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Process Optimization of Aldol-Type Reaction by Process Understanding Using in Situ IR

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Supporting Information

ABSTRACT: A high-yield robust LHMDS-mediated aldol-type reaction of benzyl maltol (**2**) and benzaldehyde (**3**) was developed using in situ IR to overcome the problems of low yield and yield fluctuation of the pilot synthesis. In situ IR studies indicated that unexpected side reactions of LHMDS and **3** reduced the yield of the aldol-type reaction. On the basis of the results, the reaction conditions were optimized.

INTRODUCTION

The lithiation-mediated aldol type reaction is well-known and useful for formation of the C−C bond to obtain the corresponding alcohol derivatives.[1] A key intermediate in the synthesis of active pharmaceutical ingredients (APIs) is 3-(benzyloxy)-2-(2-hydroxy-2-phenylethyl)-4*H*-pyran-4-one (**4**).[2] The synthetic process of **4** consists of protection of the hydroxyl group of maltol (**1**), lithiation of benzyl maltol (**2**)[3] with lithium hexamethyl disilazide (LHMDS) in THF at −70 °C and a nucleophilic reaction with **3** (Scheme 1). Excess LHMDS is generally used to complete the lithiation.[4] In accordance with the procedures, we used 1.2 equiv of LHMDS for preparation of **4** and conducted 100-kg-scale pilot production on 20 batches. In spite of the simple procedure, the yield of **4** fluctuated (72−97%), and a corresponding amount of **2** remained. To stabilize the product yield, we needed to optimize the process conditions. However, this type of reaction is often carried out under very low temperatures due to the generation of unstable intermediates, which cannot be directly detected by using at-line analytical tools such as TLC, HPLC, and GC. This prevents general optimization of these processes. What is required is an understanding of what is occurring within the reaction mixture in real time, which can offer useful information on the chemical process. Recently, process understanding by using process analytical technology (PAT),[5] such as IR,[6] NIR,[7] Raman,[8] and particle counters,[9] makes it possible for quality by design (QbD).[10] In this work, we used in situ IR, which can directly detect unstable reaction intermediates in real time, in order to clarify the chemical events taking place and develop a robust process.

RESULTS AND DISCUSSION

Consideration of the Structure of the Lithiated Intermediate and Determination of the Required Amount of LHMDS. We first investigated the lithiation of **2** with 1.2 equiv of LHMDS. The C═C stretching absorption of enolate (A 1546 cm^{-1}) and C═C stretching absorption of enolate conjugated exomethylene (B 1602 cm^{-1}) were detected as peaks of the intermediate. The IR result showed that the lithiated intermediate was not carbanion on the methyl group of **2** but a lithium enolate **5** (Figure1). The 1546 cm^{-1} of **5** increased in proportion to addition of 1.0 equiv of LHMDS (Figure 2). Although a slight excess amount of LHMDS is usually used to complete the lithiation, it was found that just 1.0 equiv of LHMDS was sufficient.

Behavior of Remaining LHMDS and 3. We next investigated the behavior of an excess amount of LHMDS using in situ IR. **3** was added to the THF solution of LHMDS at −70 °C. The absorption at 1654 cm^{-1} increased in proportion to the addition of **3**. After addition of an equivalent ratio of **3** for LHMDS. The C═O stretching absorption (1700 cm^{-1}) of **3** was detected (Figure 3). The absorption of 1654 cm^{-1} is the C═N stretching of benzaldimine **6**,[11] which is an unreactive compound for lithium enolate **5**. This means that the excess LHMDS was consumed in the reaction with the equivalent amount of **3** (Figure 4). (For further information, see Supporting Information.)

In large-scale production, however, the stirring condition differs from that of the small lab scale, and the concentration of the added **3** might be high in some portions of the reaction mixture. If the reaction does not smoothly proceed for some unforeseen reason, the reaction of **3** and LHMDS might give a result different from that of Figure 4. To evaluate the possibility of this, we changed the addition order of LHMDS and **3** and observed the behavior of **3**. A THF solution of LHMDS was added to the THF solution of **3** at −70 °C. The C═O stretching absorption (1700 cm^{-1}) of **3** decreased until half the amount of LHMDS for **3** was added, and then completely disappeared. To our surprise, no C═N stretching absorption (1654 cm^{-1}) was detected (Figure 5). The reaction mixture of enolate **5** was added to the reaction mixture, but **4** was hardly detected and **2** and **3** were recovered, which was confirmed by HPLC, in spite of no detection of carbonyl absorption of **3** by in situ IR. These results indicate that one molecule of LHMDS consumes two molecules of **3**. An unreactive complex which

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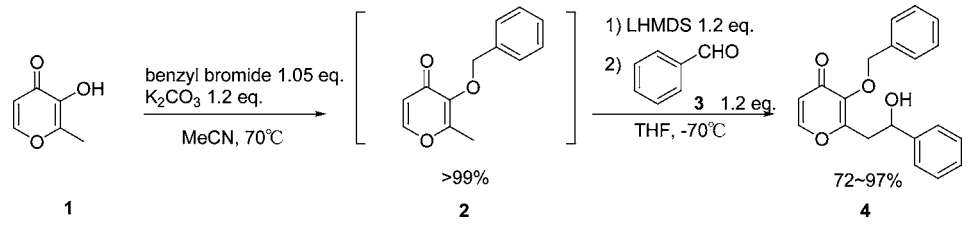
Scheme 1. Representative procedure for 4



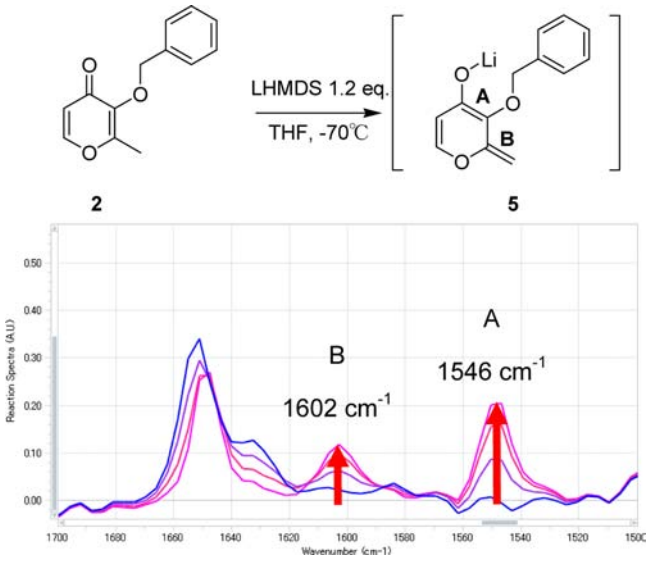


Figure 1. Structure of lithiated intermediate **5**.

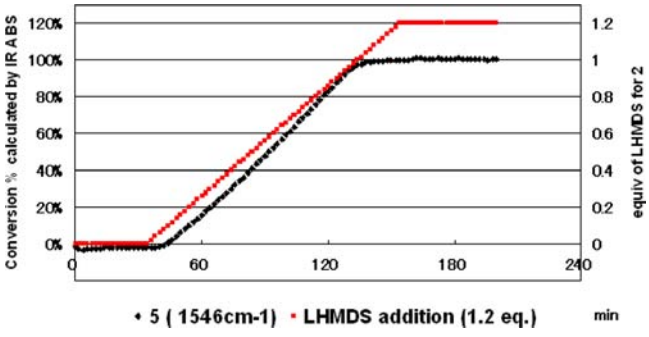


Figure 2. Plots of 1546 cm^{-1} (enolate **5**) and LHMDS addition.

can be reversed to **3** by quenching seems to be generated. We speculated that the 2:1 complex **7**, which is stabilized by six-membered ring formation, was generated under this condition

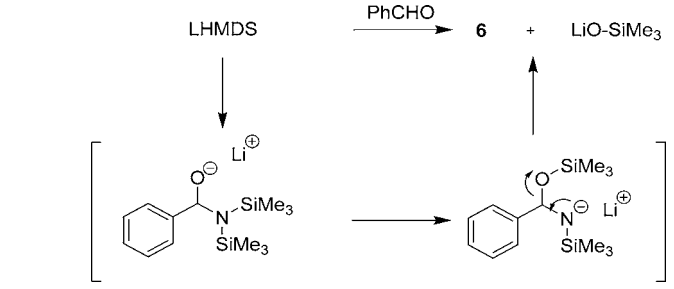


Figure 4. Generation of trimethylsilyl benzaldimine (**6**).

(Figure 6). (For further information, see Supporting Information.)

In the case where LHMDS was added into the THF solution of **3**, **3** is constantly sufficiently rich for LHMDS. Therefore, LHMDS immediately reacts with two molecules of **3** with the formation of a stable six-membered ring. It seems to be the reason for the absence of affording benzaldimine **6** in this case.

Process Optimization. According to the verification experiments for the behavior of **3** and LHMDS, complex **7** is easy to generate in the case of a high concentration of **3**. When 1.2 equiv of LHMDS was used for this reaction, the yield of product **4** might decrease by generation of complex **7** because of consumption of up to twice the amount of **3** for 0.2 equiv excess of LHMDS, and subsequent quenching of the remaining lithiated intermediate **5** affords **2**. We assumed that reduction of LHMDS is the most important factor for reducing the consumption of **3** by excess LHMDS in order to complete and stabilize the main reaction. To prove this hypothesis, the influence of the addition time of **3** and the amount of LHMDS were evaluated (Table 1). The original procedure was carried out as a controlled experiment (entry 1). As expected, fast dropwise addition of **3** (entry 2) which could generate complex **7** gave a lower yield than entry 1, and a corresponding amount of **2** was detected by HPLC. Next, the experiment with a reduced amount of LHMDS was carried out (entries 3 and 4). It gave quantitative yields without fluctuation of the yield as

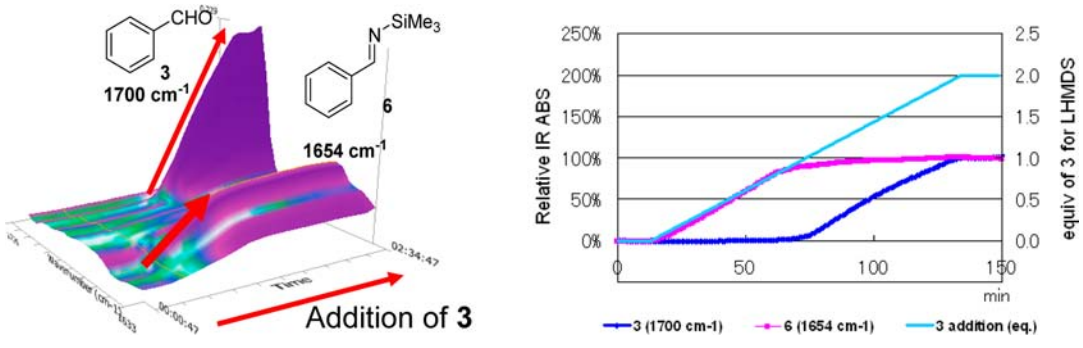


Figure 3. Observation of addition of **3** to LHMDS.

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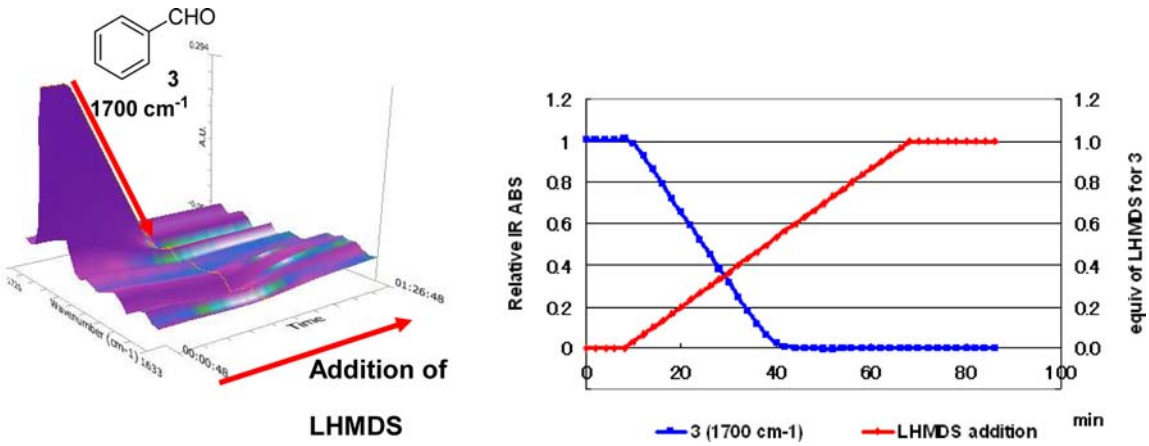

Figure 5. Observation of addition of LHMDS to **3**.

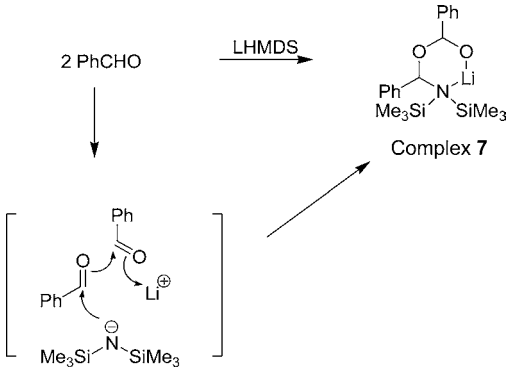

Figure 6. Generation and plausible structure of the 2:1 complex **7**.

Table 1. Evaluation of addition time of 3 and amount of LHMDS

entry	LHMDS (equiv)	3 (equiv)	addition time of 3 (min)	yield of 4 (%)[a]
1	1.20	1.2	60	92
2	1.20	1.2	10	88
3	1.05	1.2	60	>99
4	1.05	1.2	10	>99

[a]HPLC yield [4/(2 + 4)] × 100%].

with entries 1 and 2 because the consumption of **3** decreased due to the lower amount of LHMDS. In general, an excess amount of reagent is used to complete the reaction, but this is not always optimal, as we have shown here. On the basis of our findings, we were able to establish a high-yield, robust, and cost-reduced process.

CONCLUSION

In situ IR was effectively applied to the aldol-type reaction process to understand the chemical events in detail. Dependence of the reaction on relative concentrations of LHMDS and **3** were observed with in situ IR. On the basis of the findings, a high-yield, robust, and cost-reduced process was established.

EXPERIMENTAL SECTION

General. All reactions were run under a nitrogen atmosphere. Solvents and reagents were obtained from commercial sources and used without further purification. NMR spectra were measured on a 500 MHz Inova-500 or 300 MHz Varian FT spectrometer. HRMS were recorded on a LTQ-Orbitrap mass spectrometer. All in situ infrared spectra were collected using a Mettler Toledo ReactIR iC10 equipped with a 6 mm diameter Diamond attenuated total reflection (ATR) probe (DiComp).

Preparation of Benzyl Maltol (2). Potassium carbonate (131.5 g, 952 mmol) was portionwise added into the stirring surry of maltol (**1**) (100 g, 793 mmol) in acetonitrile (1400 mL) at room temperature. Then benzyl bromide (142.4 g, 833 mmol) was added into the mixturre. The mixture was heated to 70 °C, followed by stirring for 7 h. The reaction mixture was cooled to room temperature and evaporated to 500 mL. Toluene (500 mL) was added and washed with water (500 mL), followed by washing with 3%NaCl aq (500 mL). The organic layer was evaporated to 200 g. The obtained toluene solution of benzyl maltol (**2**) was used for the next step. This compound is already known, and the ^{1}H NMR data corresponded to the literature data[3] ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.04 (1H, d, J = 5.6 Hz), 7.42−7.33 (5H, m), 6.37 (1H, d, J = 5.6 Hz) 5.03 (2H, s), 2.12 (3H, s); ^{13}C NMR (500 MHz, DMSO-d_6) δ174.9, 160.19, 155.9, 144.1, 137.9, 129.6, 129.3, 129.1, 117.4, 73.6, 15.4 ; HRMS (ESI) m/z calcd for $C_{13}H_{13}O_3$ $[M]^+$: 217.0859, found 217.0851.

Preparation of 3-(Benzyloxy)-2-(2-hydroxy-2-phenylethyl)-4*H*-pyran-4-one (4). The solution of **2** (10 g containing 8.57 g of 2, 39.6 mmol) was diluted with THF (68 mL) and cooled to −70 °C. 20% lithium hexamethyl disilazide (39.81 g, 47.6 mmol) was added dropwise for 1 h, followed by stirring for 1 h at −70 °C. Benzaldehyde (5.05 g, 47.6 mmol) was added dropwise for 1 h, followed by stirring for 2 h under the same reaction conditions. The reaction mixture was added to 20% H_2SO_4 aq, keeping the temperature below 10 °C. The aqueous layer was separated and washed with 3% NaCl aq. The organic layer was evaporated. Toluene (25 mL) was added to obtain crystals of **4**, and then the slurry was evaporated to 30 mL. The slurry was cooled to 5 °C and filtrated. The filtrate was washed with toluene (25 mL) and dried under reduced pressure to yield 10.74 g of **4** (33.3 mmol, isolated yield: 84%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (1H, d, J = 5.6 Hz), 7.42−7.22 (10H, m), 6.38 (1H, d, J = 5.6 Hz), 5.62 (1H, d, J = 4.4 Hz), 4.95 (1H, d, J = 11.0 Hz), 4.88 (1H, m) 4.78 (1H, d, J = 11.0 Hz), 2.94 (1H, dd, J = 14.0, 8.5 Hz), 2.82 (1H, dd, J = 14.0, 8.5 Hz); ^{13}C NMR (500 MHz, DMSO-d_6) δ175.1, 160.5, 156.1, 145.6, 145.4, 138.1, 129.3, 129.2,

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129.1, 129.0, 128.1, 126.5, 117.4, 73.7, 71.0, 39.6 ; HRMS (ESI) m/z calcd for $C_{20}H_{19}O_4$ $[M]^+$: 323.1278, found 323.1274.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^1H NMR and ^{13}C HMR of **2** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Timothy, B. D.; Nicolas, B.; Brad, M.; Savall; Noel, A. P.; William, R. R. *J. Am. Chem. Soc.* **2004**, *126*, 9307−9317. (b) William, R. R.; Thomas, D. B.; Michael, D. W.; Jill, A. J.; Karl, A. S. *J. Org. Chem.* **2002**, *67*, 4275−4283. (c) Xuemei, C.; Andrew, J. W.; Raymond, J. H.; David, F. W. *J. Org. Chem.* **2002**, *67*, 9331−9339. (d) Darren, J. D.; Steven, V. L.; Alessandra, P.; Tom, S. *Org. Lett.* **2001**, *3*, 3749−3752. (e) Paul, M. B.; Jared, T. S.; Woerpel, K. A. *J. Org. Chem.* **1997**, *62*, 5674−5675.

(2) (a) Johns, B. A.; Wheatherhead, J. G.. WO/2010/011818 A1. (b) Aoyama, Y. WO/2010/067176 A1. (c) Yoshida, H. WO/2010/068253 A1.

(3) (a) Karine, B.; Robert, C. H.; Jan, B.; Johan, N.; Eric, D. C.; Michel, C. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4371−4374. (b) Willam, O. N.; Timothy, B. K.; Steven, J. R.; Chris, O. *Can. J. Chem.* **1988**, *60*, 123−131.

(4) (a) Brian, H.; Kenneth, L.; Kirk. *J. Org. Chem.* **2001**, *66*, 4892−4897. (b) Paul, M.; Jared, T.; Shaw, K. A.; Woerpel. *J. Org. Chem.* **1997**, *62*, 5674−5657. (c) Darren, J. D.; Steven, V. L.; Alessandra, Polara; Tom, S. *Org. Lett.* **2001**, *3*, 3749−3752. (d) Yousuke, Y.; Hisashi, Y. *J. Am. Chem. Soc.* **2010**, *132*, 5354−5356. (e) Fujioka, H.; Ohba, Y.; Nakahara, K.; Takatsuji, M.; Murai, K.; Ito, M.; Kita, Y. *Org. Lett.* **2007**, *9*, 5605−5608. (f) Ian, L. J.; Felicity, K. M.; Christina, L. L. C. *Org. Lett.* **2009**, *11*, 5526−5529. (g) David, J. M.; Samuel, J. D. *Angew. Chem., Int. Ed.* **2007**, *46*, 7789−7792.

(5) Melissa, B.; Steven, J. F.; Paul, D. H.; Neil, M.; Ivan, M. *Org. Process Res. Dev.* **2005**, *9*, 360−364.

(6) (a) Ana, C. B. S.; Ryan, C.; Thomas, W.; James, P. S.; William, E.; Thomas, C. *Org. Process Res. Dev.* **2011**, *15*, 1458−1463. (b) George, Z.; Khateeta, E.; Emily, M.; Camille, A.; Osama, S. *Org. Process. Res. Dev.* **2012**, *16*, 204−213.

(7) Michael, P.; Zhihao, L.; Yongkui, S. *Org. Process. Res. Dev.* **2005**, *9*, 141−148.

(8) Hongxun, H.; Mark, B.; Yun, H.; Weiyi, S.; Steven, F.; Barbara, W.; Brian, G. *Org. Process Res. Dev.* **2012**, *16*, 35−41.

(9) Christelle, H.; Benoît, H.; Selim, D.; Aurelie, L.; Valerie, V.; Tom, L. *Org. Process Res. Dev.* **2012**, *16*, 49−56.

(10) (a) Vince, M.; Mary, T. E.; Frank, R. B.; Jason, M.; Peter, R.; Mark, R. B. *Pharm. Eng.* **2010**, *30*, 1−16. (b) Kuroda, H. *Pharm. Tech. Jpn.* **2009**, *25*, 17−24. (c) ICH guidelines, Q8(R2) and Q9, http://www.ich.org/: *ICH Q8 Pharmaceutical Development*, (R2); U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER): Rockville, MD, Aug 2009. (d) *ICH Q9 Quality Risk Management*; U.S. Department of Health and Human Services, Food and Drug Administration,Center for Drug Evaluation and Research (CDER): Rockville, MD, June 2006.

(11) (a) Mauro, P.; Paola, Z. *Org. Process. Res. Dev.* **1998**, *2*, 49−59. (b) Ernest, W. C.; Daniel, M.; Mark, J. N. *Tetrahedron* **1988**, *44*, 4157−4172. (c) David, J. H.; Ken-ichi, K.; Dudley, G.; Thomas; Teng-Kuei, Y. *J. Org. Chem.* **1983**, *48*, 289−294. (d) Veeraraghavan, R.; Thomas, E. B. *Chem.—Eur. J.* **2005**, *11*, 4387−4395. (e) Yoshio, H.; Jun, K.; Takeo, H; Akira, T.; Kiyoko, I.; Yoshimi, T.; Michiko, M.; Hiroshi, M; Tohru, A.; Takeo, O.; Yoshimi, S.; Emiko, Y.; M.; Isao, U.; Iwao, O. *J. Med. Chem.* **1998**, *41*, 2345−2360.