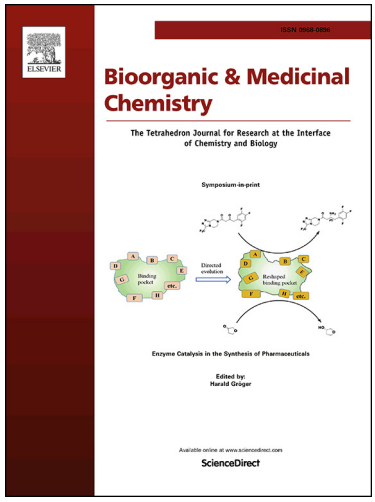
Accepted Manuscript



Synthesis of (*E*)-cinnamyl ester derivatives via a greener Steglich esterification

Andrew B. Lutjen, Mackenzie A. Quirk, Allycia M. Barbera, Erin M. Kolonko

PII: S0968-0896(18)30052-X
DOI: https://doi.org/10.1016/j.bmc.2018.04.007
Reference: BMC 14290

To appear in: *Bioorganic & Medicinal Chemistry*

Received Date: 11 January 2018
Revised Date: 30 March 2018
Accepted Date: 3 April 2018

Please cite this article as: Lutjen, A.B., Quirk, M.A., Barbera, A.M., Kolonko, E.M., Synthesis of (*E*)-cinnamyl ester derivatives via a greener Steglich esterification, *Bioorganic & Medicinal Chemistry* (2018), doi: https://doi.org/10.1016/j.bmc.2018.04.007

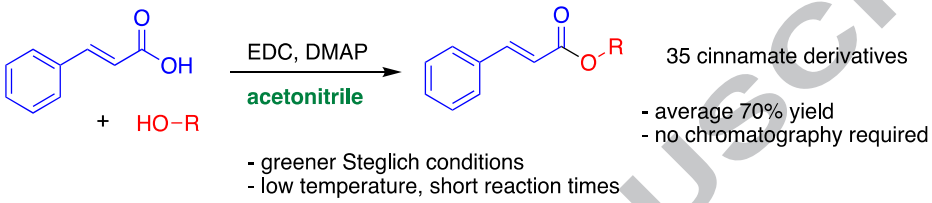
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Synthesis of (*E*)-cinnamyl ester derivatives via a greener Steglich esterification

Leave this area blank for abstract info.

Andrew B. Lutjen, Mackenzie A. Quirk, Allycia M. Barbera, Erin M. Kolonko*
Department of Chemistry and Biochemistry, Siena College, Loudonville, NY 12211, United States



Bioorganic & Medicinal Chemistry
journal homepage: www.elsevier.com

Synthesis of (*E*)-cinnamyl ester derivatives via a greener Steglich esterification

Andrew B. Lutjen, Mackenzie A. Quirk, Allycia M. Barbera, and Erin M. Kolonko*

Department of Chemistry and Biochemistry, Siena College, 515 Loudon Road, Loudonville, NY 12211, United States

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Key words:
Steglich esterification
(*E*)-Cinnamic acid
Cinnamyl ester derivatives
Green solvent

ABSTRACT

Cinnamic acid derivatives are known antifungal, antimicrobial, antioxidant, and anticancer compounds. We have developed a facile and mild methodology for the synthesis of (*E*)-cinnamate derivatives using a modified Steglich esterification of (*E*)-cinnamic acid. Using acetonitrile as the solvent, rather than the typical chlorinated solvent, and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) as the coupling agent enables ester conversion in 45 minutes with mild heating (40-45 °C) and an average yield of 70% without need for further purification. These conditions were used to couple (*E*)-cinnamic acid with 1° and 2° aliphatic alcohols, benzylic and allylic alcohols, and phenols. This work demonstrates a facile and greener methodology for Steglich esterification reactions.

1. Introduction

(*E*)-Cinnamaldehyde and (*E*)-cinnamic acid (**1**), natural products isolated from cinnamon, and their derivatives are known to have antifungal, antimicrobial, antioxidant, and anticancer properties.[1–4] The facile synthesis of libraries of cinnamic acid derivatives could enable further investigations of these properties. In order to synthesize small libraries efficiently using a routine methodology, a reaction that is general for a variety of commercially available alcohol substrates and that does not require additional purification steps is required. In addition, a primary goal for this work was to use the esterification reaction in an introductory undergraduate laboratory curriculum, and thus, a methodology that 1) uses a non-halogenated solvent system, 2) has a short reaction time (setup, reaction, and workup in < 4h), and 3) works with non-anhydrous solvents under air was needed. (*E*)-Cinnamyl ester derivatives have previously been synthesized from (*E*)-cinnamic acid and alcohols by Fischer esterification[5,6] or by the use of acyl chloride intermediates;[2,3,7] however, these methods would not fit the requirements for our methodology. In contrast, carbodiimide coupling reactions, such as the Steglich esterification, have been used to facilitate the esterification of cinnamic acid and various alcohols[8–14] and do not require high temperatures or reactive acyl halide intermediates.

1.1. Steglich esterification

The Steglich esterification (Figure 1) utilizes a carbodiimide along with *N*-(dimethylamino)pyridine (DMAP) to activate an acid and enable ester formation.[9,15–17] In this reaction, the acid is first activated by the carbodiimide, traditionally *N,N'*-dicyclohexylcarbodiimide (DCC), to form an *O*-acylisourea intermediate. For ester synthesis, the addition of *N*-(dimethylamino)pyridine (DMAP) is required to minimize the formation of the unproductive acyl migration byproduct, which is competitive with the nucleophilic attack of the alcohol on the *O*-acylisourea intermediate. The intramolecular acyl migration byproduct formation is slow compared to nucleophilic attack of amino groups. Under conditions using an excess of DMAP, an acyl pyridinium intermediate is formed,[18] which then reacts with the alcohol to regenerate DMAP and to form the ester product. Carbodiimide coupling reactions are often performed in anhydrous chlorinated solvents or dimethylformamide (DMF) under a nitrogen atmosphere. These solvent systems are hazardous to the environment and human health and are rated "undesirable" in green chemistry solvent selection guides.[19]

2. Results and discussion

2.1. Solvent modification

To develop a methodology that met our requirements of a less hazardous solvent system with short reaction times and moderate temperature, the Steglich esterification conditions were modified by substituting the solvent with a less hazardous option. Initial attempts with using recommended green solvents (e.g. ethyl acetate and acetone) did not yield product. Acetonitrile is a rated "usable" by the ACS Green Chemistry Institute and a preferable alternative to DMF.[19] This solvent has been used for Steglich esterification reactions previously, although products were

* Corresponding author. E-mail: ekolonko@siena.edu (E. Kolonko)

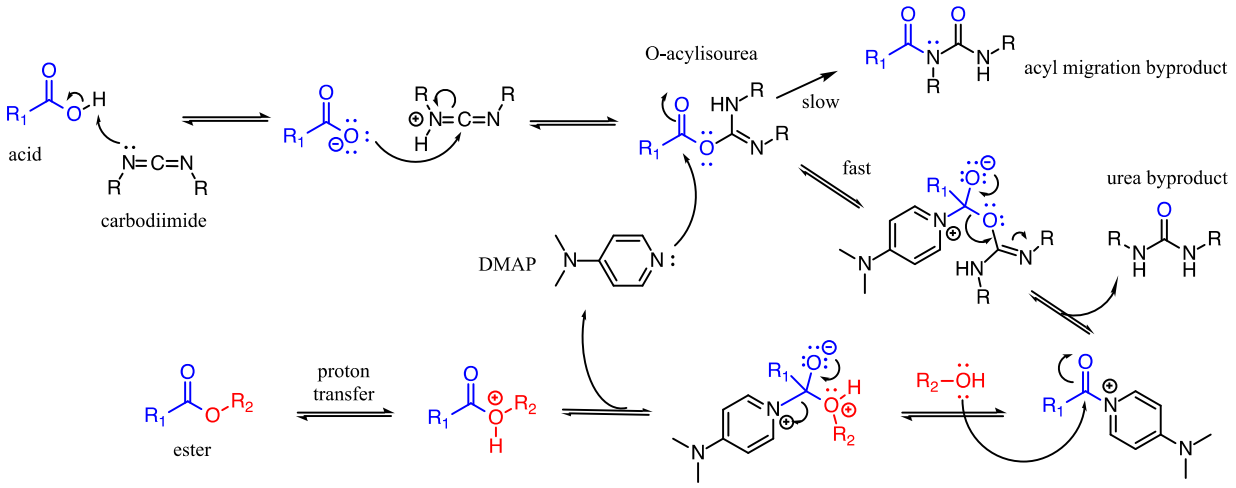


Figure 1. General mechanism of the Steglich esterification reaction

purified via chromatography after workup.[20–23] To simplify purification of the ester product, DCC was substituted for the water soluble carbodiimide reagent 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC). This reagent enables an efficient aqueous extraction workup, eliminates the need for a chromatography purification step, and generates a urea byproduct that does not pose a health or environmental hazard.[24–26] In addition, the alcohol substrates were used as the limiting reagent, as excess cinnamic acid could be removed in the extraction step and many of the alcohols used would require additional purification post-extraction if used in excess.

2.2. Relative rate comparison

The relative rates of the modified Steglich esterification reaction in different solvent systems, ACN-d_3, CD_2Cl_2, $CDCl_3$, and DMF-d_7, were determined by monitoring the reaction between (*E*)-cinnamic acid and ethanol in situ via ^{1}H NMR spectroscopy (Figure 2). Previous studies have reported that the initial nucleophilic attack of the deprotonated acid on the carbodiimide reagent is the rate-limiting step of the reaction (Figure 1).[15,27] To minimize any possible complications, the esterification reactions were performed with an excess of both alcohol and DMAP.[18] The reaction time-course was fitted to a second-order kinetic model[28] (Figure 2) of a bimolecular reaction between acid and EDC to obtain relative rate constants in each solvent (Table 1). At 25 °C, the rate of the reaction in CD_2Cl_2 and $CDCl_3$ was approximately three times and two times faster than that of the reaction in ACN-d_3 (Table 1), respectively. However, the reaction was two times faster in ACN-d_3 than in DMF-d_7. These rate data indicate that as a solvent system for the Steglich esterification reaction, acetonitrile is within the spectrum of rates

Table 1. Observed relative second order rate constants for the esterification reaction between (*E*)-cinnamic acid and ethanol[a]

Solvent	Relative rate constant ($M^{-1}s^{-1}$)
acetonitrile-d_3	0.00651 ± 0.00006
dichloromethane-d_2	0.0183 ± 0.0004
chloroform-*d*	0.0128 ± 0.0002
dimethylformamide-d_7	0.00332± 0.00003

[a]The relative rate constant data is based on a second-order kinetic model:[15,27] acid + EDC → ester + urea (d[ester]/dt = k[acid][EDC]).

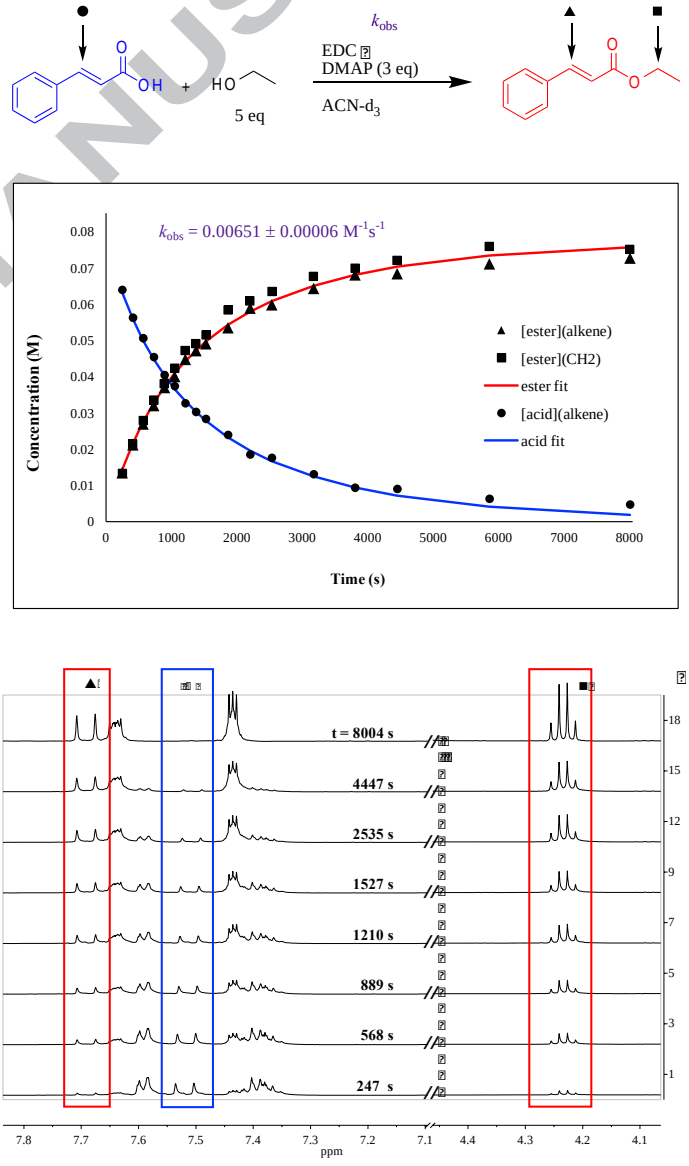


Figure 2. Modeled rate curves (middle) and ^{1}H NMR spectrum data (bottom) for the reaction between (*E*)-cinnamic acid (red) and ethanol to form (*E*)-ethyl cinnamate (blue) in acetonitrile-d_3 (top). Integrated peaks are highlighted in the ^{1}H NMR spectra and correspond to the ester alkene (1H, ▲),the acid alkene (1H, ●) , and the ester methylene (2H, ■). Relative integrations were converted to concentration (M). The rate of the reaction was modeled using a section-order reaction.

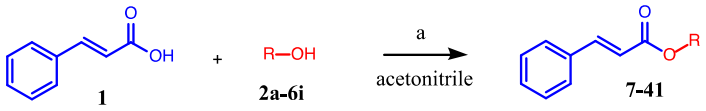
for commonly used solvents such as chloroform, dichloromethane, and dimethylformamide.

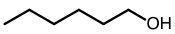
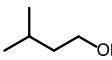
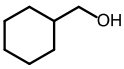
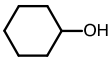
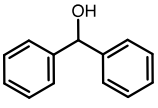
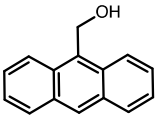
2.3. Synthesis of cinnamyl ester derivatives

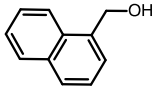
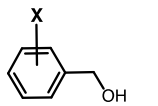
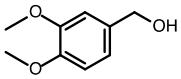
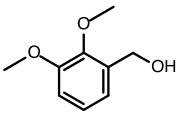
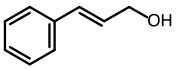
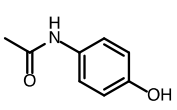
Based on this kinetic data and using a rough approximation of doubled rate for a 10 °C temperature increase, the modified Steglich esterification reaction was performed at 40-45 °C. These conditions were chosen to enable a rate similar to that of dichloromethane at room temperature, while also remaining below the boiling point of acetonitrile to avoid use of a reflux condenser. A variety of alcohols were used to assess the tolerance of the reaction to steric and electronic effects with respect to the alcohol. After 45 minutes, analysis of the reaction between cinnamic acid and benzyl alcohol by TLC demonstrated loss of the alcohol. Solvent removal followed by an acid-base extraction workup provided the ester product without the need for flash column purification, based on NMR analysis.

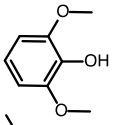
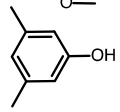
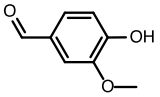
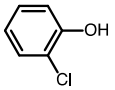
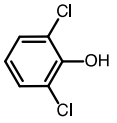
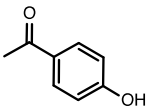
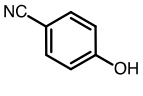
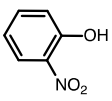
Using this method, we synthesized a series of (*E*)-cinnamyl ester derivatives (**7-41**, Table 2). Primary (**2a-g**) and secondary (**3a-c**) aliphatic alcohols and benzyl (**4a-n**) and allylic (**5**) alcohols form esters readily at 40-45 °C. Phenols containing both electron donating (**6a-d**) and electron withdrawing (**6e-i**) substituents can also be reacted readily with (*E*)-cinnamic acid under the same conditions. The reaction is tolerant to functional groups such as amide (**6a**), aldehyde (**6d**), ketone (**6g**), and nitrile (**6h**); however, strongly nucleophilic functionalities such as amino and additional hydroxy groups compete with the desired ester formation. More sterically hindered benzyl alcohols (**4b-c**) and vanillin (**6d**) required additional heat (60 °C) to enable appreciable yields at reaction times of 45 min. Moderate yields (e.g. **3b** and **6i**) under the standard conditions (40-45 °C, 45 min) can be improved with longer reaction times (room temperature, 24 h) or increased temperature (60 °C). Ester products between

Table 2. Cinnamyl ester derivatives synthesized via the modified Steglich esterification



Alcohol		Product	Yield (%)
2a		**7**	77
2b		**8**	55
2c		**9**	69
2d		**10**	95
2e		**11**	93
2f		**12**	64
2g		**13**	92
3a		**14**	62
3b		**15**	51[a] 75[b] 92[c]
3c		**16**	58
4a		**17**	65
4b		**18**	81[b]

Alcohol		Product	Yield (%)
4c		**19**	65[b]
4d	 X = H	**20**	76
4e	*o*-Br	**21**	42
4f	*m*-Br	**22**	74
4g	*p*-Br	**23**	94
4h	*o*-Cl	**24**	71
4i	*m*-Cl	**25**	51
4j	*p*-Cl	**26**	87
4k	*o*-OCH_3	**27**	89
4l	*m*-OCH_3	**28**	90
4m	*p*-OCH_3	**29**	>99
4n		**30**	51
4o		**31**	85
5		**32**	51
6a		**33**	69

Alcohol		Product	Yield (%)
6b		**34**	73
6c		**35**	58
6d		**36**	39[b]
6e		**37**	71
6f		**38**	60
6g		**39**	61
6h		**40**	72
6i		**41**	44[a] 59[b] 95[c]

[a] Standard conditions: (*E*)-cinnamic acid (1.2 eq), alcohol (1 eq), EDC (1.5 eq), DMAP (3 eq), acetonitrile, 40-45 °C, 45 min.
[b] Reaction performed at 60 °C for 45 min.
[c] Reaction performed at room temperature for 24 h.

(*E*)-cinnamic acid and tertiary alcohols could not be isolated under these conditions, which is currently a limitation compared to chlorinated solvent systems.[29] Increasing temperature to reflux, the addition of HOBt, or additional reaction time (24 h) did not yield any isolated product between *t*-butyl alcohol and (*E*)-cinnamic acid. Additional NMR kinetics and computational studies are currently underway to investigate the mechanism and constraints of this reaction in more detail.

2.4. Summary

Our group has developed modified Steglich esterification conditions using acetonitrile and EDC as the carbodiimide in an effort to eliminate the need for additional purification steps and to make the solvent system less hazardous to the environment and human health. Kinetic studies of acetonitrile compared to traditional solvent systems for the Steglich esterification demonstrated that the reaction rate was not substantially affected by the greener solvent system. The conditions were used to make a small library of (*E*)-cinnamyl ester derivatives by coupling (*E*)-cinnamic acid with 1° and 2° aliphatic alcohols, benzyl and allylic alcohols, and phenols. This work provides an alternative methodology for the preparation of (*E*)-cinnamyl ester derivatives that have potential utility in a variety of biological applications. In addition, it demonstrates the utility of acetonitrile as a less hazardous solvent system for carbodiimide coupling reactions.

3. Experimental section

3.1. General experimental procedures

All commercially available reagents and solvents were used as received without further purification. The ^{1}H and ^{13}C NMR spectra were measured on a Bruker AVANCE HD 500 MHz (126 MHz for ^{13}C) NMR Spectrometer with trimethylsilane as the internal standard. Chemical shifts (δ) are reported in ppm, and coupling constants (*J*) are reported in hertz (Hz). Signals are reported as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), or combinations of the above. HRMS data were acquired on a Bruker Maxis Impact HD Q-TOF Mass Spectrometer with a standard electrospray ionization source and are reported as *m*/*z*. Melting points (m.p.) were determined using a Mel-Temp capillary melting point apparatus with a Vernier temperature probe.

3.2. Relative rate determination

EDC (21.7 mg, 0.113 mmol, 2 eq) and DMAP (20.8 mg, 0.170 mmol, 3 eq) were dissolved in deuterated solvent (0.75 mL). Ethanol (16.55 μL, 0.283 mmol, 5 eq) was added followed by (*E*)-cinnamic acid (8.4 mg, 0.0567 mmol, 1 eq). The solution was quickly mixed by pipette and added to a 5 mm NMR tube. ^{1}H NMR spectra were acquired at 25 °C at two, five, or ten minute intervals for at least three half-lives of the reaction. To account for sample mixing and loading time, a timer was used to estimate t=0 at the addition of the cinnamic acid, and the NMR spectrum timepoints were adjusted accordingly.

Relative integrations of the ester and acid alkene ^{1}H signals and the ester methylene ^{1}H signal over time were determined using the Reaction Monitoring plugin in the Mnova NMR processing software. The relative integrations were converted to concentration (M) by comparison to the total alkene integration (ester alkene + acid alkene = 1H = 0.0756 M) for each spectrum. The rate of these reactions was simulated with COPASI[28] using a parameter estimation routine and the Levenberg-Marquardt method, and fitting acid and ester concentration to the second-order reaction:

$$\text{acid} + \text{EDC} \rightarrow \text{ester} + \text{urea} \qquad (d[\text{ester}]/dt = k[\text{acid}][\text{EDC}]).$$

^{1}H NMR time course spectra and modeled rate curves can be found in Figure 2 (acetonitrile-d_3) and in the Supplementary Information.

*3.3. General procedure for the preparation of **7-41***

(*E*)-Cinnamic acid (**1**) (0.167 g, 1.13 mmol), EDC (0.270 g, 1.4 mmol), DMAP (0.343 g, 2.8 mmol), and the alcohol (**2a-6i**) (0.97 mmol) were combined with acetonitrile (15 mL). The reaction mixture was stirred at 40-45 °C in a water bath for 45 minutes. Reactions involving aromatic alcohols were monitored for loss of alcohol by TLC (aluminum-backed silica gel plates, 1:4 ethyl acetate/hexanes). The solvent was removed under reduced pressure. The residue was dissolved in diethyl ether (25 mL), and the solution was washed with 3 M HCl (2 x 20 mL), saturated sodium bicarbonate (2 x 20 mL), and brine (20 mL). The organic layer was dried with $MgSO_4$ and filtered, and the solvent was removed under reduced pressure to yield the corresponding ester. The spectral data are summarized below for each compound. ^{1}H and ^{13}C NMR spectra can be found in the Supplementary Information.

*3.3.1. (E)-Ethyl cinnamate (**7**)*

7 was synthesized according to the general procedure using ethanol, **2a** (0.97 mmol, 0.060 mL) to yield a light yellow liquid (132 mg, 77%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 16.0 Hz, 1H), 7.63 – 7.48 (m, 2H), 7.47 – 7.34 (m, 3H), 6.46 (d, *J* = 16.0 Hz, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 1.37 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.00, 144.58, 134.51, 130.21, 128.88, 128.05, 118.32, 60.50, 14.33; HRMS ESI calcd for $C_{11}H_{12}O_2$ $(M+Na)^+$ 199.0730, found 199.0730.

*3.3.2. (E)-Methyl cinnamate (**8**)*

8 was synthesized according to the general procedure using methanol, **2b** (0.97 mmol, 0.040 mL) to yield a light yellow solid (86 mg, 55%). m.p. 31.2-32.2 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 16.0 Hz, 1H), 7.60 – 7.47 (m, 2H), 7.45 – 7.36 (m, 3H), 6.47 (d, *J* = 16.0 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.42, 144.87, 134.41, 130.28, 128.89, 128.07, 117.82, 51.70; HRMS ESI calcd for $C_{10}H_{10}O_2$ $(M+Na)^+$ 185.0573, found 185.0569.

*3.3.3. (E)-Propyl cinnamate (**9**)*

9 was synthesized according to the general procedure using propanol, **2c** (0.97 mmol, 0.073 mL) to yield a light yellow liquid (127 mg, 69%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 16.0 Hz, 1H), 7.63 – 7.50 (m, 2H), 7.45 – 7.37 (m, 3H), 6.47 (d, *J* = 16.0 Hz, 1H), 4.20 (t, *J* = 6.7 Hz, 2H), 1.76 (qt, *J* = 7.4, 6.7 Hz, 2H), 1.02 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.08, 144.55, 134.50, 130.19, 128.86, 128.04, 118.31, 66.15, 22.11, 10.45; HRMS ESI calcd for $C_{12}H_{14}O_2$ $(M+Na)^+$ 213.0886, found 213.0889.

*3.3.4. (E)-Hexyl cinnamate (**10**)*

10 was synthesized according to the general procedure using hexanol, **2d** (0.93 mmol, 0.116 mL) and corresponding amounts of cinnamic acid, EDC, and DMAP to yield a light yellow liquid (205 mg, 95%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 16.0 Hz, 1H), 7.62 – 7.49 (m, 2H), 7.46 – 7.35 (m, 3H), 6.47 (d, *J* = 16.0 Hz, 1H), 4.23 (t, *J* = 6.8 Hz, 2H), 1.79 – 1.68 (m, 2H), 1.48 – 1.39 (m, 2H), 1.39 – 1.32 (m, 4H), 0.98 – 0.88 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.09, 144.53, 134.51, 130.19, 128.86, 128.04, 118.33, 64.74, 31.48, 28.71, 25.66, 22.56, 14.01;

HRMS ESI calcd for $C_{15}H_{20}O_2$ $(M+Na)^+$ 255.1356, found 255.1359.

*3.3.5. (E)-3-Methylbutyl cinnamate (**11**)*

11 was synthesized according to the general procedure using isoamyl alcohol, **2e** (0.93 mmol, 0.100 mL) and corresponding amounts of cinnamic acid, EDC, and DMAP to yield a colorless liquid (189 mg, 93%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 16.0 Hz, 1H), 7.63 – 7.48 (m, 2H), 7.47 – 7.32 (m, 3H), 6.46 (d, *J* = 16.0 Hz, 1H), 4.27 (t, *J* = 6.9 Hz, 2H), 1.78 (nonet, *J* = 6.9 Hz, 1H), 1.63 (q, *J* = 6.9 Hz, 2H), 0.99 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.07, 144.54, 134.50, 130.19, 128.86, 128.05, 118.33, 63.23, 37.46, 25.15, 22.51; HRMS ESI calcd for $C_{14}H_{18}O_2$ $(M+Na)^+$ 241.1199, found 241.1200.

*3.3.6. (E)-2-Methylpropyl cinnamate (**12**)*

12 was synthesized according to the general procedure using isobutyl alcohol, **2f** (0.97 mmol, 0.090 mL) to yield a yellow liquid (127 mg, 64%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 16.0 Hz, 1H), 7.66 – 7.49 (m, 2H), 7.47 – 7.33 (m, 3H), 6.48 (d, *J* = 16.0 Hz, 1H), 4.02 (d, *J* = 6.7 Hz, 2H), 2.04 (nonet, *J* = 6.7 Hz, 1H), 1.02 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.07, 144.55, 134.50, 130.20, 128.86, 128.05, 118.31, 70.67, 27.86, 19.17; HRMS ESI calcd for $C_{13}H_{16}O_2$ $(M+Na)^+$ 227.1043, found 227.1044.

*3.3.7. (E)-Cyclohexylmethyl cinnamate (**13**)*

13 was synthesized according to the general procedure using cyclohexanol, **2g** (0.97 mmol, 0.114 mL) to yield a light yellow oil (209 mg, 92%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 16.0 Hz, 1H), 7.58 – 7.52 (m, 2H), 7.48 – 7.34 (m, 3H), 6.47 (d, *J* = 16.0 Hz, 1H), 4.05 (d, *J* = 6.6 Hz, 2H), 1.93 – 1.60 (m, 5H), 1.40 – 1.14 (m, 3H), 1.05 (qd, *J* = 12.1, 3.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.13, 144.53, 134.53, 130.20, 128.87, 128.06, 118.35, 69.73, 37.26, 29.75, 26.41, 25.72; HRMS ESI calcd for $C_{16}H_{20}O_2$ $(M+Na)^+$ 267.1356, found 267.1355.

*3.3.8. (E)-Isopropyl cinnamate (**14**)*

14 was synthesized according to the general procedure using isopropanol, **3a** (0.97 mmol, 0.074 mL) to yield a yellow liquid (115 mg, 62%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, *J* = 16.0 Hz, 1H), 7.59 – 7.49 (m, 2H), 7.45 – 7.34 (m, 3H), 6.44 (d, *J* = 16.0 Hz, 1H), 5.17 (heptet, *J* = 6.3 Hz, 1H), 1.34 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.52, 144.29, 134.56, 130.12, 128.85, 128.39, 128.01, 118.83, 67.80, 21.95; HRMS ESI calcd for $C_{12}H_{14}O_2$ $(M+Na)^+$ 213.0886, found 213.0886.

*3.3.9. (E)-1-Methylpropyl cinnamate (**15**)*

15 was synthesized according to the general procedure using 2-butanol, **3b** (0.97 mmol, 0.090 mL) to yield a light yellow liquid (102 mg, 51%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 16.0 Hz, 1H), 7.61 – 7.49 (m, 2H), 7.47 – 7.36 (m, 3H), 6.46 (d, *J* = 16.0 Hz, 1H), 5.01 (h, *J* = 6.3 Hz, 1H), 1.77 – 1.68 (m, 1H), 1.68 – 1.58 (m, 1H), 1.31 (d, *J* = 6.3 Hz, 3H), 0.97 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.68, 144.27, 134.57, 130.11, 128.85, 128.02, 118.82, 72.34, 28.94, 19.56, 9.73; HRMS ESI calcd for $C_{13}H_{16}O_2$ $(M+Na)^+$ 227.1043, found 227.1043.

*3.3.10. (E)-Cyclohexyl cinnamate (**16**)*

16 was synthesized according to the general procedure using cyclohexanol, **3c** (0.93 mmol, 0.100 mL) and corresponding amounts of cinnamic acid, EDC, and DMAP to yield a colorless oil (129 mg, 58%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, *J* = 16.0 Hz, 1H), 7.59 – 7.51 (m, 2H), 7.46 – 7.34 (m, 3H), 6.46 (d, *J* = 16.0 Hz, 1H), 4.92 (tt, *J* = 9.2, 3.9 Hz, 1H), 2.01 – 1.90 (m, 2H), 1.84 – 1.72 (m, 1H), 1.66 – 1.57 (m, 1H), 1.57 – 1.48 (m, 2H), 1.50 – 1.37 (m, 2H), 1.37 – 1.25 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.43, 144.24, 134.59, 130.10, 128.84, 128.02, 118.92, 72.75, 31.76, 25.45, 23.83; HRMS ESI calcd for $C_{15}H_{18}O_2$ $(M+Na)^+$ 253.1199, found 253.1199.

*3.3.11. (E)-Diphenylmethyl cinnamate (**17**)*

17 was synthesized according to the general procedure using diphenylmethanol, **4a** (0.97 mmol, 180 mg) to yield a white solid (197 mg, 65%). m.p. 79.8-80.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 16.0 Hz, 1H), 7.60 – 7.54 (m, 2H), 7.46 – 7.36 (m, 11H), 7.35 – 7.30 (m, 2H), 7.05 (s, 1H), 6.60 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.98, 145.44, 140.28, 134.37, 130.41, 128.91, 128.53, 128.17, 127.93, 127.20, 118.04, 77.00; HRMS ESI calcd for $C_{22}H_{18}O_2$ $(M+Na)^+$ 337.1199, found 337.1191.

*3.3.12. (E)-9-Anthracenemethyl cinnamate (**18**)*

18 was synthesized according to the general procedure at 60 °C using 9-anthracenemethanol, **4b** (0.97 mmol, 202 mg) to yield a yellow solid (267 mg, 81%). m.p. 127.1-127.8 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (s, 1H), 8.43 (dd, *J* = 8.9, 1.0 Hz, 2H), 8.08 (d, *J* = 8.4 Hz, 2H), 7.73 (d, *J* = 16.0 Hz, 1H), 7.62 (ddd, *J* = 9.0, 6.5, 1.4 Hz, 2H), 7.54 (ddd, *J* = 8.4, 6.5, 1.1 Hz, 2H), 7.52 – 7.44 (m, 2H), 7.43 – 7.33 (m, 3H), 6.47 (d, *J* = 16.0 Hz, 1H), 6.32 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.19, 145.30, 134.34, 131.44, 131.16, 130.30, 129.22, 129.13, 128.83, 128.08, 126.70, 126.30, 125.14, 124.01, 117.81, 58.96; HRMS ESI calcd for $C_{24}H_{18}O_2$ $(M+Na)^+$ 361.1199, found 361.1199.

*3.3.13. (E)-1-Naphthalenemethyl cinnamate (**19**)*

19 was synthesized according to the general procedure at 60 °C using 1-naphthalenemethanol, **4c** (0.97 mmol, 153 mg) to yield a light yellow solid (183 mg, 65%). m.p. 62.7-64.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (br d, *J* = 8.7 Hz, 1H), 7.90 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.87 (d, *J* = 8.3 Hz, 1H), 7.73 (d, *J* = 16.0 Hz, 1H), 7.61 (br d, *J* = 6.8 Hz, 1H), 7.58 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.53 (ddd, *J* = 8.0, 6.9, 1.3 Hz, 1H), 7.50 – 7.45 (m, 3H), 7.39 – 7.33 (m, 3H), 6.49 (d, *J* = 16.0 Hz, 1H), 5.71 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.86, 145.28, 134.35, 133.77, 131.72, 131.55, 130.34, 129.34, 128.87, 128.73, 128.11, 127.56, 126.62, 125.97, 125.32, 123.64, 117.86, 64.71; HRMS ESI calcd for $C_{20}H_{16}O_2$ $(M+Na)^+$ 311.1043, found 311.1040.

*3.3.14. (E)-Benzyl cinnamate (**20**)*

20 was synthesized according to the general procedure using benzyl alcohol, **4d** (0.93 mmol, 0.097 mL) and corresponding amounts of cinnamic acid, EDC, and DMAP to yield a light yellow liquid (175 mg, 76%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 16.0 Hz, 1H), 7.58 – 7.53 (m, 2H), 7.47 – 7.40 (m, 7H), 7.40 – 7.35 (m, 1H), 6.53 (d, *J* = 16.0 Hz, 1H), 5.29 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.78, 145.18, 136.09, 134.39, 130.35, 128.90, 128.61, 128.29, 128.26, 128.21, 128.12, 117.91, 66.37; HRMS ESI calcd for $C_{16}H_{14}O_2$ $(M+Na)^+$ 261.0886, found 261.0885.

*3.3.15. (E)-2-Bromobenzyl cinnamate (**21**)*

21 was synthesized according to the general procedure using 2-bromobenzyl alcohol, **4e** (0.93 mmol, 174 mg) and corresponding amounts of cinnamic acid, EDC, and DMAP to yield a colorless oil (125 mg, 42%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 16.1 Hz, 1H), 7.63 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.59 – 7.54 (m, 2H), 7.50 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.44 – 7.40 (m, 3H), 7.37 (td, *J* = 7.5, 1.2 Hz, 1H), 7.23 (td, *J* = 7.7, 1.7 Hz, 1H), 6.55 (d, *J* = 16.0 Hz, 1H), 5.37 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.55, 145.51, 135.46, 134.34, 132.91, 130.44, 129.91, 129.72, 128.92, 128.18, 127.54, 123.50, 117.63, 65.88; HRMS ESI calcd for $C_{16}H_{13}BrO_2$ $(M+Na)^+$ 338.9991, found 338.9990.

*3.3.16. (E)-3-Bromobenzyl cinnamate (**22**)*

22 was synthesized according to the general procedure using 3-bromobenzyl alcohol, **4f** (0.97 mmol, 0.116 mL) to yield a light yellow oil (227 mg, 74%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 16.0 Hz, 1H), 7.60 (t, *J* = 1.9 Hz, 1H), 7.58 – 7.53 (m, 2H), 7.50 (ddd, *J* = 8.0, 2.0, 1.1 Hz, 1H), 7.45 – 7.39 (m, 3H), 7.37 (ddd, *J* = 7.8, 1.8, 1.0 Hz, 1H), 7.28 (t, *J* = 7.8 Hz, 1H), 6.52 (d, *J* = 16.0 Hz, 1H), 5.24 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.58, 145.56, 138.38, 134.27, 131.32, 131.12, 130.47, 130.16, 128.93, 128.17, 126.69, 122.64, 117.84, 117.55, 65.33; HRMS ESI calcd for $C_{16}H_{13}BrO_2$ $(M+Na)^+$ 338.9991, found 338.9987.

*3.3.17. (E)-4-Bromobenzyl cinnamate (**23**)*

23 was synthesized according to the general procedure using 4-bromobenzyl alcohol, **4g** (0.93 mmol, 174 mg) and corresponding amounts of cinnamic acid, EDC, and DMAP to yield a light yellow solid (277 mg, 94%). m.p. 76.6-77.9 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 16.0 Hz, 1H), 7.60 – 7.48 (m, 4H), 7.47 – 7.37 (m, 3H), 7.37 – 7.30 (m, 2H), 6.50 (d, *J* = 16.0 Hz, 1H), 5.23 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.63, 145.46, 135.12, 134.28, 131.75, 130.46, 129.94, 128.93, 128.14, 122.30, 117.61, 65.53; HRMS ESI calcd for $C_{16}H_{13}BrO_2$ $(M+Na)^+$ 338.9991, found 338.9987.

*3.3.18. (E)-2-Chlorobenzyl cinnamate (**24**)*

24 was synthesized according to the general procedure using 2-chlorobenzyl alcohol, **4h** (0.97 mmol, 140 mg) to yield a light yellow oil (189 mg, 71%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 16.0 Hz, 1H), 7.61 – 7.53 (m, 2H), 7.52 – 7.48 (m, 1H), 7.46 – 7.43 (m, 1H), 7.43 – 7.40 (m, 3H), 7.37 – 7.29 (m, 2H), 6.54 (d, *J* = 16.0 Hz, 1H), 5.40 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.58, 145.46, 134.33, 133.80, 133.75, 130.42, 129.87, 129.61, 129.50, 128.91, 128.15, 126.91, 117.63, 63.68; HRMS ESI calcd for $C_{16}H_{13}ClO_2$ $(M+Na)^+$ 295.0496, found 295.0493.

*3.3.19. (E)-3-Chlorobenzyl cinnamate (**25**)*

25 was synthesized according to the general procedure using 3-chlorobenzyl alcohol, **4i** (0.97 mmol, 0.110 mL) to yield a colorless oil (135 mg, 51%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 16.0 Hz, 1H), 7.59 – 7.53 (m, 2H), 7.46 – 7.39 (m, 4H), 7.36 – 7.29 (m, 3H), 6.52 (d, *J* = 16.0 Hz, 1H), 5.25 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.61, 145.56, 138.12, 134.51, 134.29, 130.48, 129.89, 128.94, 128.39, 128.21, 128.17, 126.19, 117.56, 65.41; HRMS ESI calcd for $C_{16}H_{13}ClO_2$ $(M+Na)^+$ 295.0496, found 295.0495.

*3.3.20. (E)-4-Chlorobenzyl cinnamate (**26**)*

26 was synthesized according to the general procedure using 4-chlorobenzyl alcohol, **4j** (0.93 mmol, 133 mg) and corresponding amounts of cinnamic acid, EDC, and DMAP to yield a white solid (220 mg, 87%). m.p. 59.8-60.8 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 16.0 Hz, 1H), 7.58 – 7.51 (m, 2H), 7.44 – 7.40 (m, 3H), 7.38 (s, 4H), 6.50 (d, *J* = 16.0 Hz, 1H), 5.24 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.67, 145.46, 134.61, 134.30, 134.17, 130.46, 129.66, 128.93, 128.80, 128.15, 117.64, 65.51; HRMS ESI calcd for $C_{16}H_{13}ClO_2$ $(M+Na)^+$ 295.0496, found 295.0495.

*3.3.21. (E)-2-Methoxybenzyl cinnamate (**27**)*

27 was synthesized according to the general procedure using 2-methoxybenzyl alcohol, **4k** (0.97 mmol, 0.130 mL) to yield a light yellow viscous oil (231 mg, 89%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 16.0 Hz, 1H), 7.59 – 7.52 (m, 2H), 7.46 – 7.38 (m, 4H), 7.35 (ddd, *J* = 8.2, 7.5, 1.8 Hz, 1H), 7.00 (td, *J* = 7.5, 1.1 Hz, 1H), 6.94 (dd, *J* = 8.3, 1.0 Hz, 1H), 6.53 (d, *J* = 16.1 Hz, 1H), 5.34 (s, 2H), 3.89 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.93, 157.59, 144.87, 134.50, 130.23, 129.76, 129.58, 128.87, 128.08, 127.93, 124.39, 120.47, 118.19, 110.52, 61.82, 55.48; HRMS ESI calcd for $C_{17}H_{16}O_3$ $(M+Na)^+$ 291.0992, found 291.0989.

*3.3.22. (E)-3-Methoxybenzyl cinnamate (**28**)*

28 was synthesized according to the general procedure using 3-methoxybenzyl alcohol, **4l** (0.93 mmol, 174 mg) and corresponding amounts of cinnamic acid, EDC, and DMAP to yield a light yellow oil (225 mg, 90%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 16.0 Hz, 1H), 7.60 – 7.50 (m, 2H), 7.49 – 7.36 (m, 3H), 7.33 (t, *J* = 7.8 Hz, 2H), 7.03 (ddd, *J* = 7.4, 1.5, 0.8 Hz, 1H), 7.02 – 6.97 (m, 1H), 6.91 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 1H), 6.53 (d, *J* = 16.0 Hz, 1H), 5.26 (s, 2H), 3.86 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.75, 159.80, 145.22, 137.60, 134.38, 130.36, 129.66, 128.90, 128.12, 120.44, 117.87, 113.78, 113.71, 66.23, 55.27; HRMS ESI calcd for $C_{17}H_{16}O_3$ $(M+Na)^+$ 291.0992, found 291.0993.

*3.3.23. (E)-4-Methoxybenzyl cinnamate (**29**)*

29 was synthesized according to the general procedure using 4-methoxybenzyl alcohol, **4m** (0.97 mmol, 134 mg) to yield a white solid (260 mg, >99%). m.p. 59.4-60.9 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 16.0 Hz, 1H), 7.56 – 7.51 (m, 2H), 7.42 – 7.35 (m, 5H), 6.97 – 6.91 (m, 2H), 6.49 (d, *J* = 16.0 Hz, 1H), 5.21 (s, 2H), 3.84 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.86, 159.68, 145.00, 134.42, 130.28, 130.15, 128.88, 128.19, 128.08, 118.06, 114.00, 66.20, 55.30; HRMS ESI calcd for $C_{17}H_{16}O_3$ $(M+Na)^+$ 291.0992, found 291.0989.

*3.3.24. (E)-3,4-Dimethoxybenzyl cinnamate (**30**)*

30 was synthesized according to the general procedure using 3,4-dimethoxybenzyl alcohol, **4n** (0.97 mmol, 0.140 mL) to yield a white solid (142 mg, 51%). m.p. 62.6-63.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 16.0 Hz, 1H), 7.56 – 7.51 (m, 2H), 7.44 – 7.36 (m, 3H), 7.02 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.98 (d, *J* = 2.0 Hz, 1H), 6.90 (d, *J* = 8.1 Hz, 1H), 6.50 (d, *J* = 16.0 Hz, 1H), 5.21 (s, 2H), 3.93 (s, 3H), 3.91 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.87, 149.20, 149.08, 145.12, 134.40, 130.34, 128.90, 128.58, 128.10, 121.37, 118.00, 111.92, 111.11, 66.50, 55.95, 55.93; HRMS ESI calcd for $C_{18}H_{18}O_4$ $(M+Na)^+$ 321.1097, found 321.1092.

*3.3.25. (E)-2,3-Dimethoxybenzyl cinnamate (**31**)*

31 was synthesized according to the general procedure using ethanol, **4o** (0.97 mmol, 162 mg) to yield a white solid (235 mg, 85%). m.p. 68.3-69.1 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 16.0 Hz, 1H), 7.58 – 7.50 (m, 2H), 7.46 – 7.35 (m, 3H), 7.10 (t, *J* = 7.9 Hz, 1H), 7.04 (dd, *J* = 7.8, 1.6 Hz, 1H), 6.95 (dd, *J* = 8.1, 1.7 Hz, 1H), 6.51 (d, *J* = 16.0 Hz, 1H), 5.34 (s, 2H), 3.92 (s, 3H), 3.91 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.80, 152.76, 147.65, 145.00, 134.43, 130.28, 129.99, 128.88, 128.08, 124.07, 121.73, 118.05, 112.75, 61.73, 61.10, 55.84; HRMS ESI calcd for $C_{18}H_{18}O_4$ $(M+Na)^+$ 321.1097, found 321.1090.

*3.3.26. (E)-Cinnamyl cinnamate (**32**)*

32 was synthesized according to the general procedure using cinnamyl alcohol, **5** (0.97 mmol, 130 mg) to yield colorless oil (130 mg, 51%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 16.0 Hz, 1H), 7.60 – 7.55 (m, 2H), 7.48 – 7.44 (m, 2H), 7.44 – 7.40 (m, 3H), 7.40 – 7.35 (m, 2H), 7.33 – 7.29 (m, 1H), 6.76 (dt, *J* = 15.8, 1.4 Hz, 1H), 6.54 (d, *J* = 16.0 Hz, 1H), 6.41 (dt, *J* = 15.9, 6.4 Hz, 1H), 4.92 (dd, *J* = 6.4, 1.4 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.74, 145.13, 136.31, 134.44, 134.28, 130.38, 128.94, 128.66, 128.16, 128.12, 126.69, 123.36, 117.98, 65.17; HRMS ESI calcd for $C_{18}H_{16}O_2$ $(M+Na)^+$ 287.1043, found 287.1046.

*3.3.27. (E)-4-Acetimidophenyl cinnamate (**33**)*

33 was synthesized according to the general procedure using 4-acetimidophenol, **6a** (0.97 mmol, 147 mg) to yield a white solid (188 mg, 69%). m.p. 198.9-200.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 16.0 Hz, 1H), 7.66 – 7.59 (m, 2H), 7.57 – 7.52 (m, 2H), 7.48 – 7.42 (m, 3H), 7.39 (br s, 1H), 7.16 – 7.11 (m, 2H), 6.65 (d, *J* = 16.0 Hz, 1H), 2.19 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.24, 165.59, 146.95, 146.72, 135.58, 134.14, 130.75, 129.01, 128.32, 122.02, 120.87, 117.17, 24.51; HRMS ESI calcd for $C_{17}H_{15}NO_3$ $(M+Na)^+$ 304.0944, found 304.0943.

*3.3.28. (E)-2,6-Dimethoxyphenyl cinnamate (**34**)*

34 was synthesized according to the general procedure using 2,6-dimethoxyphenol, **6b** (0.97 mmol, 150 mg) to yield a white solid (202 mg, 73%). m.p. 152.2-152.8 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, *J* = 16.0 Hz, 1H), 7.68 – 7.52 (m, 2H), 7.51 – 7.33 (m, 3H), 7.19 (t, *J* = 8.5 Hz, 1H), 6.76 (d, *J* = 16.0 Hz, 1H), 6.67 (d, *J* = 8.5 Hz, 2H), 3.86 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.69, 152.51, 146.48, 134.40, 130.49, 128.91, 128.81, 128.31, 126.26, 116.99, 104.97, 56.21; HRMS ESI calcd for $C_{17}H_{16}O_4$ $(M+Na)^+$ 307.0941, found 307.0938.

*3.3.29. (E)-3,5-Dimethylphenyl cinnamate (**35**)*

35 was synthesized according to the general procedure using 3,5-dimethylphenol, **6c** (0.97 mmol, 0.118 mL) to yield a yellow oil (141 mg, 58%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 16.0 Hz, 1H), 7.71 – 7.55 (m, 2H), 7.51 – 7.40 (m, 3H), 6.92 (s, 1H), 6.82 (s, 1H), 6.65 (d, *J* = 16.0 Hz, 1H), 2.37 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.60, 150.72, 146.33, 139.28, 134.27, 130.62, 128.99, 128.28, 127.56, 119.21, 117.52, 21.27.; HRMS ESI calcd for $C_{17}H_{16}O_2$ $(M+Na)^+$ 275.1043, found 275.1043.

*3.3.30. (E)-4-Methanoyl-2-methoxyphenyl cinnamate (**36**)*

36 was synthesized according to the general procedure at 60 °C using vanillin, **6d** (0.97 mmol, 145 mg) to yield a white solid (107 mg, 39%). m.p. 90.3-91.6 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.00 (s, 1H), 7.93 (d, *J* = 16.0 Hz, 1H), 7.68 – 7.59 (m, 2H), 7.56 (d, *J* = 1.8 Hz, 1H), 7.54 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.49 – 7.41 (m, 3H), 7.34 (d, *J* = 7.9 Hz, 1H), 6.69 (d, *J* = 16.0 Hz, 1H), 3.95 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.05, 164.30, 152.18, 147.38, 145.10, 135.23, 134.07, 130.90, 129.04, 128.41, 124.80, 123.57, 116.39, 110.89, 56.16; HRMS ESI calcd for $C_{17}H_{14}O_4$ $(M+Na)^+$ 305.0784, found 305.0785.

*3.3.31. (E)-2-Chlorophenyl cinnamate (**37**)*

37 was synthesized according to the general procedure using 2-chlorophenol, **6e** (0.97 mmol, 0.100 mL) to yield a light yellow solid (178 mg, 71%). m.p. 82.3-83.1 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 16.0 Hz, 1H), 7.67 – 7.60 (m, 2H), 7.50 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.49 – 7.42 (m, 3H), 7.34 (ddd, *J* = 8.1, 7.3, 1.6 Hz, 1H), 7.28 – 7.21 (m, 2H), 6.70 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.40, 147.35, 147.13, 134.08, 130.86, 130.36, 129.01, 128.41, 127.74, 127.06, 126.98, 123.84, 116.45; HRMS ESI calcd for $C_{15}H_{11}ClO_2$ $(M+Na)^+$ 281.0340, found 281.0336.

*3.3.32. (E)-2,6-Dichlorophenyl cinnamate (**38**)*

38 was synthesized according to the general procedure using 3,5-dimethylphenol, **6f** (0.97 mmol, 158 mg) to yield a light yellow solid (172 mg, 60%). m.p. 147.3.1-148.3 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 16.0 Hz, 1H), 7.68 – 7.62 (m, 2H), 7.47 (dd, *J* = 5.0, 1.9 Hz, 3H), 7.42 (d, *J* = 8.1 Hz, 2H), 7.19 (dd, *J* = 8.4, 7.9 Hz, 1H), 6.73 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.21, 148.05, 144.20, 133.97, 131.02, 129.18, 129.04, 128.65, 128.51, 127.10, 115.65; HRMS ESI calcd for $C_{15}H_{10}Cl_2O_2$ $(M+Na)^+$ 314.9950, found 314.9945.

*3.3.33. (E)-4-Acetophenyl cinnamate (**39**)*

39 was synthesized according to the general procedure using 4-hydroxyacetophenone, **6g** (0.97 mmol, 134 mg) to yield a white crystalline solid (157 mg, 61%). m.p. 126.9-128.9 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 – 8.02 (m, 2H), 7.92 (d, *J* = 16.0 Hz, 1H), 7.66 – 7.56 (m, 2H), 7.51 – 7.42 (m, 3H), 7.35 – 7.30 (m, 2H), 6.66 (d, *J* = 16.0 Hz, 1H), 2.64 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.88, 164.80, 154.59, 147.35, 134.71, 134.01, 130.96, 129.98, 129.07, 128.40, 121.83, 116.76, 26.60; HRMS ESI calcd for $C_{17}H_{14}O_3$ $(M+Na)^+$ 289.0835, found 289.0831.

*3.3.34. (E)-4-Cyanophenyl cinnamate (**40**)*

40 was synthesized according to the general procedure using 4-cyanophenol, **6h** (0.97 mmol, 116 mg) to yield a white solid (173 mg, 72%). m.p. 99.8-101.1 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, *J* = 15.9 Hz, 1H), 7.82 – 7.70 (m, 2H), 7.68 – 7.57 (m, 2H), 7.53 – 7.43 (m, 3H), 7.40 – 7.32 (m, 2H), 6.64 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.45, 154.16, 147.86, 133.85, 133.69, 131.14, 129.11, 128.45, 122.80, 118.31, 116.32, 109.68; HRMS ESI calcd for $C_{16}H_{11}NO_2$ $(M+Na)^+$ 272.0682, found 272.0674.

*3.3.35. (E)-2-Nitrophenyl cinnamate (**41**)*

41 was synthesized according to the general procedure using 2-nitrophenol, **6i** (0.97 mmol, 135 mg) to yield a light yellow solid (114 mg, 44%). m.p. 77.3-78.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.95 (d, *J* = 16.0 Hz, 1H), 7.70 (ddd, *J* = 8.1, 7.5, 1.6 Hz, 1H), 7.67 – 7.59 (m, 2H), 7.49 – 7.41 (m, 4H), 7.36 (dd, *J* = 8.2, 1.3 Hz, 1H), 6.70 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.35, 148.20, 144.17, 142.11, 134.60, 133.90, 131.07, 129.04, 128.54, 126.52, 125.75, 125.30, 115.96; HRMS ESI calcd for $C_{15}H_{11}NO_4$ $(M+Na)^+$ 289.0853, found 289.0831.

Acknowledgments

The authors thank the Siena College Center for Undergraduate Research and Creative Activity for financial support and Dr. Thomas Hughes, Dr. Stephen Deyrup, and Dr. Kristopher Kolonko for helpful conversations. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References and notes

1. Sova M. Antioxidant and antimicrobial activities of cinnamic acid derivatives. *Mini Rev. Med. Chem.* 2012;12(8):749–67.
2. De Vita D, Simonetti G, Pandolfi F, et al. Exploring the anti-biofilm activity of cinnamic acid derivatives in Candida albicans. *Bioorg. Med. Chem. Lett.* 2016;26(24):5931–5935.
3. Qian Y, Zhang H-J, Zhang H, et al. Synthesis, molecular modeling, and biological evaluation of cinnamic acid metronidazole ester derivatives as novel anticancer agents. *Bioorg. Med. Chem.* 2010;18(14):4991–4996.
4. Peperidou A, Pontiki E, Hadjipavlou-Litina D, Voulgari E, Avgoustakis K. Multifunctional Cinnamic Acid Derivatives. *Molecules*. 2017;22(8):1247.
5. Huang X, Zhang B, Xu H. Synthesis of some monosaccharide-related ester derivatives as insecticidal and acaricidal agents. *Bioorg. Med. Chem. Lett.* 2017;27(18):4336–4340.
6. Kumar S, Singh BK, Arya P, et al. Novel natural product-based cinnamates and their thio and thiono analogs as potent inhibitors of cell adhesion molecules on human endothelial cells. *Eur. J. Med. Chem.* 2011;46(11):5498–5511.
7. Shi H, Xie D, Yang R, Cheng Y. Synthesis of Caffeic Acid Phenethyl Ester Derivatives, and Their Cytoprotective and Neuritogenic Activities in PC12 Cells. *J. Agric. Food Chem.* 2014;62(22):5046–5053.

8. Shirahata T, Nagai T, Hirata N, et al. Syntheses and mucosal adjuvant activity of simplified oleanolic acid saponins possessing cinnamoyl ester. *Bioorg. Med. Chem.* 2017;25(6):1747–1755.
9. Neises B, Steglich W. Simple Method for the Esterification of Carboxylic Acids. *Angew. Chemie Int. Ed. English*. 1978;17(7):522–524.
10. Meng L, Kamada Y, Muto K, Yamaguchi J, Itami K. C-H alkenylation of azoles with enols and esters by nickel catalysis. *Angew. Chemie - Int. Ed.* 2013;52(38):10048–10051.
11. Sova M, Perdih A, Kotnik M, et al. Flavonoids and cinnamic acid esters as inhibitors of fungal 17β-hydroxysteroid dehydrogenase: A synthesis, QSAR and modelling study. *Bioorg. Med. Chem.* 2006;14(22):7404–7418.
12. Rodrigues TS, da Silva AGM, de Oliveira LC, et al. Cu2O spheres as an efficient source of catalytic Cu(I) species for performing azide-alkyne click reactions. *Tetrahedron Lett.* 2017;58(6):590–595.
13. Glaser J, Schultheis M, Hazra S, et al. Antileishmanial Lead Structures from Nature: Analysis of Structure-Activity Relationships of a Compound Library Derived from Caffeic Acid Bornyl Ester. *Molecules*. 2014;19(2):1394–1410.
14. Wong KC, Ng E, Wong W-T, Chiu P. Copper Hydride Catalyzed Reductive Claisen Rearrangements. *Chem. - A Eur. J.* 2016;22(11):3709–3712.
15. Williams A, Ibrahim IT. Carbodiimide chemistry: recent advances. *Chem. Rev.* 1981;81(6):589–636.
16. Höfle G, Steglich W, Vorbrüggen H. 4-Dialkylaminopyridines as Highly Active Acylation Catalysts. [New synthetic method (25)]. *Angew. Chemie Int. Ed. English*. 1978;17(8):569–583.
17. Wang Z. Comprehensive Organic Name Reactions and Reagents. Hoboken, NJ, USA: John Wiley & Sons, Inc.; 2010.
18. Tsvetkova B, Tencheva J, Peikov P. Esterification of 7-theophyllineacetic acid with diethylene glycol monomethyl ether. *Acta Pharm.* 2006;56(2):251–7.
19. Byrne FP, Jin S, Paggiola G, et al. Tools and techniques for solvent selection: green solvent selection guides. *Sustain. Chem. Process.* 2016;4(1):7.
20. Williams J, Wood JA, Pandarinathan L, et al. Quantitative method for the profiling of the endocannabinoid metabolome by LC-atmospheric pressure chemical ionization-MS. *Anal. Chem.* 2007;79(15):5582–5593.
21. Benmansour F, Trist I, Coutard B, et al. Discovery of novel dengue virus NS5 methyltransferase non-nucleoside inhibitors by fragment-based drug design. *Eur. J. Med. Chem.* 2017;125:865–880.
22. Maier W, Corrie JET, Papageorgiou G, Laube B, Grewer C. Comparative analysis of inhibitory effects of caged ligands for the NMDA receptor. *J. Neurosci. Methods*. 2005;142(1):1–9.
23. Schwartz E, Koepf M, Kitto HJ, et al. Water soluble azido polyisocyanopeptides as functional β-sheet mimics. *J. Polym. Sci. Part A Polym. Chem.* 2009;47(16):4150–4164.
24. Sheehan J, Cruickshank P, Boshart G. Notes- A Convenient Synthesis of Water-Soluble Carbodiimides. *J. Org. Chem.* 1961;26(7):2525–2528.
25. El-Faham A, Albericio F. Peptide Coupling Reagents, More than a Letter Soup. *Chem. Rev.* 2011;111(11):6557–6602.
26. Wigman L, Remarchuk T, Gomez SR, et al. Byproducts of Commonly Used Coupling Reagents: Origin, Toxicological Evaluation and Methods for Determination. *Am. Pharm. Rev.* 2014;17(1).
27. Balcom BJ, Petersen NO. Solvent dependence of carboxylic acid condensations with dicyclohexylcarbodiimide. *J. Org. Chem.* 1989;54(8):1922–1927.
28. Hoops S, Sahle S, Gauges R, et al. COPASI--a COmplex PAthway SImulator. *Bioinformatics*. 2006;22(24):3067–3074.
29. Wu Y, Zhao J, Chen J, et al. Enantioselective Sequential Conjugate Addition−Allylation Reactions: A Concise Total Synthesis of (+)-Podophyllotoxin. *Org. Lett.* 2009;11(3):597–600.

Supplementary Material

Supplementary data associated with this article can be found in the online version and includes ^{1}H and ^{13}C NMR spectra, kinetic time course spectra, and modeled rate curves.

Click here to remove instruction text...