

N-Iodosuccinimide in Oxidative Dimerization of Methyl Cinnamates

Pierantonio Galgano,^[a] Alessandro Santarsiere,^[a] Maria Funicello,^[a] Paolo Lupattelli,^[b] Rosanna Ciriello,^[a] and Lucia Chiummiento*^[a]

Herein the reaction of methyl cinnamates with N-iodosuccinimide (NIS) is reported and the possible formation of dihydrobenzofuryl dimeric derivatives (DHBF), known for their biological activities, is explored. Having an oxidizing capacity, we studied the behavior of NIS with methyl ferulate and under optimized reaction conditions we obtained its DHBF dimer in 35% yield. It is worth to note that we did not obtain the DHBF in his natural form, but rather as the demethylated compound, likely due to dismutation reactions activated by the presence of water in the solvent. Methyl caffeate reacted with NIS to furnish the

DHBF dimer in 15% yield, while methyl coumarate and methyl isoferulate did not give any form of DHBF dimers, showing the importance of a hydroxyl group in *para* position on an activated system and an electron-rich aromatic ring. An electrochemical investigation by cyclic voltammetry was carried out on the three cinnamates and confirmed the correlation between dimerization and oxidation potential: methyl ferulate and methyl caffeate dimerize, while methyl coumarate, due to its higher oxidizing potential, does not.

1. Introduction

Cinnamates^[1] are phenolic compounds widely distributed in nature. Among them, phenylpropanoids such as caffeic, ferulic, p-coumaric and sinapic acids constitute essential components of plant cell walls and demonstrate significant antioxidant, anti-inflammatory, and anticancer properties.^[2] These compounds arise from the shikimic acid pathway, with phenylalanine acting as precursor (Figure 1).

In nature cinnamates give rise, to oxidative dimerization reactions, forming dimers (Figure 2) that play a fundamental structural role as cross-linkers between components of the plant cell wall.^[3–5] Such transformations are catalysed by enzymes such as peroxidases and laccases.^[6]

Among the reported dimers, 2,3-dihydrobenzofuran II (DHBF) exhibits interesting biological activities (anti-tumor, anti-parasitic, and anti-oxidant), making it a promising antimetastatic agent.^[10] Biomimetic synthesis of DHBF were obtained by employing the methyl esters of cinnamyl derivatives and enzymes as crude onion peroxidase^[2] or HRP/H₂O₂/laccase systems,^[11] with high yield and diastereoselectivity (Scheme 1a) or chemically by Ag₂O as mild oxidant^[12] (Scheme 1b).

Recently, we explored a biomimetic dimerization of resveratrol using N-iodosuccinimide (NIS) as radical initiator,^[13–14] yielding a single racemic *trans*-2,3-diaryl- DHBF, which gave ϵ -viniferin in 18% yield (Scheme 1c).^[15]

Going on the research of new strategies for the total synthesis of natural products.^[16–19] and recognizing the shortcomings of the reactivity of NIS as a radical promoter reagent, we investigated whether it was possible to use NIS in a biomimetic dimerization of cinnamates, working under air and metal-free conditions (Scheme 1d).

To confirm the correlation between the dimerization and the oxidizing potential, cyclic voltammetry of cinnamates and NIS was conducted.

1.1. Dimerization Investigation

Cinnamates used for this work were synthesized by a Wittig-Horner reaction as reported in literature.^[20]

Methyl ferulate **1a** was chosen as model substrate, the reaction was carried out at a 0.20 mmol scale. Table 1 shows the explorative dimerization conditions.

Among different solvents used, only MeCN furnished the racemic dimer **2a** in 18% yield with the simultaneous removal of the methyl from the catecholic moiety and the formation of the dihydronaphthalene **3** (7% yield), while reactions with MeCN/H₂O, toluene or without any solvent furnished **2a** in very complex mixtures. Reactions in DMF and MeOH produced principally demethylated and iodinated products, respectively.

From these preliminary results, optimization of the reaction in MeCN was carried out (Table 2): long reaction time (about a day) gave a mixture of products (entry 2), while a reaction time shorter than 1 h furnished a slightly lower yield and conversion (entry 1). Increasing the equivalents of NIS up to 3.0 eq (entries

[a] Dr. P. Galgano, Dr. A. Santarsiere, Prof. M. Funicello, Prof. R. Ciriello, Dr. L. Chiummiento
Department of Basic and Applied Sciences, University of Basilicata, Via dell'Ateneo Lucano, 10, Potenza 85100, Italy
E-mail: lucia.chiummiento@unibas.it

[b] Prof. P. Lupattelli
Department of Chemistry, Sapienza University of Rome, p.le Aldo Moro 5, Roma 00185, Italy

Supporting information for this article is available on the WWW under <https://doi.org/10.1002/slct.202403776>

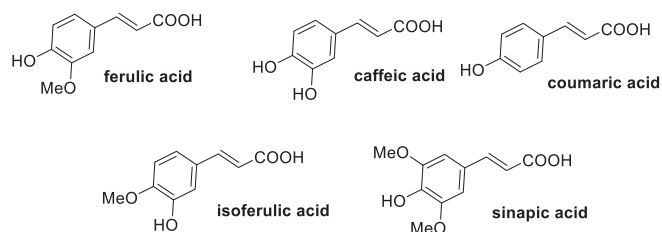


Figure 1. Natural cinnamates.

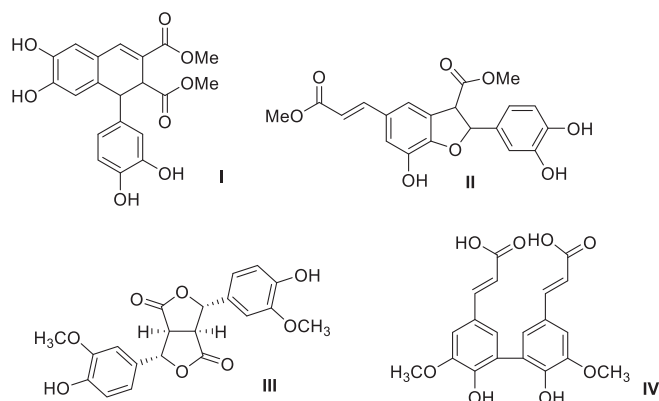


Figure 2. Structures of some dimers of phenylpropanoids.

4–6) the yield reached a maximum of 35% (entry 6), while a further increase of NIS led to lowering the yield (entry 7). At 50 °C low yield of **2a** was obtained (entry 8), while at 0 °C it raised up to 20%, together with 10% of **2b** (entry 9). The competitive dimerization to dimer **3** became more evident working with 0.5 eq of NIS, at rt and with light (up to 15% yield, entry 10).

With 0.5 eq of NIS, at rt, **2b** was produced instead of **2a** (entry 10), but at 0 °C and in dry solvent the amount of **2b** was decreased (entry 11). The yield of dimer **2b** was improved varying the eq of NIS and working at 0 °C with dry solvent and under inert atmosphere of argon (Table 2, entries 11–14).

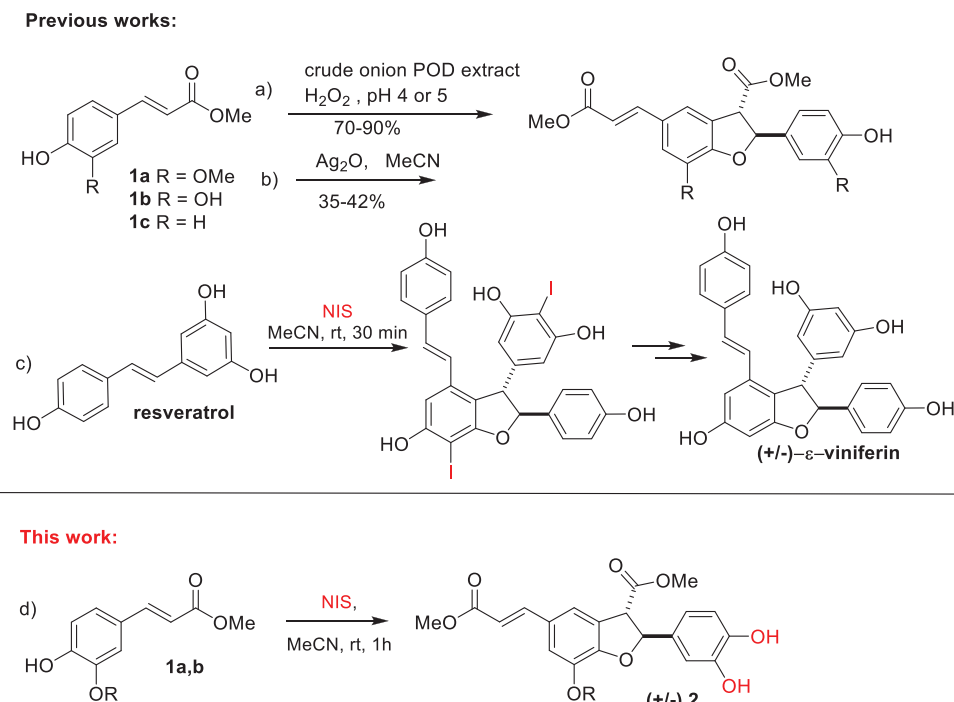
The best conditions for obtaining DHBF **2b** were those reported in the entry 12 (23%). In the entry 14 with a large excess of NIS we instead obtained the deprotected form **2a**.

Dimerization was also tried on other cinnamyl derivatives, as depicted in Table 3.

Dimerization on methyl caffeate **1b** (entry 1, Table 3) gave the corresponding desired product **5** with 15% yield and the corresponding dihydronaphthalene **6** with a 5% yield, while dimerization on other substrates didn't give any reaction, hence the importance of a hydroxyl group in *para* position on the electron-rich aromatic ring. In fact, methyl isoferulate, **1a'** furnished only the demethylated products, without any trace of dimers and compound **1c** gave rise only iodinated products (Table 3, entries 3 and 4, respectively).

To increase the yield of dimer **5** and to facilitate its isolation the crude was acetylated. Using 2 eq of NIS the reaction furnished compound **5a** (compound **5** acetylated) in 18% yield. However, extending the reaction time to 4 h furnished the dimer acetylated **6a** in 10%. A higher amount of NIS degraded the substrate **1b** (Scheme 2).

Considering the previous results, NIS acts as a radical promoter on the phenol ring of some cinnamyl derivatives. This was confirmed when the 2,2,6,6-tetramethylpiperidin-1-yl)oxy (TEMPO) was added to the mixture containing methyl ferulate **1a** and NIS, no dimerization or products were observed (Scheme 3).



Scheme 1. DHBF structures from dimerization reactions.

Table 1. Reaction with NIS in different solvents.

Entry ^{a)}	Solvent	Products (%)
1	MeCN	2a (18%)
2	Dry MeCN	2b (10%) + 3 (7%)
3 ^{b)}	MeCN/H ₂ O	2a + mix
4	MeOH	4 (70%) ^{d)}
5	DMF	1b (15%)
6	Toluene	Mix
7	DCM	No reaction
8 ^{c)}	None	2a + mix

a) All reactions were conducted with a concentration 0.1 mM of compound **1a**, 1.5 eq of NIS, for 1 h at rt, in the dark, isolated yield after chromatography.

b) 15 eq of water.

c) not in the dark.

d) yield determined by ¹H-NMR of the crude mixture.

Table 2. Optimization of dimerization conditions.

Entry ^{a)}	NIS (eq)	Time	T (°C)	Dark	Prod (%)
1	1.5	0.5 h	r.t.	Yes	2a (13%) + 3 (10%)
2	1.5	17h	r.t.	Yes	mix including 2a
3 ^{b)}	1.5	1h	r.t.	Yes	2a (6%) + 3 (7%)
4	2.0	1h	r.t.	Yes	2a (20%) + 3 (13%)
5	2.5	1h	r.t.	Yes	2a (25%)
6	3.0	1h	r.t.	Yes	2a (35%)
7	4.0	1h	r.t.	Yes	2a (27%)
8	1.5	1h	50 °C	No	mix including (2a + 3)
9	1.5	1h	0 °C	No	2a (20%) + 2b (10%)
10 ^{c)}	0.5	1h	r.t.	Yes	2b (17%) + 3 (15%)
11 ^{c)}	0.5	1h	0 °C	No	2b (10%) ^{d)}
12 ^{c)}	1.2	1h	0 °C	No	2b (23%) + 3 (10%)
13 ^{c)}	1.5	1h	0 °C	No	2b (20%)
14 ^{c)}	3.0	1h	0 °C	No	2a (19%) ^{d)}
15	/	1h	0 °C ^{e)}	No	No reaction

a) All reactions were conducted with a concentration 0.1 mM of the substrate, isolated yield after chromatography.

b) 0.2 mM of the substrate.

c) under inert atmosphere of argon and dry solvent.

d) yield determined by ¹H-NMR of the crude mixture.

e) reactions conducted at rt or at 50 °C did not give any products.

Moreover, other oxidating agents were investigated: NBS gave exclusively the brominated compound **9**, while CAN (ceric ammonium nitrate) and PIDA (phenyl iodine diacetate) gave a mixture of by-products.

From these results it can be affirmed that NIS induces the initial formation of a radical on the OH of compound **1a** which is stabilized by resonance through structures **A**, **B** and **C** (scheme 4); the coupling between **B** and **C** gives compound **D** which furnishes the DHBF **2b**. Demethylation occurs because iodine generated in situ (equation b) undergoes dismutation in water producing iodide (equation c) which acts as nucleophile causing demethylation of **2b** to **2a** and methyl iodide. In fact, only the DHBF **2b** was observed in absence of water (dry MeCN) (Table 2, entries 11–13). Demethylation occurs in presence of an excess of NIS (3.0 eq.) despite the dry condition (Table 2, entry 14).

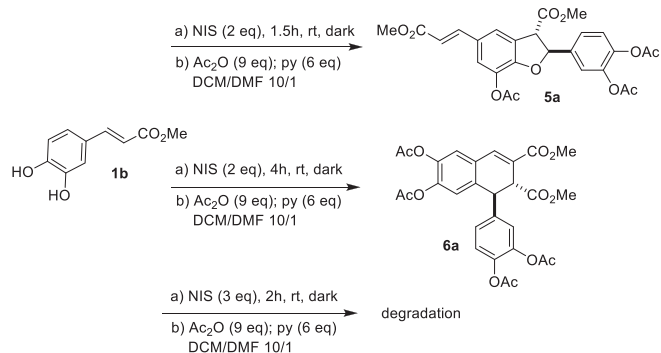
1.2. Cyclic Voltammetry

Therefore, this oxidative property of NIS in MeCN was evaluated and the electrochemical behavior of NIS and methyl coumarates **1a-c** was investigated by cyclic voltammetry at a glassy carbon electrode in acetonitrile containing tetrabutylammonium perchlorate 0.1 M as supporting electrolyte. As far as we know, this is the first electrochemical study carried out on NIS. A

Table 3. Dimerization on different substrate.

Entry ^{a)}	Substrate	Product (yield)
1	1b	5 (15%) + 6 (5%)
2	1a'	1b (7%)
3	1c	7 (15%) + 8 (22%)

^{a)} All reactions were conducted with a concentration 0.1 mM of compound **1a**, 1.5 eq of NIS, for 1 h at rt, in the dark; yields determined after chromatography.

Scheme 2. Optimization of dimerization conditions of methyl caffeate **1b**.

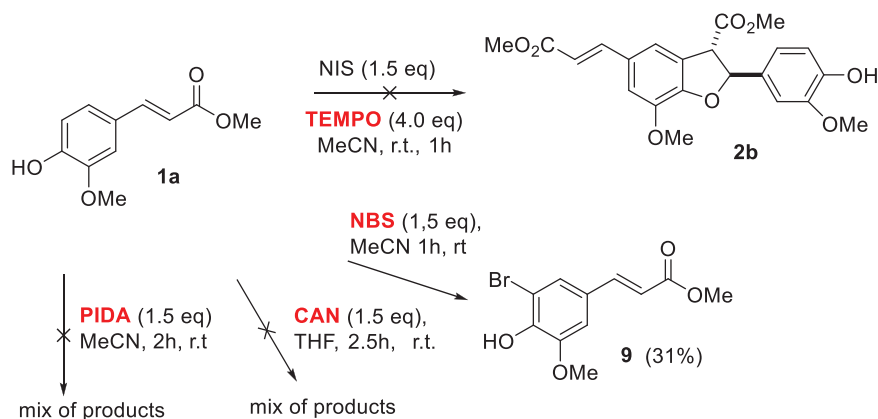
voltammetric study of NBS, an efficient mild oxidizing reagent, in hexafluoropropan-2-ol was previously reported.^[21] During the cathodic scan, an irreversible reduction process involving the transfer of a single electron was observed. Reverse anodic sweep showed a peak due to oxidation of reaction products formed during cathodic scanning.

The cyclic voltammogram recorded at a scan rate of 50 mV/s for a 5 mM NIS solution is depicted in Figure 3 along with

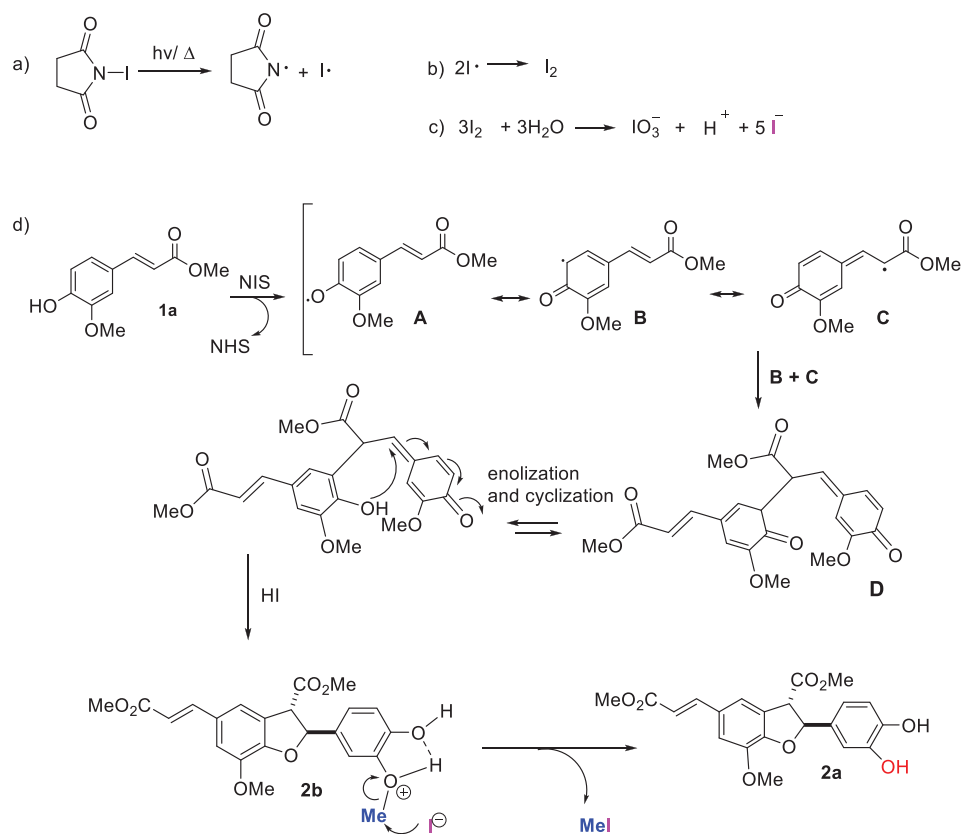
the current profile acquired in the presence of the pure solvent containing tetrabutylammonium perchlorate. As shown in Figure 3, acetonitrile has a wide potential window where no current peaks are detected and is therefore widely used as an inert non-aqueous solvent.

As already reported for NBS, a reduction peak at around -0.340 V (versus Ag/Ag⁺) is observed in the cathodic scan. This peak is thought to be due to the irreversible reduction of NIS to its radical anion, which decomposes into the succinimidyl radical and iodide ion.^[21] The iodide ion produced in the chemical reaction can reasonably oxidise to iodine in the reverse scan, giving rise to the oxidation peak detected at about 0.635 V.

It is worth noting that when the oxidation limit was extended to more anodic potentials, two poorly defined peaks were observed at about 1.8 V and 2.3 V. Electrochemical iodination with in situ generation of iodinating species by use of iodides as iodine atom source has been reported in aqueous media.^[22] In that case, the first oxidation peak was attributed to the oxidation of iodide to iodine, the second peak to the oxidation of iodine to HIO and the third peak to the oxidation of iodide to HIO₃. In the present work, the experiments were carried out in acetonitrile. The electrochemical generation of the iodinating



Scheme 3. Dimerization attempts with other oxidizing agents.



Scheme 4. Proposed mechanism for dimerization and demethylation

agents was probably due to the presence of traces of water in the organic solvent.

To justify the different oxidising activity of NIS towards the hydroxycinnamic esters studied in this work, electrochemical techniques represent an effective tool for the elucidation of the mechanisms of electron transfer. The electrochemical behavior of methyl coumarate **1c**, methyl caffeate **1b** and methyl feru-

late **1a** was then studied by cyclic voltammetry on a glassy carbon electrode in acetonitrile containing tetrabutylammonium perchlorate 0.1 M. Solutions were freshly prepared at a concentration of about 5 mM. The voltammetric profiles are shown in Figure 4.

As stated elsewhere,^[23] the oxidation potential of hydroxycinnamic esters is strictly dependent on the number and position

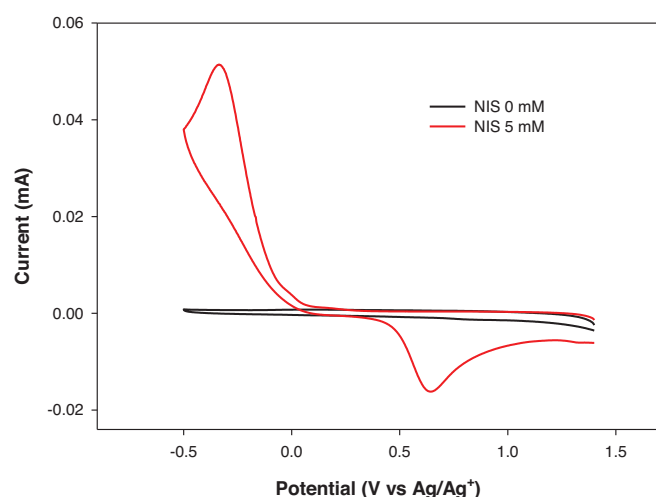


Figure 3. Cyclic voltammogram of NIS 5 mM (red curve) in acetonitrile containing tetrabutylammonium perchlorate 0.1 M at a glassy carbon electrode. The black curve represents the current profile acquired in the supporting electrolyte without NIS. Scan rate 50 mV/s.

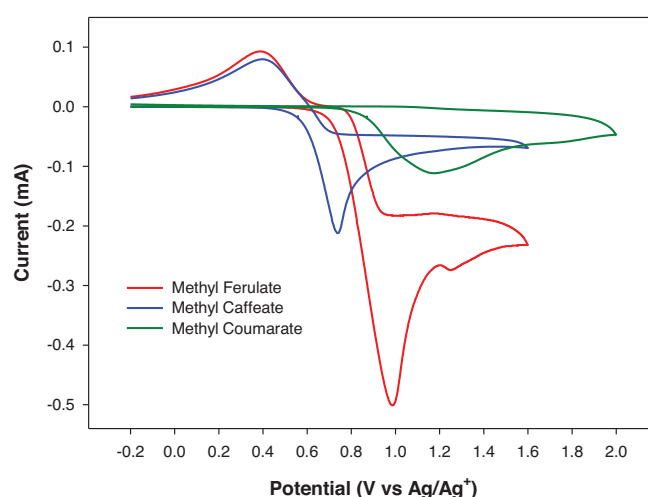


Figure 4. Cyclic voltammograms of methyl coumarate 4.45 mM, methyl caffeate 4.85 mM and methyl ferulate 5.2 mM in acetonitrile containing tetrabutylammonium perchlorate 0.1 M at a glassy carbon electrode. Scan rate 50 mV/s.

of the hydroxyl groups on the aromatic ring. The voltammetric profile of methyl coumarate **1c** shows an irreversible oxidation peak at 1.17 V due to the formation of the phenoxy radical. The absence of a cathodic peak in the reverse sweep is justified by the incoming of radical coupling processes following the electron transfer.

The introduction of a second hydroxyl group in the *ortho* position results in a significant decrease of the redox potential of methyl caffeate **1b** to 0.740 V. Oxidation of the catechol group is a two electrons and two protons process. The backscan shows a broad reduction peak at 0.400 V, due to the reduction of the previously generated catechol moiety. The ratio of anodic to cathodic peak heights above unity is consistent with an oxidation process coupled with a subsequent chemical reaction, in agreement with previous reports on caffeic acid.^[23]

Substitution of the 3-hydroxyl group of caffeic acid by a methoxy group shifts the redox potential of methyl ferulate **1a** towards more positive values, at about 0.987 V. In the anodic scan of the voltammetric profile of methyl ferulate, another weakly intense oxidation peak is evident at about 1.25 V. This feature has already been observed and attributed to the oxidation of free and adsorbed forms of methyl ferulate.^[24] The free form corresponds to the first peak, the adsorbed form, which is therefore stabilized, is oxidized at a more anodic potential. During anodic scanning, methyl ferulate is oxidized through a one electron transfer to phenoxy radical whose electronic charge distribution can be represented by different mesomeric forms. Particularly, the radical in the methoxy position undergoes a second electron transfer generating a carbocation which upon hydrolysis gives the 3,4-dioxocinnamic methyl ester and a methanol molecule. During the reverse scan, the 3,4-dioxocinnamic ester is reduced to methyl caffeate. Indeed, the potential of the reduction peak in the voltammetric profile of methyl ferulate is 0.382, and then very close to the value of the reduction potential previously reported for methyl caffeate. The extreme closeness of the reduction potentials confirms the above assumptions.

2. Conclusion

In conclusion, the scope of NIS as an oxidant agent of phenols has been demonstrated by the dimerization of methyl ferulate **1a** and methyl caffeate **1b**, giving another example of NIS as an efficient radical initiator promoting a regio-, diastereoselective biomimetic synthesis of dihydrobenzofurans and dihydronaphthalenes with a yield up to 35% and 15%, respectively. The in situ generation of iodine and the subsequent dismutation reaction to iodide and higher oxidated species are responsible for the simultaneous demethylation reaction to the catechol position of the methoxy group. Evidence of the easy oxidation of dihydroxycinnamyl derivatives promoted by NIS is provided by comparing the values of oxidation potential of these cinnamyl compounds and NIS. In fact, only methyl ferulate **1a** and methyl caffeate **1b** dimerize, while methyl coumarate **1c**, which has a higher oxidation potential, does not.

Supporting Information

The authors have cited additional references within the [Supporting Information](#).^[25–30]

Acknowledgments

Financial support has been provided by the MUR-M4C2 1.1 “PRIN PNRR 2022” funded by the European Union- Next Generation EU (Grant agreement n. P2022Y3AA8: Gold Nanostructures for Benzofuryl-based Anti-tumoral Photoinduced Drug Delivery Systems). The authors thank D. Montesano for his technical assistance.

Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

Research data are not shared.

Keywords: Biomimetic synthesis · Cinnamates · Cyclic voltammetry · Dihydrobenzofurans · N-iodosuccinimide

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Manuscript received: August 08, 2024