The Microscale Laboratory

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Two-Step Semi-Microscale Preparation of a Cinnamate Ester Sunscreen Analog

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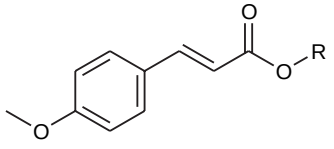
Several laboratory experiments concerning the physical properties of sunscreens have appeared in this *Journal* during the last decade *(1–5)*. These include quantification of commercial formulations by liquid chromatography *(1)* and ultraviolet (UV) spectrophotometry *(2–4)*. The photochemistry of sunscreens has also been reviewed *(6)*. Significantly, a student procedure focusing on multistep sunscreen synthesis and spectroscopic analysis has not, to our knowledge, been reported. Given the current high profile nature of skin cancer *(7)* and media attention towards sunscreens, we designed a two-step synthetic pathway towards an analog of a commercially available UV light blocker. This methodology is incorporated into a third-year undergraduate organic synthesis course at the University of Toronto.

Esters derived from *trans*-4-methoxycinnamic acid (R = H, Figure 1) are effective absorbers of UV radiation *(8)*. The 2-ethylhexyl ester **2** (commonly called octyl methoxycinnamate) is a high boiling point liquid found in many sunscreen preparations such as Bain de Soleil All Day Sunblock, Coppertone Sport, and Solbar Shield. For ease of isolation we chose to generate an analog of **2** (ethyl ester **1**, absent in sunscreens), which is obtained as a low melting point solid in two four-hour laboratory periods. Esters of *trans*-4-methoxycinnamic acid are showcased in several introductory organic chemistry textbooks *(9)*. These highly conjugated compounds absorb UVB radiation between 290–320 nm and are oil soluble. UVB radiation promotes dermal cell DNA damage, causing skin cancer *(10)*.

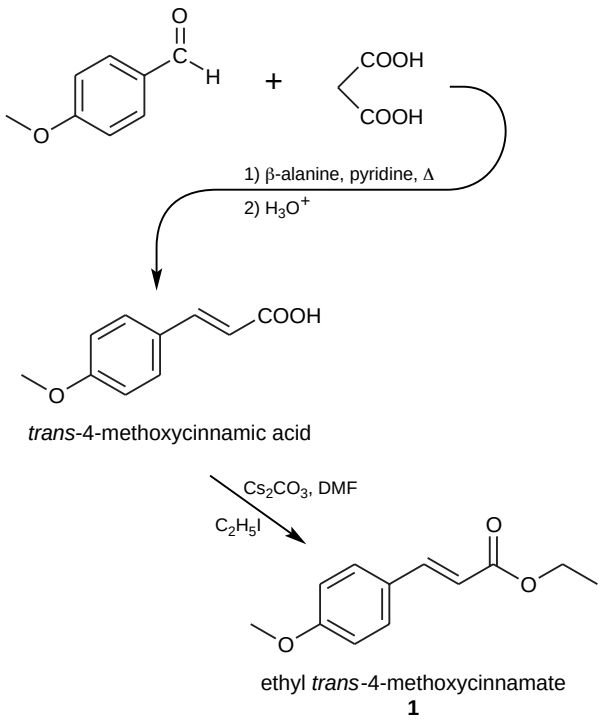


R	Compound number
$-CH_2CH_3$	**1**
$-CH_2CH(CH_2CH_2CH_2CH_3)CH_2CH_3$	**2**

Figure 1. UV light absorbers derived from *trans*-4-methoxycinnamic acid.

A two-step procedure using 4-methoxybenzaldehyde as the starting material (Scheme I) synthesizes ethyl *trans*-4-methoxycinnamate **1**. In the first laboratory session students are exposed to an important carbon–carbon bond forming condensation reaction. The Verley–Doebner modification of the Knoevenagel condensation *(11)* affords facile synthesis of *trans*-4-methoxycinnamic acid, which is isolated and characterized. During the second period, esterification is effected by a cesium base mediated O-alkylation approach. This exemplifies the so-called "cesium effect" *(12)* and the usefulness of cesium carboxylates as nucleophiles in S_N2 reactions.

In addition to stimulating class enthusiasm towards synthetic chemistry, this experiment impresses many organic pedagogical concepts, both practical and theoretical. Students become reacquainted with laboratory techniques such as heating under reflux, extraction, vacuum filtration, and thin-layer chromatography. Melting point measurements and spectro-



Scheme I. Synthesis of ethyl *trans*-4-methoxycinnamate.

scopic methods (^{1}H and ^{13}C NMR, MS, UV, IR) readily characterize both carboxylic acid and ester products. Of especial interest is the ^{1}H NMR spectrum of ethyl *trans*-4-methoxycinnamate **1**, which illustrates exceptional examples of proton shielding–deshielding and spin–spin splitting. Students may be challenged to deduce the alkene geometry in *trans*-4-methoxycinnamic acid by calculation of proton coupling constants. As this compound is commercially available,[1] the esterification reaction can be undertaken if only a single laboratory session is accessible in the curriculum.

Synthetic Overview

Verley–Doebner Synthesis of trans*-4-Methoxycinnamic Acid*

trans-4-Methoxycinnamic acid, (*E*)-3-(4-methoxyphenyl)-2-propenoic acid, is synthesized by adapting and scaling up the microscale procedure described by Kolb et al. *(13).* In a 25-mL round-bottomed flask, 4-methoxybenzaldehyde (0.804 mL, 6.61 mmol), malonic acid (1.75 g, 16.8 mmol) and β-alanine (0.1 g, 1.12 mmol) are dissolved in pyridine (3 mL, 37.1 mmol). The mixture is heated under reflux for 90 min. After cooling to room temperature and then in an ice bath, 8 mL of concentrated HCl is added slowly causing a white precipitate to form. This solid is collected by vacuum filtration, washed with cold water (2 × 10 mL), and dried thoroughly to typically yield 0.8–1.1 g pure product (68–93%).

mp 169–171 °C [lit. *(14)* 170–172 °C].

^{1}H NMR (200 MHz, $CDCl_3$, δ): 3.85 (s, 3H), 6.33 (d, 1H, J = 15.8 Hz), 6.92 (d, 2H, J = 8.8 Hz), 7.51 (d, 2H, J = 8.8 Hz), 7.75 (d, 1H, J = 16.0 Hz).

^{13}C NMR [300 MHz, DMSO-d_6 (product insufficiently soluble in $CDCl_3$), δ]: 55.98, 115.03, 117.18, 127.51, 130.65, 144.47, 161.63, 168.58.

Synthesis of Ethyl trans*-4-Methoxycinnamate*

Ethyl *trans*-4-methoxycinnamate **1**, (*E*)-ethyl 3-(4-methoxyphenyl)-2-propenate, is generated by the method of Parrish et al. *(15)* with some modification. *trans*-4-Methoxycinnamic acid (0.6 g, 3.36 mmol, product of Verley–Doebner synthesis)[1] is 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) is added followed by iodoethane (1 mL, 12.5 mmol). The flask is capped (rubber septum) and the heterogeneous mixture is stirred vigorously at 50 °C for one hour. After this time 4 mL of HCl (1 M) is added to quench the reaction. The liquid is decanted from any solid Cs_2CO_3 remaining and extracted with 3:1 hexanes/ethyl acetate (2 × 10 mL). The organic layer is washed with brine (20 mL) and dried using $MgSO_4$. Removal of the drying agent by filtration is followed by solvent removal (under vacuum). An oil remains that solidifies on standing to form colorless prisms (0.3–0.55 g, 43–80%).

mp 47–48.5 °C [lit. *(16)* 49–50 °C].

TLC: stationary phase, silica gel; eluent, 5:1 hexanes/ethyl acetate; $R_{f\text{product}}$ = 0.48 (UV lamp, 254 nm).

^{1}H NMR (200 MHz, $CDCl_3$, δ): 1.35 (t, 3H, J = 7.2 Hz), 3.84 (s, 3H), 4.26 (q, 2H, J = 7.2 Hz), 6.31 (d, 1H, J = 16.0 Hz), 6.91 (d, 2H, J = 8.6 Hz), 7.49 (d, 2H, J = 8.8 Hz), 7.66 (d, 1H, J = 16.0 Hz).

^{13}C NMR (300 MHz, $CDCl_3$, δ): 14.51, 55.50, 60.47, 114.44, 115.85, 127.31, 129.84, 144.39, 161.46, 167.49.

Hazards

All synthetic and purification procedures for both syntheses should be undertaken in an adequately ventilated fumehood. Pyridine has an obnoxious odor and is related to long-term liver, kidney, and central nervous system damage. This compound is toxic by ingestion, inhalation, and skin absorption, as is DMF. DMF is additionally a teratogen. Hydrochloric acid causes severe burns. Malonic acid is harmful if swallowed and poses a risk of serious eye damage. Iodoethane is harmful by inhalation and a vesicant. 4-Methoxybenzaldehyde, *trans*-4-methoxycinnamic acid, cesium carbonate, and ethyl *trans*-4-methoxycinnamate are irritating to the eyes, respiratory system, and skin. All liquid reactants and solvents are either flammable (iodoethane) or highly flammable (pyridine, hexanes, ethyl acetate, DMF). Liquid reagents should be dispensed using an automatic delivery syringe. Students should undertake all aspects of practical work wearing protective gloves, safety glasses, and a laboratory coat.

Discussion

A diverse range of organic chemistry concepts are underscored by the procedures reported. The high-yielding Verley–Doebner synthesis of *trans*-4-methoxycinnamic acid is illustrative of carbonyl condensation chemistry and a fundamental example of enolate anion reactivity. Students are encouraged to discuss the reaction mechanism with respect to the catalytic role of pyridine and β-alanine. Product alkene geometry can be concealed from the class to introduce an investigative feature. Trans stereochemistry is readily deduced by melting point measurements: trans isomer mp 169–171 °C, cis isomer mp 64–65 °C *(14).* Observed vinylic proton coupling constants ($J_{\text{trans H-C=C-H}}$ = 13–18 Hz versus $J_{\text{cis H-C=C-H}}$ = 6–11 Hz) are confirmatory evidence of geometry *(17).*

Cesium carboxylate O-alkylation highlights an alternative mode of esterification rather than the traditional Fischer approach *(18).* Advantages of undertaking a reaction under mild, irreversible conditions are made apparent. The "cesium effect" is a supplemental point of interest. Cesium carboxylate salts ($RCOO^-Cs^+$) have enhanced solubility in polar aprotic solvents (e.g., DMF) compared to other alkali metal carboxylates *(12).* Cesium salts are almost entirely dissociated as free ions or solvent separated ion pairs. Polar aprotic solvents solvate cations much more effectively than anions *(19).* The carboxylate anions in $RCOO^-Cs^+$ are consequently considered as being "naked" and hence highly reactive nucleophiles in S_N2 processes. This contrasts with sodium carboxylate salts that are much less soluble in polar aprotic media. Ester formation is monitored by thin-layer chromatography, which initially reveals to students UV light absorption by such compounds.

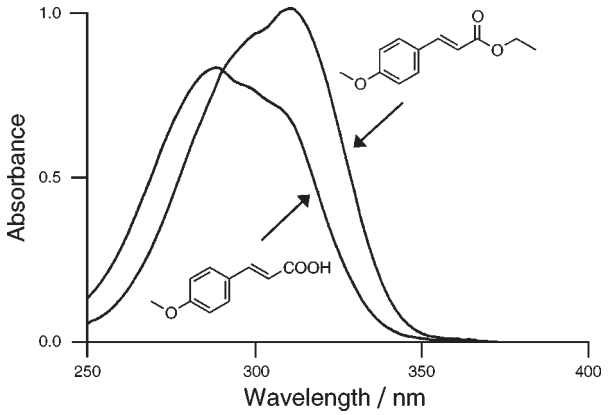


Figure 2. UV absorption spectra of equimolar *trans*-4-methoxycinnamic acid and ethyl *trans*-4-methoxycinnamate (95% C_2H_5OH).

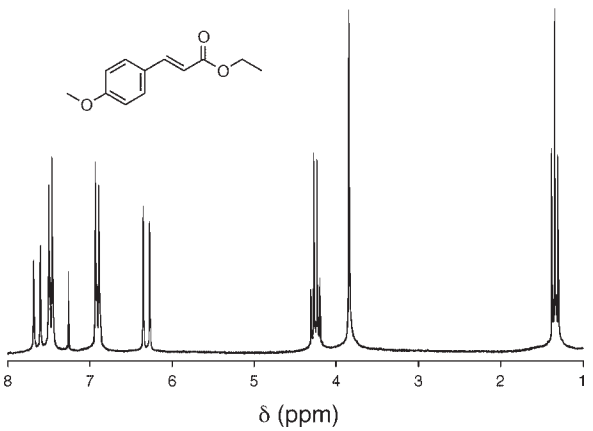


Figure 3. ^1H NMR spectrum of ethyl *trans*-4-methoxycinnamate ($CDCl_3$, 200 MHz).

Aspects of spectroscopic analysis can be combined into the critique of experimental results. Contrasting IR spectra of 4-methoxybenzaldehyde, *trans*-4-methoxycinnamic acid, and ethyl *trans*-4-methoxycinnamate **1** indicates different carbonyl-containing functional groups absorbing radiation at distinct wavenumbers (1698 cm^{-1}, 1686 cm^{-1}, and 1705 cm^{-1}, respectively). Students can rationalize lowered C=O stretch absorptions (~30 cm^{-1}) compared to nonconjugated carbonyl functionalities. UV spectroscopy stimulates appreciation of why a cinnamate ester, **2**, is chosen as a sunscreen component rather than the precursor carboxylic acid. Compounds **1** and **2** have greater molar extinction coefficients between 290–320 nm than *trans*-4-methoxycinnamic acid and therefore absorb UVB radiation more effectively (Figure 2).

The proton NMR of ethyl *trans*-4-methoxycinnamate has several features of note. A fortuitous absence of peak overlap produces a clear, unambiguous spectrum that facilitates analysis (Figure 3). An excellent opportunity exists to review concepts of proton spin–spin splitting and shielding–deshielding. A characteristic triplet ($OCH_2C\underline{H}_3$, δ 1.35) and quartet ($OC\underline{H}_2CH_3$, δ 4.26) splitting pattern reveals ethyl esterification has taken place. Methoxy protons are deshielded (δ 3.84) as predicted. Two aromatic doublets (δ 6.91 and δ 7.49, J = 8.8 Hz) are indicative of *para*-disubstitution with an electron donating (shielding) $-OCH_3$ moiety and an electron withdrawing (deshielding) $-CH=CH-$ group attached. Each alkene proton appears as a doublet (δ 6.31 and δ 7.66, J = 16 Hz) with *trans* geometry again evident.

This experiment motivates the class to connect their synthetic product structure with its ability to act as a UVB light absorber. Importantly, it is stressed that ethyl ester **1** is not an ingredient of commercial sunscreens. Students are informed that 2-ethylhexyl ester **2** is the cinnamate commonly present in over-the-counter lotions, and can be challenged to explain why experimentally. Most decide to obtain a UV spectrum of **2**,[2] which indicates that **2** has a greater molar extinction coefficient (ε_{312nm} = 30,100 M^{-1} cm^{-1}) than **1** (ε_{310nm} = 24,700 M^{-1} cm^{-1}) in the UVB range. Additionally, the larger hydrocarbon chain in **2** (compared to **1**) imparts greater lipophilic properties to the 2-ethylhexyl ester. This significantly increases oil solubility and water resistivity, allowing the sunscreen to remain on skin longer.

Summary

The preparation and analysis of a sunscreen analog is a welcome inclusion to a middle-year organic chemistry laboratory. Students are fascinated with a compound of the type that has such pertinence in the world today.

WSupplemental Material

Instructions for the students, notes for the instructor, and spectroscopic information are available in this issue of *JCE Online*.

Notes

1. *trans*-4-Methoxycinnamic acid is available from Sigma-Aldrich, product no. M1,380-7.

2. 2-Ethylhexyl *trans*-4-methoxycinnamate is available from Sigma-Aldrich, product no. 43,717-4.

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The structures of several cinnamate esters discussed in this article are available in fully manipulable Chime format as *JCE* Featured Molecules in *JCE Online*.

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