A Convenient New Synthesis of A Naproxen Precursor

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Abstract: A precursor of Naproxen, 2-(6-methoxy-2-naphthyl)propenoic acid was synthesized in good yield from commercially available 6-methoxy-2-naphthaldehyde in three steps. The synthesis includes an unprecedented one-step reduction of acrylic acid ethyl ester to propenoic acid ethyl ester in high yield.

Key words: anti-inflammatory agents, Lewis acids, organometallic reagents, catalysis, Naproxen

The synthesis of optically active α-arylpropanoic acids is of great commercial interest as they are widely used as non steroidal anti-inflammatory agents.[1] Of these, (*S*)-2-(6-methoxy-2-naphthyl)propanoic acid, commercially known as Naproxen (**2**), is a highly valued anti-inflammatory drug with annual sales of $600 million.[2] So far, the best method for the synthesis of (*S*)-Naproxen in high yield with an excellent ee was reported by Noyori.[3a] The method involved a chiral Ru catalyzed asymmetric reduction of 2-(6-methoxy-2-naphthyl)propenoic acid. Recently, Chan has patented a chiral Ru catalyst for the reduction of **1** also in very high optical yield.[3b] However, the unsaturated acid **1** is not readily accessible. Each method reported thus far either entails several steps with moderate yields[4a–c] or requires CO gas under high pressure.[4d] Herein, we would like to report a new synthesis of **1** in three simple steps from commercially available starting aldehyde in very good yields (Figure 1, **1**).

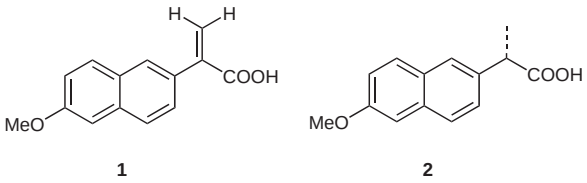
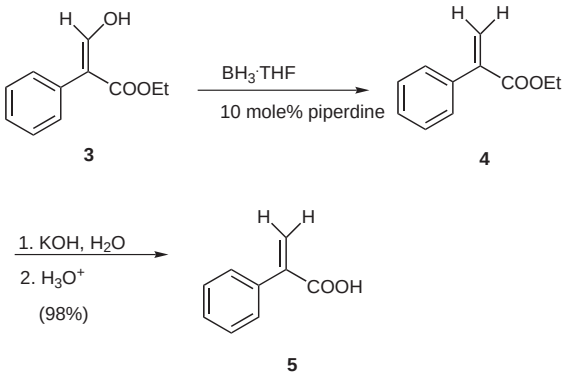
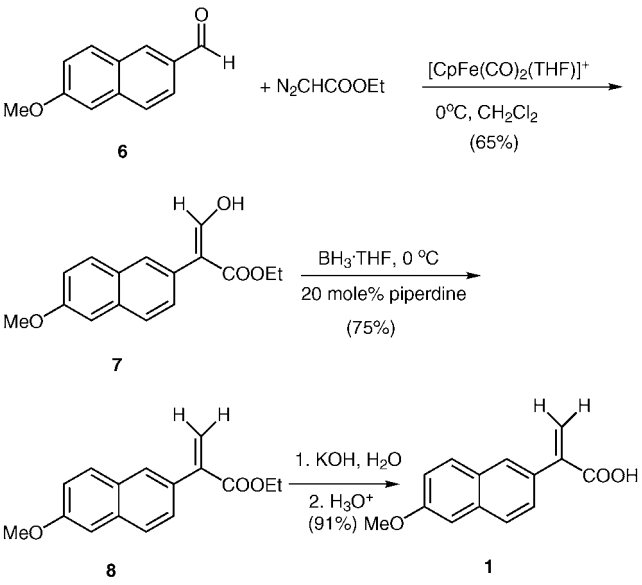


Figure 1

Recently, we have reported the synthesis of aryl-substituted 3-hydroxyacrylic acid ester **3**.[5] Now, we have found that this acid ester could be converted to propenoic acid **5** via a two step sequence (Scheme 1): first reduction by BH_3·THF in the presence of 10 mol% piperdine to propenoic acid ethyl ester **5**, followed by hydrolysis of the ester group. The one-step reduction of acrylic acid ester **4** to propenoic acid ester **5** was found to be unprecedented.



Scheme 1



Scheme 2

Based on our initial success, we decided to apply this method to synthesize 2-(6-methoxy-2-naphthyl)propenoic acid (**1**) starting from commercially available 6-methoxy-2-naphthaldehyde (**6**). Reaction of 1 equiv of 6-methoxy-2-naphthaldehyde (**6**) with 1.2 equiv of ethyldiazoacetate (EDA) in the presence of 10 mol% of the iron Lewis acid $[CpFe(CO)_2(THF)]^+$ resulted in the formation of 65% of the acrylic acid ester **7** (Scheme 2). The acrylic acid ester **7** was then converted to the propenoic ester **8** in 75% yield by BH_3·THF in the presence of 20 mol% piperdine and later, the ester **8** was hydrolyzed to the acid **1**[4b] in 91% yield.

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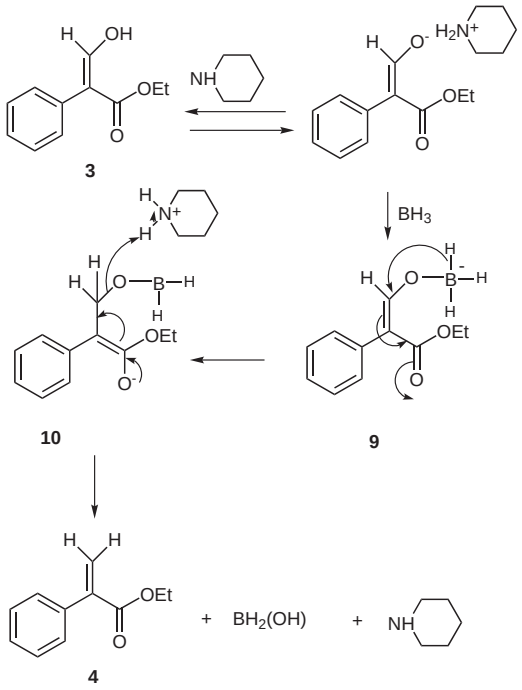

Scheme 3

Although we have not studied the mechanism of this one-step reduction, a plausible one is outlined in Scheme 3. In this proposed mechanism, the β-hydroxyacrylic acid ester **3** reacts with BH_3 in the presence of the piperdine to produce the boron complex **9**. An intramolecular migration of the hydride from the boron atom of intermediate **9** to the double bond provides the enolate **10**. In the presence of protonated piperdine, the enolate **10** undergoes an elimination reaction to form the propenoic acid ester **4**, $BH_2(OH)$ and regenerates the catalyst, piperdine.

In summary, we have reported a new method for the synthesis of 2-(6-methoxy-2-naphthyl)propenoic acid, a valuable precursor for the synthesis of (*S*)-Naproxen in three simple steps from 6-methoxy-2-naphthaldehyde in an overall yield of 45%. This method would be useful in designing a new industrial process for synthesizing the (*S*)-Naproxen. During these studies, we have developed a new one-step reaction of converting acrylic acid ester to propenoic acid ester. This new reaction is under investigation with other similar substrates and will be used in the preparation of other biologically active compounds.

All organometallic operations were performed under a dry nitrogen atmosphere using standard Schlenk techniques. All of the glass flasks were flame dried under vacuum and filled with nitrogen prior to use. Proton and carbon spectra were obtained on a 250 MHz NMR spectrometer. The chemical shifts (δ) are expressed in ppm relative to tetramethylsilane and $CDCl_3$ was used as the solvent. Previously reported compounds were identified by comparing their ^{1}H NMR with those of the known compounds. All new compounds were additionally characterized by ^{13}C NMR and elemental analysis.

Column chromatography was performed using silica gel (230–400 mesh). HPLC reagent grade CH_2Cl_2 was distilled under nitrogen from P_2O_5. Technical grade pentane was stirred with sulfuric acid overnight and then washed with sat. $NaHCO_3$ and stored over Na_2SO_4. The pentane was then distilled under nitrogen from sodium. Reagent grade Et_2O and THF were freshly distilled under a nitrogen atmosphere from sodium benzophenone ketyl. HPLC grade MeOH was distilled under nitrogen from magnesium iodide. All other reagents were used as supplied.

3-Hydroxy-2-Arylacrylic Acid Ethyl Ester (3)

We have reported this synthesis as well as the physical and spectroscopic data in an earlier publication.[5a]

2-Phenylpropenoic Acid Ethyl Ester (4)

A sample of compound **3** (0.25 g, 1.3 mmol) was dissolved in freshly distilled THF (20 mL). Piperdine (0.013 μL; 0.13 mmol) was added to the solution. The solution was cooled to 0 °C and BH_3·THF (1.56 ml, 1.56 mmol) was added. The reaction mixture was stirred for 20 h at 0 °C. H_2O (20 mL) was added to quench the reaction and organic compounds were extracted with Et_2O (3 × 20 mL). The ethereal solution was passed through a silica plug and dried (Na_2SO_4). The solvent was removed by rotary evaporation to yield 2-phenylpropenoic acid ethyl ester (**4**).

Yield: 0.216 g (86%).

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.43–7.24 (m, 5 H), 6.34 (d, 1 H, *J* = 1.3 Hz), 5.88 (d, 1 H, *J* = 1.3 Hz), 4.28 (q, 2 H), 1.32 (t, 3 H).[4d]

3-Phenylpropenoic acid (5)

A sample of **4 (**70 mg) was dissolved in acetone (15 mL). Aq KOH (1 M; 0.86 mL, 0.048 g, 0.85 mmol) was added to this solution. The mixture was allowed to stir at r.t. for 16 h. The reaction mixture was extracted with Et_2O. The aq layer was then acidified with dilute aq HCl and was extracted with Et_2O. The ethereal solution was washed with aq NaCl and dried (Na_2SO_4). The solvent was removed by rotary evaporation to get practically pure 3-phenylpropenoic acid (**5**).

Yield: 62 mg (98% yield).

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.33 (m, 5 H), 6.30 (d, 1 H, *J* = 1.0 Hz), 5.94 (d, 1 H, *J* = 1.0 Hz).[4d]

3-Hydroxy-2-(6-methoxy-2-naphthyl)acrylic Acid Ethyl Ester (7)

A sample of cyclopentadienyl dicarbonyl iron Lewis acid catalyst (0.14 g, 0.42 mmol) was dissolved in freshly distilled CH_2Cl_2 (16 mL) under nitrogen and 6-methoxy-2-naphthaldehyde (**7**) (0.77 g, 4.16 mmol) was added to it. The solution was cooled to 0 °C. A sample of ethyldiazoacetate (0.58 mL, 4.99 mmol) was diluted with freshly distilled CH_2Cl_2 (3–4 mL) and was drawn into a gas-tight syringe. It was then added to the reaction mixture dropwise over a period of 6–7 h via syringe pump. After the addition was complete, the reaction mixture was stirred for another 10–12 h at 0°C. The reaction was stopped by adding Et_2O (9–10 mL), which caused the catalyst to precipitate from the solution. Any remaining metal moiety was removed by filtration through a silica plug. The solvent was removed by rotary evaporation and the products were isolated by column chromatography (2–10% Et_2O in pentane) to get 3-hydroxy-2-(6-methoxy-2-naphthyl)acrylic acid ethyl ester (**7**).

Yield: 65% (0.74 g).

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 12.15 (d, 1 H), 7.73–7.13 (m, 6 H), 4.31 (q, 2 H), 3.96 (s, 3 H), 1.29 (t, 3 H).

^{13}C NMR ($CDCl_3$, 250 MHz): δ = 14.22, 55.38, 61.00, 105.71, 108.75, 118.97, 126.41, 127.60, 128.62, 128.87, 129.40, 129.53, 133.58, 157.84, 163.37, 171.84. Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.60; H, 5.90. Found: C, 70.77; H, 5.91.

2-(6-Methoxy-2-naphthyl)propenoic Acid Ethyl Ester (8)
A sample of compound **6** (0.18 g, 0.67 mmol) was dissolved in freshly distilled THF (20 mL). Piperdine (0.01 mL, 0.10 mmol) was added to the solution. The solution was cooled to 0 °C and BH_3·THF (1.0 mL, 1.0 mmol) was added to the solution. The reaction mixture was stirred for 20 h at 0 °C. H_2O (20 mL) was added to quench the reaction and organic compounds were extracted with Et_2O (3 × 20 mL) and the ethereal solution was dried (Na_2SO_4). The solvent was removed by rotary evaporation and the products were isolated by column chromatography (Et_2O in pentane, 2–40%) to yield **8**.

Yield: 0.13 g (75%).

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.86–7.13 (m, 6 H), 6.39 (d, 1 H, J = 1.2 Hz), 5.98 (d, 1 H, *J* = 1.2 Hz), 4.32 (q, 2 H), 3.92 (s, 3 H), 1.33 (t, 3 H).[4b]

Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.90; H, 6.30. Found: C, 74.53; H, 6.34.

2-(6-Methoxy-2-naphthyl)propenoic Acid (1)
A sample of **8 (**0.10 g, 0.40 mmol) was dissolved in acetone (15 mL). Aq KOH (1 M; 0.79 mL, 0.044 g, 0.79 mmol) was added to this solution. The mixture was allowed to stir at r.t. for 12 h. The reaction mixture was extracted with Et_2O. The aq layer was then acidified with dilute aq HCl and was extracted with Et_2O. The ethereal solution was washed with aq NaCl and dried (Na_2SO_4). The solvent was removed by rotary evaporation to give practically pure 2-(6-methoxy-2-naphthyl)propenoic acid.

Yield: 91% (0.083 g).

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.86–7.05 (m, 6 H), 6.41 (d, 1 H, J = 1.3 Hz), 6.01 (d, 1 H, J = 1.3 Hz), 3.91 (s, 3 H).[4b]

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