Journal of Zhejiang University SCIENCE A
ISSN 1673-565X (Print); ISSN 1862-1775 (Online)
www.zju.edu.cn/jzus; www.springerlink.com
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Science Letters:

Hydrogen transfer reduction of ketones using formic acid as a hydrogen donor under hydrothermal conditions*

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Received June 8, 2009; Revision accepted Aug. 7, 2009; Crosschecked Aug. 8, 2009

Abstract: The hydrothermal experiments with ketones and formic acid showed that the hydrogen transfer reduction of ketones can be conducted using formic acid as a hydride donor in the presence of NaOH at 300 °C. The yield of alcohols was considerably higher at a much lower ratio of hydrogen source to ketones than the traditional Meerwein-Ponndorf-Verley (MPV) reduction, reaching 60% for isopropanol from acetone and 70% for lactic acid from pyruvic acid. Water molecules may act as a catalyst in the hydrogen transfer reduction of ketones under hydrothermal conditions.

Key words: Hydrogen transfer reduction, Formic acid, Ketone, Hydrothermal reaction
doi:10.1631/jzus.A0920097 **Document code:** A **CLC number:** X24; O62

INTRODUCTION

The reduction of ketones to the corresponding alcohols is an important transformation in organic synthesis and industrial processes (Larock, 1989). Meerwein-Ponndrof-Verley (MPV) reduction, which involves a reversible hydride transfer via a six-membered transition state catalyzed by metal-alkoxides, is the usual method for converting ketones into alcohols (Meerwein and Schmidt, 1925; Ponndorf, 1926). The MPV reaction has real advantages over the reaction with molecular hydrogen because of the favorable properties of the organic hydrogen source. Many newer catalysts have been recently reported for improving MPV reduction (Creyghton *et al*., 1997; Campbell *et al*., 2001; Ekström, *et al*., 2007; Ruiz *et al*., 2007; Alonso *et al*., 2008a; 2008b). However, the MPV reductions are typically conducted using a stoichiometric amount of metal-alkoxides and excess isopropanol. It is inevitable that substantial side-products and environmentally undesirable salts are produced during the process (de Graauw *et al*., 1994; Sheldon, 1994). More seriously, isopropanol as a hydrogen source is obtained from fossil fuel, such as petroleum or natural gas. With the depletion of fossil fuel and the concern for the environment, it is necessary to explore other resources as a hydride donor rather than isopropanol and to develop cleaner processes for organic reactions. Fortunately, our recent researches have revealed that using an environmentally benign hydrothermal process, formic acid can be achieved easily from glucose, which is a renewable carbohydrate biomass (Jin *et al*., 2008). Accordingly, formic acid from glucose could be directly employed as a hydride donor in the reduction of ketones. In recent publications it was shown that transfer hydrogenation of ketones can be reduced by formic acid with Ru(II) complexes as catalysts (Fujii *et al*., 1996; Matharu *et al*., 2006; Naskar and Bhattacharjee, 2007). The reactions also need a high for-

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* Project supported by the State Key Laboratory of Pollution Control and Resources Reuse in China (Tongji University) (No. PCRRK08002), the National Key Technology R&D Program of China (No. 2008BAJ08B13), and the Shanghai Pujiang Elitist Program of China (No. 07pj14083)

mic acid:ketones ratio (50:1~80:1, mol/mol) and a stoichiometric amount of metal catalysts.

Recently, hydrothermal process has been attracting more attention as a medium for organic chemical because high-temperature water (HTW) is an environmentally benign solvent against less desirable organic solvents, and has remarkable properties as a reaction medium (Akiya and Savage, 2002; Watanabe *et al.*, 2004). For example, HTW has a lower dielectric constant, fewer and weaker hydrogen bonds, and a higher isothermal compressibility than ambient liquid water (Shaw *et al.*, 1991). Accordingly, many organic reactions at ambient conditions only in the presence of acidic/basic or metallic catalysts may proceed in HTW in the absence of an added catalyst (Kuhlmann *et al.*, 1994; Tsujino *et al.*, 1999; Jin *et al.*, 2004). The purpose of this research is to investigate whether the hydrogen transfer reduction of ketones can be conducted using formic acid as a hydride donor without the addition of catalysts under hydrothermal conditions.

EXPERIMENT

Acetone, the most representative of ketones, was used in this study. Butanone, acetophenone and pyruvic acid were also used for comparing the effect of different groups attached to carbonyl carbon in the hydrogen transfer reduction. Acetone (99%, AR), butanone (99%, AR), acetophenone (99%, AR), pyruvic acid (97%, AR), formic acid (99%, AR) and NaOH (96%, AR) were used, obtained from Wako Pure Chemical Industries, Osaka, Japan. In addition to an experiment for studying the effect of the reactor wall, all experiments were carried out with a batch reactor made of SUS 316 with an internal volume of 5.7 cm^3 (Jin *et al.*, 2001). Briefly, a 4 ml water mixture of test materials (70% water fill) were added into the reactor. Then the sealed reactor was put into a salt bath that had been preheated to 300 °C. After a certain reaction time, the reactor was removed from the salt bath, and then put into a cold-water bath to quench the reaction. The reaction time was defined as the period during which the reactor was kept in the salt bath. After cooling, gas and liquid samples were collected for analysis.

The gas samples were analyzed by a gas chromatography (GC) (HP 5890 Series II, USA) with a Porapak Q column or a POLA column. After filtered through a 0.45-mm filter, liquid samples were measured with a total organic carbon (TOC) analyzer (Shimadzu TOC 5000A, Japan), and high pressure liquid chromatography (HPLC) (Waters, USA) equipped with a tunable absorbance detector (UV detector) (Waters 486, USA) and a differential refractometer (RI detector) (Waters 410, USA). In the HPLC analysis, SH1011 (Shodex) column was used to separate samples with 5 mmol/L H_2SO_4.

RESULTS AND DISCUSSION

To investigate whether the hydrogen transfer reduction of ketones under hydrothermal conditions can be conducted with formic acid as a hydride donor, the experiment of acetone, the most representative ketone, and formic acid was carried out at 300 °C. As shown in Fig.1, which is the HPLC chromatogram of the solution sample after reaction with 0.25 mol/L acetone and 0.5 mol/L formic acid for 10 min in the absence of catalysts, isopropanol was detected. This shows that formic acid can be used as a hydride donor in the hydrogen transfer reduction of acetone into isopropanol without the addition of any catalysts.

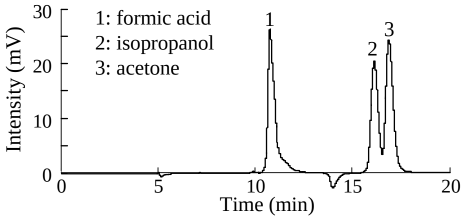

Fig.1 HPLC chromatogram for reaction sample of acetone and formic acid (RI detector; 300 °C; 10 min; acetone: 0.25 mol/L; formic acid: 0.5 mol/L)

Subsequently, a series of experiments were performed to optimize reaction conditions by varying the ratio of formic acid to acetone (F/A ratio), NaOH concentration, reaction temperature and reaction time. The addition of NaOH was used to promote the hydrogen transfer reduction of ketones because it has been recognized that base is beneficial for the MPV reduction of ketones (de Graauw *et al.*, 1994). The effects of the F/A ratio and NaOH in the hydrogen transfer reduction of acetone are illustrated in Fig.2

and Fig.3 by plotting isopropanol yield versus F/A ratio and NaOH concentration, respectively. The products yield is defined as the mole percentage of products to the initial ketones. As shown in Fig.2, the isopropanol yield drastically increased before the F/A ratio increased to 2, and then the increase became slower. This shows that the optimal ratio of hydrogen source to ketones is far lower than that of traditional MPV reduction. As shown in Fig.3, the isopropanol yield increased greatly with an increase of NaOH concentration until the concentration of 0.5 mol/L was obtained. Then the increase slowed down. The influences of the reaction time and temperature were studied at the optimal F/A ratio of 2 and NaOH concentration of 0.5 mol/L. From Fig.4, it can be seen that although the isopropanol yield at 260 °C is very low even in the reaction time of 300 min, at 300 °C the yield increased greatly as the reaction time increases. These results show that acetone can be reduced readily into isopropanol by formic acid in the presence of NaOH even in the absence of metal catalysts.

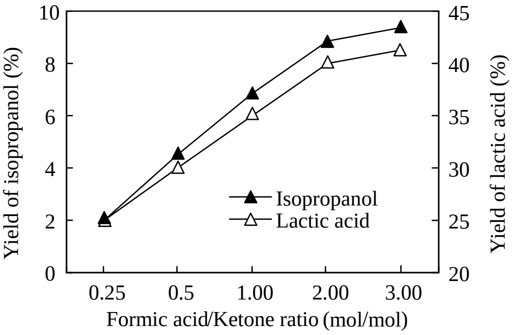

Fig.2 The effect of formic acid/ketone ratio in the hydrogen transfer reduction of ketones (300 °C; 10 min; ketones: 0.25 mol/L)

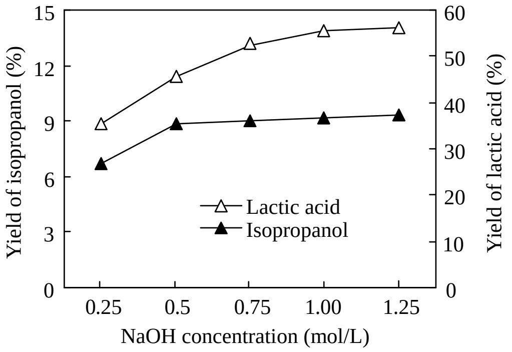

Fig.3 The effect of NaOH concentration in the hydrogen transfer reduction of ketones (300 °C; 10 min; ketones: 0.25 mol/L; formic acid: 0.5 mol/L)

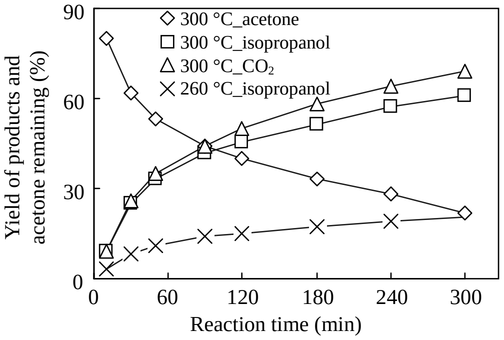

Fig.4 The effect of reaction time in the hydrogen transfer reduction of acetone (acetone: 0.25 mol/L; formic acid: 0.5 mol/L; NaOH: 0.5 mol/L)

Additionally, to compare the effect of different groups attached to carbonyl carbon in the hydrogen transfer reduction, a series of similar experiments were performed at 300 °C with other ketones and formic acid. As shown in Table 1, we find that pyruvic acid could be converted faster into lactic acid. So, a series of experiments were carried out to further study the effect of reaction conditions in the hydrogen transfer reduction of pyruvic acid. As shown in Fig.2 and Fig.3, the optimal condition is formic acid/pyruvic acid ratio of 2 and NaOH concentration of 0.75 mol/L. At the optimal conditions, a good lactic acid yield of about 70% was obtained for the reaction time of 50 min.

Table 1 Experimental results in the hydrogen transfer reduction of ketones with formic acid*

Ketone	Alcohol yield (%)
Acetone	8.9
Acetone**	1.3
Pyruvic acid	40.1
Butanone	8.5
Acetophenone	11.9

* The reaction conditions: formic acid/ketone ratio: 2; reaction temperature: 300 °C; reaction time: 10 min; ** The experiment was performed under anhydrous conditions

Further, the reaction pathway of the hydrogen transfer reduction of ketones with formic acid was discussed. In classical MPV reduction, hydride transferring of transition state is catalyzed by metal-alkoxides. To investigate the catalysis effect of reactor materials, we performed an experiment with 0.25 mol/L acetone and 0.5 mol/L formic acid at 250 °C for

24 h in a Teflon-lined reactor (Li *et al.*, 1989). No significant change in the yield of isopropanol was observed compared to that with SUS reactors, indicating that the materials of the reactor wall have no catalytic role. Then, water molecules may act as a catalyst in the hydrogen transfer reduction of ketones. To prove this, we carried out an additional experiment with acetone and formic acid at 300 °C for 10 min under anhydrous conditions. As shown in Table 1, the yield of isopropanol was only 1.3%, which is very low compared to the yield under hydrothermal conditions. The result indicated the catalytic role of water molecules in the hydrogen transfer reduction of ketones by formic acid.

On the basis of the traditional MPV reaction mechanism involving a cyclic transition state and the catalytic role of water molecules in the hydrogen transfer reduction of ketones, a mechanism of the hydrogen transfer reduction of ketones into corresponding alcohols by formic acid was proposed, as shown in Fig.5. First, two hydrogen bondings may be formed among three molecules, making the carbonyl-carbon and hydride even more positive. Then, the hydride attacked the carbonyl-carbon and a cyclic transition state may be formed. After the intramolecular hydride shift, the alcohols and CO_2 were produced, and water molecule recovered.

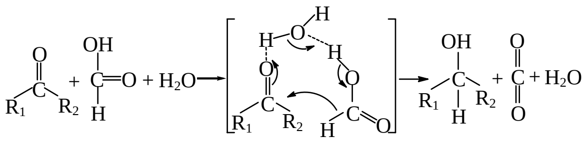

Fig.5 The reaction mechanism in the hydrogen transfer reduction of ketones with formic acid as a hyride donor

According to the mechanism proposed in Fig.5, one mole of acetone and formic acid would generate one mole of isopropanol and CO_2. To test this, CO_2 in gas and liquid compositions were analyzed for reactions at 300 °C with 0.25 mol/L acetone, 0.5 mol/L formic acid and 0.5 mol/L NaOH by varying the reaction time from 10 to 300 min. As shown in Fig.4, the isopropanol and CO_2 were generated equally at the initial stage, whereas the isopropanol was less than CO_2 at the final stage. The excess CO_2 is probably because the reaction time is longer, leading to more decomposition of formic acid as a hydride donor.

CONCLUSION

This work showed that the hydrogen transfer reduction of ketones can be conducted with formic acid as a hydride donor in the presence of NaOH at 300 °C. The yield of alcohols was considerably higher at a much lower ratio of hydrogen source to ketones than traditional MPV reduction, reaching 60% for isopropanol from acetone and 70% for lactic acid from pyruvic acid. Water molecules may act as a catalyst in the hydrogen transfer reduction of ketones under hydrothermal conditions.

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