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Large-Scale Preparation of Iodobenzene Dichloride and Efficient Monochlorination of 4-Aminoacetophenone

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Abstract:

Large-scale monochlorination of 4-aminoacetophenone using iodobenzene dichloride is described. Special emphasis was given to the characterization of the iodobenzene dichloride and to the development of a practical procedure for handling this agent from the viewpoint of hazards. This process was successfully scaled up in a pilot plant.

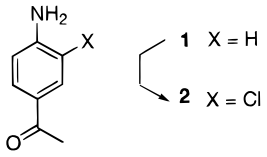
Introduction

The introduction of chlorine into an aromatic ring is a commonly used reaction in organic synthesis and medicinal chemistry. Many methods have been reported for carrying out chlorination in the chemical industry.[1] However, there are few methods amenable to the large-scale production of pharmaceutical intermediates in pilot plants, which usually do not have any special equipment.

Recently, we were interested in preparation of 4-amino-3-chloroacetophenone (**2**, Chart 1), which is a common intermediate to many of the COX-II (cyclooxygenase-2) selective inhibitors prepared in Fujisawa.[2] Whilst several methods are reported for chlorination of reactive aniline,[3] there are few reports presenting practical aromatic chlorination for deactivated anilines that are amenable to a large-scale synthesis in a pharmaceutical pilot plant.[4] Amongst several chlorinating reagents, *N*-chlorosuccinimide (NCS) is especially attractive for a large-scale preparation, since this agent is inexpensive, stable to storage for a long time, and commercially available in bulk quantities. Thus, we first selected and applied NCS to preparation of **2** by modifying the methods reported by Niokson.[4] Whilst effective for a small-scale synthesis, several complications were identified in the direct scale-up of this method. The reactions involved several byproducts that were difficult to remove and were identified as predominately side chain chlorinated products, along with traces of nuclear and side chain polychlorinated derivatives, and consequently resulted in low yield (∼40%).

To develop more efficient and cost-effective chlorination methods, our efforts turned to a search for alternative chlorinating reagents in greater detail. Amongst numerous chlorinating agents, we directed our attention to chlorine gas in that this agent is inexpensive, readily available, and involves no material which is lost as waste to be treated, except for hydrogen chloride gas. We first tried to directly react 4-aminoacetophenone with chlorine gas, but this only gave mixtures of several byproducts, and no desired monochlorinated product could be obtained. In further investigations, it was found that treating chlorine gas with iodobenzene to give iodobenzene dichloride first, followed by reaction with 4-aminoacetophenone was highly effective for selective aromatic monochlorination. Whilst chlorination of anilines by iodobenzene dichloride was reported by Murakami[5] and this agent also has proven to be applicable for several valuable reactions in pharmaceutical chemistry,[6] it has failed to achieve wide use in organic synthesis mainly because of lack of stability. To our knowledge, no application of this agent on a large scale has been described in the literature. Thus, the initial goal of process development involved evaluation of the possibility of safely applying this agent to a large scale by using exploratory chemistry prior to running reactions on the pilot plant scale.

Chart 1. **Monochlorination of 4-aminoacetophenone**



Results and Discussion

Evaluation and Characterization of Iodobenzene Dichloride. Our efforts involved initially complete evaluation and characterization of this agent, followed by designing a chemical process after evaluating several aspects: studies by differential thermal analysis (DTA), differential scanning calorimetry (DSC), accelerating rate calorimetry (ARC), and impact sensitivity test (IST). DTA was used to indicate the decomposition profile under heated conditions. As shown in Figure 1, decomposition of this agent started from about 100 °C, but the rate of heat flow was not considered serious. The potential thermokinetic description could be estimated by measuring heat liberated using DSC. The exotherm monitored was due to the decomposition of agent and was −8.26 kcal/mol (Figure 2). IST indicated that this reagent may decompose under conditions of severe impact. The detailed chemical hazard involved in running the reaction was also evaluated using ARC. As shown in Figure 3, this

(1) McBee, E. T.; Hass, H. B. *Ind. Eng. Chem.* **1941**, *33*, 137.
(2) Tsuji, K.; Nakamura, K.; Konishi, N.; Okumura, H.; Matsuo, M. *Chem. Pharm. Bull.* **1992**, *40*, 2399.
(3) Neale, R. S.; Schepers, R. G.; Walsh, M. R. *J. Org. Chem.* **1964**, *29*, 3390.
(4) Niokson, T. E.; Roche-Dolson, C. A. *Synthesis* **1985**, 669.
(5) Murakami, M.; Inukai, M.; Koda, A.; Nakano, K. *Chem. Pharm. Bull.* **1971**, *19*, 1696.
(6) Barton, D. H. R.; Miller, E. *J. Am. Chem. Soc.* **1950**, *72*, 370.

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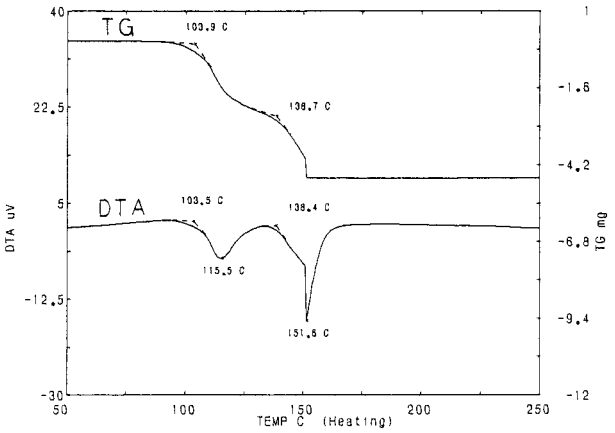

Figure 1. **DTA result.**

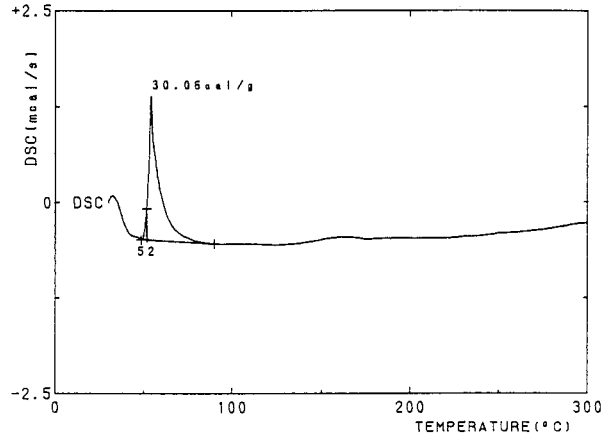

Figure 2. **DSC result.**

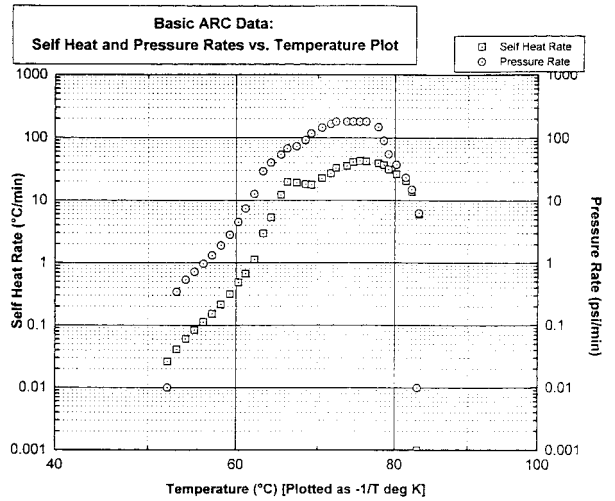

Figure 3. **ARC result.**

agent was unaffected until the temperature reached 50 °C, and the development of decomposition was slow above this temperature. The pressure data also showed the same profile (Figure 3). Other concerns were that this agent is rather unstable to light[7] and that complete removal of solvents from the product by evaporation might decrease the quality.[8] Despite these drawbacks, we finally reached the conclusion that it was possible to deal with this reagent on a pilot scale according to further investigations: (1) decomposition energy was small and partial decomposition did not lead to total reagent decomposition; (2) the impact unstability problem was overcome by using a Büchner funnel in the filtration procedure; (3) this agent cleanly precipitated from methylene chloride and could be air-dried in a light-excluded environment at room temperature; (4) chlorination reaction proceeded smoothly under cooled conditions whereby this agent could be handled without major concerns for thermal decomposition.

Practical Preparation of Iodobenzene Dichloride. Although described methods in the literature are practical and effective,[8] there still existed serious shortcomings regarding a scale-up procedure. For example, in pilot-plant work, safety concerns should be addressed regarding treatment with chlorine gas from the view of personal hazard. Therefore, the process development campaign first began with defining a practical procedure for reaction conditions for chlorine gas with iodobenzene. In our earliest studies, chlorine gas was directly bubbled into a mixture of iodobenzene and methylene chloride in order to prevent excess gas from leaking from the vessel. However, the tube at the outlet was soon clogged with products. Another potential scale-up problem was the method for determining reaction completion. Excess use might cause leakage of chlorine gas into a pilot plant; however, not enough chlorine gas sharply dropped the yield. Whilst the absorbed gas amount, roughly estimated by measuring the weight of the steel bomb, was effective as an indicator, a more exact end point of the reaction was required. HPLC analysis of the remaining amount of iodobenzene was most definite, but this required opening of the reactor in a chlorine gas atmosphere. However, further investigations indicated that the reaction speed was high enough not to require directly bubbling chlorine gas into the reaction mixture; hence, a closed system was also considered to be applicable. In effect, an internal pressure increase in the reactor was used to reveal the reaction end point. Since pilot plants usually do not include reactors suitable for working under pressure conditions, we designed the practical apparatus depicted in Figure 4 and determined the end point in the following three ways: (1) the change of the ethylene glycol surface level (indicating internal small pressure change), (2) the weight of the steel bomb, and (3) HPLC analysis. After completion was determined, the excess chlorine gas was substituted by nitrogen gas, and the precipitate was filtered using a Büchner funnel. The cake was washed with fresh methylene chloride to remove contained chlorine gas and mother liquor, followed by ventilation with fresh air in a dark space. The scale of this reaction was designed after considering three viewpoints: absorption speed of chlorine gas, heat balance between reaction exotherm, and cooling ability of the reaction vessel and productivity. Actually, this procedure was successfully conducted three times on a 20 kg scale.

Practical Application of Iodobenzene Dichloride to Chlorination of 4-Aminoacetophenone. On lab scale, 4-aminoacetophenone uneventfully reacted with iodobenzene

(7) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; Wiley: New York, 1969; Vol. 1, p 505.
(8) Lucas, H. J.; Kennedy, E. R. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, p 482.

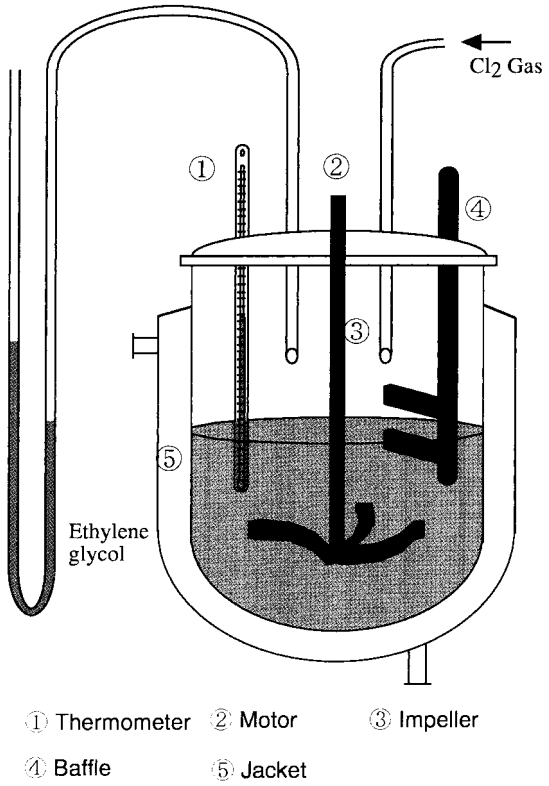

Figure 4. **Construction of reactor.**

dichloride in the presence of pyridine, involving a small exotherm to afford **2** with small amounts of byproducts. This procedure was developed into a scaled up process. Our first concern for safety in applying this agent in a pilot plant involved addressing the reaction exotherm. On a lab scale (<10 g of 4-aminoacetophenone), the heat of reaction under ice-cooled conditions almost completely dissipated to the surroundings, so that no typical exotherm was seen. However, as is well-known,[9] the heat losses from a full-scale reactor are much less compared with those from laboratory glassware. Especially, in the case of a rapid reaction using rather unstable agents, underestimation of the heat evolved can cause a reaction to run out of control. Therefore, accurate information about heat evolved was essential prior to running the pilot plant, and this should be estimated under adiabatic conditions. In a run carried out in an adiabatic reactor starting with 11.5 g of 4-aminoacetophenone, the temperature exothermed from ~3 to ~53 °C over only 3 min (Figure 5). This result indicated that the reaction might run away if the all starting materials were put into the reaction vessel at the same time, but also that reaction heat control could be achieved by addition speed. Our strategy for an operational procedure involved the addition of small amounts of iodobenzene dichloride (~1 kg) under cooled conditions (0 °C) and following the exthotherm of the reaction, followed by cooling to 0 °C again. This procedure was totally repeated 24 times with about a 10 min interval between additions. After completion of addition, the precipitated pyridine hydrogen chloride was filtered and washed with fresh THF. Next, we endeavored to remove unwanted byproducts. The filtrate contained small amounts of several

(9) Etchells, J. C. *Org. Process Res. Dev.* **1997**, *1*, 435.

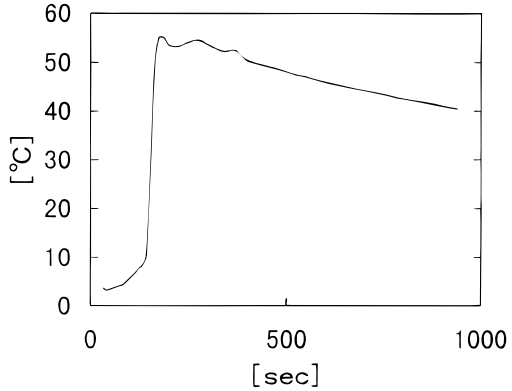

Figure 5. **Reaction of 4-aminoacetophenone with iodobenzene dichloride under adiabatic conditions.**

byproducts, which caused purification problems downstream. Removal of these impurities by recrystallization was not effective enough and resulted in necessity for chromatography purification. Therefore, we turned our effort to other, more practical purification methods in more detail and found that the hydrogen chloride salt of **2** selectively precipitated from organic solvents. In early studies, the filtration was very slow and practically impossible to apply on large scale; however, further investigation revealed that the salt produced from dioxane improved the filtration speed. Applying these findings, this process was successfully scaled up to pilot plant.

Conclusions

In this paper, we have described a practical and scaled up monochlorination of 4-aminoacetophenone using iodobenzene dichloride. This selective chlorinating agent was characterized from the viewpoint of safety issues. The results from DTA and DSC indicated the decomposition profile of this agent and called for further investigations. The defining safety data came from ARC studies and the fact that it was possible to drive the chlorination reaction under cooled conditions. These detailed safety evaluation approaches to hazards are useful when evaluating an unstable reagent for a process. The final process was successfully scaled up to afford 24.8 kg of **2** in 87% yield of 94% purity.

Experimental Section

General Procedures. 4-Aminoacetophenone of pure grade was commercially available from EMS-DOTTIKON AG. Melting points were measured on a Thomas-Hoover apparatus and are uncorrected. IR spectra were recorded on a HORIBA FT-210 spectrometer. NMR spectra were measured on a Bruker AC200P (1H, 200 MHz). Chemical shifts are given in parts per million, and tetramethylsilane was used as the internal standard. Mass spectra were measured on a Hitachi Model M-80 mass spectrometer using EI for ionization. Elemental analyses were carried out on a Perkin-Elmer 2400 CHN elemental analyzer. HPLC analyses were performed using a YMC GEL ODS 120 Å S-7 column and an acetonitrile/water phase. The water component was adjusted with KH_2PO_4 and Na_2HPO_4 to pH = 7.8. Purity of each obtained product was determined by comparison with

purified authentic samples using quantitative HPLC. Reagents and solvents were used as obtained from commercial suppliers without further purification. The DTA experiment was carried out using a Seiko Model SSC/5200H. The DSC experiment was performed on a Rigaku Model DSC-10A. The ARC experiment was conducted on a CSI 851-001 using a bomb with a 1/4 in. neck. The start temperature of the run was 27 °C, with heat step of 3 °C, a search time of 10 min, and a slope sensitivity of 0.02 °C/min. The ϕ-factor was 3.1.

Practical Preparation of Iodobenzene Dichloride. Chlorine gas (9.0 kg, 127 mol) was introduced to iodobenzene (20.0 kg, 98 mol) in methylene chloride (30 L) with stirring at −3 to +4 °C as shown in Figure 4. When the reaction was judged to be complete by HPLC, the excess chlorine gas was exchanged with nitrogen gas and the precipitate was filtered off, washed with fresh methylene chloride (6 L), and dried at room temperature to afford iodobenzene dichloride (25.3 kg, 94% yield) as a yellowish solid; mp 113−117 °C (dec.) (lit.[7] 115−120 °C (dec.)).

Large-Scale Preparation of 4-Amino-3-chloroacetophenone Hydrogen Chloride Salt. Iodobenzene dichloride (1.5 kg, 5.46 mol) was added to a solution of 4-aminoacetophenone (19.5 kg, 144 mol) in a mixture of THF (195 L) and pyridine (11.4 kg, 144 mol) at 0 °C and the internal temperature smoothly reached about 3 °C. After recooling to under 0 °C, further iodobenzene dichloride (1.5 kg, 5.46 mol) was added. Addition of iodobenzene dichloride (about 1.5 kg) was totally repeated 24 times at ∼10 min intervals. In this way, 36.8 kg (144 mol) of iodobenzene dichloride was totally consumed. After the addition was complete, the resulting mixture was further stirred at the same temperature for 1 h. The precipitate was filtered off, and the cake was washed with fresh THF (19.5 L). The filtrate was washed with brine (160 L), sodium bisulfite (15 kg, 144 mol) in water (130 L), brine (130 L), and then concentrated under reduced pressure to ∼58.5 L. After the addition of dioxane (117 L), hydrogen chloride in dioxane (4 mol/L, 78 L) was added dropwise to this solution at 15−20 °C and stirring was continued at 0 °C over 2 h. The precipitate was filtered off and washed with dioxane (19.5 L). Drying under reduced pressure afforded 4-amino-3-chloroacetophenone (**2**) as its hydrogen chloride salt (24.8 kg, 87% yield) of 94% purity as a yellowish solid: mp 165−166 °C (dec.); 1H NMR (200 MHz, DMSO-d_6) 2.43 (s, 3H), 6.87 (d, 1H, J = 4.2 Hz), 7.66 (dd, 1H, J = 8.5, 2.0 Hz), 7.79 (d, 1H, J = 2.0 Hz), 8.69 (br s, 3H); IR (KBr) 3064, 2296, 2008, 1692, 1601, 1574, 1555, 1521 cm^{-1}; MS (EI) *m/z* 170, 136, 111, 75. Anal. Calcd for $C_8H_9N_2OCl_2$: C, 46.63; H, 4.40; N, 6.80. Found: C, 46.67; H, 4.38; N, 6.63.

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