Iron-catalyzed Direct-type Hydroxymethylation of 1,3-Dicarbonyl Compounds in Water

Chikako Ogawa and Shū Kobayashi*

Graduate School of Pharmaceutical Sciences, The University of Tokyo, The HFRE Division, ERATO,
Japan Science and Technology Agency (JST), Hongo, Bunkyo-ku, Tokyo 113-0033

(Received October 5, 2006; CL-061167; E-mail: skobayas@mol.f.u-tokyo.ac.jp)

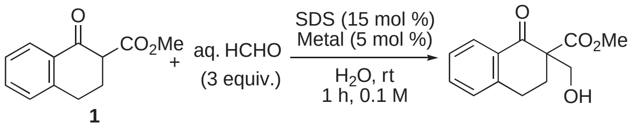
Direct-type hydroxymethylation of 1,3-dicarbonyl compounds with aqueous formaldehyde proceeded smoothly in water in the presence of $Fe(NO_3)_3 \cdot 9H_2O$ and sodium dodecylbenzenesulfate (SDBS), to afford the corresponding products in good to high yields.

The development of organic reactions in water is currently a topic of great interest in chemistry. Water offers several advantages as a solvent such as safety, low cost, reusability, and is consequently the key solvent for the realization of environmentally benign organic processes. In addition to these advantages, water has featured prominently in several Lewis acid-catalyzed reactions. For example, we have discovered water-compatible Lewis acids and achieved catalytic asymmetric reactions in aqueous media using them combined with chiral ligands.[1]

Hydroxymethylation using aqueous formaldehyde is one of the most efficient methods for the introduction of a C1 moiety,[2,3] and although several reports of hydroxymethylation by this route are known, they typically make use of paraformaldehyde and gaseous formaldehyde.[4] We have already reported that $Sc(OTf)_3$–chiral bipyridine complex[5] and $Bi(OTf)_3$–chiral bipyridine complex[6] catalyze asymmetric hydroxymethylation of silyl enol ethers using aqueous formaldehyde directly in water/THF (1/9) or water/DME (1/9) to afford the corresponding hydromethylated ketones in high yields with high enantioselectivities. However, silyl enol ethers are not necessarily suitable substrates from the viewpoint of atom economy.[7] In order to develop a truly environmentally benign system, direct-type enolate formation and its successive reaction is desirable.[8,9] In this paper, we describe direct-type hydroxymethylation of 1,3-dicarbonyl compounds using aqueous formaldehyde in water.

In the course of our studies of water-compatible Lewis acids, we succeeded in synthesizing Lewis acid–surfactant combined catalysts (LASC).[10] Based on this finding, we first tested several metal salts combined with sodium trisdodecylsulfate (SDS) in the reaction of β-keto ester **1** with aqueous formaldehyde (Table 1). Among these metal nitrates, it was found that $Fe(NO_3)_3 \cdot 9H_2O$ accelerated the reaction efficiently to give the corresponding hydroxymethylated product in 51% yield (Entry 5). We also screened counter anions of iron(III) salts and found that nitrate anion was the most effective (Entries 5 and 9–11). It was also noted that the reaction did not proceed well in the presence of a surfactant or a metal salt alone. We assume that the LASC is formed from $Fe(NO_3)_3 \cdot 9H_2O$ and SDS most efficiently among these iron(III) salts, and that this Fe-LASC promotes the desired hydroxymethylation reaction effectively.

Table 1. Effect of metal salts



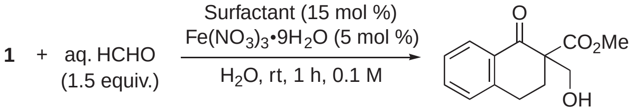
Entry	Metal Salt	Yield/%
1	$Bi(NO_3)_3 \cdot 5H_2O$	4
2	$Cu(NO_3)_2 \cdot 3H_2O$	26
3	$In(NO_3)_3 \cdot 5H_2O$	18
4	$AgNO_3$	trace
5	$Fe(NO_3)_3 \cdot 9H_2O$	51
6	none	11[a]
7	none	3[b]
8	$Fe(NO_3)_3 \cdot 9H_2O$	6[b]
9	$Fe(acac)_3$	4
10	$FeCl_3$	42
11	$Fe(OTf)_3$	14

[a] Only SDS was added. [b] In the absence of SDS.

The effect of surfactants was next examined using the same substrate with 1.5 equiv. of aqueous formaldehyde. As a result, SDS gave the corresponding product in 18% yield with several unknown by-products, while sodium dodecylbenzenesulfate (SDBS) promoted the desired reaction cleanly to give the product in 35% yield (Table 2). Therefore, we decided to use $Fe(NO_3)_3 \cdot 9H_2O$ with SDBS instead of SDS as the catalyst.[11]

Several substrates were examined in the direct-type hydroxymethylation in water in the presence of 5 mol % of $Fe(NO_3)_3 \cdot 9H_2O$ combined with 15 mol % of SDBS as shown in Table 3. The yield of the hydroxymethylated product from β-keto ester **1** was improved to 90%, when the reaction was carried out for 4 h. β-Keto ester **2** was reported as an intermediate for the synthesis of *anti*-HIV agents.[12] This substrate is relatively hydrophilic, and the yield according to this method was poor. On the other hand, β-keto ester **3** having benzyl ester instead of methyl ester gave the corresponding product in better yield because of its higher hydrophobicity. Diketone **5** also worked

Table 2. Effect of surfactants



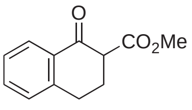
Entry	Surfactant	Yield/%
1	$C_{12}H_{25}OSO_3Na$ (SDS)	18
2	$C_{12}H_{25}C_6H_4SO_3Na$ (SDBS)	35
3	$C_{11}H_{23}SO_3Na$	17
4	$C_{12}H_{25}SO_3Na$	12
5	$C_{13}H_{27}SO_3Na$	16
6	$C_{14}H_{29}SO_3Na$	8

Table 3. Fe-catalyzed hydroxymethylation

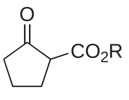
$$\text{Substrate} + \underset{(x\ \text{equiv.})}{\text{aq. HCHO}} \xrightarrow[\text{H}_2\text{O, rt, Conc.}]{\substack{\text{SDBS (15 mol \%)} \\ \text{Fe(NO}_3)_3\cdot 9\text{H}_2\text{O (5 mol \%)}}} \text{Product}$$

Substrate	x/equiv.	Conc./M	Time/h	Yield/%
1	3	0.1	4	90 (7)[a]
2	5	1.0	5	34[b]
3	5	0.2	5	79
4	1.5	0.5	3	87
5	10	1.0	48	63
6	5	1.0	5	92
7	5	1.0	5	91

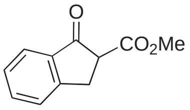
[a]In the absence of $Fe(NO_3)_3 \cdot 9H_2O$ and SDBS. [b]Yield was determined after TBDPS protection.



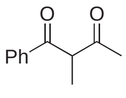
1



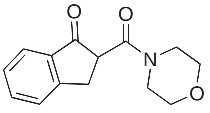
2: R = Me
3: R = Bn



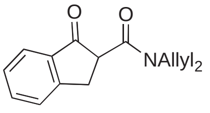
4



5



6



7

well in this system, although the reaction proceeded very slowly. Furthermore, solid ketoamides **6** and **7** reacted with aqueous formaldehyde in water successfully to afford the corresponding hydroxymethylated ketoamides in excellent yields.

A typical experimental procedure is described for the hydroxymethylation of β-keto ester **1**. $Fe(NO_3)_3 \cdot 9H_2O$ (11.6 mg, 0.029 mmol) and SDBS (30.0 mg, 0.086 mmol) were combined in water (5.6 mL) at room temperature for 10 min. To this solution, **1** (116.4 mg, 0.57 mmol) and 35% aqueous formaldehyde (146.0 mg, 1.71 mmol) were added, and the mixture was stirred for 4 h. The color of the reaction pot changed from colorless to bright purple when **1** was added. Water was then added to quench the reaction, and the product was extracted with dichloromethane (DCM). The combined organic layer was washed with brine (twice) and dried over Na_2SO_4. After usual work-up, the crude product was purified by neutral silica-gel column chromatography (hexane/ethyl acetate = 5/1) to afford the desired hydroxymethylated product (120.2 mg, 90% yield). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 2.12–2.18 (m, 1H), 2.39–2.43 (m, 1H), 2.97–3.01 (m, 2H), 3.22 (dd, $J = 9.6$, 3.1 Hz, 1H), 3.69 (s, 3H), 3.85 (dd, $J = 10.5$, 9.6 Hz, 1H), 3.98 (dd, $J = 10.5$, 3.1 Hz, 1H), 7.26–7.28 (m, 1H), 7.33–7.36 (m, 1H), 7.51–7.54 (m, 1H), 8.02–8.04 (m, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 26.3, 29.6, 52.9, 59.6, 66.6, 127.2, 127.8, 129.3, 132.2, 134.4, 143.9, 172.1, 197.7; IR (neat) 3519, 1732, 1681 cm^{-1}; HRMS (ESI) m/z calcd for $C_{13}H_{14}O_4$ ($M + Na^+$), 257.0784, found: 257.0789.

In conclusion, we have developed direct-type hydroxymethylation of 1,3-dicarbonyl compounds with aqueous formaldehyde in water by using $Fe(NO_3)_3 \cdot 9H_2O$ combined with SDBS. Further studies directed towards the realization of truly efficient environmentally benign processes including asymmetric versions are now in progress.

This work was partially supported by Grant-in-Aid for Scientific Research from the Japan Society of the Promotion of Sciences (JSPS).

This paper is dedicated to Professor Teruaki Mukaiyama for his great contribution to this journal on the occasion of his 80th birthday.

References and Notes

1 a) S. Kobayashi, S. Nagayama, T. Busujima, *J. Am. Chem. Soc.* **1998**, *120*, 8287. b) S. Kobayashi, K. Manabe, *Acc. Chem. Res.* **2002**, *35*, 209. c) S. Kobayashi, C. Ogawa, *Chem. Eur. J.* **2006**, *12*, 5954.
2 For example: a) T. Akeboshi, Y. Ohtsuka, T. Sugai, H. Ohta, *Tetrahedron* **1998**, *54*, 7387. b) M. Ora, E. Mäki, P. Poijärvi, K. Neuvonen, M. Oivanen, H. Lönnberg, *J. Chem. Soc., Perkin Trans. 2* **2001**, 881. c) P. Poijärvi, E. Mäki, J. Tomperi, M. Ora, M. Oivanen, H. Lönnberg, *Helv. Chim. Acta* **2002**, *85*, 1869.
3 a) H. Gault, J. Skoda, *Bull. Soc. Chim. Fr.* **1946**, *13*, 308. b) J. Casas, H. Sundén, A. Córdova, *Tetrahedron Lett.* **2004**, *45*, 6117. c) H. Torii, M. Nakadai, K. Ishihara, S. Saito, H. Yamamoto, *Angew. Chem., Int. Ed.* **2004**, *43*, 1983.
4 a) G. Stork, J. d'Angelo, *J. Am. Chem. Soc.* **1974**, *96*, 7114. b) K. Maruoka, A. B. Concepcion, N. Hirayama, H. Yamamoto, *J. Am. Chem. Soc.* **1990**, *112*, 7422. c) T. Okachi, K. Fujimoto, M. Onaka, *Org. Lett.* **2002**, *4*, 1667. d) T. Okachi, M. Onaka, *J. Am. Chem. Soc.* **2004**, *126*, 2306.
5 a) K. Manabe, S. Ishikawa, T. Hamada, S. Kobayashi, *Tetrahedron* **2003**, *59*, 10439. b) S. Ishikawa, T. Hamada, K. Manabe, S. Kobayashi, *J. Am. Chem. Soc.* **2004**, *126*, 12236.
6 S. Kobayashi, T. Ogino, H. Shimizu, S. Ishikawa, T. Hamada, K. Manabe, *Org. Lett.* **2005**, *7*, 4729.
7 T. Isoda, H. Oyamada, R. Akiyama, S. Kobayashi, *Adv. Synth. Catal.*, in press.
8 a) R. Kuwano, H. Miyazaki, Y. Ito, *Chem. Commun.* **1998**, 71. b) R. Kuwano, H. Miyazaki, Y. Ito, *J. Organomet. Chem.* **2000**, *603*, 18.
9 For reviews of direct type reactions, see: a) W. Notz, F. Tanaka, C. F. Barbas, III, *Acc. Chem. Res.* **2004**, *37*, 580. b) M. Shibasaki, S. Matsunaga, *Chem. Soc. Rev.* **2006**, *35*, 269.
10 a) S. Kobayashi, T. Wakabayashi, *Tetrahedron Lett.* **1998**, *39*, 5389. b) K. Manabe, Y. Mori, T. Wakabayashi, S. Nagayama, S. Kobayashi, *J. Am. Chem. Soc.* **2000**, *122*, 7202. c) K. Manabe, Y. Mori, S. Kobayashi, *Tetrahedron* **1999**, *55*, 11203. d) K. Manabe, N. Aoyama, S. Kobayashi, *Adv. Synth. Catal.* **2001**, *343*, 174.
11 N. Aoyama, K. Mabnabe, S. Kobayashi, *Chem. Lett.* **2004**, *33*, 312.
12 H. Kuwano, K. Haraguchi, H. Tanaka, T. Nitanda, M. Baba, G. E. Dutschman, Y.-C. Cheng, K. Kato, *Nucleoside, Nucleotides Nucleic Acids* **2005**, *24*, 73.

Published on the web (Advance View) December 16, 2006; doi:10.1246/cl.2007.56