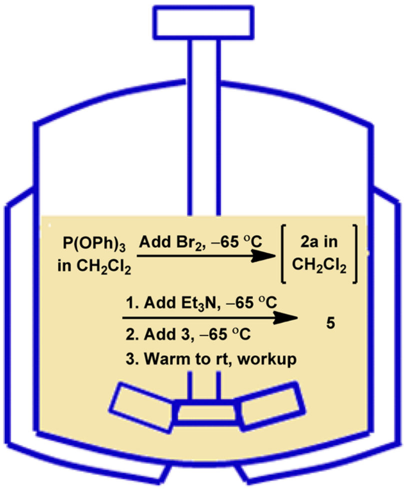


Figure 1. First-generation batch process.

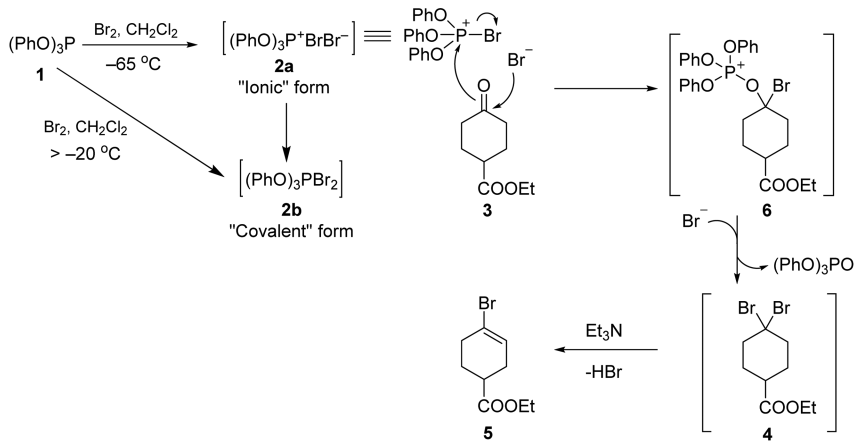
the addition rate needed to be controlled carefully to maintain the reaction temperature below −60 °C; for example, one plant-scale batch (17 kg input) required an 8 h addition sequence followed by an additional 8–9 h for warming the reaction mass to ambient temperature, and resulted in a significantly lower yield (55%) of the desired bromide **5**. This result prompted us to closely examine the reaction pathway and the unit operations in the process in an effort to develop a more robust and efficient process for the synthesis of **5**.

In this reaction, it is believed that the reaction of bromine and triphenyl phosphite leads to the active brominating agent, bromotriphenoxyphosphonium bromide [$(PhO)_3P^+BrBr^-$, **2a**] (Scheme 2).[4,7] According to the literature, this active, ionic species reacts with the substrate (**3** in this case) to form the oxyphosphonium bromide **6**. Elimination of triphenylphosphate from **6** provides the intermediate *gem*-dibromide **4**, which upon base-promoted dehydrobromination affords vinyl bromide **5** (Scheme 2). The ionic species **2a** is reported to convert to the inactive covalent form, dibromotriphenoxyphosphorane [$(PhO)_3PBr_2$, **2b**] over time even at low temperatures (Scheme 2), and the ratio of the two species appears to be temperature-dependent (**2a**:**2b** is reported to be 4:1 at −60 °C, and 1:3 at −20 °C).[4,7] Thus, in order for the bromination process to be efficient, the bromination reaction should be faster than the conversion of **2a** to **2b**.

Preliminary investigations revealed that the capricious performance of the bromination reaction on scale may be attributed to the long addition times in the pilot plant. We presume that the root cause of this loss in reactivity is the depletion of the reactive ionic form, **2a**. A series of experiments was conducted to gain further insights into the nature and stability of the brominating reagent and its reactivity with **3**. In one experiment, **2a** was generated and maintained at −60 °C for 16 h prior to the addition of triethylamine and **3**. This reaction, upon warming to ambient temperature, provided **5** in ca. 75% yield. However, in instances where **2a** was generated at −60 °C and was allowed to warm to −50 or −35 °C and held at those temperatures for 16 h prior to the addition of triethylamine and **3**, a much lower yield (~45%) was obtained upon workup, suggesting deterioration in the reactivity of the system presumably by means of conversion of **2a** into the inactive form **2b** above −50 °C, consistent with literature reports.[4] While these experiments are consistent with prior observations, they do not discount a loss of activity via other pathways.

Analysis of the mechanism of reagent formation and its reaction with **3** led to the hypothesis that there is both a time and temperature variable associated with the stability of the active brominating agent. This led us to investigate the instantaneous reaction of the brominating reagent **2a** with the substrate **3**, in hopes of circumventing the possible loss of reagent quality associated with on-scale processing times between reagent formation and substrate addition. The goal of this work was to develop a fundamentally robust process, unencumbered by tight

Scheme 2



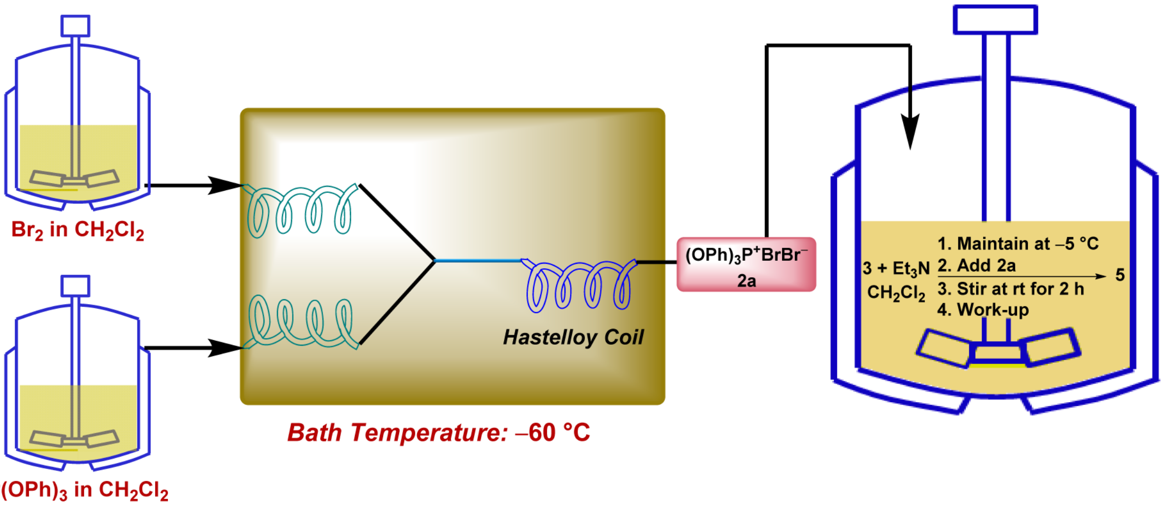


Figure 2. First-generation semibatch process.

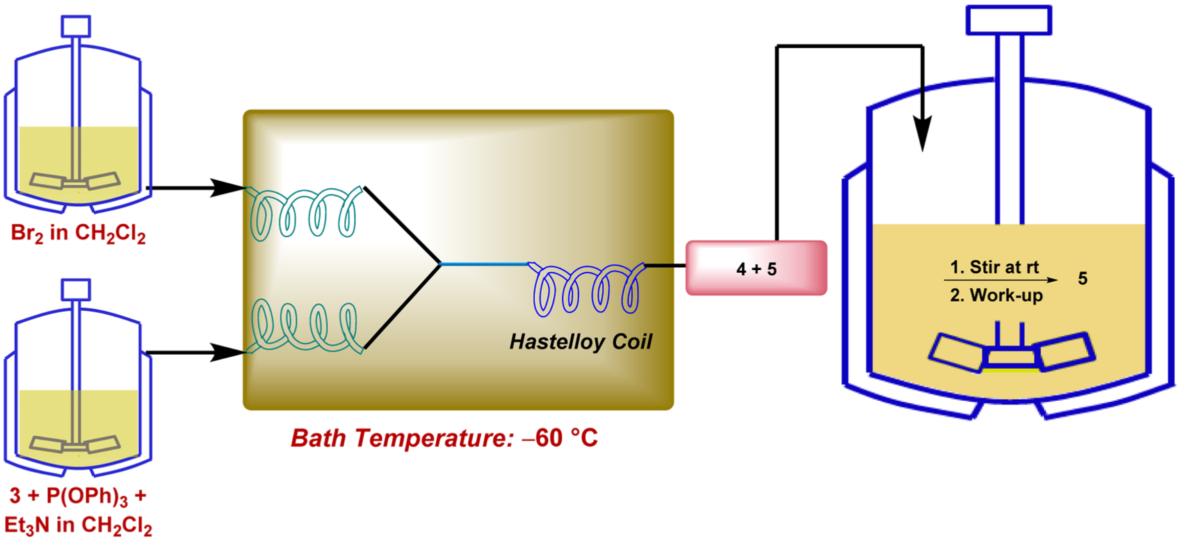


Figure 3. Second-generation semibatch process.

processing requirements (such as rigid control over processing times). Since this appeared challenging in batch mode, we evaluated the possibility of generating the active reagent **2a** under a continuous process prior to charging the active stream into a batch reactor containing substrate **3** and triethylamine (Figure 2). Accordingly, precooled solutions of bromine in dichloromethane (2.1 M, flow rate = 29 mL/min) and triphenyl phosphite **1** in dichloromethane (2.1 M, flow rate = 45 mL/min)[8] were pumped and circulated through a 100 mL flow reactor (Hastelloy coil), which was maintained at −50 to −60 °C (residence time = 1.35 min) before being charged into a batch reactor containing a solution of **3** and triethylamine in dichloromethane at −5 °C. This mixture was warmed to ambient temperature, and afforded **5** upon workup. This first-generation semibatch process was found to be significantly more efficient than the original batch process, resulting in ~85% isolated yield of the desired product **5**.

Interestingly, a sample analyzed immediately after completion of addition of **2a** showed almost complete consumption of ketone **3**, even after minimal aging of the reaction stream post bromine addition. This indicated that the reaction of **2a** with **3** was kinetically fast. Thus, we explored the possibility of generating the active brominating agent **2a** in the presence of ketone **3**. A second-generation semibatch process was therefore developed, wherein two dichloromethane streams—one containing bromine and the other a mixture of **3**, triphenyl phosphite, and triethylamine—were circulated through a flow reactor in similar manner at −50 to −60 °C (bath temperature) and charged into a batch reactor for further reaction and workup (Figure 3). This second-generation semibatch process was also found to be more efficient than the first-generation batch process and led to ~85% isolated yield of product **5**.

The flow chemistry protocols enabled us to successfully generate reagent **2a** at −50 to −60 °C and treat it with ketone **3** instantaneously, resulting in both faster reactions and improved yields.

With this new knowledge, we sought to develop a more robust and efficient second-generation batch process in an effort to increase throughput. We postulated that charging molecular bromine to a batch reactor containing a mixture of **3**, triphenyl phosphite, and triethylamine in dichloromethane at −40 to −50 °C may result in a reactivity and stability profile suitable for reproducibly forming the desired bromide in a safe and efficient manner. Gratifyingly, this subtle modification gave a further improvement in yield and quality, providing **5** in ~90% yield. After further parameter screening, we were able to increase the reaction temperature and therefore significantly improve reaction rate (time) and develop a second-generation batch process, wherein molecular bromine was charged at −20 to −5 °C to a mixture of **3**, triphenyl phosphite, and triethylamine in dichloromethane. This reaction proceeded to completion within 1 h at 20 °C and generated vinyl bromide **5** in 90% yield (Figure 4).[9] This modified second-generation batch process was found to be more efficient than the first-generation batch process in many aspects as evident from Table 1.

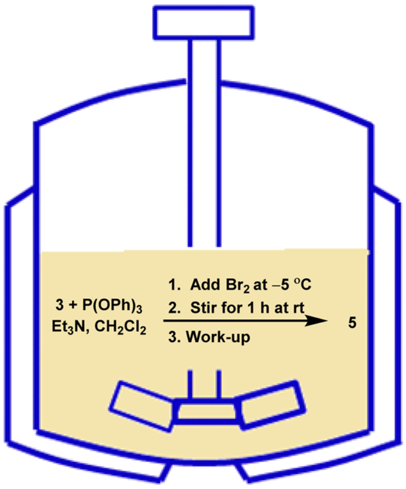


Figure 4. Second-generation batch process.

CONCLUSION

In summary, we have successfully implemented the use of a mild brominating reagent **2a** derived from triphenyl phosphite−bromine for the noncryogenic preparation of an important vinyl bromide intermediate **5** in batch mode. We have demonstrated the use of continuous flow chemistry tools for instantaneous generation of the brominating reagent, thus avoiding its storage and potential decomposition prior to reaction with the substrate. Understanding the instability of the preformed brominating agent was critical to this process, along with the ability to form the active agent in situ. We believe that the modified addition sequence described herein will be generally applicable for the large scale conversion of a variety of ketones to the corresponding vinyl bromides.

EXPERIMENTAL SECTION

First-Generation Batch Process (Figure 1). Molecular bromine (6.2 L, 121.0 mol) was charged to a solution of triphenyl phosphite (37.2 kg, 119.9 mol) in dichloromethane (347 L) in a Hastelloy reactor while maintaining the mass temperature between −65 and −75 °C. The reaction mixture was stirred for 30 min at −65 to −75 °C, and triethylamine (14.2 kg, 139.8 mol) was added while maintaining the mass temperature at −65 to −75 °C. Compound **3** (17 kg, 99.8 mol) was charged to the reactor while maintaining the mass temperature at −65 to −75 °C. The reaction mass was maintained at −65 to −75 °C for 1 h and warmed to ambient temperature over a period of 10 h and stirred for 23 h. The reaction was quenched by charging 0.5 N HCl (85 L). The layers were separated, and the organic layer was washed with water (85 L). The organic layer was passed through a silica gel bed (60−120 mesh size, 51 kg), and the bed was washed with dichloromethane (87 L). The combined filtrate was concentrated under vacuum to provide **5** (59.2 kg, assay by HPLC: 21.7% w/w) as a viscous liquid in 55% yield.[6]

First-Generation Semibatch Process (Figure 2). Reagent solution A: a solution of bromine (25 mL, 485 mmol) in dichloromethane (230 mL). Reagent solution B: a solution of triphenyl phosphite (165 g, 531 mmol) in dichloromethane (250 mL).

Reagent solution A was pumped at a rate of 29 mL/min through one head of a double-headed Ceram pump Q2 V with two Q1CTC pump heads and one V300 Stroke controller (Make: Fluid Metering, Inc.). Reagent solution B was pumped through the other head at 45 mL/min.[8] The reagent solutions A and B were flowed through 100 mL precooled tube reactors maintained at −50 to −60 °C. These precooled solution streams were mixed through a T-joint (static mixer). The mixed stream was passed through a 100 mL coil maintained at −50 to −60 °C. The outlet of the coil was drained to a reactor containing **3** (50 g, 294 mmol), triethylamine (75 mL, 538 mmol) in dichloromethane (500 mL) and maintained at −5 to 0 °C. Upon completion of the transfer, the mass was warmed to ambient temperature and stirred for 2 h. Upon reaction completion, the reaction mixture was quenched with 0.5 N HCl (500 mL), the layers were separated, and the organic layer was washed with water (500 mL). The organic layer was filtered through a silica gel pad (60−120 mesh size, 150 g), and the filtrate was concentrated under vacuum to provide **5** (206 g, assay by HPLC: 28% w/w) as a viscous liquid in 85% yield.[6]

Second-Generation Batch Process (Figure 4). A solution of **3** (500 g 2.94 mol), triethylamine (580 mL, 4.16 mol), and triphenyl phosphite (1100 g, 3.50 mol) in dichloromethane (10 L) was stirred at −20 to −15 °C. To the solution was charged bromine (180 mL, 3.49 mol) in a dropwise manner while maintaining the mass temperature below −5 °C. Upon completion of the addition, the mixture was warmed to ambient temperature and stirred for 1 h. Upon reaction completion, the reaction mixture was quenched with 0.5 N HCl (2.5 L), the layers were separated, and the organic layer was washed with water (2.5 L). The organic layer was filtered through a silica gel pad (60−120 mesh size, 900 g) and the filtrate was concentrated under vacuum to afford **5** (1950 g, assay by HPLC: 32% w/w) as a viscous liquid in 90% yield.[6]

Table 1. Comparison of First- and Second-Generation Batch Processes

parameter	first-gen batch process (Figure 1)	second-gen batch process (Figure 4)	advantages of second-gen batch process
operating temperature	−75 to 30 °C	−20 to 30 °C	cryogenic conditions are not required
number of cryogenic reactors required (operating below −50 °C)	one	none	
reaction time (after addition of reagents)	18−24 h	∼1 h	significant reduction in reaction time
cycle time/batch (500 g scale)	∼3 days	1 day	∼66% reduction in cycle time
yields	55−74%	85−90%	up to 35% yield improvement

Analytical Data of Purified 5. IR (cm^{-1}): 2933, 1727, 1652, 1168, 1030.

^{1}H NMR (400 MHz, DMSO-d_6): δ 6.04 (s, 1 H), 4.08 (q, J = 7.2 Hz, 2 H), 2.58−2.61 (m, 1 H), 2.38−2.51 (m, 2 H), 2.19−2.33 (m, 2 H), 1.96−2.0 (m, 1 H), 1.72−1.81 (m, 1 H), 1.19 (t, J = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ 173.81, 127.17, 120.95, 59.93, 36.81, 33.53, 29.00, 26.31, 13.94.

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Notes

The authors declare no competing financial interest.

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(5) Quenching the reaction mixture at − 60 °C led to only 5% of isolated product. Quenching of the reaction immediately after warming to room temperature led to ca. 40% yield of **5**.

(6) The potency of the product in the crude was determined by HPLC assay (typical range: 28−30%), and the yield of the reaction was corrected for the potency of product **5** as well as starting material **3**. The subsequent base mediated hydrolysis of ester **5** to the corresponding carboxylic acid led to complete cleanup of the product upon acid−base workup and purification of the crude by water slurry.

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(8) These flow rates correspond to a 1:1.1 mol ratio of bromine to triphenylphosphite.

(9) The reaction was extremely rapid at this temperature. We have not investigated the exact nature of the brominating species generated under these conditions as part of this work.

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