Organic Process Research & Development **2004**, *8,* 18–21

Articles

Environmentally Friendly and Efficient Process for the Preparation of β-Hydroxyl Ketones

Guan-Wu Wang,* Ze Zhang, and Ya-Wei Dong

Department of Chemistry, University of Science and Technology of China, Hefei, Anhui 230026, P.R. China

Abstract:

An environmentally benign and efficient process for the preparation of β-hydroxyl ketones was developed by the practical cross-aldol reactions of 2-acetylpyridine, acetophenone, and cyclohexanone with 4-nitro-, 3-nitro-, and 2-nitrobenzaldehydes in water catalyzed by Na_2CO_3 in very high yields.

Introduction

Environmentally friendly chemical process is the vital part of the current chemical research and development.[1] Organic reactions in water[2] have attracted more and more attention from chemists because there are many potential advantages and benefits in terms of cost, safety, environmental concerns, efficiency, and selectivity when the common organic solvents are replaced by water in organic reactions.[3]

The aldol reaction is one of the most powerful and useful reactions utilized in the construction of the carbon−carbon bond.[4] Aldol reaction has been classically conducted in the presence of strong base or acid.[5] However, under such strong basic or acidic condition, the synthesis of the desired aldol product is plagued by the concomitant α,β-unsaturated ketone, formed through aldol dehydration,[5a,c] and other side products from polycondensation, self-condensation of the ketone, Michael addition to the formed enone, and so on.[5a] To overcome these problems, various Lewis acids[6] or Lewis bases[7] have been explored as alternative catalysts, but in most cases the ketones need to be modified as silyl enol ethers, ketene silyl acetals, etc.

The K_2CO_3-induced intramolecular aldol reaction in CH_3OH/H_2O was reported to give a mixture of α,β-unsaturated ketones resulting from the dehydration of the initially formed β-hydroxyl ketones.[8] Alkali and earth alkali metal salts including Na_2CO_3 have also been used to promote aldol reaction of dimethylsilyl enolates in aqueous dimethylformamide.[9] However, a certain amount of diol was formed by the tandem aldol−reduction reaction in the case of Na_2CO_3. Aldol reactions in pure water have been reported; however, the substrates have to be modified as silyl enol ethers, ketene silyl acetals, and boron enolates.[10] Most recently, proline-catalyzed aldol reactions in aqueous micelles has been reported.[11] To the best of our knowledge, there is no report of aldol reaction in pure water promoted by Na_2CO_3 at ambient temperature. Herein we present the highly efficient and practical aldol reaction of unmodified ketones with reactive aldehydes bearing strong electron-withdrawing groups in water catalyzed by Na_2CO_3 at room temperature.

Results and Discussion

Recently we have reported the efficient synthesis of chalcone and azachalcone by the aldol reactions of ketones with various aldehydes catalyzed by Na_2CO_3 at elevated temperatures.[12] When the reactions were conducted at ambient temperature, a mixture of β-hydroxyl ketones and the dehydration products, that is, chalcones and azachalcones, was obtained in most cases. However, we found that the reactions

* To whom correspondence should be addressed. E-mail: gwang@ustc.edu.cn.

(1) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford, 1998.

(2) (a) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; John Wiley & Sons: New York, 1997. (b) *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blackie Academic and Professional: London, 1998. (c) Lubineau, A.; Augé, J. *Top. Curr. Chem.* **1999**, *206*, 1−59.

(3) Lindström, U. M. *Chem. Rev.* **2002**, *102*, 2751−2772.

(4) Healthcock, C. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, pp 133−238.

(5) (a) For an early work on aldol reactions under strong basic conditions, see: House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc*. **1973**, *95*, 3310−3324. (b) For a work on intramolecular aldol reaction in the THF/H_2O systems under strong basic and acidic conditions, see: Denmark, S. E.; Lee, W. *Tetrahedron Lett*. **1992**, *33*, 7729−7732. (c) For a work on NaOH-activated aldol reaction affording a mixture of initially produced ketol and the dehydrated product, see: Fringuelli, F.; Pani, G.; Piermatti, O.; Pizzo, F. *Tetrahedron* **1994**, *39*, 11499−11508. (d) For a work on solvent-free aldol reaction attaining chalcone by grinding with NaOH, see: Raston, C. L.; Scott, J. L. *Green Chem.* **2000**, *2*, 49−51.

(6) (a) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc*. **1974**, *96*, 7503−7509. (b) Kobayashi, S.; Manabe, K. *Acc. Chem. Res*. **2002**, *35*, 209−217.

(7) For recent examples, see: (a) Denmark, S. E.; Stavenger, R. A.; Wong, K.-T.; Su, X. *J. Am. Chem. Soc*. **1999**, *121*, 4982−4991. (b) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc*. **2001**, *123*, 5260−5267.

(8) Gil, M. V.; Román, E.; Serrano, J. A. *Tetrahedron Lett*. **2001**, *41*, 4625−4628.

(9) Miura, K.; Nakagawa, T.; Hosomi, A. *J. Am. Chem. Soc.* **2002**, *124*, 536−537.

(10) For some examples, see: (a) Lubineau, A.; Meyer, E. *Tetrahedron* **1988**, *44*, 6065−6070. (b) Manabe, K.; Kobayashi, S. *Synlett* **1999**, 547−548. (c) Tian, H.-Y.; Chen, Y.-J.; Wang, D.; Zeng, C.-C.; Li, C.-J. *Tetrahedron Lett*. **2000**, *41*, 2529−2532. (d) Manabe, K.; Mori, Y.; Wakabayashi, T.; Nagayama, S.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 7202−7207. (e) Loh, T.-P.; Feng, L.-C.; Wei, L.-L. *Tetrahedron* **2000**, *56*, 7309−7312. (f) Mori, Y.; Manabe, K.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2001**, *40*, 2816−2818.

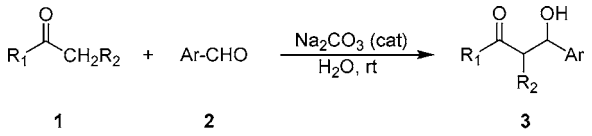
(11) Peng, Y.-Y.; Ding, Q.-P.; Li, Z.-C.; Wang, P. G.; Cheng, J.-P. *Tetrahedron Lett*. **2003**, *44*, 3871−3875.

(12) Zhang, Z.; Dong, Y.-W.; Wang, G.-W. *Chem. Lett*. **2003**, *32*, 966−967.

Published on Web 11/20/2003

10.1021/op0341263 CCC: $27.50

Scheme 1. **Cross-aldol reactions of ketones 1a−c and aldehydes 2a−c in water catalyzed by Na_2CO_3**



1 **2** **3**

1a: R_1 = 2-pyridyl, R_2 = H
1b: R_1 = Ph, R_2 = H
1c: R_1, R_2 = $(CH_2)_4$

2a: Ar = 4-NO_2-Ph
2b: Ar = 3-NO_2-Ph
2c: Ar = 2-NO_2-Ph

Table 1. **Reaction times, yields and purities for the cross-aldol reactions of ketones 1a−c with nitrobenzaldehydes 2a−c in water in the presence of 0.017 mol/L of Na_2CO_3**

entry	ketone	aldehyde	reaction time (h)	product	yield (%)[a]/ purity (%)[b]
1	**1a**	**2a**	1	**3aa**	98 (>99)
2	**1a**	**2b**	2	**3ab**	98 (>99)
3	**1a**	**2c**	18	**3ac**	87 (>98)
4	**1b**	**2a**	3	**3ba**	95 (>99)
5	**1b**	**2b**	10	**3bb**	94 (>99)
6	**1b**	**2c**	24	**3bc**	92 (>98)
7	**1c**	**2a**	8	**3ca**	94[c] (>99)
8	**1c**	**2b**	26	**3cb**	96[d] (>99)
9	**1c**	**2c**	45	**3cc**	87[e] (>98)

[a] Isolated yield. [b] Determined by ^{1}H NMR. [c] *threo*:*erythro* = 5:1. [d] *threo*:*erythro* = 1:1. [e] *threo*:*erythro* = 2:1.

of 2-acetylpyridine (**1a**), acetophenone (**1b**), and cyclohexanone (**1c**) with 4-nitro- (**2a**), 3-nitro- (**2b**), and 2-nitrobenzaldehyde (**2c**) could proceed very well under the same conditions to afford cross-aldol products **3** in very high yields (Scheme 1).

The role of Na_2CO_3 is a catalyst, and one molar equivalent of Na_2CO_3 was not necessary for the aldol reaction. In fact, a concentration of 0.017 mol/L of Na_2CO_3 (25% mol equiv) was enough for the reaction to proceed with completion. The reaction times, yields, and purities for the cross-aldol reactions of ketones **1a−c** (1.05 mmol) with nitrobenzaldehydes **2a−c** (1 mmol) in 15 mL of water catalyzed by 0.017 mol/L of Na_2CO_3 are listed in Table 1.

From Table 1, it can be seen that the isolated yields are nearly quantitative with very high purity under the given reaction conditions. The reactivity orders for the ketones and aldehydes are **1a** > **1b** > **1c** and **2a** > **2b** > **2c**, respectively. The lower reactivity of 2-nitrobenzaldehyde relative to that of 3-nitro- and 4-nitrobenzaldehyde is probably due to the steric effect of the ortho nitro group. The identities of all aldol products were unequivocally ascertained by ^{1}H NMR, ^{13}C NMR, HRMS, and FT-IR spectra. In the ^{1}H NMR spectra of the β-hydroxyl ketones from 2-acetylpyridine and acetophenone, the two methylene protons are magnetically nonequivalent due to the neighboring chiral methine group, and each proton has a double-doublet splitting pattern, the methine proton shows a double-triplet splitting, and the hydroxy proton is a doublet, fully consistent with their structures. There are two diastereoisomers for the aldol products of cyclohexanone and nitrobenzaldehydes, and the *threo*/*erythro* ratios for **3ca**, **3cb**, and **3cc** were determined by the ^{1}H NMR integrals of the proton of the methine group

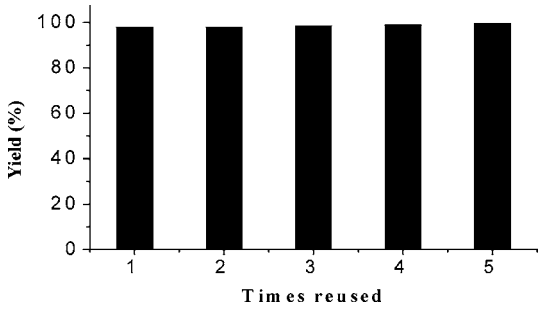


Figure 1. **Yields of cross-aldol reactions between ketone 1a and aldehyde 2b in reused aqueous phase.**

connecting hydroxy group.[10a,13] It is interesting to observe that the methine group bearing hydroxy group of **3ac**, **3bc**, and **3cc** downfield shifted about 0.5 ppm in the ^{1}H NMR spectra and upfield shifted about 4 ppm in the ^{13}C NMR spectra compared to that of the corresponding **3aa**/**3ab**, **3ba**/**3bb**, and **3ca**/**3cb**, reflecting the strong influence of the ortho nitro group of the benzene ring on the chemical shifts of neighboring methine group in both ^{1}H and ^{13}C NMR spectra.

Besides nitrobenzaldehydes, other reactive aldehydes bearing strong electron-withdrawing groups could undergo Na_2CO_3-catalyzed aldol reactions at room temperature and give selectively the β-hydroxyl ketones. For example, 3,4-dichlorobenzaldehyde reacted with 2-acetylpyridine in the presence of 0.017 mol/L of Na_2CO_3 in water at ambient temperature for 9 h to produce 3-(3,4-dichlorophenyl)-3-hydroxy-1-(2-pyridyl)-1-propanone in 98% yield.

Despite the extremely low solubility of both ketones and aldehydes used in water, the Na_2CO_3-catalyzed aldol reactions could still proceed efficiently at ambient temperature. The aldol reaction might take place at the interface of organic reactants with water in the heterogeneous system. The sparsely dissolved ketone and aldehyde in water could also react to give the aldol product in the presence of Na_2CO_3. It was found that vigorous stirring was required for the success of the aldol reaction. The aldol products **3** could be obtained in practical pure form by simple Büchner filtration of the final water suspension mixture. The purities of the aldol products were higher than 98%, as determined by ^{1}H NMR spectroscopy. On the basis of the ^{1}H NMR measurement, the ethyl acetate extract of the aqueous filtrate was the slightly excess unreacted ketone along with trace of the aldol product in a ratio of ~50:1. It should be noted that the aqueous filtrate could be reused for the next batch reaction. As an example, the reaction of **1a** with **2b** afforded aldol **3ab** quantitatively in all four subsequent runs (Figure 1). In fact, there was a slight increase of the yield in the subsequent runs, probably due to the accumulation of the excess unreacted ketone in the aqueous filtrate. The purity of aldol **3ab** was still over 99% in the fifth run.

The use of Na_2CO_3 in the aldol reaction is superior to NaOH for the preparation of β-hydroxyl ketones because byproducts are obtained in the latter case. For example, the reaction of **1a** with **2b** in the presence of 0.017 mol/L of NaOH afforded 54% of **3ab** and 38% of dehydration product

(13) Stiles, M.; Winkler, R. R.; Chang, Y.-L.; Traynor, L. *J. Am. Chem. Soc.* **1964**, *86*, 3337−3342.

3-(3-nitrophenyl)-1-(2-pyridyl)-2-propen-1-one. K_2CO_3 can also be used as catalyst in the above aldol reaction and behaves similarly to Na_2CO_3.

The aldol synthetic method reported here does not require the preformed silyl enol ethers or ketene silyl acetals which generate significant amount of metal salts as waste and usually demand the use of potentially polluting solvents and low temperatures. Catalyzed reactions of acetophenone and cyclohexanone with aromatic aldehydes are known to give chalcones and α,α′-bis(substituted)benzylidenecyclohexanones under nonaqueous solution[14] or solvent-free conditions.[14e,15] Under our reaction conditions, no traces of dehydration products from the initially formed β-hydroxyl ketones **3aa**−**cc**, self-condensation products of ketones **1a**−**c**, and diols resulting from the tandem aldol−reduction reactions by Na_2CO_3 were identified for the reactions of ketones **1a**−**c** and nitrobenzaldehydes **2a**−**c**. β-Hydroxyl ketones **3aa**−**cc** were the single isolated products with nearly quantitative yields.

Conclusions

The present contribution describes the utilization of Na_2CO_3 as an efficient catalyst for the aldol reactions of unmodified ketones and reactive aldehydes in pure water at ambient temperature. An environmentally friendly and efficient process for the synthesis of β-hydroxyl ketones has been proven to be practical from the aldol reaction of ketones and reactive aldehydes bearing strong electron-withdrawing groups. The current method presents a very attractive and appealing synthetic process for β-hydroxyl ketones because of the following advantages: (1) 100% atom economical reaction, (2) very high yield and chemoselectivity, (3) simplicity of product isolation, (4) usage of water as environmentally benign reaction medium, (5) catalytic usage of very cheap and readily available Na_2CO_3. The protocol reported in this paper can be easily developed into large-scale preparation of β-hydroxyl ketones, and the work along this line is under way.

Experimental Section

General. Reagents and solvents were obtained from commercial suppliers and were used without further purification. All melting points were determined on a XT-4 binocular microscope (Beijing Tech Instrument Co., China) and are not corrected. Infrared spectra were recorded on a VECTOR-12 infrared spectrometer in KBr pellet and reported in cm^{-1}. ^1H NMR spectra were recorded on BRUKER AV400 (400 MHz) spectrometer, chemical shifts (δ) are reported in parts per million relative to tetramethylsilane. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. ^{13}C NMR spectra were recorded on BRUKER AV400 (100 MHz) spectrometer with complete proton decoupling, chemical shifts are reported in parts per million relative to the solvent resonance as the internal standard ($CDCl_3$, δ 77.16 ppm). High-resolution mass spectra (HRMS) were recorded on a BRUKER VPEXII spectrometer with positive CI mode. Analytical TLC and column chromatography were performed on silica gel GF254, and silica gel H60, respectively.

Representative Procedure for the Preparation of β-Hydroxyl ketones 3, 3-(4-Nitrophenyl)-3-hydroxy-1-(2-pyridyl)-1-propanone (3aa). A mixture of **1a** (128 mg, 1.05 mmol) and **2a** (151 mg, 1 mmol) in 10 mL of water was stirred vigorously at room temperature for several minutes to form enough turbidity and a good dispersion. Then a solution containing 26.5 mg (0.25 mmol) of sodium carbonate and 5 mL of water was added. The reaction was followed and monitored by TLC. After the reaction was completed (1 h), the aldol product was collected by Büchner filtration, washed with water (20 mL × 3), air-dried to give 267 mg (98%) of **3aa** as white powder. The purity of the **3aa** was over 99%, as determined by ^1H NMR spectroscopy.

Other aldol products were prepared similarly. The *threo (anti)* and *erythro (syn)* isomers of aldols **3ca**, **3cb**, and **3cc** were further separated by column chromatography on silica gel with 2:1 petroleum ether/ethyl acetate.

The identities of **3ca** isomers were confirmed by comparison of their spectral data with those reported before.[10a,13,16] Part of the ^1H NMR spectral data of **3ba** were reported,[17] but it seems that the reported data are not consistent with its structure. The melting points and spectral data of all adol products **3** except those of **3ca** as well as of 3-(3,4-dichlorophenyl)-3-hydroxy-1-(2-pyridyl)-1-propanone are listed below.

3-(4-Nitrophenyl)-3-hydroxy-1-(2-pyridyl)-1-propanone (3aa): mp 107−109 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.69 (ddd, J = 4.7, 1.7, 0.9 Hz, 1 H), 8.22 (d, J = 8.7 Hz, 2 H), 8.08 (dt, J = 7.9, 1.0 Hz, 1 H), 7.90 (td, J = 7.7, 1.7 Hz, 1 H), 7.63 (d, J = 8.7 Hz, 2 H), 7.54 (ddd, J = 7.6, 4.7, 1.2 Hz, 1 H), 5.39 (dt, J = 8.8, 3.4 Hz, 1 H), 4.72 (d, J = 3.6 Hz, 1 H), 3.65 (dd, J = 16.8, 3.1 Hz, 1 H), 3.57 (dd, J = 16.8, 8.8 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.37, 152.82, 150.81, 148.97, 147.40, 137.61, 127.88, 126.66 (2C), 123.81 (2C), 122.45, 69.62, 47.61; FT-IR (cm^{-1}) 3332, 1697, 1509, 1347; HRMS (+CI) calcd for $C_{14}H_{13}N_2O_4$ (M + 1): 273.0875, found: 273.0867.

3-(3-Nitrophenyl)-3-hydroxy-1-(2-pyridyl)-1-propanone (3ab): mp 62−63 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.70 (ddd, J = 4.7, 1.7, 0.9 Hz, 1 H), 8.36 (t, J = 1.9 Hz, 1 H), 8.15 (ddd, J = 8.2, 2.2, 1.0 Hz, 1 H), 8.10 (dt, J = 7.9, 1.1 Hz, 1 H), 7.91 (td, J = 7.7, 1.7 Hz, 1 H), 7.80 (dt, J = 8.4, 1.0 Hz, 1 H), 7.55 (ddd, J = 7.6, 4.7, 1.2 Hz, 1 H), 7.54 (t, J = 8.0 Hz, 1 H), 5.39 (dt, J = 8.8, 3.2 Hz, 1 H), 4.70 (d, J = 3.5 Hz, 1 H), 3.67 (dd, J = 16.8, 3.1 Hz, 1 H), 3.57 (dd, J = 16.8, 8.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.54, 152.85, 149.05, 148.52, 145.70, 137.66,

(14) (a) Davey, W.; Gwilt, J. R. *J. Chem. Soc.* **1957**, 1008−1014. (b) Sinisterra, J. V.; Garcia-Raso, A.; Cabello, J. A.; Marinas, J. M. *Synthesis* **1984**, 502−504. (c) Natekar, R. S.; Samant, S. D. *Indian J. Chem.* **1996**, *35B*, 1347−1348. (d) Zheng, M.; Wang, L.; Shao, J.; Zhong, Q. *Synth. Commun*. **1997**, *27*, 341−354. (e) Iranpoor, N.; Zeynizadeh, B.; Aghapour, A. *J. Chem. Res. (S)* **1999**, 554−555. (f) Li, Z.; Zhang, Y.; Li, Q. *J. Chem. Res. (S)* **2000**, 580−581.

(15) (a) Toda, F.; Tanaka, K.; Hamai, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 3207−3209. (b) Iranpoor, N.; Kazemi, F. *Tetrahedron* **1998**, *54*, 9475−9480.

(16) Nakadai, M.; Saito, S.; Yamamoto, H. *Tetrahedron* **2002**, *58*, 8167−8177.

(17) Sugasawa, T.; Toyoda, T.; Sasakura, K. *Synth. Commun*. **1979**, *9*, 515−528.

132.11, 129.56, 127.95, 122.64, 122.49, 121.04, 69.53, 47.75; FT-IR (cm^{-1}) 3436, 1697, 1529, 1351; HRMS (+CI) calcd for $C_{14}H_{13}N_2O_4$ (M + 1): 273.0875, found: 273.0879.

3-(2-Nitrophenyl)-3-hydroxy-1-(2-pyridyl)-1-propanone (3ac): mp 107−109 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (ddd, J = 4.7, 1.7, 0.9 Hz, 1 H), 8.09 (dt, J = 7.9, 1.1 Hz, 1 H), 7.97 (dd, J = 8.2, 1.3 Hz, 1 H), 7.94 (dd, J = 7.9, 1.4 Hz, 1 H), 7.89 (td, J = 7.7, 1.7 Hz, 1 H), 7.65 (td, J = 7.6, 1.3, Hz, 1 H), 7.52 (ddd, J = 7.6, 4.8, 1.3 Hz, 1 H), 7.43 (td, J = 8.2, 1.4 Hz, 1 H), 5.88 (d, J = 8.9 Hz, 1 H), 4.52 (s, 1 H), 3.84 (dd, J = 17.5, 2.4 Hz, 1 H), 3.55 (dd, J = 17.5, 9.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.26, 152.84, 148.87, 147.31, 139.02, 137.29, 133.62, 128.32, 128.15, 127.61, 124.42, 122.20, 65.83, 46.91; FT-IR (cm^{-1}) 3534, 1684, 1523, 1341; HRMS (+CI) calcd for $C_{14}H_{13}N_2O_4$ (M + 1): 273.0875, found: 273.0871.

3-(4-Nitrophenyl)-3-hydroxy-1-phenyl-1-propanone (3ba): mp 112−114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 8.7 Hz, 2 H), 7.95 (dd, J = 8.4, 1.3 Hz, 2 H), 7.63 (d, J = 8.7 Hz, 2 H), 7.62 (tt, J = 8.4, 1.2 Hz, 1 H), 7.49 (t, J = 8.0 Hz, 2 H), 5.46 (dt, J = 8.8, 3.2 Hz, 1 H), 3.82 (d, J = 3.2 Hz, 1 H), 3.42 (dd, J = 17.9, 3.2 Hz, 1 H), 3.33 (dd, J = 17.9, 8.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.52, 150.17, 147.41, 136.19, 134.03, 128.85 (2C), 128.16 (2C), 126.56 (2C), 123.82 (2C), 69.24, 46.97; FT-IR (cm^{-1}) 3497, 1669, 1514, 1340; HRMS (+CI) calcd for $C_{15}H_{14}NO_4$ (M + 1): 272.0923, found: 272.0914.

3-(3-Nitrophenyl)-3-hydroxy-1-phenyl-1-propanone (3bb): mp 82−84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1 H), 8.17 (d, J = 8.2 Hz, 1 H), 7.96 (d, J = 7.9 Hz, 2 H), 7.80 (d, J = 8.0 Hz, 1 H), 7.62 (t, J = 7.4 Hz, 1 H), 7.57 (t, J = 7.8 Hz, 1 H) 7.50 (t, J = 7.8 Hz, 2 H), 5.46 (dt, J = 8.9, 3.1 Hz, 1 H), 3.83 (d, J = 3.0 Hz, 1 H), 3.45 (dd, J = 17.8, 3.0 Hz, 1 H), 3.36 (dd, J = 17.8, 8.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.78, 148.54, 145.15, 136.27, 134.17, 132.10, 129.69, 128.97 (2C), 128.30 (2C), 122.76, 121.02, 69.22, 47.10; FT-IR (cm^{-1}) 3511, 1672, 1528, 1350; HRMS (+CI) calcd for $C_{15}H_{12}NO_3$ (M − 18 + 1): 254.0817, found: 254.0809.

3-(2-Nitrophenyl)-3-hydroxy-1-phenyl-1-propanone (3bc): mp 106−107 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96−8.01 (m, 3H), 7.70 (td, J = 7.6, 1.3, 1 H), 7.60 (tt, J = 7.4, 1.3 Hz, 1 H), 7.45−7.50 (m, 3H), 5.86 (dt, J = 9.4, 2.6 Hz, 1 H), 4.01 (d, J = 3.1 Hz, 1 H), 3.73 (dd, J = 17.7, 2.2 Hz, 1 H), 3.22 (dd, J = 17.7, 9.3 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.90, 147.32, 138.58, 136.34, 133.82 (2C), 128.75 (2C), 128.43, 128.31, 128.24 (2C), 124.44, 65.95, 46.46; FT-IR (cm^{-1}) 3507, 1661, 1530, 1351; HRMS (+CI) calcd for $C_{15}H_{14}NO_4$ (M + 1): 272.0923, found: 272.0922.

2-(Hydroxyl(3-nitrophenyl)methyl)-cyclohexanone (3cb) (*threo*): mp 84−85 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (t, J = 1.8 Hz, 1 H), 8.16 (ddd, J = 8.0, 2.3, 1.1 Hz, 1 H), 7.68 (dt, J = 8.0, 1.0 Hz, 1 H), 7.53 (t, J = 8.0 Hz, 1 H), 4.90 (dd, J = 8.4, 3.1 Hz, 1 H), 4.10 (d, J = 3.1 Hz, 1 H), 1.34−2.66 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.90, 148.40, 143.37, 133.27, 129.38, 122.96, 122.11, 74.15, 57.23, 42.76, 30.84, 27.71, 24.76; FT-IR (cm^{-1}) 3436, 1693, 1532, 1352; HRMS (+CI) calcd for $C_{13}H_{16}NO_4$ (M + 1): 250.1079, found: 250.1078.

2-(Hydroxyl(3-nitrophenyl)methyl)-cyclohexanone (3cb) (*erythro*): mp 63−64 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (t, J = 1.8 Hz, 1 H), 8.12 (ddd, J = 8.0, 2.3, 1.1 Hz, 1 H), 7.67 (dt, J = 8.2, 1.0 Hz, 1 H), 7.52 (t, J = 8.0 Hz, 1 H), 5.49 (t, J = 2.4 Hz, 1 H), 3.17 (d, J = 3.3 Hz, 1 H), 1.49−2.68 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.20, 148.44, 143.88, 132.03, 129.24, 122.18, 120.97, 70.02, 56.86, 42.71, 27.97, 26.01, 24.86; FT-IR (cm^{-1}) 3434, 1691, 1525, 1353; HRMS (+CI) calcd for $C_{13}H_{16}NO_4$ (M + 1): 250.1079, found: 250.1078.

2-(Hydroxyl(2-nitrophenyl)methyl)-cyclohexanone (3cc) (*threo*): mp 123−125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, J = 8.2, 1.2 Hz, 1H), 7.77 (dd, J = 7.9, 1.4 Hz, 1 H), 7.63 (td, J = 7.7, 1.1 Hz, 1 H), 7.43 (td, J = 8.2, 1.4 Hz, 1 H), 5.44 (d, J = 7.1 Hz, 1 H), 3.95 (br, 1 H), 1.57−2.79 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.97, 148.84, 136.70, 133.12, 129.09, 128.46, 124.15, 69.87, 57.39, 42.90, 31.20, 27.83, 25.06; FT-IR (cm^{-1}) 3430, 1701, 1523, 1344; HRMS (+CI) calcd for $C_{13}H_{16}NO_4$ (M + 1): 250.1079, found: 250.1076.

2-(Hydroxyl(2-nitrophenyl)methyl)-cyclohexanone (3cc) (*erythro*): mp 86−87 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, J = 8.2, 1.3 Hz, 1 H), 7.84 (dd, J = 7.9, 1.4 Hz, 1 H), 7.65 (td, J = 7.7, 1.3 Hz, 1 H), 7.43 (td, J = 8.2, 1.5 Hz, 1 H), 5.96 (d, J = 2.1 Hz, 1 H), 2.95(br, 1 H), 1.48−2.90 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.05, 147.21, 137.08, 133.19, 129.68, 127.99, 124.71, 66.73, 54.90, 42.62, 28.05, 26.57, 24.92; FT-IR (cm^{-1}) 3422, 1701, 1523, 1336; HRMS (+CI) calcd for $C_{13}H_{16}NO_4$ (M + 1): 250.1079, found: 250.1076.

3-(3,4-Dichlorophenyl)-3-hydroxy-1-(2-pyridyl)-1-propanone: mp 41−43 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (ddd, J = 4.7, 1.7, 0.9 Hz, 1 H), 8.08 (dt, J = 7.9, 1.1 Hz, 1 H), 7.88 (td, J = 7.7, 1.7 Hz, 1 H), 7.57 (d, J = 2.1 Hz, 1H), 7.52 (ddd, J = 7.6, 4.8, 1.3 Hz, 1 H), 7.41 (d, J = 8.3 Hz, 1 H), 7.27 (ddd, J = 8.3, 2.1, 0.6 Hz, 1 H), 5.24 (dt, J = 7.8, 3.9 Hz, 1 H), 4.52 (d, J = 3.5 Hz, 1 H), 3.59 (dd, J = 16.8, 4.1 Hz, 1 H), 3.54 (dd, J = 16.8, 7.9 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.50, 152.86, 148.90, 143.75, 137.41, 132.56, 131.29, 130.39, 127.91, 127.68, 125.17, 122.28, 69.20, 47.52; FT-IR (cm^{-1}) 3352, 1704; HR MS (+CI) calcd for $C_{14}H_9NO^{37}Cl_2$ (M − 18): 281.0002, found: 280.9993.

Acknowledgment

This project is supported by the National Science Fund for Distinguished Young Scholars (20125205), Anhui Provincial Natural Science Foundation (00045306), and Anhui Provincial Bureau of Personnel Affairs.

Received for review September 5, 2003.

OP0341263