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## Ruthenium catalysed redox transformation of cinnamaldehyde to 3-phenylpropionic acid and methyl ester.

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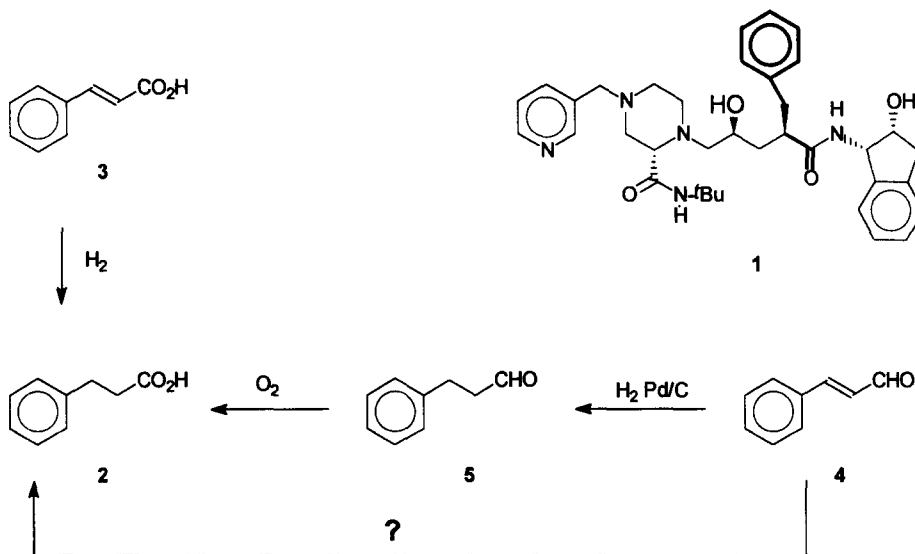
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### Abstract

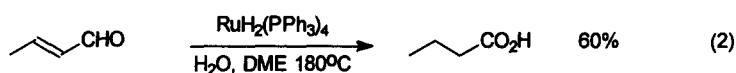
3-Phenylpropionic acid (**2**) is an intermediate for the anti-aids drug Indinavir. The one step conversion of cinnamaldehyde (**4**) into **2** was attempted using homogeneous ruthenium catalysts. Use of  $[H_2Ru(Ph_3P)_4]$  induced mainly decarbonylation of **4** to give styrene. Use of  $RuCl_3/PCy_3$  gave a mixture of **2** and cinnamic acid (**3**). Performing the same reaction in methanol, instead of water/dimethoxyethane mixtures afforded methyl 3-phenylpropionate in 70% yield. © 1998 Elsevier Science Ltd. All rights reserved.

Indinavir (**1**) is a highly successful anti-aids agent which is currently used in combination therapy [1]. The compound and its building blocks have inspired many interesting synthetic efforts [2]. One of the less conspicuous constituents is 3-phenylpropionic acid (**2**). Though **2** can be easily produced by hydrogenation of cinnamic acid (**3**), cinnamaldehyde (**4**) is a much

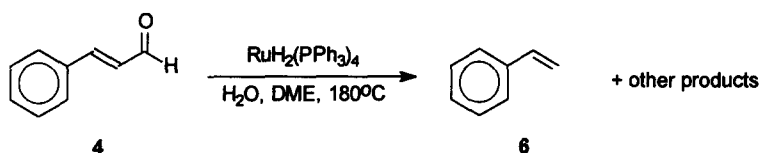


Scheme 1. Preparation of 3-phenylpropionic acid, a building block for Indinavir.

cheaper raw material than **3**. For this reason we have developed a simple and high yielding route to 3-phenylpropionic acid based upon the hydrogenation of **4** to 3-phenylpropionaldehyde (**5**), followed by air oxidation of **5** to **2** (Scheme 1.) [3]. Unfortunately, the higher number of reaction steps offsets the price advantage of cinnamaldehyde over cinnamic acid. Our aim was therefore to design a catalytic one step process for the conversion of cinnamaldehyde to 3-phenylpropionic acid. This would seem a viable venture as the net reaction works out thermodynamically advantageous and the hydrogen equivalents could be transferred via known transition metal catalysed steps. In fact, we could find one earlier reported instance of the desired transformation. In a paper by Murahashi *et al.* on the ruthenium catalysed oxidative transformation of alcohols and aldehydes to esters and lactones the transformation of crotonaldehyde to butyric acid catalysed by  $[\text{RuH}_2(\text{PPh}_3)_4]$  [4] is described to take place in 68% yield (Scheme 2.) [5].



Application of these conditions to **4** led to quite different results, however. Only minor amounts of **2** were formed, and styrene (**6**) was found to be the main product. At later stages in the reaction the amount of **6** diminished, presumably due to polymerisation (Fig. 1).



Conditions: 3 mmol  $[\text{RuH}_2(\text{PPh}_3)_4]$ , 50 mmol cinnamaldehyde, 2ml  $\text{H}_2\text{O}$  and 18ml DME,  $180^\circ\text{C}$ , 2h

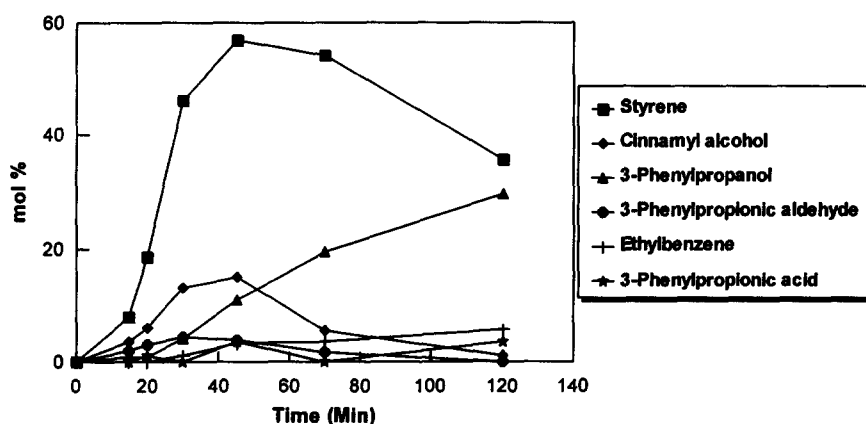
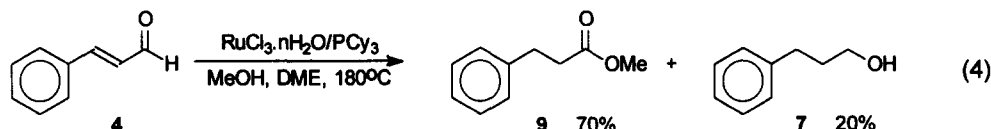
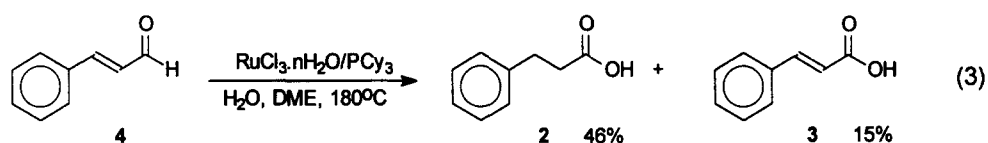


Figure 1. Decarbonylation of cinnamaldehyde.

The ruthenium and rhodium catalysed decarbonylation of saturated aldehydes has been reported by Prince and Raspin [6]. The catalytic decarbonylation of cinnamaldehyde has been reported using Pd/C [7], Pt/C, Ra-Ni [8] and [RhCl(PPh<sub>3</sub>)<sub>3</sub>] [9]. However, we also considered the possibility that styrene is formed by decarboxylation of **2** [6, 10]. Treatment of **2** with the catalyst under the same reaction conditions afforded no styrene. Finally, the possibility that **6** is formed via a radical pathway was investigated by the addition of 2,6-di-*t*-butylphenol as radical inhibitor. This did not stop the decarbonylation reaction but had the surprising side effect of inducing the reduction of styrene to ethylbenzene (25% yield). Ruthenium catalysed decarbonylation of cinnamaldehyde therefore seems the most likely mechanism for this synthetically useful transformation.

A number of other ruthenium catalysts were tested for the desired conversion under the same conditions [11]. From this search the catalyst obtained by stirring a solution of RuCl<sub>3</sub> and 3 equivalents of tri-cyclohexylphosphine (PCy<sub>3</sub>) in CH<sub>3</sub>OH under N<sub>2</sub> for 1 hr, followed by evaporation of CH<sub>3</sub>OH to leave a dark green solid, gave the best results [12]. With 0.5 mol% of catalyst the aldehyde **4** was fully converted after 28 hr at 180°C in a water dimethoxyethane (DME) mixture (Scheme 3). In addition to the desired **2** (46%) some **3** (15%) was also obtained. Analysis of the reaction mixtures over time using <sup>1</sup>H NMR and GC showed that the formation of **2** and **3** continues even after all **4** has been converted. This can be explained by the formation of a stable intermediate product. As it is known that ruthenium complexes can catalyse the Tishchenko reaction [13] we independently synthesised cinnamyl cinnamate. However, this compound was not found in any quantities, nor did we find **5**, 3-phenylpropanol (**7**) or cinnamyl alcohol (**8**).

The poor mass balance can be a result of retro-condensation of cinnamaldehyde to give acetaldehyde and benzaldehyde, which both react to a multitude of other products. To suppress this reaction we next decided to investigate the formation of methyl 3-phenyl-propionate (**9**) by carrying out the transformation of **4** in CH<sub>3</sub>OH instead of water (Scheme 4.).



This reaction proceeds much faster than the one in water, resulting in a much higher selectivity. The main side product was **7** (20%). From this mixture **2** can be obtained in pure form by basic hydrolysis (NaOH/CH<sub>3</sub>OH), work-up by evaporation, partitioning between ether and water, followed by acidification of the aqueous layer.

In conclusion, direct redox transformation of cinnamaldehyde in DME/H<sub>2</sub>O at 180°C catalysed by a catalyst made *in situ* from RuCl<sub>3</sub>/PCy<sub>3</sub> gave an inseparable mixture of 3-phenylpropionic acid and cinnamic acid. Performing the same reaction in CH<sub>3</sub>OH gave a useful 70% yield of methyl 3-phenylpropionate, from which 3-phenylpropionic acid can be isolated in pure form. Treatment of cinnamaldehyde with RuH<sub>2</sub>(PPh<sub>3</sub>)<sub>4</sub> in DME/water induced decarbonylation to styrene.

## Experimental Section

**Preparation of methyl 3-phenylpropionate:** To RuCl<sub>3</sub>·nH<sub>2</sub>O (0.1g, 0.4 mmol) and PCy<sub>3</sub> (0.3 g, 1.2 mmol) in a Schlenk tube degassed CH<sub>3</sub>OH (15 ml) was added under N<sub>2</sub> and the solution was stirred for 1h at ambient temperature. The green solution was transferred to an autoclave (Parr Hastelloy C) and **4** (9.0g, 68 mmol) and CH<sub>3</sub>OH (10 ml) were added. The autoclave was brought to 180°C and the mixture was stirred at this temperature till completion of the reaction (5h). Samples were taken for GC analysis after 0.5, 1, 2, 3 and 5 h. GC was performed on a Chrompac wcot fused silica column, using the following temperature program: T<sub>init</sub> 70°C 1 min, 10<sup>0</sup>/min, T<sub>final</sub> 220°C. 1,2,4 trichlorobenzene was added to the samples as internal standard.

## References

- [1] Vacca JP, Dorsey BD, Schleif WA, Levin RB, McDaniel SL, Darke PL, Zugay J, Quintero JC, Blahy OM, Sardana VV, Schlabach AJ, Graham PI, Condra JH, Gotlib L, Holloway MK, Lin J, Chen IW, Vastag K, Ostovic D, Anderson PS, Emini EA, Huff JR. Proc. Natl. Acad. Sci. USA. 1994;91:4096-4100.
- [2] a) Askin D, Eng KK, Rossen K, Purick RM, Wells KM, Volante RP, Reider P. Tetrahedron Lett. 1994;35:673-676. b) Malignes PE, Upadhyay V, Rossen K, Cianciosi SJ, Purick RM, Eng KK, Reamer RA, Askin D, Volante RP, Reider PJ, Tetrahedron Lett. 1995;36:2195-8. c) Rossen K, Weissman SA, Sager J, Reamer RA, Askin D, Volante RP, Reider PJ. Tetrahedron Lett. 1995;36:6419-6422. d) Malignes PE, Weissman SA, Upadhyay V, Cianciosi SJ, Reamer RA, Purick RM, Sager J, Rossen K, Eng KK, Askin D, Volante RP, Reider PJ. Tetrahedron 1996;52:3327-3338. e) Rossen K, Reamer RA, Volante RP, Reider PJ. Tetrahedron Lett. 1996;37:6843-6846.
- [3] a) Castelijns AMCF, Hogeweg JM, van Nispen SPJM. WO 96 11898 (to DSM). b) Castelijns AMCF, Hogeweg JM, Van Nispen SPJM. WO 96 11900 (to DSM).
- [4] Harris RO, Hota NK, Sadavoy L, Yuen JMC. J. Organomet. Chem. 1973;54:259.
- [5] Murahshi SI, Naota T, Ito K, Maeda Y, Taki H. J. Org. Chem. 1987;52:4319-4327.
- [6] Prince RH, Raspin KA, J. Chem. Soc. Chem. Commun. 1966: 156-157.
- [7] Hoffmann NE, Kanakkanatt AT, Schneider RF. J. Org. Chem. 1962;27:2687-2689.
- [8] Mailhe A. Bull. Soc. Chim. Fr. 1926;39:922.
- [9] Tsuji J, Ohno K. Tetrahedron Lett. 1967;23:2173-2176.
- [10] Miller JA, Nelson JA, Byrne MP. J. Org. Chem. 1993;58:18-20.
- [11] The following catalysts were tested but gave lower yields of the desired product: [RuCl<sub>2</sub>(DMSO)<sub>4</sub>], [CpRuCl(PPh<sub>3</sub>)<sub>2</sub>], [Ru<sub>3</sub>O(OAc)<sub>6</sub>(H<sub>2</sub>O)<sub>3</sub>]<sup>+</sup>OAc<sup>-</sup>, [Ru(CO)<sub>2</sub>(Ph<sub>4</sub>CpOH)]<sub>2</sub>, [RuCl<sub>2</sub>(p-Cymene)]<sub>2</sub>, RuCl<sub>3</sub> with 3 eq. of PPh<sub>3</sub>, *i*-Pr<sub>3</sub>, or *n*-Bu<sub>3</sub>.
- [12] <sup>31</sup>P NMR analysis of the catalyst showed several species. The most abundant (50%) was [RuHCl(CO)(PCy<sub>3</sub>)<sub>2</sub>]. See: James BR, Preece M, Robinson SD. Adv. Chem. Ser. 1982;196:145-161.
- [13] a) Horino H, Takashi I, Yamamoto A. Chem Lett. 1978:17-20. b) Ito T, Horino H, Koshiro Y, Yamamoto A. Bull. Chem. Soc. Jpn. 1982;55:504-512. c) Menashe N, Shvo Y. Organometallics 1991;10:3885-3891. d) Nozaki K, Yoshida M, Takaya H. J. Organomet. Chem. 1994;473:253-256.