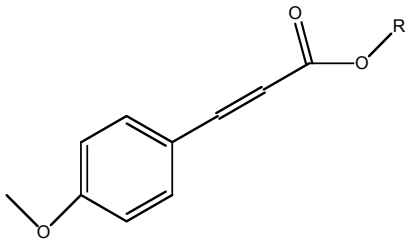
Experiment 2: Two-step Synthesis of Ethyl 4-Methoxycinnamate

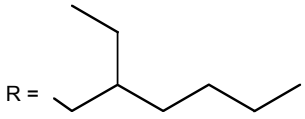
Background

Why is ethyl 4-methoxycinnamate (**1**) interesting?

First, it is the analog of octyl 4-methoxycinnamate (**2**), a UV light blocker found in Bain de Soleil All Day Sunblock and Coppertone Sport. The derivatives of 4-methoxycinnamic acid absorb UVB radiation due to their high level of conjugation. They are also oil soluble. UVB radiation promotes dermal cell DNA damage causing skin cancer. Octyl 4-methoxycinnamate is used in sunscreen over ethyl 4-methoxycinnamate because of its higher molar absorptivity ε and its greater lipophilicity.



R = $-CH_3CH_3$ ethyl 4-methoxycinnamate (**1**)



octyl 4-methoxycinnamate (**2**)

Figure 1: Derivatives of 4-methoxycinnamic acid

Second, a two-step synthesis is put forth so that you can practice multi-step synthesis using a variety of laboratory techniques before diving into Honors Cup.

Step 1 is the Verley-Doebner modification of the Knoevenagel condensation.[1] The Knoevenagel condensation reaction dates from 1896 and is a facile one-step method of forming new carbon-carbon bonds under mild reaction conditions. It utilizes a weak amine base such as piperidine to initially form an enolate anion derived from a 1,3-dicarbonyl compound. The enolate subsequently acts as a nucleophile in the condensation with another carbonyl compound. This carbonyl is often an aldehyde and the reaction mechanism bears striking similarity to that of the aldol condensation. The isolated product is generally an α,β-unsaturated carboxylic acid, formed by ready dehydration of the intermediate β-hydroxydicarbonyl compound and subsequent saponification and decarboxylation.

[1] Jones, G. *Organic Reactions*; Wiley: New York, 1967; Vol. 15, pp 204-599.

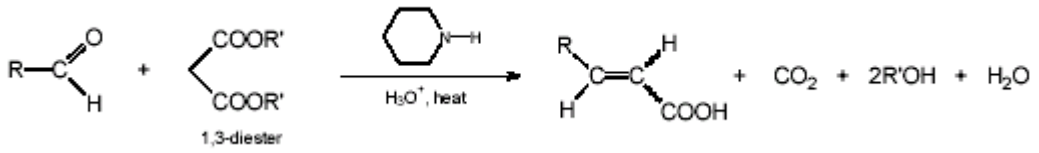


Figure 2: A Generalized Knoevenagel Condensation

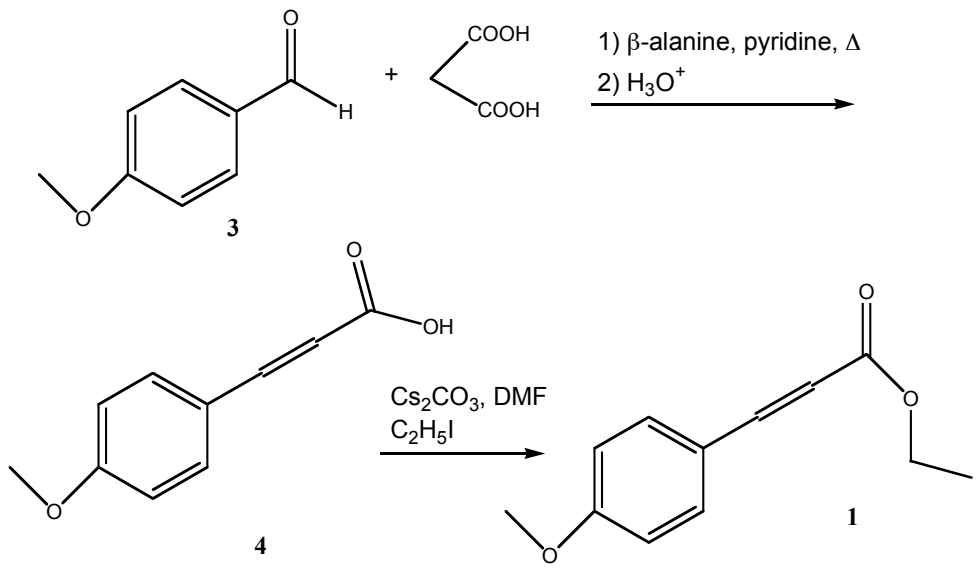
The Verley-Doebner modification of this condensation employs pyridine as solvent and catalyst and a cocatalyst such as β-alanine. With this procedure malonic acid itself, rather than its diester can be efficiently condensed with 4-methoxybenzaldehyde (*p*-anisaldehyde) to generate 4-methoxycinnamic acid.

Experimental

4-Methoxycinnamic Acid [3-(4-Methoxyphenyl)-2-proenoic Acid] (4): In a 25-mL, round-bottomed flask, 4-methoxybenzaldehyde (0.804 mL, 6.61 mmol) (**3**), malonic acid (1.75 g, 16.8 mmol), and β-alanine (0.10 g, 1.12 mmol) were dissolved in pyridine (3.0 mL, 37.1 mmol) and heated under reflux for 90 minutes. After cooling to room temperature, the reaction mixture was placed in an ice bath and 8.0 mL of concentrated HCl was *slowly* added. The resulting white precipitate was collected by vacuum filtration, washed with cold water (2 x 10mL) and dried thoroughly. The product was recrystallized from absolute ethanol (~20 mL). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.75 (d, 1H, J = 16.0 Hz), 7.51 (d, 2H, J = 8.8 Hz), 6.92 (d, 2H, J = 8.8 Hz), 6.33 (d, 1H, J = 15.8 Hz), 3.85 (s, 3H).

Hint: For best results dry your product thoroughly by spreading it out on a watch glass/filter paper between lab days.

Ethyl 4-Methoxycinnamate [(*E*)-Ethyl 3-(4-Methoxyphenyl)-2-propenate (1): **4** (0.60 g, 3.36 mmol) was dissolved in 10 mL of dry *N*,*N*-dimethylformamide (DMF) in a 25-mL, round-bottomed flask. Cesium carbonate (1.65 g, 5.06 mmol) was added followed by iodoethane (1.0 mL, 12.5 mmol). The flask was capped (rubber septum) and the heterogeneous mixture stirred vigorously at 50 °C for one hour. After this time, HCl (1.0 M, 4.0 mL) was added to quench the reaction. The liquid was decanted from any remaining solid and extracted with 3 : 1 hexanes/ethyl acetate (2 x 10 mL). The organic layer was washed with brine (20 mL), dried with $MgSO_4$, filtered, and solvent removed. The remaining oil solidified on standing to form colorless prisms. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.66 (d, 1H, J = 16.0 Hz), 7.49 (d, 2H, J = 8.8 Hz), 6.91 (d, 2Hz, J = 8.6 Hz), 6.31 (d, 1 H, J = 16.0 Hz), 4.26 (q, 2H, J = 7.2 Hz), 3.84 (s, 3H), 1.35 (t, 3H, J = 7.2 Hz).



Scheme 1: Synthesis of ethyl 4-methoxycinnamate

Questions to be addressed in your report:

Is the double bond in **1** trans, cis, or a mixture? How did you deduce this? Make sure you're your report reflects your method of deducing this information. (Hint: The stereochemistry of the double bond can be deduced in two different ways so find out as much as you can about each of the possibilities.)

Why was a cesium salt used in step 2?[2]

The ^{1}H NMR data is given. What other characterization techniques give you useful information?

What is your overall yield?

[2] Dijkstra, G.; Kruizinga, W. H.; Kellogg, R. M. *J. Org. Chem.* **1987**, *52*, 4230-34.