

A simple and convenient approach for the synthesis of *trans*-cinnamic acids from aromatic aldehydes utilizing dehydroacetic acid

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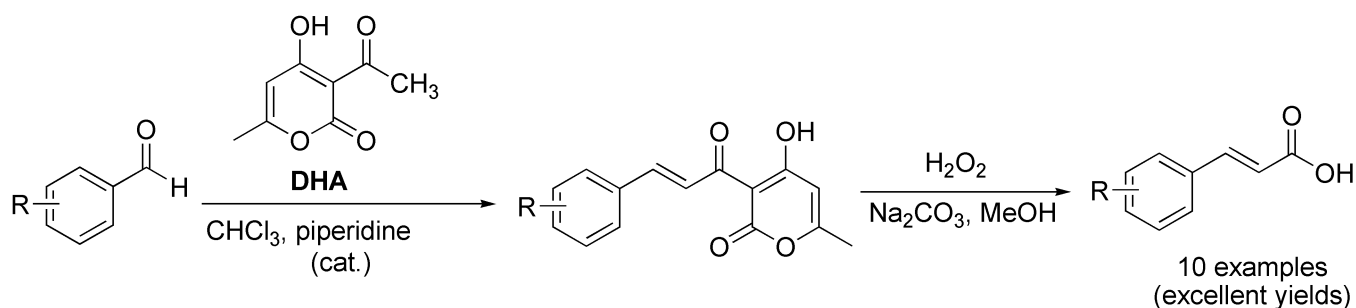
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Abstract

A simple and convenient protocol for the synthesis of *trans*-cinnamic acids from aromatic aldehydes utilizing dehydroacetic acid (DHA) has been developed. Cinnamic acids have been synthesized through the alkaline hydrogen peroxide oxidation of dehydroacetic acid (DHA) chalcones. All the cinnamic acid derivatives were obtained in good to excellent yields (72-89%). A key advantage of the developed protocol is that it avoids the need for pyridine and metal salts.



- pyridine-free
- metal-free
- H₂O as 'by-product' in second step from H₂O₂
- excellent selectivity

Keywords: DHA, chalcones, *trans*-cinnamic acids, alkaline hydrogen peroxide

Introduction

Cinnamic acid, a naturally occurring plant metabolite, have found widespread applications in pharmaceuticals, agrochemicals, and pharmaceutical intermediates production sectors.¹⁻⁶ Cinnamic acid and their derivatives have been associated with diverse range of biological applications, such as, antimicrobial⁷⁻⁹, anticancer¹⁰, UV absorption¹¹, antioxidant¹², antimetastatic¹³, and anti-inflammatory¹⁴. Biosynthesis of cinnamic acid involves phenylalanine ammonia-lyase (PAL) enzyme - catalyzed shikimate pathway.

Due to the widespread applications, synthesis of cinnamic acids is quite valuable and certain synthetic methods have been reported in the literature so far. Inarguably, the Doebner- Knoevenagel reaction has been one of the most broadly used procedures for the preparation of cinnamic acids.¹⁵ Generally, ammonia, amines (primary or secondary) and their salts are employed as base in the Knoevenagel reaction.¹⁶ Besides, use of pyridine as a solvent as well as a base is commonly used in conducting the Knoevenagel condensation.¹⁷ Continuous research has been made in this direction by chemists in order to develop more green, safe and convenient protocols. These developments include: (i) condensation of malonic acid and aromatic aldehydes in the presence of pyridine and piperidine using ultrasound and conventional heating¹⁸; (ii) microwave assisted condensation using silicon carbide vessel¹⁹, and (iii) use of microwave reactors as well as silicon carbide autoclaves for the synthesis of cinnamic acids in the presence of piperidine in ethanol²⁰. Chiriac synthesized cinnamic acids using boron tribromide as reagent, 4-dimethylaminopyridine (4-DMAP) and pyridine (Py) as bases and N-methyl-2-pyrrolidinone (NMP) as solvent.²¹

Furthermore, several advancements have been made to develop pyridine-free protocols to avoid the environmental health and safety issues associated with pyridine due to its carcinogenic effect, hazardous nature and complexity in handling at the bulk scale. These methods include use of ammonium acetate²², bismuth chloride under solvent-free conditions²³, ammonium chloride²⁴, tetrabutylammonium bromide (TBAB) and K₂CO₃²⁵, and combination of β -alanine and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)²⁶. Lu and Toy developed Doebner-Knoevenagel reaction mediated by a bifunctional polymeric catalyst²⁷. Bhat research group reported an iron (III) - catalyzed synthesis of cinnamic acids using cyclic 1,3-diester (Meldrum's ester).²⁸ Lali *et al* developed a synthetic protocol using triethyl amine as a potential N-base surrogate for pyridine in the synthesis of cinnamic acids.²⁹

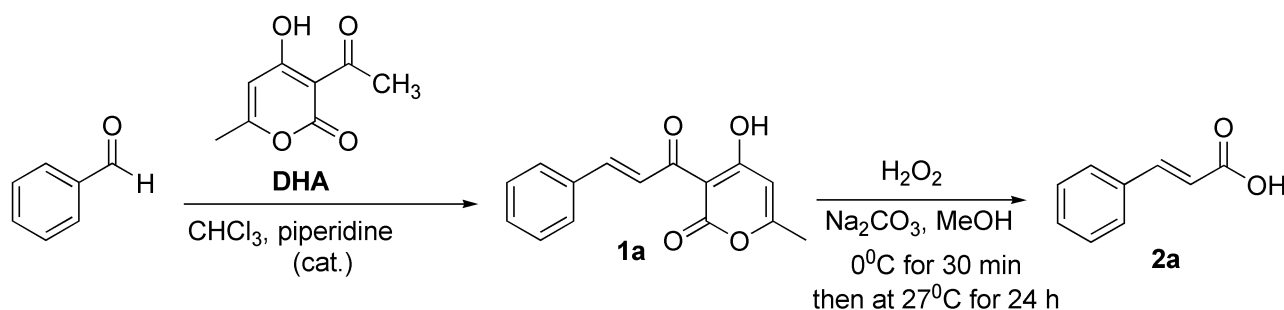
In the present work, a simple and convenient pyridine-free and metal-free protocol for the synthesis of *trans*-cinnamic acids from aromatic aldehydes utilizing dehydroacetic acid (DHA) has been developed. Further, one of key advantages of the developed protocol is the utilization of alkaline hydrogen peroxide for the cleavage that gave 'water' as by-product.

Results and Discussion

Flavonoids, a class of polyphenols obtained *via* secondary metabolism pathways, are present in our diet and possess various biological properties.³⁰ Their synthesis has been of utmost significance due to their rich and diverse chemistry as well as their diverse medicinal and photochemical properties.³¹⁻³³ The Algar, Flynn and Oyamada reaction (AFO) is one of the most commonly used methods to synthesize flavonols *via* oxidation of 2'-hydroxychalcones in alkaline hydrogen peroxide.

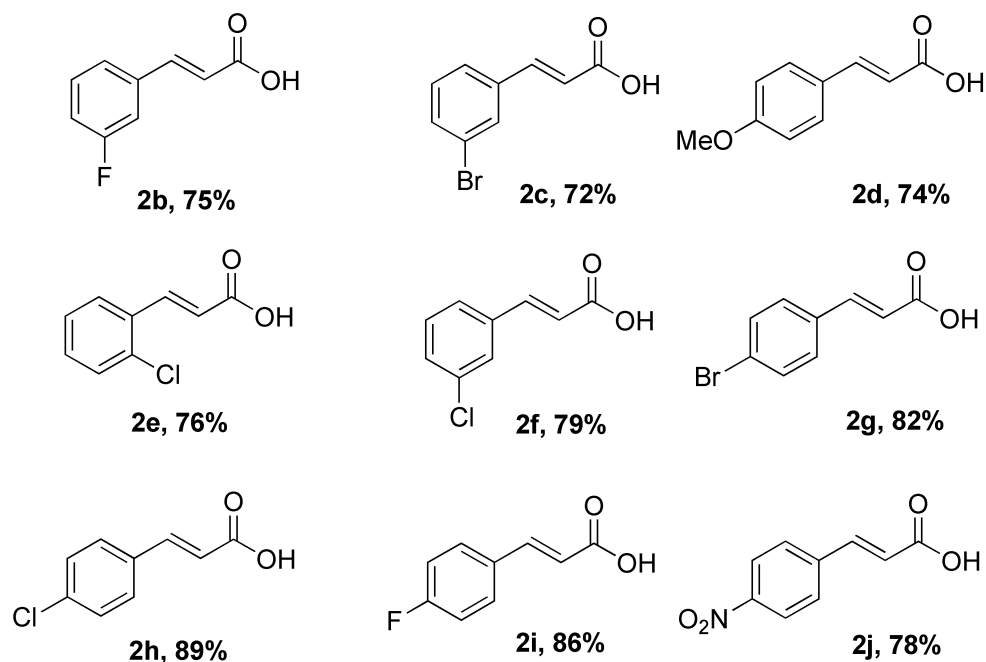
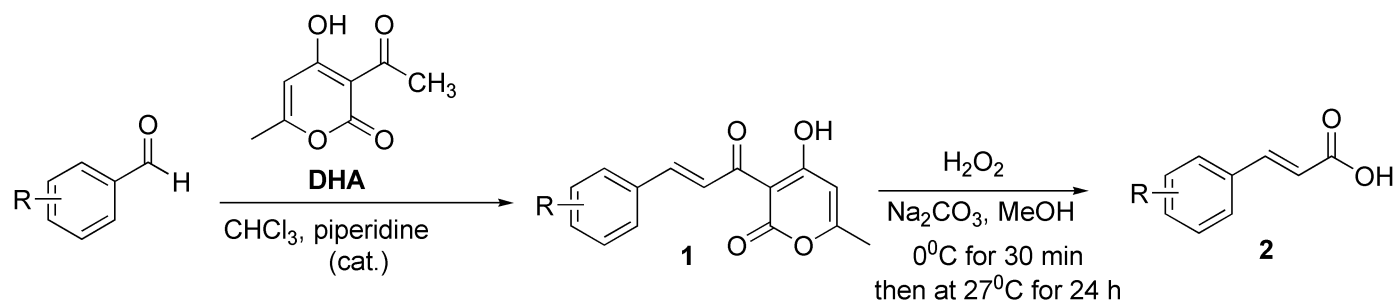
The present study began with an objective of synthesizing flavanols from DHA-chalcones utilizing Algar-Flynn-Oyamada (AFO) reaction conditions. Hence, the DHA-chalcone **1a** was treated with hydrogen peroxide in sodium carbonate using methanol as solvent following the procedure reported by Wang *et al* for

the synthesis of 5-substituted flavonols.³⁴ DHA-chalcone **1a** underwent cleavage under these oxidative conditions leading to formation of *trans*-cinnamic acid **2a** in 75% yield (**Scheme 1**). Structure of the compound **2a** was confirmed by comparing its m.pt. and spectral data (IR, ¹HNMR) data with the reported values. In the ¹HNMR spectrum of **2a**, a doublet appeared at δ 6.48 ppm with J = 16.0 Hz for one proton and another doublet appeared at δ 7.82 ppm with J = 16.0 Hz thereby confirming the *trans* -CH=CH- bond. Further, two multiplets appeared in the aromatic region for five protons of the phenyl ring.



Scheme 1. Synthesis of *trans*-cinnamic acids from aromatic aldehydes

The result obtained was quite encouraging as these simple reaction conditions gave a modified convenient way of achieving the synthesis of useful cinnamic acid under pyridine - free conditions. To check the substrate scope and functional group tolerance, other DHA-chalcones **1b-j** were reacted with alkaline hydrogen peroxide under similar reaction conditions. Interestingly, the reaction went well for all these substrates affording corresponding *trans*-cinnamic acids **2b-j** in excellent yields (72-89%) (**Table 1**). Structures of the compound **2b-j** were confirmed by comparing their m.p. and spectral data (IR, ¹HNMR) data with the reported values. The mechanism of this transformation is not fully understood till now and further experimentation in this direction is still underway.

Table 1. Substrate Scope for the synthesis of *trans*-cinnamic acids

DHA-chalcones **1a–j** can be obtained from the aromatic aldehydes on reaction with DHA in chloroform and catalytic amounts of piperidine.³⁵

Conclusions

Synthesis of cinnamic acids is quite valuable and certain synthetic methods have been reported in the literature, however, many of these methods either involve pyridine or metal salts. Several advancements have been made to develop pyridine-free protocols to avoid the environmental health and safety issues associated with pyridine due to its carcinogenic effect, hazardous nature and complexity in handling at the bulk scale. We have now developed a simple and approach for the synthesis of *trans*-cinnamic acids utilizing dehydroacetic acid and, alkaline hydrogen peroxide as a reagent. The developed method is a valuable addition towards the synthesis of *trans*-cinnamic acids.

Experimental Section

General. All the chemicals used in the synthesis were of analytical grade and procured from Sigma Aldrich and CDH and were used without further purification. Progress of each reaction was checked by thin layer chromatography (TLC), using (Merck) silica plates. A mixture of petroleum ether and ethyl acetate was used as eluent. Melting points were recorded with open glass capillaries in melting point apparatus. IR spectra were recorded using Perkin Elmer Spectrophotometer, Central Research Facility, J. C. Bose University of Science and Technology, YMCA, Faridabad.

Synthesis of DHA chalcones (1a-j). To a stirred solution of dehydroacetic acid (DHA, 1.0 eq) and the appropriately substituted benzaldehyde (1.0 eq) in chloroform, a catalytic amount of piperidine (3-4 drops, 0.1-0.2 eq) was added. The resulting reaction mixture was refluxed for 12-15 hours. After the completion of the reaction (as monitored by TLC), the solvent was removed and the resulting crude residue was recrystallized from methanol to get pure DHA Chalcones (1a-j).

Synthesis of cinnamic acids (2a-j). To a stirred solution of DHA-chalcone (1, 2.0 g, 9.36 mmol) in methanol (20 mL), sodium carbonate (4.9 g, 46.8 mmol) was added and the mixture was allowed to stir for 30 minutes at 0°C. Subsequently, 30% aqueous hydrogen peroxide (30%, 35 mL) was added dropwise to the reaction mixture. The resulting solution was stirred at (0-5 °C) for 4-5 hrs and then slowly rising the temperature to room temperature. The reaction mixture was further stirred for 10-12 hrs. Upon completion of the reaction (as monitored by TLC), the mixture was acidified with 1M HCl until a pH of 5 was reached. The aqueous layer was then extracted with ethyl acetate, concentrated and was washed with small amounts of ethyl acetate to afford the pure product 2.

Characterization data of cinnamic acids (2a-j)

Cinnamic acid (2a). White solid, m.p. 127-129°C (lit. m.p. 130-131°C);³⁶ IR ($\nu_{\max}$, cm^{-1}): 2925, 1673 (C=O), 1628, 1285, 1219; ¹H NMR (400 MHz) δ (ppm) : 7.82 (d, 1H, J_{trans} 16.0 Hz), 7.57-7.61 (m, 2H, Ar-H), 7.42-7.45 (m, 3H, Ar-H), 6.48 (d, 1H, J_{trans} 16.0 Hz); ¹³C NMR (125 MHz) δ (ppm) : 172.28 (C=O), 147.13, 134.06, 130.77, 128.98, 117.28.

3-Fluorocinnamic acid (2b). White solid, m.p. 162-163°C (lit. m.p. 165-168°C);³⁷ IR ($\nu_{\max}$, cm^{-1}): 2514, 1681 (C=O), 1630, 1294, 1216; ¹H NMR (500 MHz) δ (ppm) : 7.74 (d, 1H, J_{trans} 15.5 Hz), 7.32-7.40 (m, 2H, Ar-H), 7.10-7.24 (m, 3H, Ar-H), 6.45 (d, 1H, J_{trans} 16.0 Hz); ¹³C NMR (125 MHz) δ (ppm) : 171.39 (C=O), 164.02, 145.66, 136.29, 130.52, 124.33, 118.61, 117.56, 114.69.

3-Bromocinnamic acid (2c). White solid, m.p. 172-175°C (lit. m.p. 177-179°C);³⁷ IR ($\nu_{\max}$, cm^{-1}): 2515, 1674 (C=O), 1627, 1473, 1318, 1299, 1219; ¹H NMR (500 MHz) δ (ppm) : 12.46 (bs, 1H), 7.94 (s, 1H, Ar-H), 7.71 (d, 1H, J 8.0 Hz, Ar-H), 7.60 (d, 1H, J 16.0 Hz), 7.36-7.39 (m, 2H, Ar-H), 6.62 (d, 1H, J 16.0 Hz); ¹³C NMR (125 MHz) δ (ppm) : 167.25 (C=O), 142.17, 136.71, 132.64, 130.87, 130.64, 127.02, 122.22, 120.89.

4-Methoxycinnamic acid (2d). White solid, m.p. 168-171°C (lit. m.p. 174°C);³⁸ IR ($\nu_{\max}$, cm^{-1}): 2514, 1673 (C=O), 1627, 1298, 1219; ¹H NMR (500 MHz) δ (ppm) : 7.63 (d, 1H, J_{trans} 9.0 Hz), 7.56 (d, 2H, Ar-H, J =16.0 Hz), 6.97 (d, 2H, Ar-H, J 9.0 Hz), 6.37 (d, 1H, J_{trans} 16.0 Hz), 3.79 (s, 3H, -OCH₃); ¹³C NMR (125 MHz) δ (ppm) : 167.69 (C=O), 160.82, 143.61, 129.81, 126.71, 116.39, 114.24, 55.19 (-OCH₃).

2-Chlorocinnamic acid (2e). White solid, m.p. 203-207°C (lit. m.p. 208-212°C);²⁹ IR ($\nu_{\max}$, cm^{-1}): 2525, 1682 (C=O), 1616, 1275, 1224; ¹H NMR (500 MHz) δ (ppm) : 12.63 (bs, 1H), 7.54 (dd, 1H, Ar-H J_1 8.0, J_2 1.5 Hz), 7.45 (dd, 1H, Ar-H, J_1 7.5, J_2 1.5 Hz), 7.38-7.43 (m, 3H, Ar-H), 6.61 (d, 1H, J_{trans} 16.0 Hz); ¹³C NMR (125 MHz) δ (ppm) : 167.03 (C=O), 138.56, 133.44, 131.75, 131.56, 129.82, 128.12, 127.65, 122.22.

3-Chlorocinnamic acid (2f). White solid, m.p. 155-159°C (lit. m.p. 161-164°C);³⁹ IR ($\nu_{\max}$, cm^{-1}): 2535, 1684 (C=O), 1623, 1285, 1217; ¹H NMR (500 MHz) δ (ppm) : 12.53 (bs, 1H), 7.81 (s, 1H, Ar-H), 7.67 (d, 1H, J 7.0 Hz,

Ar-H), 7.58 (d, 1H, J_{trans} 16.0 Hz), 7.42-7.48 (m, 2H, Ar-H), 6.50 (d, 1H, J_{trans} 16.0 Hz); ^{13}C NMR (125 MHz) δ (ppm) : 171.66 (C=O), 145.48, 135.83, 135.05, 130.63, 130.22, 128.11, 126.51, 118.70.

4-Bromocinnamic acid (2g). White solid, m.p. 257-261°C (lit. m.p. 264-265°C); ^{38} IR (ν_{max} , cm^{-1}): 2514, 1682 (C=O), 1623, 1283, 1219; ^1H NMR (500 MHz) δ (ppm) : 12.45(bs, 1H), 7.66 (d, 2H, J 8.5 Hz, Ar-H), 7.61 (d, 2H, J 8.5 Hz, Ar-H), 7.57 (d, 1H, J_{trans} 16.0 Hz), 6.57 (d, 1H, J_{trans} 16.0 Hz); ^{13}C NMR (125 MHz) δ (ppm) : 167.29 (C=O), 142.49, 133.44, 131.74, 130.04, 123.40, 120.03.

4-Chlorocinnamic acid (2h). White solid, m.p. 236-239°C (lit. m.p. 241°C); ^{38} IR (ν_{max} , cm^{-1}): 2514, 1678 (C=O), 1625, 1283, 1206; ^1H NMR (400 MHz) δ (ppm) : 12.47 (bs, 1H), 7.73 (d, 2H, J 8.4 Hz, Ar-H), 7.59 (d, 1H, J_{trans} 16.0 Hz), 7.48 (d, 2H, J 8.4 Hz, Ar-H), 6.56 (d, 1H, J_{trans} 16.0 Hz); ^{13}C NMR (125 MHz) δ (ppm) : 167.38 (C=O), 142.48, 134.67, 133.15, 129.88, 128.89, 120.01.

4-Fluorocinnamic acid (2i). White solid, m.p. 199-204°C (lit. m.p. 207°C); ^{38} IR (ν_{max} , cm^{-1}): 2603, 1680 (C=O), 1626, 1285, 1226; ^1H NMR (500 MHz) δ (ppm) : 12.39 (bs, 1H), 7.77 (dd, 2H, Ar-H, J 8.5, 5.5 Hz), 7.60 (d, 1H, J_{trans} 16.0 Hz), 7.25 (t, 2H, Ar-H, J 8.8 Hz), 6.50 (d, 1H, J_{trans} 16.0 Hz); ^{13}C NMR (125 MHz) δ (ppm) : 167.32 (C=O), 142.42, 134.62, 133.12, 129.84, 128.84, 119.98.

4-Nitrocinnamic acid (2j). White solid, m.p. 274-280°C (lit. m.p. 284°C); ^{38} IR (ν_{max} , cm^{-1}): 2587, 1682 (C=O), 1631, 1283, 1228; ^1H NMR (500 MHz) δ (ppm) : 12.69 (bs, 1H), 8.24 (d, 2H, J 9.0 Hz, Ar-H), 7.98 (d, 2H, J 8.5 Hz, Ar-H), 7.70 (d, 1H, J_{trans} 16.0 Hz), 6.75 (d, 1H, J_{trans} 16.0 Hz); ^{13}C NMR (125 MHz) δ (ppm) : 166.78 (C=O), 147.74, 141.05, 140.57, 129.03, 123.67, 123.43.

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Supplementary Material

The ^1H NMR and ^{13}C NMR spectra of the compounds **2a-j** are given in the supporting information.

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