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Direct electrosynthesis of a series of novel caffeic acid analogues through a clean and serendipitous domino oxidation/thia-Michael reaction†

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A series of novel caffeic acid analogues have been synthesized in an experimentally simple electrochemical procedure employing electrons as the only reagents in aqueous solution without introducing any catalyst or oxidant. It has been shown that the reactions proceed *via* a domino of electrochemical and chemical events (EC mechanism) with an interesting regioselectivity in the formation of arylsulfonyl-functionalized *N*-caffeoyl amides and caffeate esters. All products were purely obtained at the surface of anode (carbon rods) in excellent yields and no extra purification was needed. Structural characterization of these novel compounds was also performed using various spectroscopic techniques: FT-IR, ^{1}HNMR, ^{13}CNMR and HR-mass.

Introduction

Caffeic acid and its naturally occurring derivatives are the main representatives of the hydroxycinnamic and phenolic acids and widely distributed in plants, vegetables, and propolis as simple derivatives such as esters, amides, glycosides, and sugar esters.[1] The physiological functionality of caffeic acid and its analogues has attracted a great deal of attention in recent years. They are known to have many biological activities like antibacterial,[2,3] antifungal,[4,5] antiviral,[6] anti-oxidative,[7–10] and proteins cross-linker properties.[11] On the other hand, sulfone fragments are important building blocks in medicinal chemistry[12] and also useful intermediates in a wide range of fields such as polymers[13] and organic synthesis.[14–16] By considering the unique synthetic and biomedical potential of caffeic acids and sulfones, we envisioned that cross-combination of these moieties through biocompatible approaches might lead to the formation of novel compounds possessing dual synthetic and biological potential functionalities. A literature survey revealed that despite their promising biological features, the synthesis of polyfunctional adducts bearing caffoeyl and arylsulfonyl groups have not been subjected to detailed investigations and only one study of Zeng and co-workers in 2007 has reported the electrochemical synthesis of two caffeic acid derivatives.[17]

The advances in electrochemical-induced synthesis in the last few years have provided organic chemists with a clean and convenient synthetic device of great promise.[18–22] Electrochemical reaction works based on the electron transfer in the Helmholtz layer at the electrode–solution interface.[23] Several features of electron-transfer reactions between ions and molecules in solution have been widely explored in chemical and electrochemical systems.[24] For example, many rate constants of electron transfer reactions in solution and at electrodes have been measured and some quantitative comparisons of the data in these two fields have been performed.[25,26] Furthermore, many experimental and theoritical efforts have been made to develop various aspects of electron-transfer processes.[27,28] Through these chemical and electrochemical processes, highly reactive intermediates (*i.e.*, cation-radicals, anion-radicals, *etc.*) can be generated under very mild conditions, such as ambient temperatures, normal pressure, and often in non-halogenated solvents. Electrochemical oxidation reactions of organic compounds such as catechol, hydroquinone, phenols and aminophenols in aqueous solution are biocompatible and similar to enzymatic oxidation in biological systems.[29,30] Since the basic of electrochemical reactions and principal biological function of cytochromes P450 is electron transfer,[31] they often parallel the cytochrome P450-catalyzed oxidation in liver microsomes.[32] Direct electrochemical oxidation/reduction of substrates utilizes practically electrons as the only reagents in synthetic organic reactions. For instance, the concept of electrochemical oxidation of catechols and subsequent trapping of their nascent *o*-benzoquinones with nucleophiles goes back at least as far as 1976 when, for the first time, Tabakovic and co-workers reported that electrochemically-generated *o*-benzoquinones could simply undergo 1,4-Michael addition reactions with a variety of nucleophiles.[33] In this sense, electrochemistry

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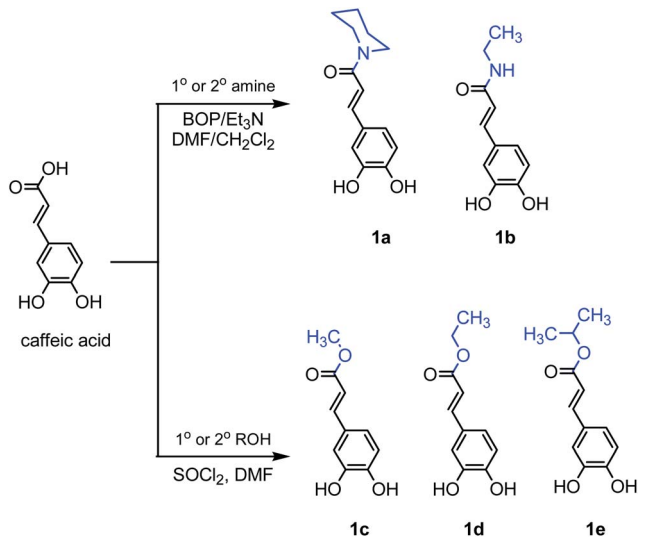
is frequently referred to as one of the prototypical simple and green procedures for synthesizing various organic molecules and structures.[34] Therefore, the electrochemical feasible approach to functionalized novel caffeic acid analogues seems to be a highly attractive approach from a mechanistic and synthetic point of view as it allows the combination of the synthetic virtues of a mild electrooxidation protocol with the benefits and convenience of green chemistry.

Inspired by the above facts and in continuation of our ongoing research program in the field of chemical and electrochemical domino reactions,[35–38] herein we report an experimentally simple and clean method for the synthesis of a series of amides and esters analogues of caffeic acid bearing arylsulfonyl moiety with pharmaceutical applications. All reactions occur in a domino of electrochemical and chemical events in aqueous solution and ambient conditions with high atom economy and excellent current efficiencies.

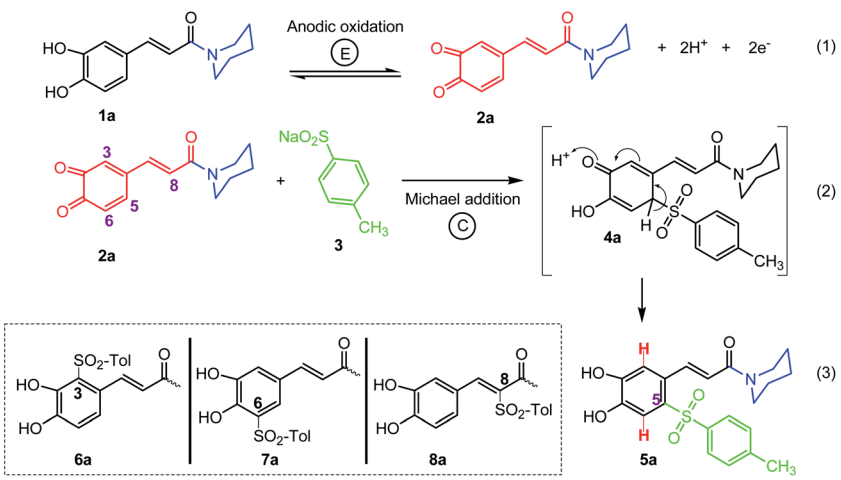


Scheme 1 Procedures for the synthesis of starting *N*-caffeoyl amides and caffeate esters.

Results and discussion

The starting *N*-caffeoyl amides (**1a**, **1b**) and alkyl caffeate esters (**1c–e**) were simply synthesized following the previously reported procedures[9,39] (Scheme 1) and then used in our further electrochemical investigations and in final preparative electrolyses as electroactive starting materials.

Cyclic voltammogram of a 1 mM solution of *N*-caffeoyl piperidine (**1a**) in water–acetonitrile (80/20) solution containing sodium phosphate (0.2 M, pH = 7) shows one anodic peak (A_1) and a corresponding cathodic peak (C_1), which correspond to the transformation of **1a** to its corresponding *o*-benzoquinone (**2a**) (Scheme 2) and *vice versa* through a quasi-reversible two-electron process (Fig. 1, curve a). A peak current ratio (IpC_1/IpA_1) of nearly unity can be considered as a criterion for the stability of *o*-benzoquinone produced at the surface of electrode, under the experimental conditions. In other words, any side reactions such as hydroxylation and/or dimerization reactions are too slow to be observed at the time scale of cyclic voltammetry. To get further support on the electrochemical oxidation of **1a**, it was studied in the presence of sodium *p*-toluenesulfinate (**3**). Although *o*-benzoquinones are extremely reactive and often difficult to isolate, they can be easily generated *in situ* by oxidation of their corresponding catechols and then trapped by sulfur nucleophiles.[38,40,41] Fig. 1, curve b, shows the cyclic voltammogram obtained for a 1 mM solution of **1a** in the presence of 1 mM of **3**. As seen, the voltammogram exhibits two anodic (A_1) and (A_2) and one cathodic (C_1) peaks. The new anodic (A_2) peak is attributed to the electrooxidation of product which is formed at the surface of electrode. Also notably, comparison of the cathodic part of curves a and b shows a complete decrease in the current density for curve b. This clearly reveals that, compared to the back-reduction of **2a** to **1a**, the intermolecular Michael-type addition of **3** to **2a** is dominant and fast process and as result cathodic part of curve b is completely disappeared. These facts are in a good agreement with the high reactivity of electrogenerated *o*-benzoquinone **2a** toward **3** and the formation of Michael adduct through an interfacial reaction



Scheme 2 Proposed mechanism for the electrochemical oxidation of *N*-caffeoyl piperidine in the presence of sodium *p*-toluenesulfinate.

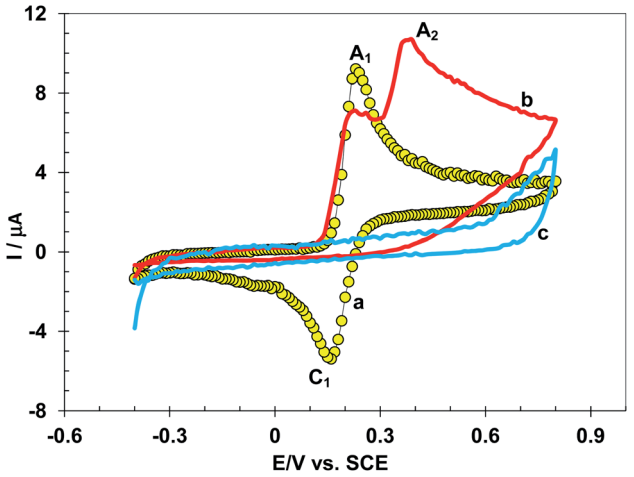


Fig. 1 Cyclic voltammograms of 1 mM of **1a**: (a) in the absence; (b) in the presence of 1 mM of **3**; and (c) 1 mM of **3** in the absence of **1a** at a glassy carbon electrode in sodium phosphate solution (0.2 M, pH = 7); scan rate: 100 mV s^{-1}; $T = 25 \pm 1$ °C.

at the electrode surface. The cyclic voltammogram of a 1 mM solution of **3** is shown in Fig. 1, curve c, for comparison.

Furthermore, our investigations on the preparative electrolysis of **1a** in the presence of **3**, began with the optimization of the reaction conditions. According to the aforementioned cyclic voltammetry studies, we found that the optimum conditions required a graphite anode, water–acetonitrile (80/20 v/v) as the solvent, and sodium phosphate solution (0.2 M, pH = 7) as the supporting electrolyte. In addition, 0.5 equivalent of **1a** and 0.5 equivalent of nucleophile **3** were a good reagent combination for this reaction. In the meantime, the anode potential was maintained at +0.21 V *vs.* SCE, which is at a potential for which **1a** could be oxidized to the corresponding *o*-benzoquinone form and *vice versa* within a reversible two-electron process. The continuously low concentration of the electrogenerated *ortho*-benzoquinone **2a**, together with the large excess of **3**, promotes the Michael-type reaction at the expense of other side reactions and this intermolecular event seems to be much faster than the other side reactions.

As seen in Fig. 2, the electrolysis progress was simply monitored using cyclic voltammetry, and it was found that proportional to the advancement of coulometry, the anodic peak decreases and disappears when the charge consumption becomes about $2e^-$ per molecule of **1a**.

In addition to the above-mentioned electrochemical observations, some additional experimental tests were performed to allow us to understand more about the mechanism and the rate-determining step (RDS) of this reaction. The mechanism and RDS of the sequential oxidation/Michael addition reactions of *o*-benzoquinones with N- and S-nucleophiles have been previously investigated in details by Mavri's group using computational calculations employing modern quantum chemical methods.[42,43] Their calculations nicely demonstrated that RDS of these sequential reactions is Michael addition between quinones and nucleophiles.[43] Having this in mind, we assumed that in the present study, among three steps shown in Scheme 2: (i) anodic oxidation of **1a** to **2a**, (ii) nucleophilic Michael addition of **3** to **2a** and (iii) rearomatization of **4a** to **5a**, the rate-limiting step is the Michael addition of **3** to **2a**. The accuracy of this assumption was

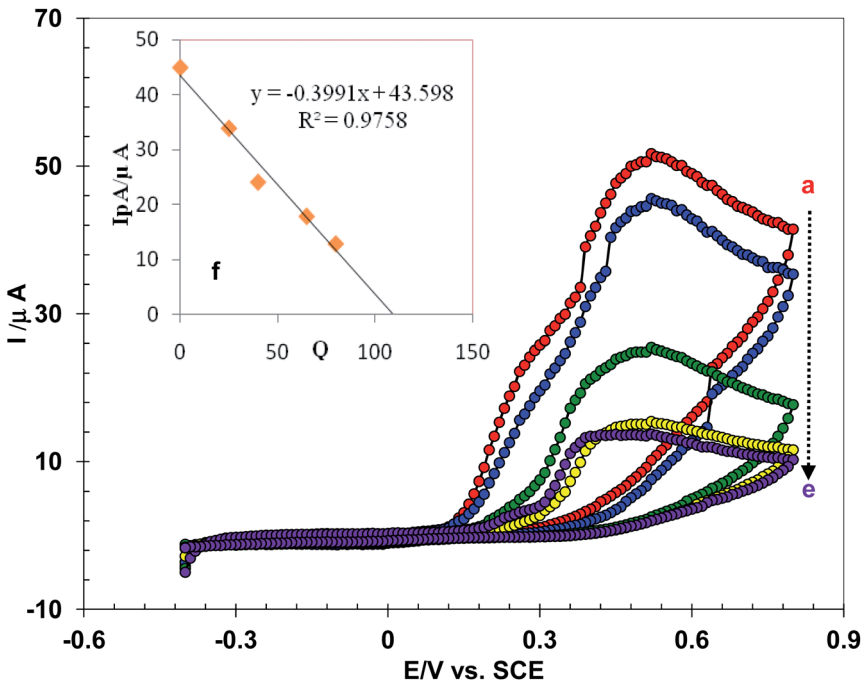


Fig. 2 Cyclic voltammograms of 0.5 mmol amide **1a** in the presence of 0.5 mmol of nucleophile **3**, at a glassy carbon electrode during controlled potential coulometry at 0.21 V *vs.* SCE. After consumption of: (a) 0, (b) 25, (c) 40, (d), 65 and (e) 80 C. Scan rate 100 mV s^{-1}; $T = 25 \pm 1$ °C; (f) variation of peak current (IpA1) *versus* charge consumed.

Table 1 Experimental and theoretical ^{1}H NMR data for possible structures **5a–8a**

Structure	Experimental		Theoretical	
	δ (ppm)	J (Hz)/(multiplicity)	δ (ppm)	J (Hz)/(multiplicity)
	7.21, 7.49	0.0 / (s)		
6a			6.9–7.6	^3J = 7.5–8 (d)
7a			7.2–8.1	^4J = 2–3 (d)
8a			7.0–8.0	^3J = 7.5–8 (d), ^4J = 2–3 (d), ^5J = <1 or (s)
5a			7.3–7.5	^5J = <1 or (s)

evaluated experimentally by varying the ratio of starting materials (**1a** : **3**). According to the basic principals of chemical kinetic,[44] it was expected that, if the Michael nucleophilic addition of **3** to **2a** is the RDS, then any change made in the concentration of **3** should directly affect the overall rate of the reaction and total time of the electrolysis. To explore this, we carried out the electrolysis of **1a** in the presence of **3** using two different ratio (1 : 1 and 1 : 5) under the potential-controlled condition. It was found that, proportional to the increasing of **3** to **1a** concentration ratio, the electrolysis was completed in much shorter time indicating the dependence of the overall rate of reaction to the concentration of nucleophile **3**. On the other hand, changing the starting material from **1a** to **1b** had no remarkable effect on the time of electrolysis, confirming that the overall rate is independent of the concentration of **1a**. All together, these experimental evidences clearly proved that the rate-limiting step of the three-step sequential reaction between **1a** and **3** was nucleophilic Michael addition rather than anodic oxidation or rearomatization steps and the overall rate of reaction was therefore more or less equal to the rate of the nucleophilic Michael addition step. Therefore, this three-step one-pot coupling reaction was considered as a sequential reaction composed of at least one electron transfer step (E) at the electrode and a preceding and follow-up C–S bond forming step (C) (Scheme 2). The irreversible bond formation is the most common following coupled chemical reaction in EC mechanism.[45]

The overoxidation of **5a** was circumvented during the preparative reaction (anode potential maintained at +0.28 V), since its oxidation seems to be more difficult than the parent starting molecule **1a**, by virtue of the presence of tolylsulfonyl group with electron-withdrawing character on the dihydroxybenzene ring. The electrochemical efficiency (current efficiency) of this controlled-potential coulometry was simply calculated using the Faraday's law and found to be >95% (EC mechanism needs at least two electrons, n = 2 and 2F charge consumption per each mol of **1a**). Under these reaction conditions, a highly functionalized caffeic acid analogue **5a** bearing an aryl sulfonyl moiety was purely obtained in excellent yield and no extra purification was needed. The product was characterized by various spectroscopic techniques: FT-IR, ^{1}HNMR, ^{13}CNMR and HRMS.

From the mechanistic point of view, it is worthy to mention that the existence of an unsaturated substituent at C-4 position of **2a** would probably cause this Michael acceptor to be attacked by **3** at one of the four possible electrophilic sites (C-3, C-5, C-6, or C-8, Scheme 2) and formation of four regioisomers (**5a–8a**).

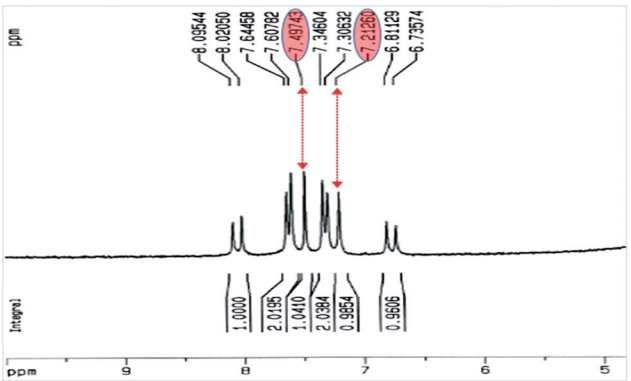


Fig. 3 Experimental ^{1}HNMR spectrum of **5a** in DMSO-d_6 (expanded 5–10 ppm).

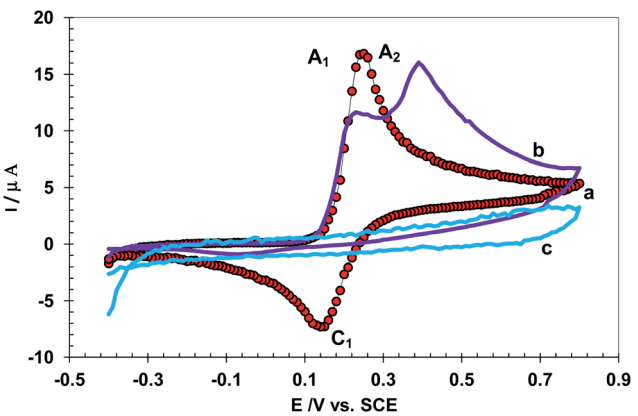


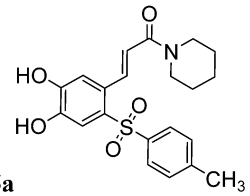
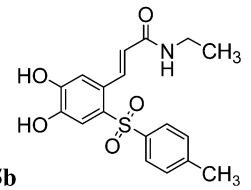
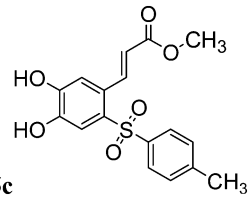
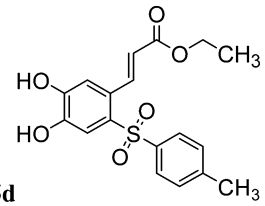
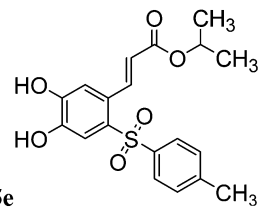
Fig. 4 Cyclic voltammograms of 1 mM of **1e**: (a) in the absence; (b) in the presence of 1 mM of **3**; and (c) 1 mM of **3** in the absence of **1e** at a glassy carbon electrode in sodium phosphate solution (0.2 M, pH = 7); scan rate: 100 mV s^{-1}; T= 25 ± 1 °C.

Since the substituent at C-4 position has an electron-withdrawing character, we suggest **2a** to be more electropositive at C-5 position and selectively attacked from this site by **3** leading to the formation of regioisomer **5a**. The accuracy of this suggestion was proved by means of theoretical[46] and experimental ^{1}H NMR studies. Addition of **3** to C-3 position in generation of **6a**, once ortho hydrogens would couple, may result in two doublets with a coupling constant of about 7–8 Hz in ^{1}H NMR spectrum, however, addition of **3** to the C-6 position may lead to the formation of **7a** with two doublets with a coupling constant of about 3–4 Hz. Also, addition of **3** to C-8 position gives a complex signal pattern with various possible coupling in product **8a** (Table 1).

On the other hand, ^{1}H NMR spectrum of the obtained product (Fig. 3) shows two singlets appeared at 7.21 and 7.49 ppm which is in a good agreement with two aromatic protons in *para* position[47] and formation of the single regioisomer **5a**.

With a reliable set of conditions in hand, and in examining the scope and generality of the developed protocol as well as the influence of structural variation of caffeic acid amides and esters on their reactivity toward **3**, we studied the reaction of other caffeic acid derivatives (**1b–1e**) with **3**. It was found that the electro-oxidation of these caffeic acid derivatives in the presence of **3** proceed in a way similar to that of **1a**. For instance, Fig. 4, curve b, shows the cyclic voltammogram obtained for a 1 mM solution of isopropyl caffeate (**1e**) in the

Table 2 Electroanalytical and preparative electrolysis data for preparation of **5a–e**[a]

Starting material	Peak potentials[b] (V)		Peak potentials[c] (V)			Applied potential at carbon rods[d]	Product	C.E.[e]/ Yield[f] (%)
	Ep_{ox}	Ep_{red}	Ep_{ox1}	Ep_{ox2}	Ep_{red1}			
1a	0.24	0.16	0.24	0.41	—	+0.21	 **5a**	96/78
1b	0.26	0.11	0.25	0.40	—	+0.24	 **5b**	93/89
1c	0.28	0.22	0.29	0.44	—	+0.25	 **5c**	98/90
1d	0.29	0.22	0.30	0.49	—	+0.28	 **5d**	96/92
1e	0.25	0.15	0.24	0.40	—	+0.24	 **5e**	96/78

[a] Cyclic voltammetry measurements were performed in 4 : 1 (v/v) of 0.2 M phosphate buffer solution (pH = 7) and CH_3CN, glassy carbon (GC) working electrode; scan rate 100 mV s^{-1}. Reference electrode: SCE. [b] 1 mM **1** in the absence. [c] In the presence of 1 mM **3**. [d] Controlled-potential coulometries were carried out in 0.2 M phosphate buffer solution, at carbon rods; reference electrode: SCE. [e] Calculated using the Faraday's law. [f] Isolated yields.

presence of 1 mM of **3**. As it is seen, similar to that of **1a**, the voltammogram exhibits two anodic (A_1) and (A_2) peaks and a cathodic peak (C_1). Comparison of the cathodic part of curves a and b shows a considerable decrease in the case of curve b which is in a good agreement with the electrooxidation of **1e** to its relevant *o*-benzoquinone, interfacial Michael addition of **3** to the intermediate **2e**, followed by a re-aromatization process to form the Michael adduct **5e** at the electrode surface through an EC mechanism. Furthermore, the electrochemical investigation of the other starting materials (**1b**, **1c**, **1d**) in the presence of **3** was pursued in more details and the results are summarized in Table 2.

From mechanistic points of view, it was also found that changing the functionalities on the starting materials has no subtle electronic and steric effects on the reactivity of their relevant *o*-benzoquinones and almost similar current efficiencies and mechanistic pathways (EC) can be considered for these structures. Also, in preparative electrolysis, four novel and highly functionalized caffeic acid analogues **5b–e** were purely obtained in excellent yields *via* the EC mechanistic fashions with high atom economy and no extra purification was needed. In all cases, the reaction proceeds smoothly under very mild conditions without introducing any acid, base, or metal catalyst.

Experimental

All experiments were carried out in a conventional electrochemical cell using traditional three-electrode system. The working electrode used in voltammetry experiments was a glassy carbon disc (1.8 mm diameter) and platinum wire was used as the counter electrode. The working electrode used in controlled-potential coulometry and bulk electrolysis (using an electronic potentiostat) was an assembly of four rods, 6 mm diameter, and ~10 cm length and a large platinum gauze constituted the counter electrode. The working electrode potentials were measured *versus* SCE.

^{1}H and ^{13}C NMR spectra were recorded on a spectrometer operating at 200 MHz and 50 MHz for proton and carbon nuclei. Chemical shifts were recorded as δ values in parts per million (ppm). ^{1}H NMR spectra are reported as follows: chemical shift (δ) [multiplicity (where multiplicity is defined as: br = broad; s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet), coupling constant(s) J (Hz), relative integral, and assignment]. Mass spectra and exact masses were recorded on a MAT 8200 Finnigan (EI, 70 eV) high resolution mass spectrometer; the latter employed a mass of 120 000 for carbon and the data are listed as follows: mass-to charge ratio (m/z). Infrared spectra were recorded neat and are reported in wavenumbers (cm^{-1}). All chemicals were reagent-grade materials and solvents and reagents were of pro-analysis grade. These chemicals were used without further purification.

Typical electrolysis procedure

In a typical experiment, controlled potential electrolysis (CPE) was carried to a 100 mL of suitable buffer solution in water–acetonitrile mixture containing 0.5 mmol of caffeic acid derivatives (**1a–e**) and 0.5 mmol of sodium *p*-toluenesulfinate (**3**), in an undivided cell equipped with a carbon anode (an assembly of four rods, 6 mm diameter, and 10 cm length) and a large platinum gauze at suitable potential (*V*) *vs.* SCE (see Table 2) at ambient condition. In order to minimize the ohmic drop, the reference electrode was kept in close proximity to the working electrodes.

The progress of electrolysis was followed by recording periodically the decreases in current with time and eventually, the electrolysis was terminated when the current decreased by more than 95% (also monitored by TLC). The process was interrupted during the electrolysis and the graphite anode was washed in acetone in order to reactivate it. At the end of electrolysis, a few drops of acetic acid were added to the solution and the cell was placed in a refrigerator overnight. The precipitated solid was collected by filtration and washed copiously with distilled water and with no extra purification process this protocol led to the desired Michael adducts **5a–e**.

3-[4,5-Dihydroxy-2-(toluene-4-sulfonyl)-phenyl]-1-piperidin-1-yl-propenone (5a). The product was isolated as a pale white solid in 78% yield (156.44 mg): mp = 207 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.42 (m, 4H), 1.55 (m, 2H), 2.31 (s, 3H), 3.47 (m, 4H), 4.22–4.30 (br, OH), 6.77 (d, J = 15 Hz, 1H), 7.21 (s, 1H), 7.32 (d, J = 8 Hz, 2H), 7.49 (s, 1H), 7.62 (d, J = 8 Hz), 8.05 (d, J = 15 Hz, 1H); ^{13}C NMR (50 MHz, DMSO-d_6) δ (ppm) 21.4, 24.6, 32.1, 48.2, 115.7, 116.4, 120.3, 126.9, 127.4, 129.5, 130.2, 137.1, 139.7, 144.1, 147.2, 151.2, 164.4; IR (neat) ν 3319, 3105, 2947, 1637, 1572, 1446, 1335 (SO_2), 1290, 1146 (SO_2), 1088 cm^{-1}; HRMS (EI): m/z calcd for $C_{21}H_{23}NO_5S$: 401.1296; found: 401.1173.

3-[4,5-Dihydroxy-2-(toluene-4-sulfonyl)-phenyl]-*N*-ethyl-acrylamide (5b). The product was isolated as a white solid in 89% yield (160.69 mg): mp = 214 °C; ^{1}H NMR (200 MHz, DMSO-d6) δ 1.03 (t, J = 7 Hz, 3H), 2.31 (s, 3H), 3.15 (m, 2H), 6.16 (d, J = 15 Hz, 1H), 6.96 (s, 1H), 7.34 (d, J = 8 Hz, 2H), 7.52 (s, 1H), 7.62 (d, J = 8 Hz, 2H), 8.01 (d, J = 15 Hz, 1H); IR (neat) ν 3394 (NH), 3313, 33 086, 2978, 1660, 1587, 1330 (SO_2), 1140 (SO_2), 1086 cm^{-1}; HRMS (EI): m/z calcd for $C_{18}H_{19}NO_5S$: 361.0983; found: 361.0914.

3-[4,5-Dihydroxy-2-(toluene-4-sulfonyl)-phenyl]-acrylic acid methyl ester (5c). The product was isolated as a white solid in 90% yield (156.63 mg): mp = 240–242 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.35 (s, 3H), 3.72 (s, 3H), 6.21 (d, J = 15.7 Hz, 1H), 7.18 (s, 1H), 7.4 (d, J = 8 Hz, 2H), 7.55 (s, 1H), 7.65 (d, J = 8 Hz, 2H), 8.28 (d, J = 15.7 Hz, 1H); ^{13}C NMR (50 MHz, DMSO-d_6) δ (ppm) 20.0, 52.0, 114.0, 116.0, 118.0, 124.0, 127.0, 129.0, 130.0, 140.0, 140.0, 143.0, 149.0, 152.0, 166.0; IR (neat) ν 3292, 2949, 1709, 1581, 1442, 1308, 1132, 1086 cm^{-1}; HRMS (EI): m/z calcd for $C_{17}H_{16}O_6S$: 348.0667; found: 348.0612.

3-[4,5-Dihydroxy-2-(toluene-4-sulfonyl)-phenyl]-acrylic acid ethyl ester (5d). The product was isolated as a light brown solid in 92% yield (166.56 mg): mp = 214–216 °C; ^{1}H NMR (200 MHz, $CO(CD_3)_2$) δ 1.29 (t, J = 7 Hz, 3H), 2.35 (s, 3H), 4.19 (q, J = 7 Hz, 2H), 5.50 (br, OH), 6.09 (d, J = 15.7 Hz, 1H), 7.16 (s, 1H), 7.32 (d, J = 8 Hz, 2H), 7.63 (s, 1H), 7.72 (d, J = 8 Hz, 2H), 8.5 (d, J = 15.7 Hz, 1H); ^{13}C NMR (50 MHz, $CO(CD_3)_2$) δ (ppm) 13.8, 20.5, 59.9, 114.2, 116.3, 118.2, 124.8, 127.2, 129.6, 130.4, 140.3, 140.6, 143.6, 149.4, 152.1, 166.0; IR (neat) ν 3330, 3007, 2983, 1697,

1587, 1473, 1315, 1136, 1086 cm^{-1}; HRMS (EI): *m*/*z* calcd for $C_{18}H_{18}O_6S$: 362.0824; found: 362.0911.

3-[4,5-Dihydroxy-2-(toluene-4-sulfonyl)-phenyl]-acrylic acid isopropyl ester (5e). The product was isolated as a white solid in 90% yield (169.92 mg): mp = 193–195 °C; ^1H NMR (200 MHz, DMSO-d_6) δ 1.26 (d, $J = 6$ Hz, 6H), 2.35 (s, 3H), 4.99 (septet, $J = 6$ Hz, 1H), 6.11 (d, $J = 15.7$ Hz, 1H), 7.16 (s, 1H), 7.38 (d, $J = 8$ Hz, 2H), 7.57 (s, 1H), 7.65 (d, $J = 8$ Hz, 2H), 8.25 (d, $J = 15.7$ Hz, 1H); ^{13}C NMR (50 MHz, DMSO-d_6) δ (ppm) 21.4, 22.1, 68, 115.2, 116.6, 119.7, 125, 127.2, 130.2, 130.4, 139.4, 139.8, 139.9, 144.5, 148, 151.1, 165.8; IR (neat) ν 3373, 3280, 3011, 2981, 1655, 1577, 1448, 1350, 1136, 1086 cm^{-1}; HRMS (EI): *m*/*z* calcd for $C_{19}H_{20}O_6S$: 376.0980; found: 376.0920.

Conclusion

In summary, we have established a successful use of electric current as a clean tool in oxidation of amides and esters derivatives of caffeic acid to produce a series of highly substituted novel caffeic acid analogues. The developed synthetic protocol is based on a feasible and clean approach employing electrons as the only reagents in aqueous solution without introducing any catalyst or oxidant. We think that this simple electrooxidative coupling protocol with its advantages of complementary reactivity, and especially dramatically technical feasibility may find potential applications in synthetic organic chemistry. In addition, we hope that because of the diversity of this procedure and the possibility of introducing variations in both Michael-addition partners, it can be adopted in bioorganic chemistry to synthesize and screen libraries of related biologically important structures.

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