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

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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 α-iodo-α,β-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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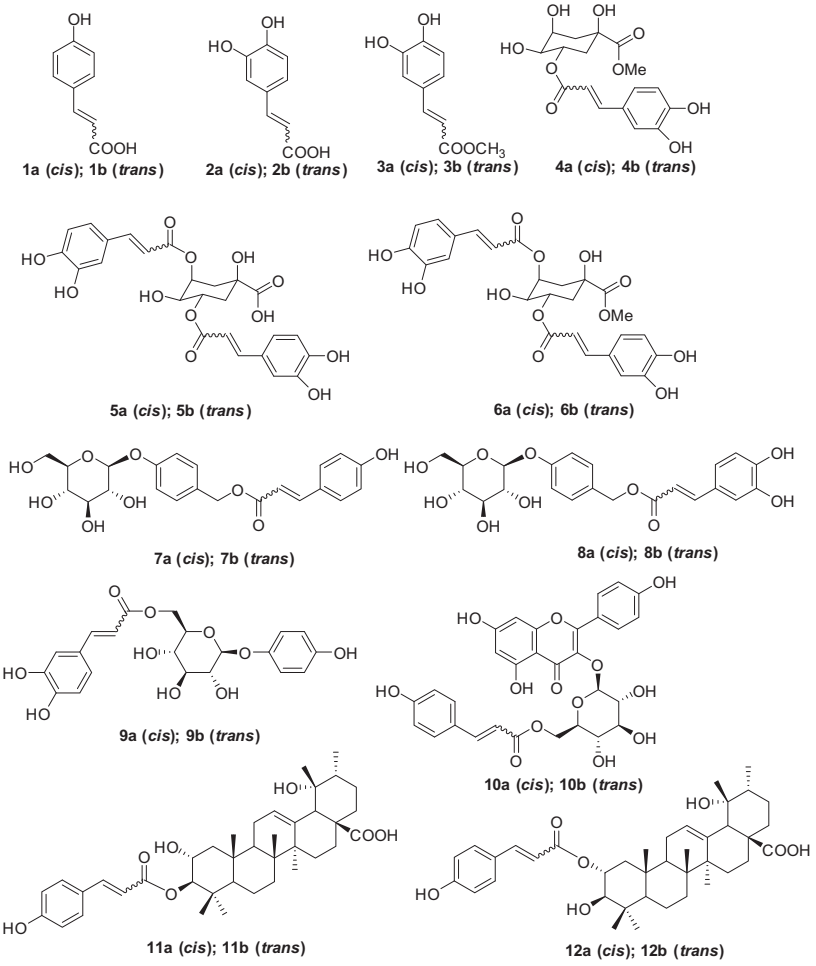
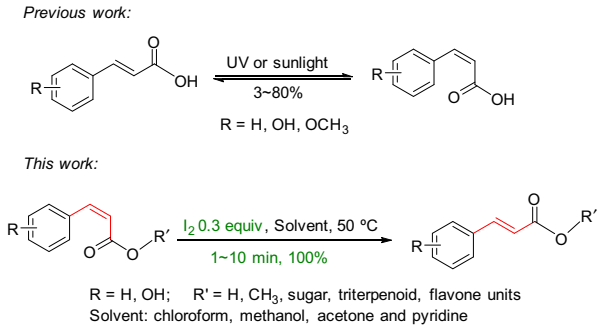


Figure 1. Structures of compounds **1**–**12**.



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

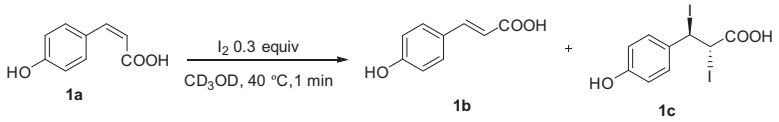
to obtain 100% conversion of *trans*-*p*-hydroxy-cinnamic acid (**1b**) were I_2 (0.3 equiv) and 10 min at 50 °C (Table 1, entry 12). The reaction could occur in several solvents, including chloroform, methanol, acetone, and pyridine. However, when the reaction was conducted in dimethyl sulfoxide (DMSO), 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.

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 ^{1}H and ^{13}C NMR spectra of the mixture of *cis*- and *trans*-chlorogenic acid methyl ester (**4a** and **4b**).

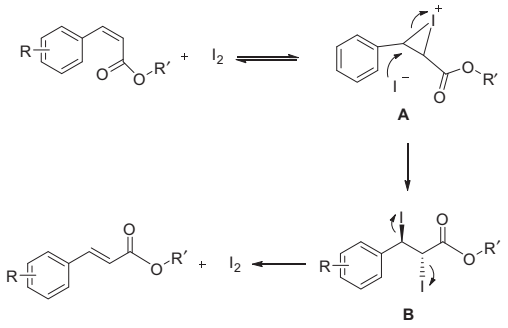
Table 1
The reaction of *cis*-*p*-hydroxy-cinnamic acid (**1a**) and iodine in NMR tubers at 50 °C

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 ^{1}H NMR analysis.



Scheme 2. Addition reaction of iodine and *cis*-*p*-hydroxy-cinnamic acid (**1a**).



Scheme 3. Reaction mechanism of *cis*- to *trans*-isomerization.

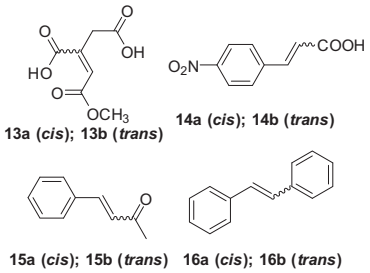


Figure 2. Structures of compounds **13**–**16**.

After reacting with 0.3 equiv weight of iodine for 2 min at 50 °C, the ^{1}H and ^{13}C NMR spectra of the above mixture became simple and pure (Fig. S2), indicating that all the *cis*-chlorogenic acid methyl ester (**4a**) was converted to its *trans*-isomer (**4b**). Therefore, this reaction could be a very convenient method that natural product chemists could use to study CAs. This reaction could also be utilized in organic synthesis researches.

To investigate the applicability of this reaction on gram scale, 1.05 g of a mixture of *cis*- and *trans*-caffeic acids (**2a**:**2b** = 43:57) were transformed by iodine (41.3 mg, 0.16 mmol). Results indicated that all the *cis*-caffeic acid was converted to its *trans*-isomer within 5 min, which indicated that this reaction could be scaled up commendably. Particularly, iodine in catalytic amounts could be taken away along with solvent evaporation after the reaction because of its sublimation property, which made the post-treatment easy. Thus, this reaction is green, efficient, and has potential industrial applications.

In view of the speed of the iodine transformation, the reaction was first considered to proceed via a radical anion intermediate. If this conversion was a radical reaction, other radical initiators should also promote this conversion. Therefore, two additional radical initiators, azobisisobutyronitrile and *tri*-*n*-butyltin hydride, were used to react with *cis*-*p*-hydroxy-cinnamic acid (**1a**) and 4-hydroxy-*cis*-cinnamomic acid 4-*β*-D-glucopyranosyloxybenzyl ester (**7a**). Unexpectedly, the transformation did not occur. Additionally, an efficient radical-trapping reagent, 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), was further involved in this mechanism study.[54,55] The result indicated that TEMPO could not prevent the transformation from *cis*-*p*-hydroxy-cinnamic acid (**1a**) to its *trans*-isomer (**1b**), which was consistent with results of azobisisobutyronitrile and *tri*-*n*-butyltin hydride experiment. The above two experiments incontrovertibly confirmed that this conversion was not promoted by a free radical.

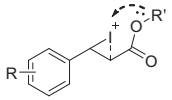
Therefore, the iodonium cation was suggested as an intermediate in this reaction. When the reaction temperature was deceased to 40 °C, the signals of a key anti-7,8-diiodo intermediate (**1c**) were detected in ^{1}H NMR spectrum (δ_H 4.45, d, J = 10.5 Hz and δ_H 4.34, d, J = 10.5 Hz, Fig. S3). Compound **1c** was unstable and two labile iodine groups were eliminated to form *trans*-*p*-hydroxy-cinnamic acid (**1b**) (Scheme 2). The above experiments definitely confirmed that the iodine-catalyzed transformation of *cis*-CAs occurred via an iodonium cation (**A**), followed the production of the key *trans*-diiodo intermediate (**B**) (Scheme 3).

Table 2
Investigation on the effect of vicinal moieties

Entry	Starting material	Reaction time	Product	Percent conversion[a] (%)
1	Oleinic acid	5 h	—	—
2	**13a**	1 h	**13b**	—
3	**14a**	2 h	**14b**	30
4	**15a**	4 min	**15b**	100
5	**16a**	2 h	**16b**	100

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

To evaluate the effect of vicinal moieties on the transformation of *cis*-double bonds to their *trans*-isomers, various compounds (**13**–**16**) (Fig. 2) were screened in this reaction (Table 2). The phenyl group was supposed to facilitate the formation of an iodonium cation because of its electron donating effect. *Cis*-4-nitrocinnamic acid (**14a**), whose electron donating ability was significantly decreased, could not be completely transformed to its *trans*-form (30%), indicating that the electron donating effect of the phenyl group was very important to this reaction. Two *cis*-vinyl compounds, *cis*-aconitic acid methyl ester (**13**) and oleinic acid, which both contain no phenyl linking with the *cis*-double bond, could not be transformed to their *trans*-isomers by iodine which further suggested that the phenyl group was essential for the success of this transformation. To examine the effect of the carboxyl group on this transformation, *cis*-stilbene (**16a**), which has no carboxyl group adjacent to the double bond, was used in this transformation. The result showed that the transformation could be completed in 2 h, which was much longer than for CAs, indicating that carboxyl was positive to this conversion. The reason might be that carboxyl unit increased the polarization of π electron cloud in vinyl, which facilitated the formation of the iodonium cation. Another compound, 4-phenyl-*cis*-3-buten-2-one (**15a**), whose hydroxyl group in the carboxyl moiety was replaced by a methyl, could also be converted to its *trans*-isomer in 4 min, which was slightly longer than common CAs, implying the hydroxyl in carboxyl was also positive to this transformation. This might be caused by the stabilization of the iodonium cation by the lone pair electrons in the hydroxyl oxygen (Scheme 4). It can be concluded that two substitutions adjacent to the *cis*-double bond had a significant influence on the transformation capabilities, which decreased in the following order: phenyl, carboxyl > phenyl, carbonyl > phenyl, phenyl ≫ carboxyl, carboxyl = alkyl, alkyl (no reaction).



Scheme 4. Stabilization of the iodonium cation by the lone pair electrons in the hydroxyl oxygen.

In summary, using iodine, we have developed an efficient, quick, and convenient approach to completely transforming *cis*-CAs to their corresponding *trans*-forms in this study. This conversion was shown to proceed via an iodonium cation intermediate and could be used in the lab to obtain pure *trans*-CAs in an efficient manner. Meanwhile, easy scale-up and convenient post-treatment provided potential industrial applications for this reaction.

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Supplementary data

Supplementary data (experimental procedures and spectral data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.11.050.

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