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L-Proline as an eco-friendly catalyst for microwave-assisted synthesis of *trans*-cinnamic acid derivatives

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Abstract: A simple and green synthesis of *trans*-cinnamic acid derivatives from aldehydes and malonic acid using L-proline as a green catalyst under solvent-free conditions is described. This method has the advantage of good to excellent yields, short reaction time and using of an eco-friendly catalyst.

Keywords: *Trans*-cinnamic acid; Microwave-assisted; L-proline; Tetrabutylammonium bromide; Knovenagel-Doebner.

Introduction

Cinnamic acids compose a relatively large family of organic acids which appear to have antibacterial, antifungal and antiparasitical activities [1]. Cinnamic acid and its derivatives are important reagents in organic synthesis both as intermediates and final products. Routinely, they were obtained from the reaction between aromatic aldehydes and malonic acid (Knoevenagel–Doebner reaction) [2] or acetic anhydride (Perkin reaction) [3]. The classic Knoevenagel–Doebner reaction was carried out in organic solvents catalysed by secondary or primary amines [4].

However, organic solvents used in these transformations, *e.g.* pyridine, are high on the list of damaging chemicals because of their volatile nature, considerable toxicity and use in large quantities for the reaction. On the other hand, the secondary amines employed as catalysts in these procedures are difficult to recover and often entail severe environmental pollution during the process of waste disposal. Therefore, the introduction of new methods, inexpensive reagents and environmentally friendly conditions for such transformations is still in demand. Because of the volatile and toxic nature of many organic solvents, ionic liquids are emerging as effective solvents for 'green' processes [5]. These solvents are nonflammable, nonvolatile, easy to handle and possess high thermal stability [6]. However, the high cost of most conventional room temperature ionic liquids and apprehension about their toxicity [7] have led us to use of more benign salts in the molten state as practical alternatives. For example molten tetrabutylammonium bromide was used as a low toxic and cost-effective ionic liquid in a number of useful synthetic transformations [8].

Microwave heating has emerged as a powerful technique to promote a variety of chemical reactions [9]. Many reactions that typically need many hours to reach completion with conventional heating can be brought to full conversion in only seconds to minutes by utilizing this powerful tool.

In continuation of our ongoing efforts in this area, by using microwave technique, we have developed a very efficient synthetic method for the preparation of *trans*-cinnamic acid derivatives in solvent-free conditions (Scheme 1).

This method involves the use of L-proline as an eco-friendly catalyst, and gives desired products in a short period with good to excellent yields.

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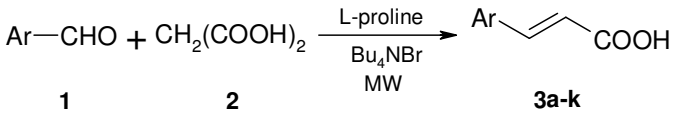


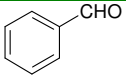
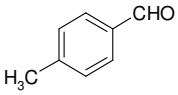
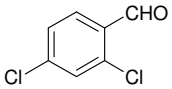
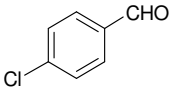
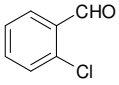
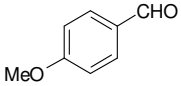
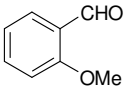
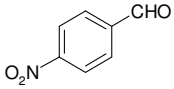
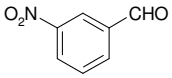
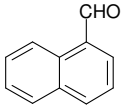
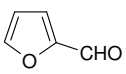
Scheme 1: Microwave-assisted synthesis of trans-cinnamic acid derivatives.

In this method, microwave irradiation plays an important role in significantly enhancing the reaction rate as well as avoiding the use of toxic or flammable organic solvents, for example, pyridine or ethanol.

Results and Discussion

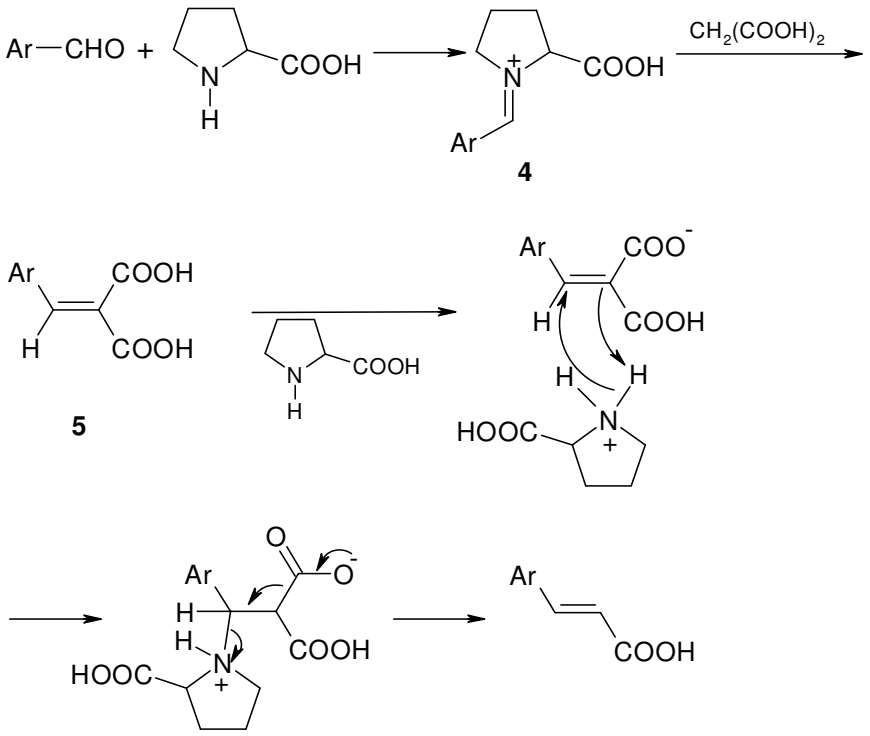
To optimize the conditions, reaction of benzaldehyde and malonic acid was selected as a model to investigate the effects of different amounts of L-proline and tetrabutylammonium bromide on the yield and time of reaction. The best results were obtained in the presence of 10 mol% of L-proline and tetrabutylammonium bromide with 600 W microwave power. To test the general scope and versatility of this procedure in the synthesis of a variety of substituted cinnamic acids, we examined a number of differently substituted aryl aldehydes. The experimental results showed the presence of electron-withdrawing or -releasing groups on the substrates had only a slight influence on the yields. The results are summarized in Table 1.

Table 1: L-proline catalyzed synthesis of *trans*-cinnamic acid derivatives

Entry	Ar	Product	Yield (%)[a]	mp (°C)	Lit. mp. (°C)[ref.]
1		**3a**	95	130-132	133 [10]
2		**3b**	94	195-197	197 [11]
3		**3c**	85	228-230	232-234 [12]
4		**3d**	96	245-247	248 [12]
5		**3e**	92	205-208	208-210 [4]
6		**3f**	94	169-172	171 [10]
7		**3g**	88	180-183	184-186 [13]
8		**3h**	95	283-285	285-286 [12]
9		**3i**	92	196-198	197-199 [4]
10		**3j**	95	207-209	211-212 [14]
11		**3k**	80	136-138	140 [11]

[a] All yields refer to isolated products which were characterized by mp data, NMR and IR spectral analysis.

This reaction may proceed via iminium intermediate **4**, formed by the reaction of the aldehyde and proline. Then malonic acid reacts with this iminium ion to form α, β-unsaturated dibasic acid **5**. Apparently, this α, β-unsaturated dibasic acid readily decarboxylated by proline to the *trans*-cinnamic acid. A reasonable mechanism is shown in Scheme 2.



Scheme 2: Mechanism of proline-catalyzed synthesis of *trans*-cinnamic acids

The experimental procedure is very simple and all reactions were performed in an open vessel in the absence of any organic solvents. After the reaction was completed the cinnamic acids extracted with NaOH solution from the reaction mixture. The corresponding *trans*-cinnamic acid derivatives were obtained by acidification of solution with high purity and do not require any chromatographic purification.

It is pertinent to note that L-proline is a green and nontoxic compound in comparison with amines, e.g piperidine, which were previously used as catalyst in this reaction [11].

Conclusions

In conclusion, we have demonstrated a simple, convenient and efficient protocol for the synthesis of wide range of *trans*-cinnamic acids in molten salt media. The simplicity, efficiency, mild reaction condition, high yields of products, easy work up procedure and using small amounts of catalyst make it the preferred procedure for the preparation of different kind of *trans*-cinnamic acids. Another important feature of this methodology is the use of molten tetrabutylammonium bromide as a low cost ionic liquid and avoidance of hazardous organic solvent.

Experimental

All products are known compounds and were characterized by comparison of thier physical properties and spectral data with authentic samples. All reagents were purchased from Merck chemical company and were used without further purification. IR spectra were recorded on a Mattson 1000 FT-IR spectrometer (KBr). ^{1}H NMR and ^{13}C NMR spectra were recorded on a BRUKER DRX-500 AVANCE spectrometer in DMSO-d_6.

Typical experimental procedure:
Malonic acid (1.5 mmol), aldehyde (1 mmol), L-proline (0.1 mmol) and tetrabutylammonium bromide (1 mmol) were mixed in a flask. This mixture was exposed to microwave irradiations at 600 W for 50 s. Then 20 ml of hot NaOH (1N) solution was added to the reaction mixture and was shaken vigorously and then filtered. The filtration was cooled and acidified (PH 5) by aqueous HCl. The resulting cinnamic acid derivative was filtered and recrystalyzed by ethanol 25%.

Spectral data for selected compounds

Cinnamic acid **(3a)**:
ν_{max} (KBr, cm^{-1}): 3230-2485, 1692, 1625; ^{1}H NMR (DMSO, d_6): δ (ppm) 12.41 (s, 1H, OH), 7.69-7.67 (m, 2H, CH_{arom}), 7.60 (d, J = 16.0 Hz, 1H, CH), 7.42-7.40 m, 3H, CH_{arom}), 6.54 (d, J = 16.0 Hz,1H, CH); ^{13}C NMR (DMSO, d_6): δ (ppm) 168.4, 144.7, 135.1, 133.1, 129.7, 129.1, 120.1.

2-Chloro cinnamic acid **(3e)**:
ν_{max} (KBr, cm^{-1}): 3156-2506, 1716, 1641; ^{1}H NMR (DMSO, d_6): δ (ppm) 12.65 (s, 1H, OH), 7.92 (m, 1H, CH_{arom}), 7.88 (d, J = 16.0 Hz, 1H, CH), 7.55 – 7.36 (m, 3H, CH_{arom}), 6.61(d, J = 16.0, 1H, CH); ^{13}C NMR (DMSO, d_6): δ (ppm) 168.0, 139.5, 134.4, 132.7, 132.5, 130.8, 129.1, 128.6, 123.2.

4-Methoxy cinnamic acid **(3f)**:
ν_{max} (KBr, cm^{-1}): 3250-2550, 1693, 1637 ; ^{1}H NMR (DMSO, d_6): δ = 12.22 (s, 1H, OH), 7.64 (d, J = 8.55 Hz, 2H, CH_{arom}), 7.55 (d , J = 15.95 Hz, 1H , CH), 6.97 (d, J = 8.55 Hz, 2H, CH_{arom}), 6.38 (d, J = 15.95 Hz, 1H, CH), 3.97 (s, 3H, OCH_3); ^{13}C NMR (DMSO, d_6): δ (ppm) 168.6, 161.8, 144.6, 130.7, 127.7, 117.3, 115.2, 56.1.

3-Nitro cinnamic acid **(3i)**:
ν_{max} (KBr, cm^{-1}): 3106-2610, 1702, 1649; ^{1}H NMR (DMSO, d_6): δ (ppm) 12.64 (s, 1H, OH), 8.47 (s, 1H, CH_{arom}), 8.20 (d, 1H, CH_{arom}), 7.71 – 7.66 (m, 1H, CH_{arom}), 7.68 (d, J = 16.0 Hz, 1H, CH), 6.72 (d, J = 16.0 Hz, 1H, CH); ^{13}C NMR (DMSO, d_6): δ (ppm) 167.9, 149.1, 142.2, 136.9, 134.8, 131.1, 125.1,123.5, 123.1.

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