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## Michael addition reactions of acetoacetates and malonates with acrylates in water under strongly alkaline conditions

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Abstract—Michael addition reactions of acetoacetates and malonates with acrylates in a 5 M KOH aqueous solution without using any other catalysts are described. When they are either *tert*-butyl or benzyl esters, the reaction proceeded very rapidly to afford moderate to high yields of the corresponding bis-Michael adducts that are unexpectedly stable under these conditions. © 2005 Elsevier Ltd. All rights reserved.

Whereas water is an environmentally benign, non-toxic, and cheaper solvent than any other organic solvents, its use as the solvent for organic reactions has been quite limited until the most recent decade. Since then, there are numerous reports on the reactions successfully carried out in water in the presence of newly developed catalysts or surfactants.<sup>1,2</sup> Many of these reports refer to superior properties of water over organic solvents such as the ability to increase reaction rate or yield, or to decrease the steps of the workup procedure. Michael addition reaction is one of the most frequently studied reactions found to be suitable for the reaction in water.<sup>3-6</sup> However, there has been a limited number of reports on the reactions in water under simply basic conditions.<sup>7,8</sup> In this letter, we report an efficient Michael reaction of acetoacetates and malonates with acrylates in KOH aqueous solution without any kind of organometallic catalysts.

In the course of our investigations to design and synthesize new polyester dendrimers, we found that the Michael reaction of benzyl acetoacetate with *tert*-butyl acrylate in the presence of *t*-BuOK in THF gave bisadduct **1** (see Eq. 1 in Table 1) in over 90% yield. The new polyester dendrimers were successfully synthesized using the AB<sub>2</sub> type building block derived from subsequent hydrogenolysis and decarboxylation of **1**.<sup>9</sup>

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Although 1 was obtained in high yield, 1 was often contaminated with yellowish substance (structure unidentified), which required time-consuming column chromatographic process for separation. However, 1 has to be supplied in bulk by the simple purification process since it is the starting material for the synthesis of our dendrimers. Looking for more efficient and by-product-free reaction procedure, we found that the reaction proceeded efficiently in 5-7 M KOH aqueous solution within 2 h to give almost pure and colorless 1 in over 60% yield. In addition to the often referred advantages of using water as a solvent, this procedure has the following remarkable features compared with other reactions in water: (1) no organometallic or phase-transfer catalyst used by many others is necessary, (2) although both the starting materials and the product are esters, hydrolysis is almost suppressed during the reaction, (3) the reaction proceeded very rapidly. We then investigated the optimum reaction conditions and the availability of this reaction medium to the Michael reaction of other compounds.

The dependency of the product yield on the concentration of KOH was first tested and the results are shown in Table 1.<sup>10</sup> The reaction in a 5 M KOH solution at room temperature gave the adduct 1 in the highest yield (entry 4). Although the reaction at 40 °C also afforded 1 in good yield (entry 5), the reaction at 0 °C proceeded very slowly to give a trace amount of 1. The reactions in solutions of higher than 5 M resulted in lower yields (entries 6 and 7). While any kind of reaction products was obtained from the organic extract from a 0.1 M KOH solution, a very small amount of the organic

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Table 1. Dependency of concentration of aqueous KOH and temperature<sup>a</sup>

	$\bigcup_{OBn}^{O} + 2 = 0 + \frac{aq.K}{2.5}$	(OH) $(OH)$	(1)
Entry	KOH aq (M)	<i>T</i> (°C)	Yield of <b>1</b> (%)
1	0.1	20	b
2	1	20	11
3	5	0	Trace
4	5	20	68
5	5	40	63
6	7	20	42
7	10	20	38°

<sup>a</sup> Benzyl acetoacetate (0.13 mmol) and *tert*-butyl acrylate (3.9 mmol) were reacted in a KOH aqueous solution (3 mL). After the reaction, the product was isolated by chromatography.

<sup>b</sup> Almost no reaction took place.

<sup>c</sup> Yield after 24 h of reaction.

extract consisting of both 1 and mono-adduct 2 was collected from a 1 M KOH solution suggesting that hydrolysis of the esters is the major reaction.

We next examined the time dependency of the product yield in a 5 M KOH solution. The reaction was stopped after certain intervals and the reaction mixture was extracted with AcOEt. The total weight was measured after washing and evaporation of the solvent under reduced pressure. The amount (%) of constituents of the organic extracts was calculated from the NMR spectra that consisted of the signals assigned to 1, benzyl alcohol, benzyl acetoacetate, and/or mono-adduct 2. Although *tert*-butyl acrylate was detected by the HPLC analysis of the organic extract before evaporation, it was not found in NMR spectra taken after evaporation. As shown in Figure 1, benzyl acetoacetate was almost consumed and the yield of 1 reached over 80% after 90 min. Contrary to our expectation, the yields of 1 stayed at the same level thereafter up to 240 min, suggesting that 1 is stable against hydrolysis under these conditions. Although a small amount of mono-adduct 2 was found in the organic extracts of the reactions for 15 and 30 min when enough acetoacetate remained unreacted in the reaction medium, it was completely converted to 1 as the reaction proceeded. The amount of benzyl alcohol was increased during the first stage of the reaction and stayed almost constant after 60 min. Since the increase of benzyl alcohol is almost coincident with the decrease of benzyl acetoacetate, benzyl alcohol is mainly derived from the hydrolysis of the acetoacetate but not from 1.

Several examples of the Michael reactions in a KOH solution are summarized in Table 2. While the reactions of *tert*-butyl acetoacetate with benzyl or *tert*-butyl acrylate proceeded as well (entries 1 and 2), the reaction of ethyl acetoacetate with *tert*-butyl acrylate resulted in hydrolysis of acetoacetate (entry 3). Therefore, the



Figure 1. Change in amount (%) of constituents of organic extract with progress of the reaction (1).

Table 2. Michael reactions in aqueous KOH solution<sup>a</sup>



<sup>a</sup> Reactions were conducted on a dicarbonyl compound (0.13 mmol) and acrylate (0.39 mmol) in 3 mL of 5–7 M KOH solution.

<sup>b</sup> Isolated yields.

<sup>c</sup> The organic layer was disappeared.

<sup>d</sup> No reaction occurred.

<sup>e</sup> Mono-adduct was obtained.

<sup>f</sup>Bis-adduct obtained from the reaction in 7 M KOH.

presence of the protecting groups stable under strongly basic conditions such as benzyl or *tert*-butyl is necessary for the reaction. The similar situation was found for malonates (entries 4–7). Dibenzyl and di-*tert*-butyl malonate reacted with *tert*-butyl and benzyl acrylate, respectively, to afford bis-adducts (entries 4 and 5), which can be useful precursors of tricarboxylates having one free and two protected carboxyl groups. Due to lower acidity of  $\alpha$ -hydrogen of 1,3-diester (p $K_a \sim 13$ ) than that of 1,3-ketoester (p $K_a \sim 11$ ), the reaction of dibenzyl malonate in a 5 M KOH solution gave a mono-adduct as a major product, and a 7 M KOH solution is necessary to obtain a satisfactory yield of bisadduct.

In summary, Michael reactions of acetoacetates and malonates with acrylates proceeded smoothly to afford bis-adducts in an aqueous 5–7 M KOH solution, when they are the esters of benzyl or *tert*-butyl that are fairly stable in strongly basic solution. As far as we know, this is the first example of Michael reactions successfully carried out in a strongly alkaline aqueous solution to afford a bis-adduct without a noticeable amount of by-products. Although its application is rather limited for the time being, it will offer a new concept for the reaction in a strongly basic aqueous medium. Application of this simple procedure to other reactions are now in progress in our laboratory.

## Supplementary data

Experimental procedure for the syntheses of  $\mathbf{1}$ , <sup>1</sup>H NMR of  $\mathbf{1}$ ,  $\mathbf{2}$ , and bis-adducts made by the reactions in Table 2 are available. Supplementary data associated with this article can be found, in the online version at doi:10.1016/j.tetlet.2005.07.045.

## **References and notes**

- (a) Grieco, P. A. Organic Synthesis in Water; Blackie Academic and Professional: London, 1998; (b) Li, C.-J.; Chan, T.-H. Organic Reactions in Aqueous Media; John Wiley & Sons: New York, 1997.
- 2. Kobayashi, S.; Manabe, K. Acc. Chem. Res. 2002, 35, 209–217.
- 3. Keller, E.; Feringa, B. L. Tetrahedron Lett. 1996, 37, 1879–1882.
- 4. Mori, Y.; Kakumoto, K.; Manabe, K.; Kobayashi, S. *Tetrahedron Lett.* **2000**, *41*, 3107–3111.
- Shimizu, S.; Shirakawa, S.; Suzuki, T.; Sasaki, Y. Tetrahedron 2001, 57, 6169–6173.
- (a) Naidu, B. N.; Sorenson, M. E.; Connolly, T. P.; Ueda, Y. J. Org. Chem. 2003, 68, 10098–10102; (b) Naidu, B. N.; Li, W.; Sorenson, M. E.; Connolly, T. P.; Wichtowski, J. A.; Zhang, Y.; Kim, O. K.; Matiskella, J. D.; Lam, K. S.; Bronson, J. J.; Ueda, Y. Tetrahedron Lett. 2004, 45, 1059– 1063.
- Elder, U.; Sauer, G.; Wiechert, R. Angew. Chem., Int. Ed. Engl. 1971, 10, 496–497.
- Ballini, R.; Barboni, L.; Giarlo, G. J. Org. Chem. 2003, 68, 9173–9176.
- Hirayama, Y.; Nakamura, T.; Uehara, S.; Sakamoto, Y.; Yamaguchi, K.; Sei, Y.; Iwamura, M. Org. Lett. 2005, 7, 525–529.
- 10. A typical experimental procedure for the Michael reaction in a 5 M KOH solution is described: To a mixture of benzyl acetoacetate (25 mmol) and *tert*-butyl acrylate (75 mmol), 40 mL of 5 M KOH aqueous solution is added. The emulsified reaction mixture is stirred at room temperature for 2 h to give a clear organic layer separated from the aqueous layer. Then the organic layer is separated and the aqueous layer is extracted with ethyl acetate. The combined organic extract is washed with water, 1 M HCl, and brine successively and dried over MgSO<sub>4</sub>. The solution is concentrated under reduced pressure and chromotographed on silica-gel to afford 1.