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# A highly efficient transformation of *cis*- to *trans*-cinnamic acid derivatives by iodine

Zhen-Jie Li [1], Le Cai [1], Rui-Feng Mei, Jian-Wei Dong, Shu-Quan Li, Xue-Qiong Yang, Hao Zhou, Tian-Peng Yin, Zhong-Tao Ding *

*Key Laboratory of Medicinal Chemistry for Nature Resource, Ministry of Education, School of Chemical Science and Technology, Yunnan University, Kunming 650091, PR China*

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ABSTRACT

Cinnamic acid derivatives (CAs), which have proven to be versatile components, are present in abundance in biologically active natural products, and are widely used as intermediates in the manufacture of pharmaceuticals, and chemicals. The presence of *cis*- and *trans*-CAs created difficulties for natural product and organic synthetic studies. A highly efficient method that utilized iodine to entirely convert *cis*- CAs into their *trans*-forms was developed to solve this problem. The mechanism of study revealed this conversion occurred via an *anti*-diiodo intermediate.

Cinnamic acid derivatives (CAs) have attracted a great deal of interest over the years due to their widespread occurrence in plants[1–7] and are widely used as intermediates for the manufacture of pharmaceuticals, and chemicals.[8–10] From a chemical point of view, CAs possess an enormous degree of structural diversity, although their molecular backbone consists only of one phenylpropane ($C_6$–$C_3$) unit. Previous studies showed CAs exist as both *cis*- and *trans*-forms in nature.[1,11,12] The *trans*-CAs have been shown to be the predominant form in nature (>99%), because they are much more stable than the *cis*-isomers.[13,14] The *trans*-CAs were shown to photoisomerize to *cis*-forms under sunlight[15] or ultraviolet light[16,17], which led to the isolation of numerous *cis*-CA derivatives, including triterpenoids,[1,18–21] alkaloids,[18] flavonoids,[22–25] steroids,[26] cyclic peptides,[27] and phenolic compounds.[28–33] The highly selective synthesis of *trans*-CAs is a hot topic and it is difficult to obtain the pure *trans*- or *cis*-isomer for chemists. The mixtures of *cis*- and *trans*-CAs refer to natural products[18,19,34,35] and organic synthetic products[36–42] were reported. It was indicated that it was difficult to separate these isomers to obtain pure CAs.

During our phytochemical investigations on the plant material, twelve pairs of *cis*- and *trans*-CAs (**1**–**12**) were isolated (Fig. 1).[21,29,33,43] The overlapped and complex NMR signals of the *cis*- and *trans*-isomers created difficulties in assigning signals for these CAs (see Supplementary information). It took a great amount of time and energy to separate these isomers by silica gel column chromatography and semi-preparative HPLC. Undoubtedly, completed transformations to *cis*- or *trans*-isomers would facilitate to obtain pure CAs. Studies of the transformation of *trans*-CAs to their *cis*-forms have been reported. However, a photostationary equilibrium was maintained after the transformation.[12,44,17] *Cis*-ionic liquid ammonium cinnamates were reported to be converted partly to *trans*-forms.[44] Two ionic liquids with photoisomerizable *p*-hydroxycinnamic acid moieties were synthesized and their photochemistry transformations were studied in solution and neat conditions.[45] Nevertheless, these methods were helpless to obtain pure *cis*- or *trans*-CAs (Scheme 1). Hence, developing a straightforward and efficient approach to converting the mixture to pure *cis*- or *trans*-form is intensely required.

Iodine is a friendly catalyst and a remarkable radical initiator in synthetic chemistry.[46–48] Rando and Chang reported the $I^2$-catalyzed isomerization of the retinal isomers with a rate constant of $1.9 \times 10^{-4}\ s^{-1}$.[49] Puri et al. reported the iodo-Meyer–Schuster rearrangement of 3-alkoxypropargyl alcohols to $\alpha$-iodo-$\alpha,\beta$-unsaturated esters using iodine.[46] Herein we report for the first time a highly efficient and green method using iodine to completely transform *cis*-CAs to their corresponding *trans*-forms (Scheme 1).

*Cis*-*p*-hydroxy-cinnamic acid (**1a**), prepared from commercially available *trans*-*p*-hydroxy-cinnamic acid (**1b**) using a previous described method[12,50] was selected for the optimization of the reaction conditions. Reactions of *cis*-*p*-hydroxy-cinnamic acid (**1a**) with 0.1, 0.2, 0.3, 0.4 and 0.5 equiv of iodine were screened at 50 °C in NMR tubes. In the end, the optimal reaction conditions

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* Corresponding author. Tel.: +86 871 65033910.
*E-mail address:* ztding@ynu.edu.cn (Z.-T. Ding).

[1] These authors contributed equally to this work.

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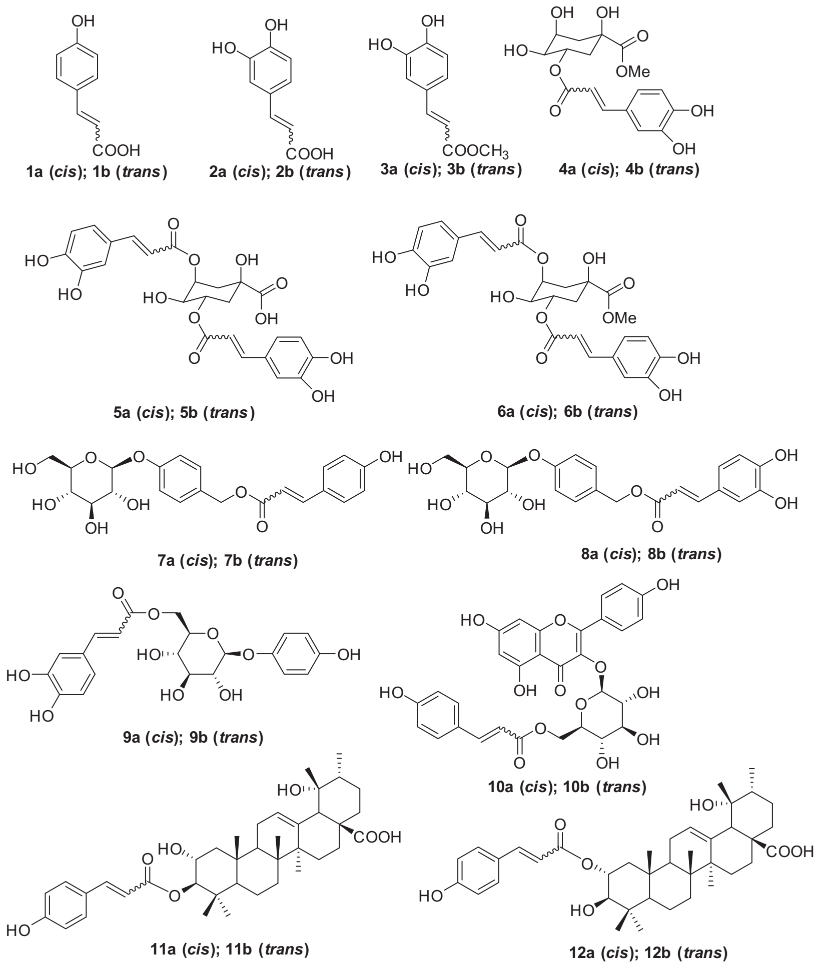
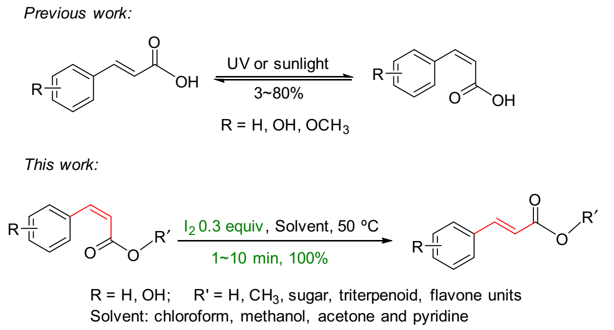


**Figure 1.** Structures of compounds **1**–**12**.



**Scheme 1.** Transformation between *cis*- and *trans*-cinnamic acid derivatives.

to obtain 100% conversion of *trans*-*p*-hydroxy-cinnamic acid (**1b**) were $I_2$ (0.3 equiv) and 10 min at 50 °C (Table 1, entry 12). The reaction could occur in several solvents, including chloroform, methanol, acetone, and pyridine. However, when the reaction was conducted in dimethyl sulfoxide (DMSO), percent conversion was very low. The unsatisfactory solvent was related with iodine–DMSO complex[51–53] and dimethyl sulfoxide should be avoided in order to obtain excellent conversion.

**Table 1**
The reaction of *cis*-*p*-hydroxy-cinnamic acid (**1a**) and iodine in NMR tubers at 50 °C

| Entry | $I_2$ (equiv) | Time (min) | Percent conversion[a] (%) |
|---|---|---|---|
| 1 | 0.1 | 2 | 8 |
| 2 | 0.1 | 4 | 11 |
| 3 | 0.1 | 8 | 14 |
| 4 | 0.1 | 10 | 51 |
| 5 | 0.2 | 2 | 35 |
| 6 | 0.2 | 4 | 57 |
| 7 | 0.2 | 8 | 76 |
| 8 | 0.2 | 10 | 92 |
| 9 | 0.3 | 2 | 51 |
| 10 | 0.3 | 4 | 73 |
| 11 | 0.3 | 8 | 88 |
| 12 | 0.3 | 10 | 100 |
| 13 | 0.5 | 2 | 84 |
| 14 | 0.5 | 4 | 86 |
| 15 | 0.5 | 8 | 84 |
| 16 | 0.5 | 10 | 90 |
| 17 | 1.0 | 2 | 74 |
| 18 | 1.0 | 4 | 72 |
| 19 | 1.0 | 8 | 72 |
| 20 | 1.0 | 10 | 80 |

[a] Percent conversion was determined by $^1H$ NMR analysis.

To investigate the scope of the above transformation, an additional eleven pairs of natural CAs (**2a**–**12a**) were treated with 0.3 equiv of iodine for a few minutes in NMR tubes. The result indicated that all the *cis*-CAs were completely transformed to the corresponding *trans*-forms and the original complex NMR spectra became simple and unambiguous (see Supporting information). For example, Fig. S1 showed the $^1H$ and $^{13}C$ NMR spectra of the mixture of *cis*- and *trans*-chlorogenic acid methyl ester (**4a** and **4b**).