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The synthesis of a chiral fluoxetine intermediate by catalytic enantioselective hydrogenation of benzoylacetamide

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Abstract

In the presence of a chiral BINAP–ruthenium(II) catalyst, asymmetric hydrogenation of β-keto propanoic acid *N*-methyl amide under 200 psi of hydrogen pressure furnished the corresponding 3-hydroxypropanoic acid *N*-methyl amide as the single enantiomer. The product can be used as an intermediate for chiral fluoxetine.

1. Introduction

Fluoxetine and analogues belong to a class of selective serotonin (5-HT) reuptake inhibitors (SSRI), and have been widely used as antidepressants.[1] Although fluoxetine hydrochloride is currently sold as the racemate (Prozac),[2] related studies showed that the two enantiomers have different activities and rates of metabolism.[3] In recent years, non-racemic fluoxetine and its intermediates have been prepared by chemical,[4–6] enzymatic,[7] and microbiological[8] methods. Recently, Lily submitted an approval application for (*R*)-fluoxetine in the US for the treatment of bulimia.[4] Due to its medical potential, non-racemic fluoxetine still attracts considerable interest for organic and medicinal chemists. In this paper, we describe a convenient procedure for the preparation of a homochiral β-hydroxy amide as an intermediate for fluoxetine by asymmetric hydrogenation of a β-keto amide.

2. Results and discussion

Hydrogenation of β-keto carboxylates aided by chiral catalysts affords the corresponding enantiomerically pure 3-hydroxy esters with high enantioselectivity.[9,10] However, hydrogenation of β-keto amides and the application of this methodology for the synthesis of chiral compounds have not been reported in

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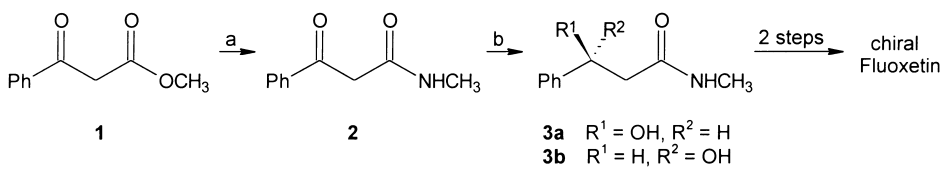
literature.[9] In fact, asymmetric hydrogenation of a β-keto amide followed by reduction of the amide to an amine should be a good pathway for the preparation of chiral 3-amino alcohols. In addition, because most primary and secondary amides are solid, these amides can be conveniently purified by a simple crystallization. Herein, we report our preliminary study on the asymmetric hydrogenation of a β-keto amide with a chiral catalyst.

The β-keto amide **2** was prepared from the reaction of *N*-methylamine and β-keto methyl ester **1** (Scheme 1). The crude solid was recrystallized several times until a colorless compound **2** was obtained. Asymmetric hydrogenation of the β-keto amide **2** in the presence of (*R*)-BINAP–$RuCl_2$ under 200 psi of hydrogen at 100°C (in a sealed reaction vessel) gave **3a**. The reaction mixture was chromatographed over silica gel to afford a crude chiral alcohol **3a**. After repeated recrystallization to remove colored impurities, (*S*)-alcohol **3a** was obtained as white needles in 50% yield. Analysis by chiral HPLC (Daicel Chiralcel OD column, *iso*-propanol:hexanes, 9:1) showed that this (*S*)-alcohol **3a** is a single enantiomer and is not contaminated by the other enantiomer **3b**. The high purity of this chiral alcohol **3a** was also confirmed by its specific rotation value (−29.1, see Table 1), which was higher than that of the literature value (−25.5).[8] We observed that the stereoselectivity in the enantioselective hydrogenation of the β-keto amide **2** and the configuration of the β-hydroxy amide **3** in this reaction are similar to those in the reduction of β-keto esters to the corresponding β-hydroxy esters. (*R*)-Alcohol **3b** was also prepared in an enantiomerically pure form when an (*S*)-BINAP–$RuCl_2$ complex was used as the catalyst. In a test experiment, we found that the enantioselectivity of this asymmetric hydrogenation was still very high (>99.9% ee) if this reaction was performed in a Parr shaker at 80°C and under 60 psi of hydrogen, but the yield of the product was not satisfactory.



Reagents and conditions: (a) 40% methyl amine, refluxed, 72 hr, 50%;
(b) (*R*)- or (*S*)-BINAP-$RuCl_2$, methanol, H_2 (200 psi), 100 °C, 18 h, 50%.

Scheme 1.

3. Experimental section

3.1. General

All reactions were carried under nitrogen unless otherwise stated. Thin layer chromatography (TLC) was performed on 0.2 mm aluminum sheets precoated with silica gel 60 (Kieselgel-60 F_{254}, E. Merck Art. 5554). Visualization was performed with UV light, 5% ninhydrin, or 5% vanillin ethanolic solution.

Table 1
Asymmetric hydrogenation of β-keto amide **2** to chiral alcohol **3**

entry	Chiral Ligand	product, configuration	yield (%)	ee (%)	$[\alpha]_D^{25}$ (c 1.25, CH_3OH)
1	(*R*)-BINAP	**3a**, *S*	50	>99.9	-29.1 (Lit.[8] -25.5)
2	(*S*)-BINAP	**3b**, *R*	50	>99.9	+28.3

Flash chromatography was carried out using 0.040–0.063 mm (230–400 mesh) silica gel 60 (Kieselgel-60, E. Merck Art. 9385). High-performance liquid chromatography (HPLC) analysis was performed on a Shimadzu LC-10At solvent delivery system equipped with an SPD-10A UV–Vis detector and an IT-500 integrator. Proton and carbon-13 NMR spectra were recorded using a Bruker AC-200 or AVANCE DRX-500 spectrometer at room temperature. Chemical shifts are reported in ppm relative to $Si(CH_3)_4$. Coupling constants are reported in hertz. The specific rotation value was measured at the sodium D-line (589 nm) using a Dr. Kernchen's Propol automatic polarimeter.

3.2. *3-Oxo-3-phenylpropanoic acid* N-*methyl amide* ***2***

A mixture of 10 mL of methyl benzoylacetate and 50 mL of aqueous 40% methylamine solution was refluxed for 72 h. The solution was extracted with ethyl acetate several times. The organic layer was washed with a brine solution and dried over magnesium sulfate. After evaporation of ethyl acetate, the viscous liquid was diluted with ethyl acetate/hexanes and stored in the freezer overnight. The solid was collected, and recrystallized from ethyl acetate and hexanes (50% yield): mp 80.8–81.0°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.05–7.95 (m, 2H), 7.70–7.30 (m, 3H), 7.16 (br s, 1H), 3.97 (s, 2H), 2.87 (d, *J*=4.8 Hz, 3H).

3.3. *(3*S*)-(−)-3-Hydroxy-3-phenylpropanoic acid* N-*methyl amide* ***3a***

To a 400 mL reaction vessel in an AtmosBag under argon was added 2 g of compound **2**, 100 mg of (*R*)-BINAP–$RuCl_2$ complex,[10b] and 100 mL of dry methanol. The reaction vessel was tightly sealed, and hydrogen was filled to about 30 psi and then released after shaking. This process was repeated three times, then hydrogen was introduced into the reaction vessel until the pressure reached about 200 psi. The solution was stirred at 100°C for 18 h. The reaction vessel was allowed to cool to room temperature and excess hydrogen was carefully bled off. The solvent was evaporated and the residue was chromatographed over silica gel. After evaporation, the crude product was recrystallized from ethyl acetate and hexanes several times until colorless needles were obtained (50% yield): mp 125.8–126.0°C; $[\alpha]_D^{25}=-29.1$ (c 1.25, CH_3OH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.25–7.17 (m, 5H), 5.81 (br s, 1H), 5.11 (dd, *J*=4.9, 7.5 Hz, 1H), 2.82 (d, *J*=4.8 Hz, 3H), 2.56 (m, 2H).

3.4. *(3*R*)-(+)-3-Hydroxy-3-phenylpropanoic acid* N-*methyl amide* ***3b***

The procedure was similar to that of compound **3a** except the (*S*)-BINAP–$RuCl_2$ complex was used as the catalyst: mp 126.0–126.2°C; $[\alpha]_D^{25}=+28.3$ (c 1.25, CH_3OH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.25–7.17 (m, 5H), 5.81 (br s, 1H), 5.11 (dd, *J*=4.9, 7.5 Hz, 1H), 2.82 (d, *J*=4.8 Hz, 3H), 2.56 (m, 2H).

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