Organic Process Research & Development **2005**, *9,* 216–218

Scale-Up of a Reformatsky Reaction to an Indenyl Butanoate[†]

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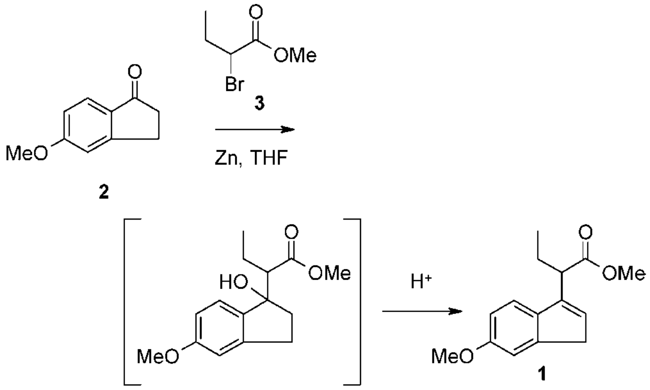
Abstract:

A safe process for the Reformatsky reaction of 5-methoxy-1-indanone and methyl 2-bromo butyrate giving an indenyl butanoate was developed. It was scaled-up from the lab to the pilot plant. The results from two campaigns on pilot-plant scale are presented.

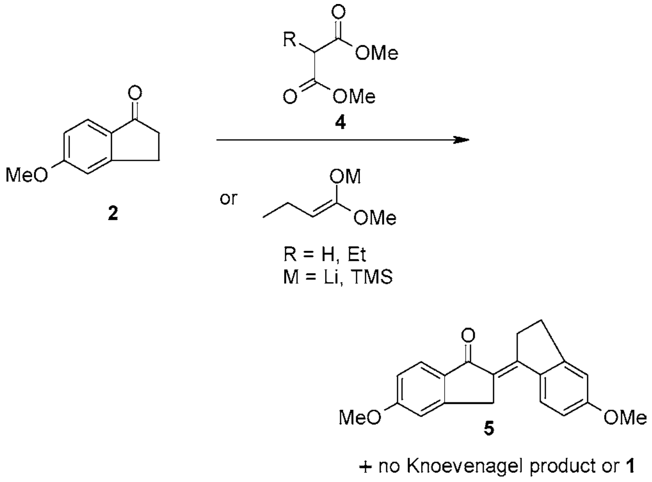
Introduction

The original synthesis of methyl 2-(6-methoxy-1H-inden-3-yl)butanoate (**1**) was carried out in a drug discovery project (Scheme 1) by Zhang, Lei, and Ma[1] using the Zn-mediated condensation of indanone **2** and bromoester **3**. This type of reaction is named after its inventor Reformatsky.[2] The reaction sequence consists of three individual steps: (1) formation of the Reformatsky reagent from Zn metal and a bromoester, (2) addition of this Reformatsky reagent to a carbonyl compound, and (3) the acidic quench. The formation of the Reformatsky reagent is known to be a synthetic challenge in those reactions.[3a] The Zn metal must be activated to react smoothly with the bromoester. The literature describes several methods[3] to accomplish this problematic step. Despite the fact that the Reformatsky reaction has been developed as early as 1887 and is well-known even to undergraduate students. this reaction is not used very often on pilot-plant[4] or production scale. The most serious drawback for scalability is the highly exothermic reaction after an unpredictable time of induction. This poses the risk of a runaway reaction.

Scheme 1. **Reformatsky reaction to an indenyl butanoate**



Scheme 2. **Failed reaction of indanone 2 to butanoate 1**



We needed access to large amounts of **1** as a synthetic intermediate for a development project. Our first choices to circumvent this problematic step were Zn-free approaches. Knoevenagel reactions[5] with malonates such as **4** or enolate-type condensations failed to produce **1** (Scheme 2). If the indanone **2** was exposed to basic or Lewis acidic conditions, we could only obtain the product **5** arising from self-condensation of **2**.

Only the Zn-mediated approach proved to give access to **1**. The production of **1** was time-critical at that stage of development. Therefore, we were faced with the task of developing a pilot-plant synthesis of **1** based on the Reformatsky reaction.

In the approach by Zhang et al.,[1] an aliquot of already reacted material was kept in the flask before feeding the flask with a new batch of starting materials. While this "seed process" worked very well on smaller scale, we decided to quench every batch at the end of the reaction. We did not want to charge a vessel containing unquenched material for safety reasons. Our only option for a rapid scale-up with a safe process was the development of a reproducible method for activating the Zn metal to reliably initiate the reaction.

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[†] This paper is dedicated to Professor Reinhard Brückner on the occasion of his 50th birthday.

(1) Zhang, M.; Zhu, L.; Ma, X *Tetrahedron: Asymm.* **2003**, *14,* 3447−3453.

(2) (a) Reformatsky, S. *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 1210−1211. (b) for a recent review: Ocampo, R.; Dolbier, W. R., Jr. *Tetrahedron* **2004**, *60*, 9325−9374.

(3) (a) Erdik, E. *Tetrahedron* **1987**, *43*, 2203−2212. (b) Newman, M. S. *J. Am. Chem. Soc.* **1942**, *64*, 2131−2133. (c) Gawronsky, J. K. *Tetrahedron Lett.* **1984**, *25*, 2605−2608. (d) Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1984**, *25*, 1475−1478.

(4) Reformatsky reaction on pilot-plant scale has been used in: (a) Clark, J. D.; Weisenburger, G. A.; Anderson, D. K.; Colson, P.-J.; Edney, A. D.; Gallagher, D. J.; Kleine, H. P.; Knable, C. M.; Lantz, M. K.; Moore, M. V.; Murphy, J. B.; Rogers, T. E.; Ruminski, P. G.; Shah, A. S.; Storer N.; Wise, B. E. *Org. Process Res. Dev.* **2004**, *8*, 51−61. (b) Atkins, R. J.; Breen, G. F.; Crawford, L. P.; Grinter, T. J.; Harris, M. A.; Hayes, J. F.; Moores, C. J.; Saunders: R. N.; Share A. C.; Walsgrove T. C.; Wicks, C. J. *Org. Process Res. Dev.* **1997**, *1*, 185−197.

(5) Basu, B.; Maity, S. K.; Mukherjee, D. *Synth. Commun.* **1981**, *11*, 803−809.

10.1021/op049778l CCC: $30.25

Results and Discussion

At the very beginning we established the general order of adding the reagents. Experiments of preparing the Reformatsky reagent separately and adding indanone **2** later failed to give any **1**. Despite consumption of the bromoester **3**, no addition reaction to **2** could be observed. Therefore, we decided to perform the reaction in a Barbier-type fashion,[6] meaning that the electrophile **2** must be available to the Reformatsky reagent while the latter is formed.

We tried activating Zn by heating it with I_2, TMS-Cl, MeMgBr, 1,2-dibromoethane, CuCl, CuI[3] either prior to the addition of indanone **2** or in its presence. None of these procedures resulted in an immediate initiation when applied to our reaction.

A typical first-generation process on 50-g scale was performed as follows. The metal was activated by various methods (vide supra). For instance, the Zn metal was heated in the presence of iodine. THF and indanone **2** were added after the mixture was cooled to room temperature. The reaction mixture was heated to reflux, and **3** was added. The reaction initiated typically after addition of 30−70%[7] of the total amount of **3** and started to boil very violently. Although we had only one runaway reaction out of 200 experiments on lab scale, it was obvious that this process could not be scaled up due to its unpredictable point of initiation, which made efficient cooling impossible.

Even when we tried Zn−Cu[8] couple as the activated metal, we observed an initiation of the reaction after only 10% of the bromoester was added to the reaction mixture. This slightly shorter induction period led us to try the formation of the Zn−Cu couple in situ. When we added sulfuric acid[9] to Zn and CuCl in THF, we observed a slightly exothermic reaction accompanied by evolution of hydrogen gas. Indanone **2** was then added and the mixture heated to reflux. On addition of bromoester **2** to this mixture, we observed the immediate formation of **1** by HPLC. This second-generation process allowed the synthesis of **1** up to 350 g per batch.

To evaluate its suitability for further scale-up, a reaction calorimetry experimentwas carried out. However, the results were rather disappointing. The heat produced during dosing of the bromoester **3** was $Q_R = -241$ kJ/kg and resulted in a maximum adiabatic temperature rise of $\Delta T_{adj} = 178$ K. Since at that time we could not be sure that the reaction would always start immediately when starting the dosing of bromoester **3**, this was not considered to be a safe process!

To always be on the safe side, our idea was to use a more diluted, iterative process. We used half the concentration of the original process while sequentially adding the bromoester in three equal amounts. Our rough estimate was that doubling the dilution will halve ΔT_{adj}, and addition of three sublots will further decrease it by factor three. Starting from $\Delta T_{adj} = 178$ K, we should end up with $\Delta T_{adj} = 178\ \text{K}/6 \approx 30$ K.[10] We decided to add each sublot of the bromoester at 45 °C.[11] An increase in temperature would prove that the reaction had successfully initiated. After each addition of a sublot of **3**, we expected a maximum increase of 30 K corresponding to only a few K above the boiling point of the reaction mixture of $T = 66$ °C. In a number of experiments performed this way, we observed no initiation after the third addition, while the first sublots of **3** initiated the reaction very well. This meant that the Zn was aging during the reaction. While we had developed a safe process, it was not reliable with regard to conversion. To avoid aging of the Zn, we would need to add the bromoester in a single lot. However, to keep it safe, we had to dilute the reaction mixture again by a factor of 3.[12]

When the process was diluted six more times in comparison to the original procedure, it was still concentrated enough for a reasonable throughput. While considering scale-up to pilot-plant scale, we made final adjustments to the workup. The first was to add diluted sulfuric acid to the reaction mixture after all indanone **2** was consumed. First, the acidic conditions will eliminate water from the tertiary alcohol formed during the addition of the Reformatsky reagent of **3** to indanone **2**, and second the excess of Zn is oxidized to $ZnSO_4$. After addition of sulfuric acid, Cu residues and the $ZnSO_4$ formed are filtered off.[13] Toluene was added to the mixture in a second vessel, which was then concentrated by distillation and washed three times with water. Further distillation and addition of toluene yielded a ca. 30 wt-% solution of **1** in toluene. We applied this method to three batches starting from 5 kg of indanone **2** and a fourth from 4 kg of **2** and observed almost ideal results for a dosage-limited reaction. The temperature prior to the addition of bromoester was ca. 43 °C and started to rise after the first drops of bromoester were dosed. We observed $T_{max} = 56-63$ °C (cf. Figure 1) at the end of the addition (total dosing time 15−30 min). This resulted in an observed $\Delta T = 13-20$ K, which is lower than our estimate from the calculated ΔT_{adj} after dilution of 30 K, and can be explained by the dosing time and a significant heat transfer to the vessel.

During the campaign we rinsed the reaction vessel only with THF followed by drying in vacuo after every run. Small amounts of sediments of Cu- and Zn-salts did not affect further batches and were removed completely after the final batch by boiling with aqueous ammonia. This campaign yielded 28 kg of **1** in toluene corresponding to an average yield of 98%.

We learned from this campaign that even on pilot-plant scale, the reaction was strictly dosage limited. For the next

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(6) Oda, Y.; Matsuo, S.; Saito K. *Tetrahedron Lett.* **1992**, *33*, 97−100.

(7) The induction period and the necessary amount of bromoester **3** needed for initiation of the reaction varied between experiments. No correlation to any reaction parameter (such as concentration or addition rate) could be observed.

(8) (a) For a use of Zn−Cu couple in a Reformatsky reaction see: Santaniello, E.; Manzocchi A. *Synthesis* **1977**, 698−699. (b) We prepared the Zn−Cu couple according to McMurry, J. E.; Lectka, T.; Rico, J. G. *J. Org. Chem.* **1989**, *54*, 3748−3749.

(9) No other acids were tried for the activation of the Zn metal in situ.

(10) This was supported by a further reaction calorimetry experiment: addition of first sublot **3**: $Q_R = -48$ kJ/kg, $\Delta T_{adj} = 36$ K; addition of second sublot **3**: $Q_R = -46$ kJ/kg, $\Delta T_{adj} = 35$ K; addition of third sublot **3**: $Q_R = -42$ kJ/kg, $\Delta T_{adj} = 33$ K.

(11) Addition of **3** at 20 °C failed to initiate the reaction; 45 °C was chosen as a compromise of safety and reliability.

(12) The results of the reaction calorimetry of this process are in good accordance with our prediction: $Q_R = -58$ kJ/kg, $\Delta T_{adj} = 36$ K.

(13) Most of the Zn residues were precipitated as $ZnSO_4$ as estimated by mass balance. The contamination of Zn ions in the aqueous waste was not investigated.

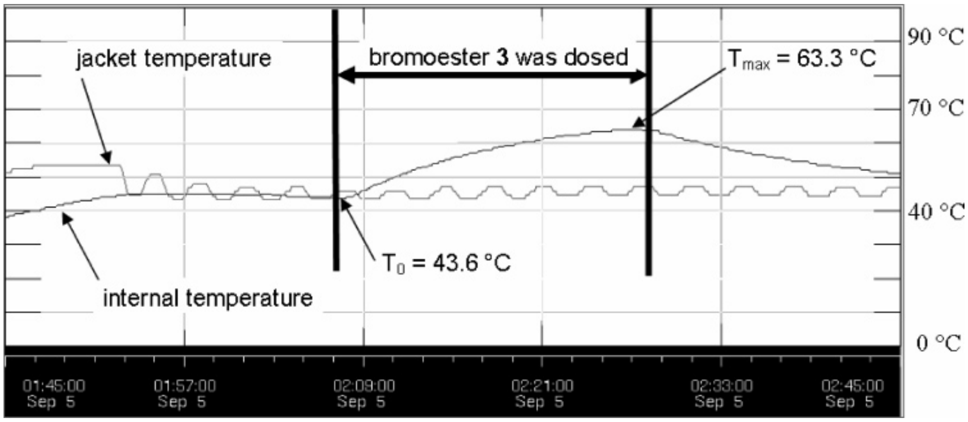

Figure 1. **Temperature graphs during dosing bromoester 3 (typical run of second pilot-plant campaign).**

campaign, we returned to higher concentration to increase throughput and efficacy of the process. In the same vessels, we performed 24 batches starting from 10 kg of indanone **2** for each. The reaction mixture was 1.5 times as concentrated as in the first campaign. All 24 batches showed dosage-limited behavior during addition of the bromoester **3**. The dosing time varied between 6 and 43 min, and the observed ΔT varied between 7.8 K (43 min dosing) and 24.2 K (6 min dosing). The large variations of the dosing time are a result of varying adjustments at the dosing pump and emphasize the robustness of the process. The yield varied between 89 and 96%, while the average yield was 92%. In total we obtained 329 kg (net weight) of the title compound as solution in toluene.

In conclusion, we have developed a process that enables us to supply **1** in sufficient amounts for further synthetic steps. Furthermore, this process is an application of the Reformatsky reaction on pilot-plant scale and circumvents usual drawbacks of this reaction. The key to a successful activation of the Zn metal is the use of CuCl in combination with sulfuric acid. Our process is safe and dosage limited even on pilot-plant scale. The reaction can be performed at a higher concentration to increase the throughput. Waste treatment with regard to Zn contamination should be considered before further scale-up.

Experimental Section

Analytics. Methyl 2-(6-methoxy-1H-inden-3-yl)butanoate (**1**) was quantified by HPLC against an external reference standard. HPLC analysis was performed on a Phenomenex ODS III RP-18, 3 μm column (150 mm × 3 mm) at 45 °C with a flow rate of 0.5 mL/min, UV-detection at 210 nm, and the following linear gradient (solvent A = 10 mM phosphate buffer pH = 2.4; solvent B = methanol): 0 min A:B 80:20; 15 min A:B 20:80. All other analytical data are in accordance to **1** (CAS-RN 496060-58-3)[1].

Representative Procedure on Pilot-Plant Scale for Methyl 2-(6-Methoxy-1*H*-inden-3-yl)butanoate. CuCl (1.2 kg, 12 mol, 0.2 equiv) was charged into a 250 L alloy 59 vessel. THF (40.0 kg) was added at 20 °C. To this solution, Zn powder (US-Zinc, 7.1 kg, 106 mol, 1.7 equiv) was added, followed again by THF (48.8 kg). Concentrated sulfuric acid (1.1 kg, 12 mol, 0.2 equiv) was added, and the mixture was heated to 45 °C. When the target temperature was reached, a solution of indanone **2** (9.8 kg, 60 mol) in THF (88 kg) was added. This latter solution was prepared prior to the reaction and tempered at 45 °C. After addition of the indanone solution, bromoester **3** (13.4 kg, 73 mol, 1.2 equiv) was dosed over approximately 15 min. The pump and pipes were rinsed with THF (2.0 kg). The reaction mixture was stirred with a jacket temperature of 45 °C for 1.5 h and subsequently cooled to 20 °C. Diluted sulfuric acid (c = 20%, 33.3 kg) was added, and the mixture was stirred at 20 °C for 10 h. The mixture was transferred via a filter nutsche to a 650 L alloy 59 vessel. The first vessel, the filter nutsche, and all pipes were rinsed with toluene (64.8 kg). The mixture was concentrated in vacuo (150 mbar) by distilling off THF (90 kg). Water (3 × 30 kg) was added, and the layers were separated. The aqueous layers were disposed of. THF and toluene (97 kg) were distilled off in vacuo (150 mbar), resulting in a solution of **1** in toluene (32.70 kg, 41.9 wt % of **1**), corresponding to an assay-corrected yield of 92% (13.70 kg of **1**).

Acknowledgment

We thank Dieter Heitkamp for performing the calorimetry experiments and DTA-measurements and Clemens Bothe for his support in preparing the pilot-plant campaign. We thank Joachim Rehse and his team in the pilot plant for performing two campaigns so well and for many fruitful discussions.

Received for review December 7, 2004.

OP049778L