Organic Process Research & Development

ARTICLE

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Pilot Plant Preparation of *tert*-Butyl-4-(2-hydroxyethyl)-4-(pyrrolidin-1-yl)-piperidine-1-carboxylate, An Intermediate of Novel Antiarteriosclerotics, Via a Safe, Scalable Reformatsky-Type Reaction

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Supporting Information

ABSTRACT: Reported here is a safe, scalable process via a Reformatsky-type reaction of iminium salt (**4**) followed by Red-Al reduction giving *tert*-butyl-4-(2-hydroxyethyl)-4-(pyrrolidin-1-yl)-piperidine-1-carboxylate (**6**), an intermediate of novel antiarteriosclerotics (**1**). The key points of this safe process are the use of trifluoroacetic acid (TFA) for the iminium salt formation, vigorous stirring for the Reformatsky reaction, and slow addition of methyl bromoacetate. Pilot manufacturing on the 500 L scale was achieved.

INTRODUCTION

β-Hydroxyalkanoates can be obtained by nucleophilic reaction with α-haloester and ketone, which is well-known as the Reformatsky reaction.[1] However, this reaction is difficult to apply to scale-up production because of inherent safety concerns. Particularly serious problems are the large reaction heat and the unpredictable induction period of the reaction, which make it difficult to safely control the reaction.[2] The synthesis of *tert*-butyl-4-(2-hydroxyethyl)-4-(pyrrolidin-1-yl)-piperidine-1-carboxylate (**6**), which is an intermediate of novel antiarteriosclerotics (**1**)[3] discovered by IMMD Inc. and Shionogi & Co., Ltd., also posed some problems for scale-up production. To obtain alcohol (**6**), the Reformatsky-type reaction with unstable iminium salt (**4**) and methyl bromoacetate had to be carried out (Scheme 1). Although scale-up investigations of the Reformatsky reaction have been reported,[2e−g,4] this reaction using iminium salt[5] seems to be more difficult than the conventional Reformatsky reaction using ketones or aldehydes because of the unstable character of iminium salt. Therefore, attention must be paid to the stability of the iminium salt (**4**), and a robust process needs to be established to obtain alcohol (**6**). Our first trial pilot production was unsuccessful, but improvement of the procedure led to successful scale-up production of alcohol (**6**) in a pilot plant. Here we report the development of the process including investigation of the failed trial and practical application for scale-up production of methyl ester (**5**) via iminium salt (**4**) by the Reformatsky-type reaction.

RESULTS AND DISCUSSION

Original Procedure Employed by the Medicinal Chemistry Group. The synthesis of alcohol (**6**) consists of four sequential reactions: (1) enamine formation, (2) iminium salt formation, (3) Reformatsky reaction, and (4) Red-Al reduction. Three issues were identified for scale-up production. First, when 35% hydrochloric acid solution was used for zinc activation in a flask experiment, agglomeration of the zinc powder occurred, and hydrogen gas was uncontrollably generated. This would have been difficult to apply to scale-up production in a pilot plant. Second, the reaction heat of the Reformatsky reaction is large and uncontrollable, and there is a potential risk of a runway reaction.[2] Third, heptane was used for the isolation of alcohol (**6**), and the reproducibility of the crystallization step was poor. As the low electric conductivity of heptane might cause an explosion due to a static electric spark, heptane should not be used for the isolation, if possible.[6] After considering these problems, we started the scale-up investigation.

Process Development for the First Trial. *Iminium Salt Formation.* As strong acids can decompose Boc protection, acetic acid was selected as well as the original procedure.

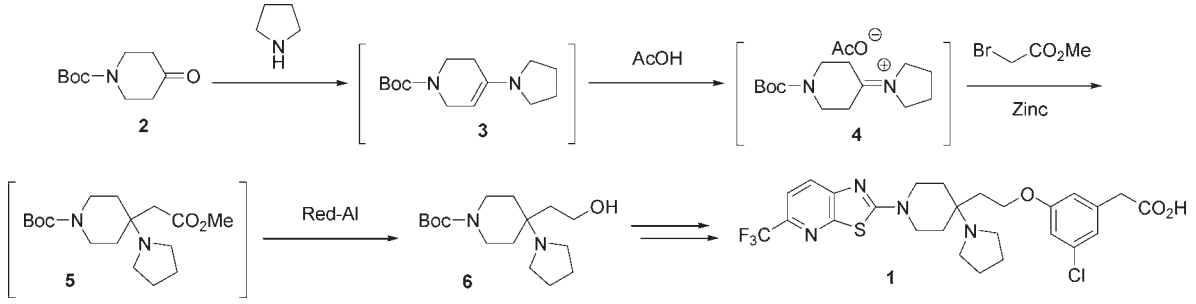
Reformatsky Reaction. First, we screened some activators[7] for zinc powder, for example, I_2, TMS−Cl, 1,2-dibromoethane, and CuCl, to avoid using a 35% hydrochloric acid solution. We found that TMS−Cl could successfully activate zinc powder and selected it as an activator. The next issue was the control of the reaction heat. We tried to add preformed Reformatsky reagent to iminium salt (**4**), but the reagent was unstable and the chemical conversion not good (∼40%). If methyl bromoacetate was added slowly to a mixture of activated zinc and iminium salt (**4**), the Reformatsky reagent could react with iminium salt (**4**) immediately after being formed, and the reaction heat could be controlled easily. On the basis of this approach, we attempted optimization of the reaction conditions and measured the reaction heat by RC1e, with the results shown in Figure 1. The procedure was as follows. TMS−Cl (2.2 mol %) was added to a slurry of zinc (1.5 equiv) in THF (8.5 vol.) at 5 °C, and the mixture was aged for 10 min at the same temperature. Iminium

Special Issue: Safety of Chemical Processes 11

Received: June 28, 2011
Published: August 01, 2011

dx.doi.org/10.1021/op2001723 | *Org. Process Res. Dev.* 2011, 15, 1433–1437

Scheme 1



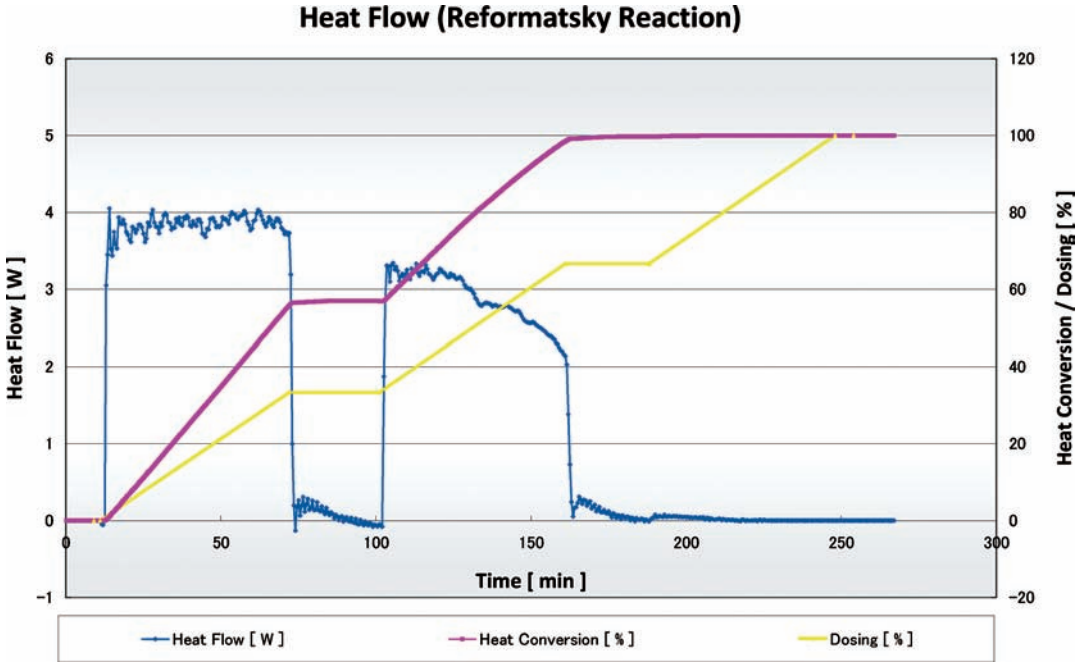


Figure 1

salt solution, prepared by mixing enamine solution and acetic acid (1.1 equiv), was added to the slurry of activated zinc in THF, and then this mixture was cooled to 5 °C. Finally, methyl bromoacetate (1.8 equiv) was added dropwise to the mixture. It should be noted that the pause of methyl bromoacetate addition for a few minutes to remove the sample sometimes impeded the reaction. To confirm the effect of discontinuation of reagent addition, methyl bromoacetate was added in three portions; 0.6 equiv of methyl bromoacetate was added dropwise for 1 h; and the mixture was aged for 30 min. This procedure was repeated two more times.

The reaction heat only occurred during addition of the first two portions of methyl bromoacetate. After completion of the first methyl bromoacetate (0.6 equiv) addition, the reaction heat generation ceased immediately. This indicates that the reaction heat of the formation and the reaction of the Reformatsky reagent were well-controlled by the slow addition of the bromide reagent. During addition of the second portion (0.6−1.2 equiv), the reaction heat was also as well-controlled as for the first portion. However, during addition of the third portion (1.2−1.8 equiv), no reaction heat was observed. This indicates that continuing the addition of methyl bromoacetate is important. The total reaction calorie level was 298 kJ/mol (Reformatsky reagent formation and Reformatsky reaction), and the adiabatic temperature rise (ΔT_{ad}) was 75.9 °C.

Red-Al Reduction. The reaction mixture was used for the next Red-Al reduction without extraction or purification. As excess methyl bromoacetate (1.8 equiv), which also has an ester moiety, was used at the Reformatsky step, and 4.3 equiv of Red-Al reagent needs to be used to complete the reaction. Although Red-Al reduction is also a highly exothermic reaction, the reaction heat was well-controlled by the slow addition of Red-Al. Completion of the reduction was confirmed by HPLC, and acetone was added to quench the excess Red-Al reagent.

*Quenching and Isolation of Alcohol (**6**).* Under basic conditions, zinc and aluminum metals were not dissolved completely, and phase separation was difficult. Several acidic conditions were investigated, and citric acid solution was chosen because the condition after quenching was good enough for extraction and the alcohol (**6**) stable under this condition. After several extractions to remove metals, the combined organic solution was concentrated, and the solvent was replaced by MeOH, which

dx.doi.org/10.1021/op2001723 |*Org. Process Res. Dev.* 2011, 15, 1433–1437

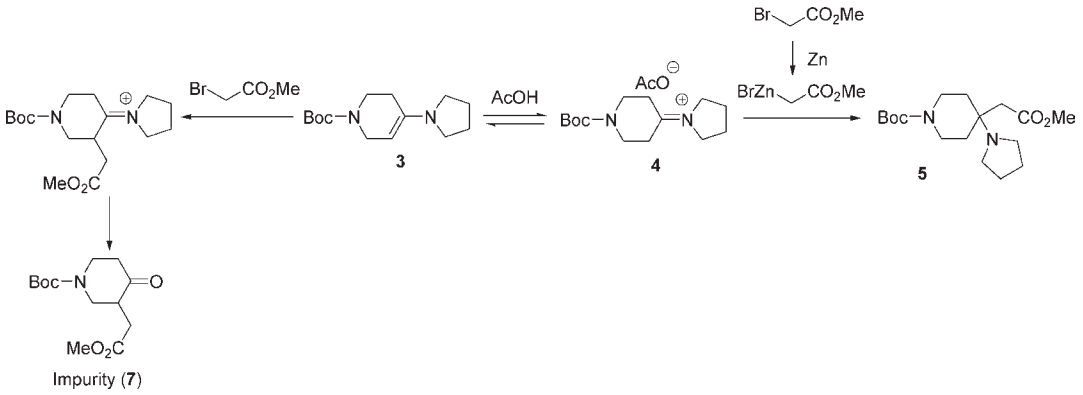


Figure 2

shows a much lower risk of explosion due to static electricity than heptane. The solution was cooled to 20 °C, and water was added. After confirmation of crystal precipitation, the slurry was cooled to 5 °C, water added, and the mixture stirred for a few hours. The crystals were collected, washed with a mixture of water and MeOH, and dried. This procedure provided the alcohol (**6**) in 40−50% yield on a lab scale. However, the reproducibility of the crystallization step was still poor. Unknown organic impurities in the crude solution before crystallization seemed to have caused the poor reproducibility. Therefore, after removal of metals by the first extraction, aqueous citric acid solution and ethyl acetate were added to the mixture. As alcohol (**6**) has a basic functional group at pyrrolidine, it could be extracted in the aqueous layer under the acidic condition, with the other impurities remaining in the organic layer. These operations greatly improved the purity of the extract, and alcohol (**6**) could be reproducibly crystallized from MeOH and water. This optimized sequential process was applied to the first scale-up trial.

Result of the First 500 L Scale Pilot Trial. In the first 500 L scale pilot trial, the first step of enamine formation was successful. In-process tests for the disappearance of the starting material (**2**) by NMR and water content by the Karl Fischer test gave the same results as the flask experiment. Zinc was activated by a catalytic amount of TMS−Cl, and the enamine solution was added. The reaction mixture was cooled to 5 °C, and methyl bromoacetate was added dropwise. Although the reaction heat was observed at the beginning of the reagent addition, the reaction temperature gradually decreased, indicating impedance of the reaction. When 0.6 equiv of methyl bromoacetate was added, an aliquot was sampled, and HPLC analysis showed that unexpected impurities were generated in large amounts (HPLC (PA%) result; starting material/impurity/methyl ester (**5**) = 56.6:31.7:11.7). Due to this unexpected trouble, addition of the remaining methyl bromoacetate was stopped. A small amount of the reaction mixture was obtained for the flask experiments to investigate the cause of the trouble and to recover the product.

Investigation of the Cause of Failure in the Pilot Scale Trial. First, we tried to identify the structure of the impurity. It was isolated by reversed-phase UV trigger, and the structure identified it as compound (**7**) which was formed via "Stork Enamine Alkylation."[8] The plausible reaction mechanism is shown in Figure 2.

This could occur only when both enamine (**3**) and methyl bromoacetate were present together. Thus, the iminium salt (**4**) was not completely formed, and methyl bromoacetate remained intact. Iminium salt formation was examined with enamine (**3**) in the presence of acetic acid in THF-d_6 at 0 °C. The result showed that only 50% was iminium salt (**4**), and the remaining 50% was enamine (**3**). This indicates that a much stronger acid is necessary for complete iminium salt formation. Another dubious point is the incomplete formation of the Reformatsky reagent in the 500 L scale trial. The sample from the 500 L reactor was a clear solution and was different from that in the flask experiment. From this observation, "zinc aggregation" was suspected, and this might have caused the failure of this 500 L scale trial. Examination of conditions causing zinc aggregation has revealed the role of acetic acid, which would disqualify zinc from the Reformatsky reagent formation. From previous NMR analyses of our system, 0.75−0.85 equiv of acetic acid works as a free acid and might cause zinc aggregation. Second, TMS−Cl is easily hydrolyzed and forms HCl and TMS−OH with small amounts of water, and this also might cause the aggregation. We concluded that the choices of the appropriate acid for iminium salt formation and the catalyst for zinc activation would be the key points to avoid byproduct formation and zinc aggregation. Another disputable point is the agitation. In the first trial, suspending the agitation for a few minutes to conduct the in-process test might be one of the reasons for this failure,[9] and we decided to keep the agitation vigorously during the reaction at the next trial. For improvement of these points, we next conducted process optimization.

Process Optimization for the Second 500 L Scale Pilot Trial. First, the reagent to activate zinc was changed to 1,2-dibromoethane from TMS−Cl. The disappearance of 1,2-dibromoethane was confirmed by GC to confirm the successful zinc activation. The new zinc activation method constantly works well. The next important point was to identify the acid suitable for iminium salt formation. As a weak acid like acetic acid cannot lead to the complete formation of iminium salt, we selected TFA as a strong organic acid. NMR analysis was conducted to confirm the ratio of iminium salt in the presence of different amounts of TFA. The result, summarized in Figure 3, indicates that the ratio of iminium salt formation depends on the amount of TFA.

The iminium salt formed with TFA proved to be stable at 25 °C for 3 h. TFA fulfills two roles. First, complete iminium salt formation prevents the generation of "Stork enamine alkylation compound (**7**)". Second, zinc aggregation is inhibited because of the absence of free acid. The iminium salt formation was also confirmed by React IR (Figure 4).

Increase of the absorption of iminium (1700 cm^{-1}) and decrease of that of enamine (1650 cm^{-1}) were observed when

dx.doi.org/10.1021/op2001723 |*Org. Process Res. Dev.* 2011, 15, 1433–1437

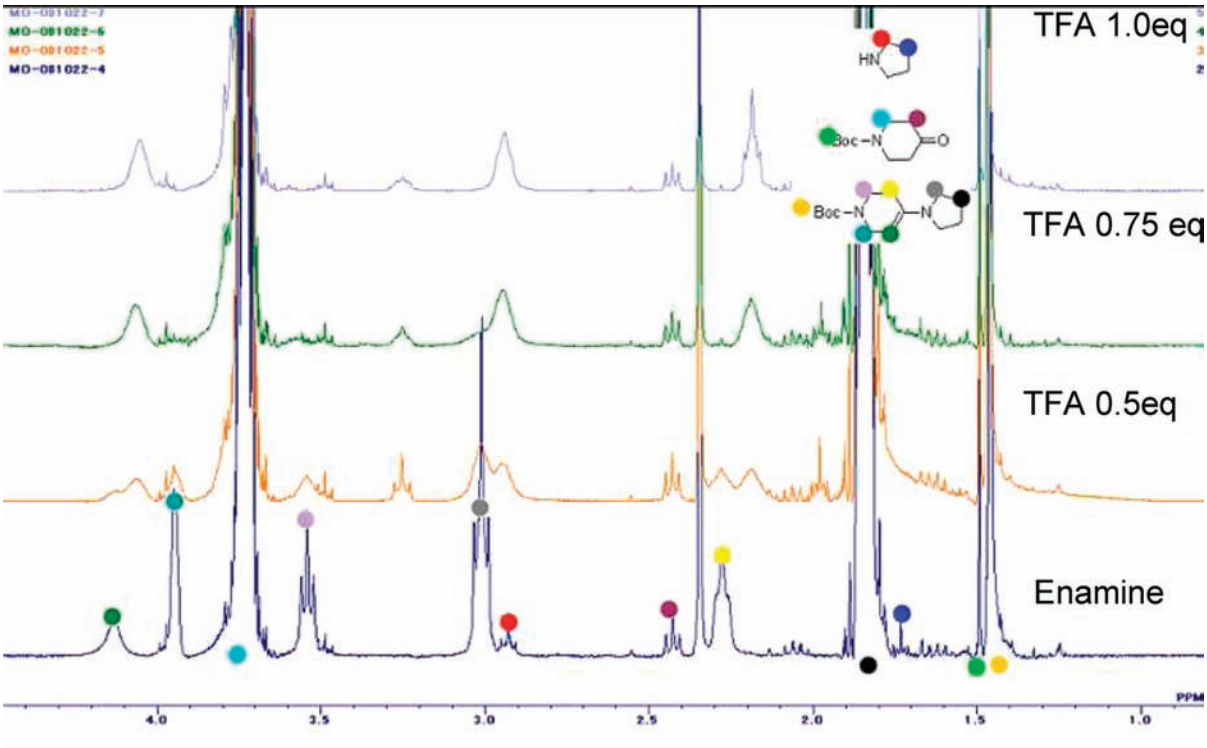


Figure 3

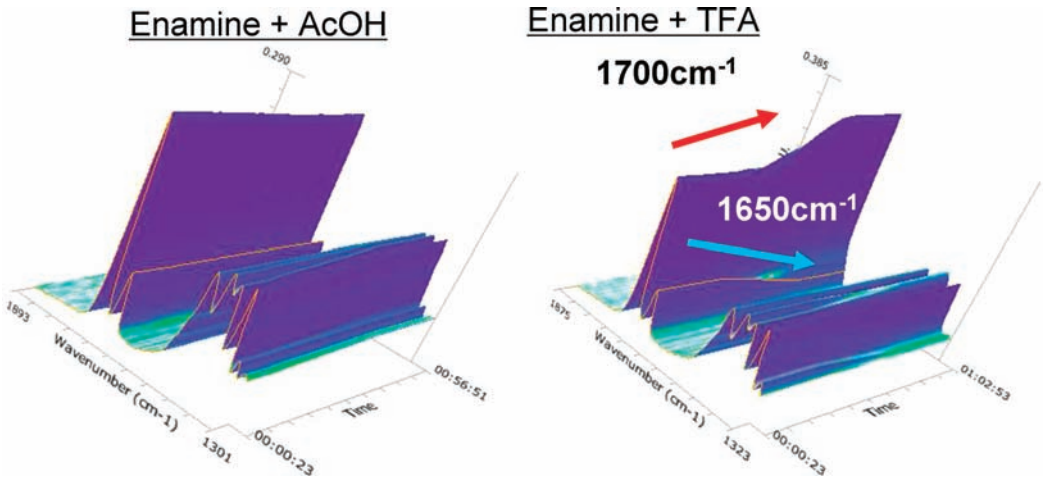


Figure 4

TFA was added. By contrast, no significant change was observed when acetic acid was added.

Result of the Second 500 L Scale Pilot Trial. The new procedure was applied to pilot manufacturing. The reactor was charged with 15 kg of *N*-Boc-piperidone (**2**), and enamine formation was successfully achieved as in the first trial. Zinc activation was conducted with a catalytic amount of 1,2-dibromoethane under THF reflux for 3 h. After activation, the absence of 1,2-dibromoethane was confirmed by GC. TFA was added to enamine solution below 5 °C to form iminium salt (**4**). This iminium salt solution was added to the activated zinc in THF solution below 5 °C, and methyl bromoacetate was added dropwise for 2 h while keeping the agitation vigorous. The constant generation of reaction heat was observed during the addition of methyl bromoacetate unlike in the first trial. After addition of the reagent, the absence of the starting material was confirmed by HPLC, which also indicated the absence of target impurities in this trial. Next, 4.3 equiv of Red-Al was added to the crude solution kept at below 5 °C for 3 h. Excess Red-Al was destroyed by acetone. This reaction mixture was poured into the 28.5 w/w % citric acid solution at 0 °C. The organic phase was separated and washed with water repeatedly to remove zinc and aluminum residues. After several extractions to remove organic impurities, the combined organic solution was concentrated and replaced with MeOH solution. This solution was cooled to 5 °C, and water was added for crystallization. The crystals were obtained by filtration and dried under reduced pressure at 60 °C. By this procedure, 9.25 kg of alcohol (**6**)

dx.doi.org/10.1021/op2001723 |*Org. Process Res. Dev.* 2011, 15, 1433–1437

was obtained. The yield (42.3%) of the product was comparable to those of laboratory runs (yield: 40−50%).

CONCLUSION

A safe, scalable process including Reformatsky reaction was applied to pilot manufacturing of *tert*-butyl-4-(2-hydroxyethyl)-4-(pyrrolidin-1-yl)-piperidine-1-carboxylate (**6**), which is an intermediate of novel antiarteriosclerotics (**1**). Iminium salt formation was successfully achieved by TFA, and the reaction heat could be successfully controlled by slow addition of methyl bromoacetate. This led to successful scale-up manufacturing to a scale of 15 kg.

EXPERIMENTAL SECTION

NMR spectra were measured on a Varian MERCURY-300VX. High-performance liquid chromatographic (HPLC) analysis was carried out using a Shimadzu LC-10ADVP.

Procedure for Manufacturing Alcohol (6) in a Pilot Plant. *Enamine Formation and Iminium Salt Formation.* *N*-Boc-piperidone (**2**) (15.0 kg, 75.3 mol) was dissolved in THF (85 L) at 25 °C, and pyrrolidine (10.7 kg, 150.6 mol) was added to the THF solution. This reaction mixture was heated azeotropically over 3 h. After the confirmation of the absence of starting material by NMR and the absence of the water by a Karl Fischer test, this enamine solution was cooled to 5 °C, and TFA (10.3 kg, 90.4 mol) was added dropwise over 1 h at below 5 °C. This iminium salt solution was used for Reformatsky reaction without purification.

Zinc Activation, Reformatsky Reaction, and Red-Al reduction. 1,2-Dibromoethane (2.8 kg, 15.1 mol) was added to a slurry of zinc (7.4 kg, 112.9 mol) in THF (100 L), and this mixture was refluxed for 3 h. The absence of 1,2-dibromoethane was confirmed by GC, and this slurry was cooled to 5 °C. Iminium salt solution was added to activated zinc slurry at below 10 °C, and methyl bromoacetate (20.7 kg, 135.5 mol) was added dropwise over 2 h at below 5 °C. The mixture was aged for 1 h at the same temperature. After the completion of the reaction had been confirmed by HPLC, Red-Al (65.4 kg, 323.7 mol) in toluene (112 L) was added dropwise over 3 h. After the completion of the reaction had been confirmed by HPLC, acetone (15.7 kg, 271.0 mol) was added to the reaction mixture at the same temperature.

*Quenching and Isolation of Alcohol (**6**).* The reaction mixture was poured into a solution of citric acid hydrate (84.0 kg, 399.7 mol) in water (210 L) dropwise over 2 h at below 5 °C. The pH of the aqueous layer was adjusted to 10 with aqueous 48% NaOH, and then the mixture was warmed to 20 °C. The organic layer was separated and washed subsequently with aqueous 1% NaOH (150 kg) and water (150 kg). The organic layer was extracted by aqueous 19% citric acid solution (2 × 33 kg), and a combined aqueous layer was diluted by ethyl acetate (65 L). The pH of the aqueous layer was adjusted to 10 with aqueous 10% NaOH, and then the separated organic layer was washed by aqueous 5% NaCl and evaporated to around 40 L. MeOH (45 L) was added to the residue, and this mixture was evaporated to around 40 L. This procedure was repeated to remove ethyl acetate. After less than 1 wt % of ethyl acetate was confirmed by GC, MeOH (30 L) and water (30 L) were added to the solution at 20 °C, and the alcohol (**6**) was observed to precipitate. This slurry was cooled to 5 °C and aged for 3 h. The mixture of water (36 L) and MeOH (9 L) was added dropwise over 3 h to the slurry at 5 °C and aged for 30 min. Water (45 L) was added dropwise over 1 h and aged for 30 min. The crystals were filtrated, washed by the mixture of water (81 L) and MeOH (9 L), and dried using a double-cone dryer under reduced pressure at 60 °C. By this procedure, 9.25 kg of alcohol (**6**) was obtained (isolated 42.3%). Mp 125 °C; ^{1}H MNR (300 MHz, $CDCl_3$) δ 6.29 (s, 1H), 4.05−3.90 (m, 2H), 3.83 (t, J = 6.0 Hz, 2H), 2.95−2.80 (m,2H), 2.75−2.65 (m, 4H), 1.88 (t, J = 6.0 Hz, 2H), 1.80−1.60 (m, 8H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.68, 79.52, 59.86, 56.80, 44.36, 30,58, 29.74, 28.50, 23.42.

ASSOCIATED CONTENT

Supporting Information. Copies of ^{1}H and ^{13}C NMR of compound (**6**) and copies of HPLC results. This material is available free of charge via the Internet at http://pubs.acs.org.

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ACKNOWLEDGMENT

We thank Natsuko Suzuki, Yutaka Yokota, and Dr. Yoshinori Murata in Shionogi CMC development laboratories for helpful discussion on process development studies.

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(9) Rapid agitation has a high probability of success on Reformatsky reaction; however, slow agitation sometimes gave a poor result in the lab runs. Rapid agitation seems to minimize the risk of the activated zinc surface becoming coated with salts/oxide etc. and thus stopping the reaction.

NOTE ADDED AFTER ASAP PUBLICATION

This paper was published on the Web on August 15, 2011. Additional corrections were made in the Abstract, Results and Discussion, and Experimental sections. The corrected version was reposted on August 31, 2011.