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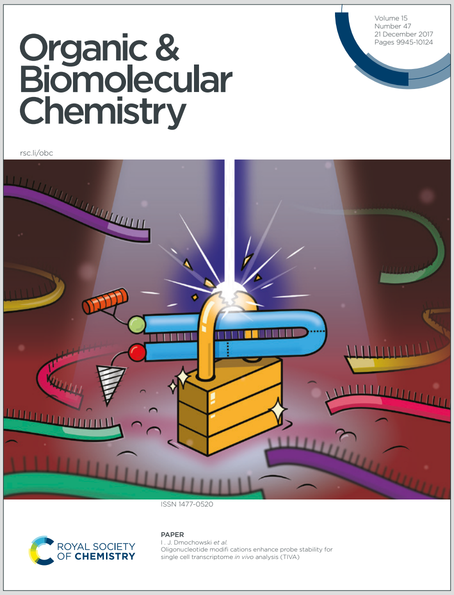

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Electricity-Driven Sustainable Synthesis of 2-Aminobenzonitriles through C-C bond cleavage of isatins: Post-Functionalization via One-Pot Integration with Enzyme Catalysis

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Abstract

Herein, we report an electricity-mediated sustainable synthesis of 2-aminobenzonitriles, which serve as essential building blocks for numerous pharmaceuticals, by using isatins and hydroxylamine as starting materials. Furthermore, electricity served as an efficient and environmentally friendly mediator, promoting the C-C cleavage of isatin derivatives to afford the desired products in good to excellent yields. The scope and practicality of the method have been validated through a screening of isatins bearing different substituents. Moreover, this electrochemical protocol was successfully integrated with an α-amylase-catalyzed aza-Michael addition in a one-pot system, providing pharmaceutically relevant β-aminocarbonyl compounds via C–N bond formation. Additionally, mechanistic insights obtained from control experiments and cyclic voltammetry studies suggest that the formation of 2-(2-aminophenyl)-2-oxoacetate serves as a key intermediate during the electrochemical step.

Introduction

The carbon–carbon bond serves as the fundamental backbone of organic molecules, and its cleavage or functionalization offers an effective way of structural modification.[1] In recent years, considerable attention has been directed toward developing novel and efficient methods for achieving selective C–C bond cleavage. Besides, isatin is recognized as a crucial and privileged scaffold in synthetic chemistry, as it incorporates both a keto group and a lactam moiety within its structure.[2] The coexistence of these functional groups, along with the easy availability of isatin, makes it a highly versatile starting material for generating clinically important molecules.[3] Consequently, a wide range of chemical transformations is being carried out, targeting either the keto or the lactam functionality of isatin to broaden its synthetic and medicinal applications. However, the selective cleavage of C–C bonds in isatin remains relatively underexplored compared to other chemical transformations.[4] Nevertheless, the molecular scaffolds generated through the selective cleavage of the C–C bond of isatin have

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significant importance, as they constitute the core structures of various pharmacologically active compounds, including several non-steroidal anti-inflammatory drugs (NSAIDs).[5] Numerous methods have been previously reported for cleaving the carbon–carbon bond in isatin; however, most of these approaches are limited by drawbacks such as the use of costly transition metal catalysts, stoichiometric chemical oxidants, and harsh reaction conditions.[6]

On the other hand, electrochemistry in organic synthesis has experienced remarkable growth and garnered widespread attention over the past decade, primarily due to its environmentally benign nature.[7] Unlike conventional methods that rely on stoichiometric oxidants or reductants, electrochemical processes generate reactive intermediates directly via anodic oxidation or cathodic reduction, thereby minimizing hazardous reagents and improving overall atom economy.[8] Consequently, electrochemical methods have been successfully developed for the selective cleavage of carbon–carbon bonds of isatin.[9] In this context, Wang et al. reported the electricity-driven cleavage of the C-C bond in isatin for the synthesis of anthranilic acid derivatives (**Scheme 1a**).[10] Along with this, Liu et al. reported an efficient and convenient method for the ring opening of isatin using organic amines in an acidic buffer solution for the synthesis of methyl 2-ureidobenzoates (**Scheme 1b**).[11] Moreover, the integration of electrosynthesis with enzyme catalysis has emerged rapidly, reflecting a shift towards sustainable and efficient chemical transformations.[12] This merged system leverages the complementary strengths of both domains, where electrosynthesis provides a clean and green source of redox equivalents, and enzyme catalysis contributes exceptional selectivity and mild reaction conditions.[13] With respect to this, Tyagi et al. reported the synthesis of chiral sulphur-containing organofluorine acids in good yields using fluorine-based unsaturated alkenes and thiophenols by combining electrosynthesis and biocatalysis **(Scheme 1c)**.[13b] Additionally, Guan et al. reported the synthesis of 2,2-disubstituted 3-carbonyl indoles by integrating the non-natural catalytic activity of lipase with electrosynthesis, affording the products in good isolated yields as well as excellent enantio- and diastereoselectivities **(Scheme 1d)**.[13c]

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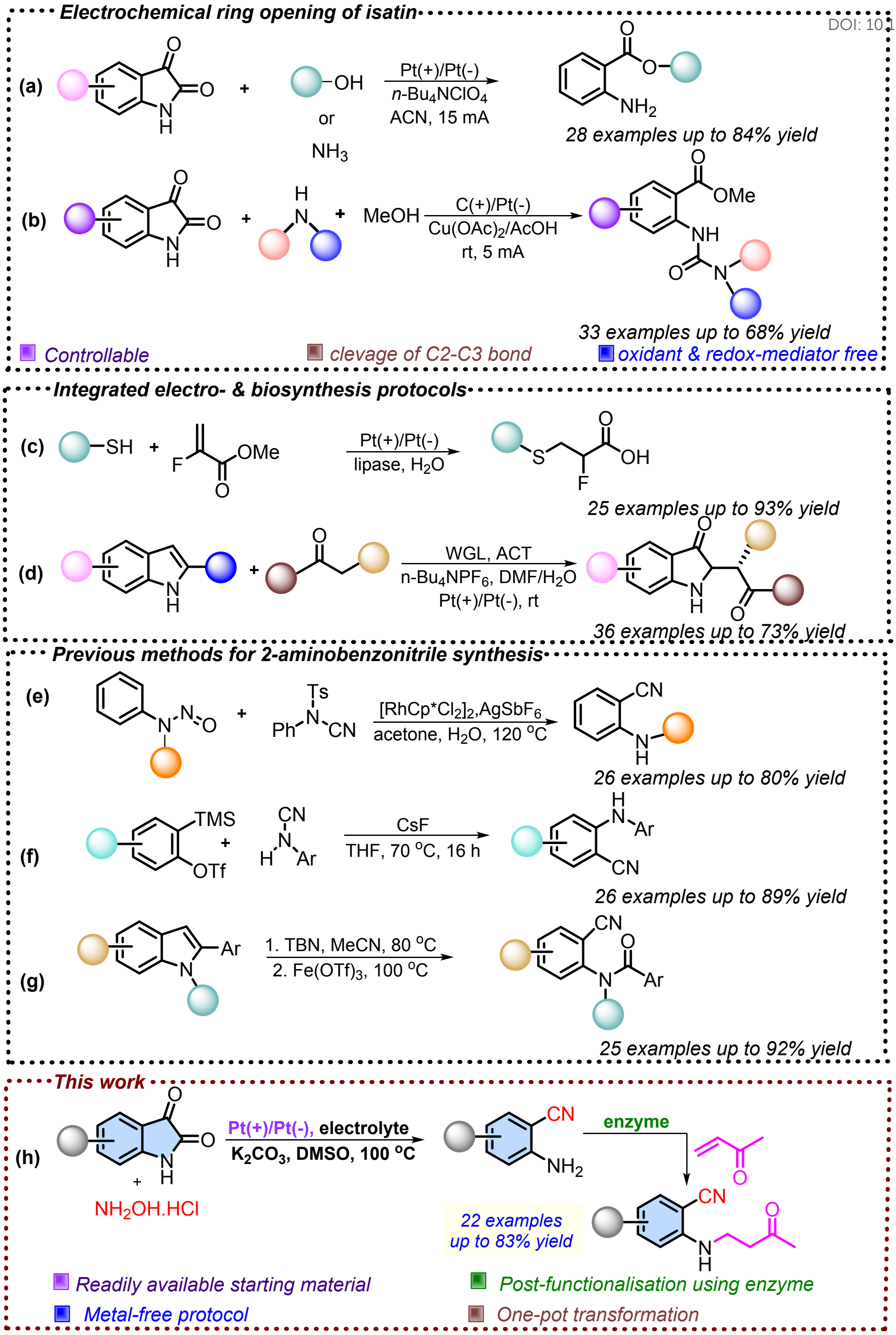

Scheme 1: Examples of oxidative ring opening of isatin and strategies to synthesize 2-aminobenzonitrile

Next, 2-aminobenzonitrile is one of the important moieties that have been used as a precursor for the synthesis of potent anti-inflammatory, antidiabetic, anti-HIV, antibacterial, and antiviral compounds, as shown in Figure 1.[14] Traditionally, 2-aminobenzonitriles have been synthesized

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via coupling or reduction of *o*-nitrobenzonitriles or related *o*-nitro derivatives.[15-20] In this context, Sun et al. reported a rhodium-catalyzed cyanation of aromatic C–H bonds, followed by denitrosation of nitrosoarylamines, using the nitroso group as a directing moiety. This strategy enabled the synthesis of 2-(alkylamino) benzonitriles, with N-cyano-N-phenyl-p-methylbenzenesulfonamide serving as the cyano source (**Scheme 1e**).[21] In addition to this, Zeng et al. demonstrated an aminocyanation method for the synthesis of bifunctional aminobenzonitriles by direct addition of aryl cyanamides to arynes, which embeds both amino and cyano groups simultaneously (**Scheme 1f**).[22] Furthermore, Mo et al. reported a one-pot tert-butyl nitrite (TBN)-mediated nitrosation followed by Fe-catalyzed cleavage of the carbon-carbon bond for the synthesis of 2-aminobenzonitriles in excellent yields, using 2-aryl indoles as the starting material (**Scheme 1g**).[23] While the aforementioned methods have been successfully established for the synthesis of 2-aminobenzonitriles, they still have certain limitations, such as many of these approaches rely on starting materials that are not easily accessible, which restricts their broader applicability.[24] The frequent use of costly transition-metal catalysts further diminishes the practicality and economic feasibility of these protocols.[25a-b] Therefore, there is a need to devise alternative strategies for the synthesis of 2-aminobenzonitrile derivatives that not only employ readily available and inexpensive starting materials but also utilize more affordable catalytic systems, thereby offering a more sustainable approach.

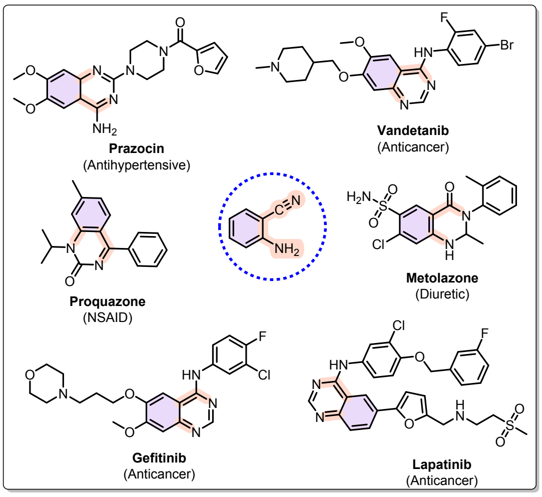

Figure 1: Important pharmaceuticals containing 2-aminobenzonitrile

Inspired by the wide-ranging applications of 2-aminobenzonitriles and recognizing the limitations of conventional approaches, we propose an electricity-mediated, sustainable strategy for synthesizing 2-aminobenzonitrile derivatives from readily available isatins.

Furthermore, by coupling the electrochemical step with enzyme catalysis, this approach enables an efficient two-step, one-pot synthesis of pharmaceutically significant β-amino carbonyl compounds (**Scheme 1h**).

Result and Discussion

We began our study by establishing a model reaction in which isatin (**1a**) and hydroxylamine (**2a**) were electrolyzed using Pt/Pt electrodes and DMSO as solvent at 120 °C. The reaction proceeded smoothly at a constant current of 10 mA in the presence of potassium iodide (KI) as the electrolyte and K_2CO_3 as the base, affording the desired product (**3a**) in 69% yield (entry 1, Table 1). It might be due to the limited solubility of KI in organic solvents, whereas nBu_4NI is highly soluble due to the lipophilic tetrabutylammonium cation, ensuring a uniform distribution of iodide ions throughout the reaction medium.[25c] To further improve the yield, several reaction parameters were optimized, as summarized in Table 1. First, various electrolytes were screened. The use of tetrabutylammonium iodide (n-Bu_4NI) instead of KI significantly enhanced the yield to 82% (entry 2, Table 1). In contrast, when bromide salts such as KBr and n-Bu_4NBr were used in place of KI, no product formation was observed (entries 3 and 4, Table 1), while lithium perchlorate as an electrolyte afforded the product only in trace amounts (entry 5, Table 1). Importantly, no product (**3a**) formation was observed in the absence of current, highlighting the essential role of electricity in the process (entry 6, Table 1). Next, the effect of the current was examined. Decreasing the current from 10 mA to 5 mA led to a noticeable drop in yield (entries 7 and 8, Table 1), whereas increasing the current to 15 mA resulted in no significant improvement in the yield of product (entry 9, Table 1). Furthermore, solvent screening revealed that replacing DMSO with acetonitrile (ACN) or 1,2-dichloroethane (DCE) gave no product, while DMF and THF provided significantly reduced yields compared to DMSO (entries 10-13, Table 1). Next, the electrolyte concentration was also optimized. Lowering the loading of TBAI from 1.0 to 0.5 equiv. decreased the yield of (**3a)** (entry 14, Table 1), whereas increasing it to 1.5 equiv. furnished (**3a**) in 87% yield (entry 15, Table 1). Moreover, a further increase to 2.0 equiv. slightly reduced the yield of product (**3a**) (entry 16, Table 1). Moreover, optimization of the base showed that replacing K_2CO_3 with Na_2CO_3 decreased reaction efficiency, while organic bases such as Et_3N and DBU completely suppressed product formation (entries 17-19, Table 1). Notably, in the absence of a base, there was no product formation, confirming the requirement of a base in this protocol (entry 20,

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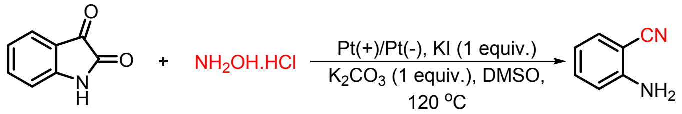
Table 1). Additionally, temperature studies revealed that lowering the reaction temperature to 80 °C decreased the yield to 55% (entry 21, Table 1), whereas operating at 100 °C yielded (**3a**) with an up to 87% yield (entry 22, Table 1). However, increasing the temperature further to 140 °C led to a reduced yield of (**3a**) up to 79% (entry 23, Table 1). Finally, the stoichiometry of hydroxylamine was investigated, reducing its amount to 0.5 equiv. or 1.0 equiv. decreased product (**3a**) formation (entries 24 and 25, Table 1), whereas 1.5 equiv. gave yields comparable to 2.0 equiv., establishing 1.5 equiv. as sufficient for optimal yield (entry 26, Table 1).

Table 1 Optimisation of reaction conditions



1a **2a** **3a**

Entry	Divergence from standard conditions	[b]Yield of 3a (%)
1.	[a]No change	69
2.	*n*-Bu_4NI instead of KI	82
3.	KBr instead of KI	nr
4.	*n*-Bu_4NBr instead of KI	nr
5.	$LiClO_4$ instead of KI	traces
6.	No current	nr
7.	5 mA instead of 10 mA	12
8.	8 mA instead of 10 mA	67
9.	15 mA instead of 10 mA	80
10.	ACN instead of DMSO	traces
11.	DCE instead of DMSO	nr
12.	DMF instead of DMSO	19
13.	THF instead of DMSO	23
14.	TBAI (0.5 equiv.) instead of TBAI (1 equiv.)	49
15.	TBAI (1.5 equiv.) instead of TBAI (1 equiv.)	87
16.	TBAI (2 equiv.) instead of TBAI (1 equiv.)	79
17.	Na_2CO_3 instead of K_2CO_3	34
18.	Et_3N instead of K_2CO_3	nr
19.	DBU instead of K_2CO_3	nr
20.	no base	nr
21.	80 ℃ instead of 120 ℃	55
22.	100 ℃ instead of 120 ℃	87

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23.	140 ℃ instead of 120 ℃	79
24.	0.5 equiv. of hydroxylamine instead of 2 equiv.	42
25.	1 equiv. of hydroxylamine instead of 2 equiv.	69
26.	1.5 equiv. of hydroxylamine instead of 2 equiv.	87
27.	2.5 equiv. of hydroxylamine instead of 2 equiv.	85

[a]Standard reaction conditions: Isatin (**1a**) (20 mg, 1 equiv.), hydroxyl amine (19 mg, 2 equiv.) (**2a**), KI (23 mg, 1 equiv.), K_2CO_3 (19 mg, 1 equiv.) in 1 mL of DMSO under constant current 10 mA in an undivided cell having Pt electrodes as cathode and anode at 120 ℃, [b]Yields were calculated using HPLC.

After optimizing the reaction conditions, the substrate scope of the electro-catalyzed reaction was thoroughly investigated, as shown in **Scheme 2**. First, we examined the influence of various electron-donating groups, such as $-OCH_3$ and $-CH_3$, at the C-5, C-6, and C-7 positions of isatin. Notably, the presence of $-OCH_3$ groups at the C-6 position reaction provided in good yield i.e. 71% (**3b,** Scheme 2). In the case of the CH_3 group at the C-5 position of isatin, the product (**3c**) was obtained in an isolated yield of 77%, whereas the CH_3 group at the C-7 position led to a significantly lower yield of the corresponding product (**3d**). Next, we investigated the electron-withdrawing effect at the C-5 position, where the $-NO_2$ group present at this position afforded the product with a 58% yield (**3e**, Scheme 2). The influence of various halides, including -F, -Cl, and -Br, was examined at the C-4, C-5, and C-6 positions. It was observed that halide substitutions at the C-4 position resulted in lower yields (**3g** and **3i**, Scheme 2). In contrast, isatins having F, Cl, and Br at the C-5 position produced products in good yields (**3f, 3h,** and **3j**, Scheme 2). Additionally, halide substitutions at the C-6 position resulted in lower product efficiency (**3k**, Scheme 2). However, no product formation was observed when N-methyl-substituted isatin was employed in the reaction (**3l**, Scheme 2).

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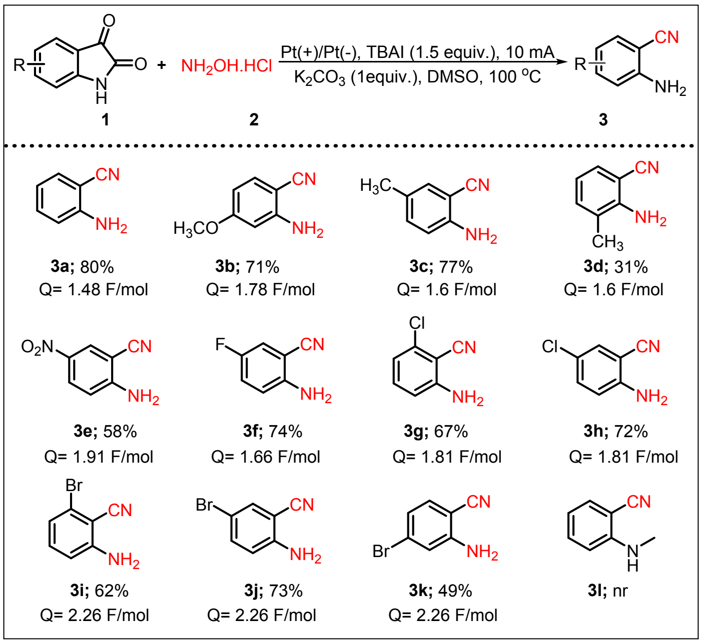

Scheme 2: Substrate scope of electricity-mediated synthesis of 2-aminobenzonitrile

Reaction conditions: Isatin (**1**) (100 mg, 1 equiv.), hydroxyl amine (**2**), (71 mg, 1.5 equiv.), TBAI (377 mg, 1.5 equiv.), K_2CO_3 (95 mg, 1 equiv.) in 5 mL of DMSO under constant current of 10 mA in an undivided cell having Pt electrodes as cathode and anode at 100 °C.

In the second phase of our study, we conducted a reaction integrating electrochemical and α-amylase-catalyzed reaction conditions within a single vessel to synthesize a pharmaceutically relevant β-amino carbonyl compound (Scheme S1).[26] Conversely, the one-pot procedure produced the aza-Michael product with a notably low yield of only 12%. To improve the yield of the integrated protocol, the reaction conditions were modified. In this context, after completion of the electrochemical reaction, as confirmed by TLC, α-amylase (2 mg/mL), methyl vinyl ketone (1.5 equiv.), and water (1 mL) were added to the reaction mixture. The resulting mixture was stirred at 50 °C for 12 hours. Encouragingly, we obtained the aza-Michael product (**4a**) with improved yield, i.e., 45% (entry 1, Table 2). Further, no reaction was observed when the enzyme concentration was reduced to 1 mg/mL (entry 2, Table 2). However, increasing the enzyme loading to 4 mg/mL and 6 mg/mL resulted in 56% and 52% isolated product yields, respectively (entries 3–4, Table 2). Additionally, the reaction medium was optimized for the enzymatic step by varying the amount of water. Reducing the volume of H_2O from 1 mL to 0.5 mL decreased the yield of **(4a)** to 39%. Although increasing the H_2O volume to 2 mL improved the yield up to 61% (entry 6, Table 2). However, further increases beyond 2 mL did not significantly affect the yield of **(4a)** (entry 7, Table 2). Furthermore, increasing the amount of methyl vinyl ketone up to 2.5 equivalents improved the isolated yield

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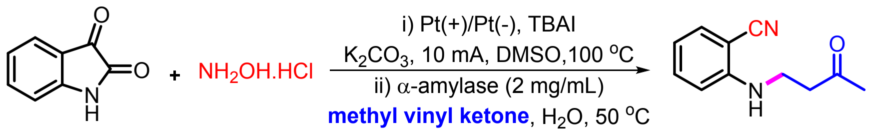
of the product (entries 8–9, Table 2). However, further increasing the methyl vinyl ketone, i.e., 3.0 equivalents in comparison to isatin, did not significantly change the outcome of the reaction (entry 10, Table 2).

Table 2: Optimisation of reaction conditions for integrated protocol



1a **2a** **4a; 70%**

Entry	Divergence from standard reaction conditions	Isolated Yield of 4a (%)
1.	No change	45
2.	α-amylase (1 mg/mL)	No reaction
3.	α-amylase (4 mg/mL)	56
4.	α-amylase (6 mg/mL)	52
5.	H_2O (0.5 mL)	39
6.	H_2O (2 mL)	61
7.	H_2O (2.5 mL)	60
8.	MVK (2 equiv.)	68
9.	MVK (2.5 equiv.)	76
10.	MVK (3 equiv.)	74

Standard reaction conditions: Isatin (**1a**) (20 mg, 1 equiv.), hydroxyl amine (14 mg, 1.5 equiv.) (**2a**), TBAI (75 mg, 1.5 equiv.), K_2CO_3 (19 mg, 1 equiv.) in 1 mL of DMSO under constant current 10 mA in an undivided cell having Pt electrodes as cathode and anode at 100 °C, after completion of electrocatalytic step: α-amylase (2 mg/mL), methyl vinyl ketone (18 μL, 1.5 equiv.), 1 mL water (v/v) at 50 °C for overnight, error = ± 4% (reaction performed in triplicates).

Further, the substrate scope of the integrated protocol has been thoroughly investigated under optimal electro-biocatalytic reaction conditions, as shown in Scheme 3. In this context, electron-donating groups like methoxy and methyl facilitated the synthesis of the aza-Michael product with high yields (**4b–c**, Scheme 3). Additionally, halide substituents such as F, Cl, and Br at the C-4 and C-5 positions were well tolerated, affording the desired product with isolated yields ranging from 55% to 75% (**4d–h**, Scheme 3). Additionally, Michael acceptors such as cyclohexanone and cyclopentanone were investigated, along with differently substituted isatin, and as a result, the corresponding products were obtained with low to moderate yields (**4i-k**, Scheme 3). However, only a trace amount of product formation was observed when cyclopentanone was employed in combination with 5-NO_2-substituted isatin (**4l**, Scheme 3).

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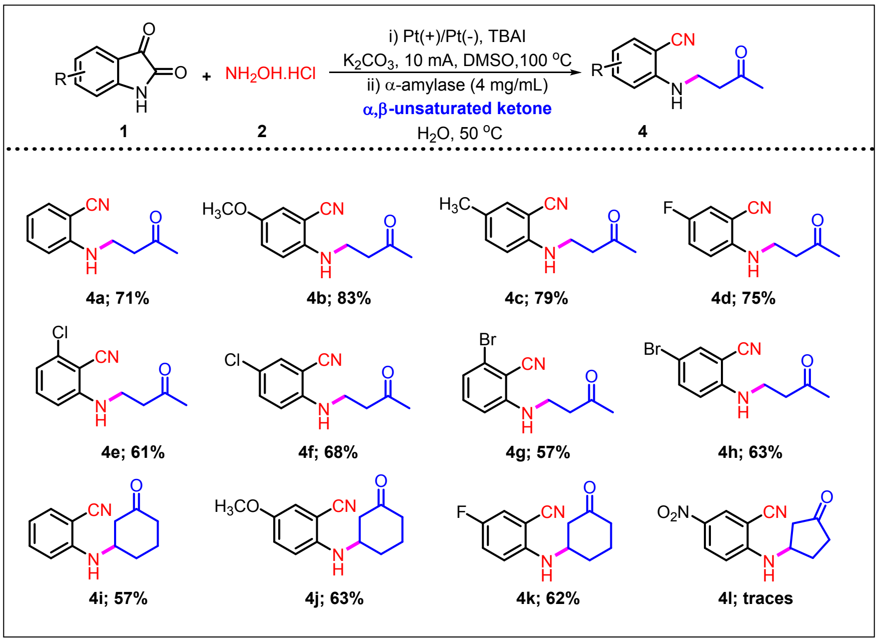

Scheme 3: Substrate scope of integrated electro-biocatalytic synthesis of β-amino carbonyl

Reaction conditions: i) Isatin (**1a**) (100 mg, 1 equiv.), hydroxyl amine (71 mg, 1.5 equiv.) (**2a**), TBAI (367 mg, 1.5 equiv.), K_2CO_3 (95 mg, 1 equiv.) in 5 mL of DMSO under constant current 10 mA in an undivided cell having Pt electrodes as cathode and anode at 100 ℃, ii) after completion of the electrocatalytic step: α-amylase (4 mg/mL), methyl vinyl ketone (150 μL, 2.5 equiv.), 10 mL water (v/v) at 50 ℃ for overnight.

To investigate the rate and influence of electricity and enzyme at different reaction stages leading to the formation of **(3a)** and **(4a)**, we conducted a systematic study by designing a series of controlled reactions under optimized conditions, as illustrated in Figure 2. In the first experiment, substrates **(1a)** and **(2a)** were subjected to electrochemical conditions, resulting in the formation of **(3a)** within 2 hours. Along with the formation of **(3a)**, the consumption of isatin **(1a)** and the formation of isatin-3-oxime, an intermediate, were also monitored. The reaction showed complete consumption of isatin and formation of the corresponding isatin-3-oxime intermediate within 20 minutes. Subsequently, **(3a)** was treated under enzymatic conditions, facilitating the conversion to **(4a)** in 12 hours. Next, to validate the role of electricity and the enzyme in a one-pot two-step protocol, we conducted different control experiments. First, an experiment was set up in the absence of electricity; however, the enzyme was still added to the reaction, and no formation of **(3a)** was observed, confirming the necessity of electricity in the formation of **(3a)**. Similarly, in the second experiment, electricity was employed without the addition of the enzyme, and no formation of **(4a)** took place, thereby verifying the essential role of the enzyme in the aza-Michael addition step. Finally, in the third experiment, where electricity and enzyme were both absent, neither **(3a)** nor **(4a)** was formed.

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These control experiments suggested that electricity plays a role in the formation of product **(3a)**, while the enzyme is necessary for the formation of **(4a)** via an aza-Michael addition reaction.

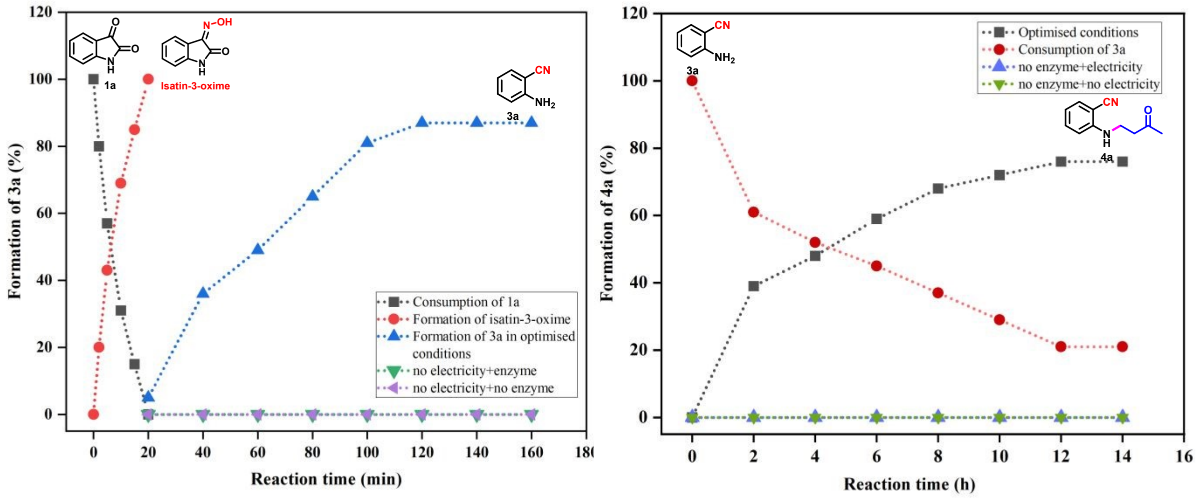

Figure 2. (a) Role of electricity and enzyme on the formation of **(3a)** with time (b) Role of electricity and enzyme on the formation of **(4a)** with time; **Optimised reaction conditions**: Isatin (**1a**) (20 mg, 1 equiv.), hydroxyl amine (14 mg, 1.5 equiv.) (**2a**), TBAI (75 mg, 1.5 equiv.), K_2CO_3 (19 mg, 1 equiv.) in 1 mL of DMSO under constant current 10 mA in an undivided cell having Pt electrodes as cathode and anode at 100 °C, ii) after completion of the electrocatalytic step: α-amylase (4 mg/mL), methyl vinyl ketone (30 µL, 2.5 equiv.), 2 mL of water (v/v) at 50 °C for overnight.

Next, based on the information available in the literature, we propose a plausible reaction mechanism for the electricity-mediated synthesis of 2-aminobenzonitrile, as illustrated in Scheme 4.[27] [10] The process begins with the condensation of substrates (**1a)** and **(2a)**, resulting in the formation of isatin-3-oxime **(I)**. [28]At the cathode, water undergoes reduction, generating hydroxide ions. The electrogenerated hydroxide ion subsequently attacks intermediate **(I)**, producing intermediate **(II)**. Next, the base K_2CO_3 interacts with intermediate **(II)**, leading to electron redistribution and ring opening to yield intermediate **(III)**. Meanwhile, the iodide ion derived from tetrabutylammonium iodide (TBAI) is oxidised to molecular iodine (**I_2**), which reacts with intermediate **(III)**, and provides intermediate **(IV)**.[10] This intermediate is unstable and readily eliminates an iodine radical with the concurrent release of carbon dioxide, affording intermediate **(V)**.[27] The carbon-centred radical in **(V)** then loses an electron to generate intermediate **(VI)**, which, upon dehydration, furnishes the desired product **(3a).**

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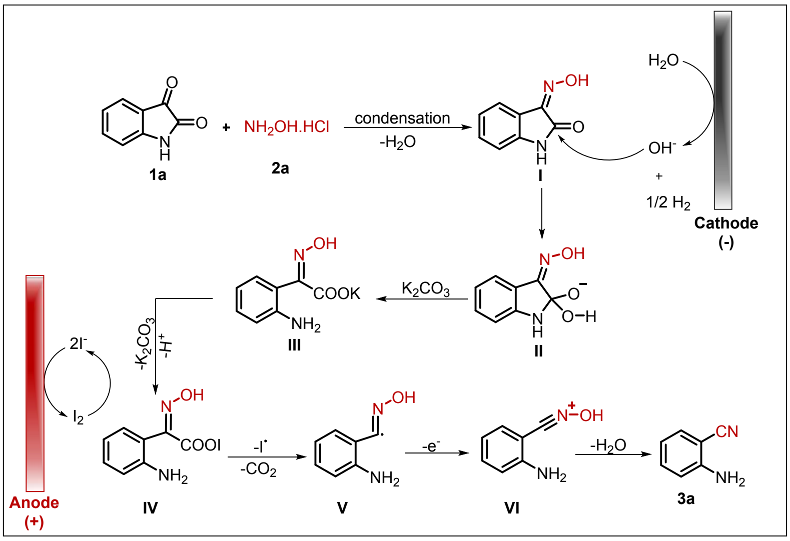

Scheme 4: Proposed mechanism for the electro-synthesis of 2-aminobenzonitriles

Besides, to gain further insight into the proposed reaction mechanism, various control experiments were conducted. First, radical-scavenging experiments were conducted in which 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) and butylated hydroxytoluene (BHT) were used as additives in the reaction. In the presence of TEMPO, product **(3a)** was obtained in only 5% yield, whereas no reaction was observed with BHT, thereby indicating the involvement of radical species in the reaction mechanism (**Scheme 5a**). Further, the electricity-driven reaction was initiated with the sodium salt of 2-(2-aminophenyl)-2-oxoacetate and hydroxylamine hydrochloride, yielding the product (**3a**) in 65% yield (**Scheme 5b**). This experiment suggested the formation of intermediate (**III**) in the reaction, as determined by HRMS, also, and supports the proposed mechanistic pathway. Along with this, when the reaction of the sodium salt of 2-(2-aminophenyl)-2-oxoacetate was set in the absence of electricity, there was no formation of product (**3a**), which depicts the necessity of electricity for this reaction (**Scheme 5c**). Furthermore, when N-methyl-substituted isatin was used in the electrochemical reaction, no formation of product (**3a)** was observed (**Scheme 5d**). It was observed that no oxime formation occurred with N-methyl isatin, thereby suppressing the subsequent decarboxylation and electrochemical reduction steps. In addition to the above experiments, control reactions were performed to verify the enzyme's role in the formation of the aza-Michael products. In this context, the first experiment was set up by adding starch in an equimolar amount, and in the second experiment, urea was used in a 4.0 equivalent ratio corresponding to the enzyme. As a result, product (**4a)** was obtained in 29% and 7% isolated yields, respectively (**Schemes 5e and 5f**). Besides, when BSA was used as a catalyst in place of α-amylase, only a trace amount of (**4a)** was observed (**Scheme 5g**). Subsequently, to verify the role of the active site in catalyzing

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the reaction, the enzyme was thermally denatured, and the product (**4a**) was obtained only in a trace amount when denatured α-amylase was used as a catalyst (**Scheme 5h**).

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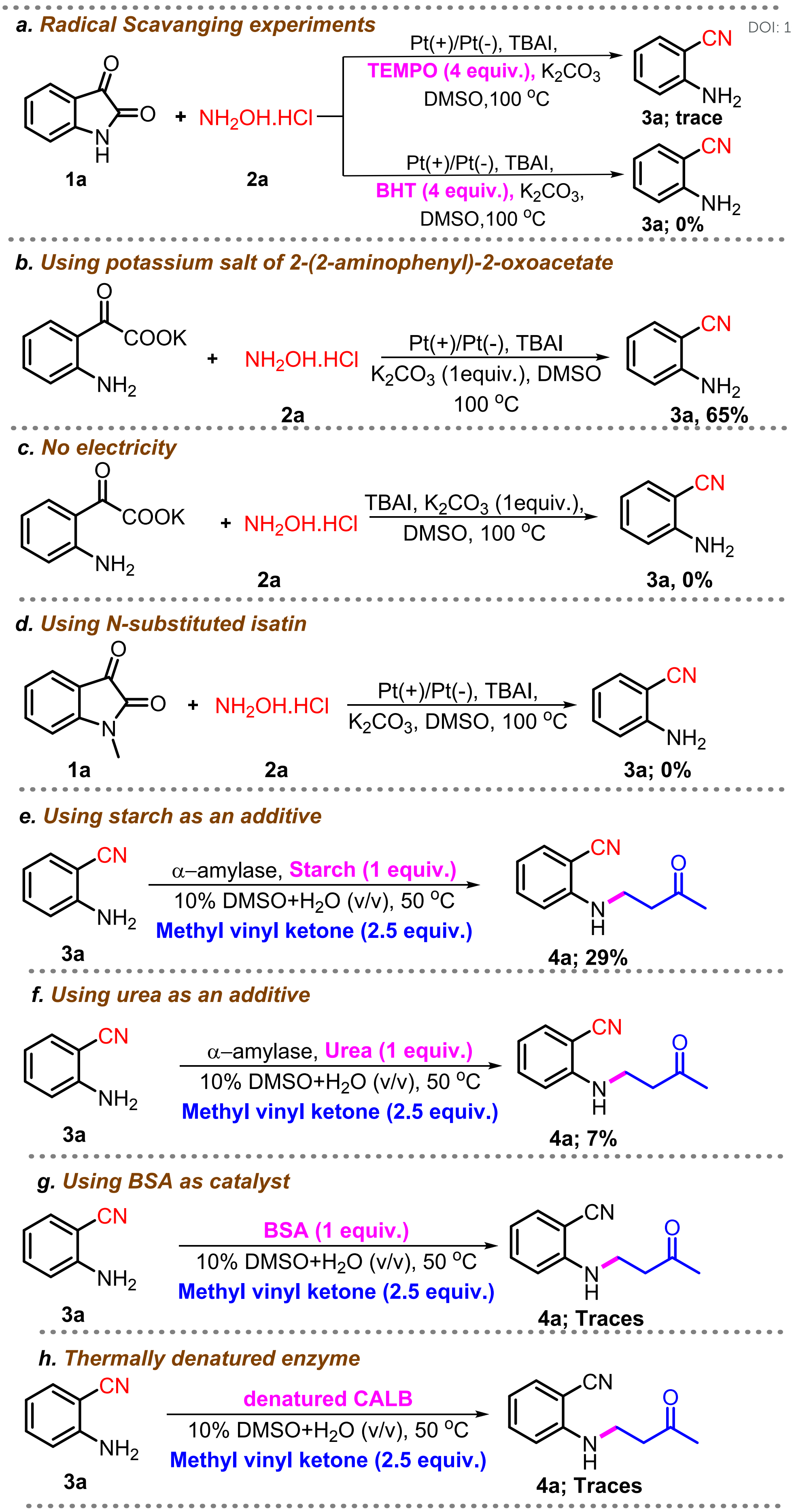

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Scheme 5: Control Experiments

Furthermore, a cyclic voltammetry (CV) study was conducted to investigate the underlying mechanism involved in the electrosynthesis of 2-aminobenzonitrile (Figure 3).[27 29 30] The CV profiles of potassium (E)-2-(2-aminophenyl)-2-(hydroxyimino)acetate (blue line) which is an intermediate, tetrabutylammonium iodide (TBAI, red line), and a blank sample ($LiClO_4$ in DMSO, black dotted line) were recorded using a platinum disc as the working electrode, a platinum wire as the counter electrode, and Ag/AgCl as the reference electrode. In the blank sample containing only background electrolyte $LiClO_4$ and DMSO, no oxidation peak was observed, confirming the electrochemical inactivity of the solvent under the applied conditions. The cyclic voltammogram of TBAI revealed two characteristic anodic peaks at 0.535 V and 0.752 V vs Ag/AgCl. These features are assigned to the stepwise redox processes involving oxidation of iodide ions to I_2 ($I^- \rightarrow I_2$) followed by oxidation of triiodide species to iodine ($I_3^- \rightarrow I_2$).[29] Notably, the CV of the mixture containing both TBAI and potassium (E)-2-(2-aminophenyl)-2-(hydroxyimino)acetate displayed an excessive oxidation potential peak at 1.378 V. Since, during the reaction mechanism there is formation of potassium (Z)-2-(2-aminophenyl)-2-(hydroxyimino)acetate salt which undergoes halogenation to form hypoiodite species due to in situ electrogenerated I_2 and I_3^- with potassium salt.[30]

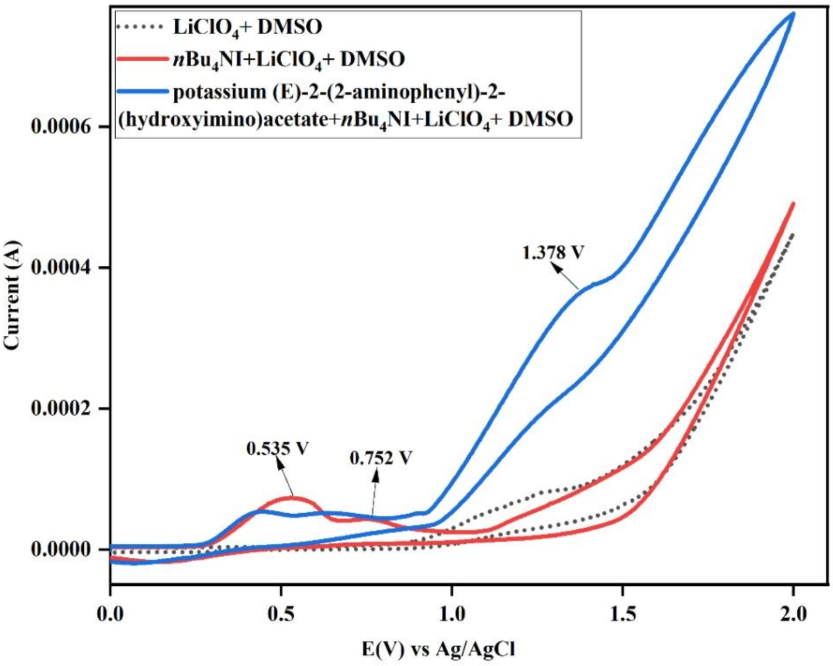

Figure 3: Cyclic voltammogram using Pt disc as working electrode, Pt as counter electrode & Ag/AgCl as reference electrode, initial potential= zero-volt, scan direction= 0 to +2 (oxidative), room temperature. A cyclic voltammogram of potassium (E)-2-(2-aminophenyl)-2-(hydroxyimino) acetate (0.05 M) in DMSO with TBAI (0.01 M) and $LiClO_4$ (0.1 M) (background electrolyte), 0.05 V sec^{-1} scan rate, 0 to 2 V.

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Experimental

General Information. All chemicals and solvents employed in this study were purchased from Sigma-Aldrich and used without further purification. The α-amylase from *Aspergillus oryzae* (≥150 U/mg, CAS NO.: 232-588-1, Product code: A9857) utilized for the functionalization of 2-aminobenzonitriles, was also procured from Sigma-Aldrich and used as received.

The electrochemical reactions were carried out on the OWON (P4305) instrument fitted with an undivided cell, magnetic stirrer, and a set of platinum electrodes (2.5 cm length, 0.7 cm width and 0.05 mm thickness). Furthermore, the cyclic voltammetry study was performed using the DY2300 potentiostat instrument. The progress of the reaction was monitored using Thin Layer Chromatography (TLC, Silica 254G was coated on the glass slide). The ^{1}H and ^{13}C NMR characterisation of compounds was recorded using a JEOL or a Bruker spectrometer, where 1H at 400 MHz and 500 MHz, and ^{13}C at 100 MHz and 125 MHz. The samples were recorded in solvents $CDCl_3$ and d^6- DMSO using trimethyl silane as an internal standard (TMS). The chemical shift was denoted by δ (ppm) and the coupling constant was denoted by *J* (Hz). The Chemical shift values of residual solvent peaks: for ^{1}H NMR, for $CDCl_3$ 7.26 ppm and for d^6-DMSO 2.50 ppm; ^{13}C NMR, for $CDCl_3$ 77.16 ppm and for d^6-DMSO 39.51 ppm. The abbreviations used for peak description of NMR are as follows: brs, broad singlet; s, singlet; d, doublet; t, triplet; dd, doublet of doublet. The HRMS data of the compounds were characterised using the QTOF mass spectrometer (XEVO G2 XS) in ESI(+ve) mode.

1.1 General procedure for the synthesis of 2-aminobenzonitriles (3a-3k). In a reaction vial containing a magnetic bar added isatin (**1**) (100 mg, 1 equiv.), hydroxyl amine hydrochloride (**2**) (71 mg, 1.5 equiv.), *n*Bu_4NI (376 mg, 1.5 equiv.) and base K_2CO_3 (95 mg, 1 equiv.) in 5 mL DMSO, and is stirred at 100 ℃ at a constant current of 10 mA in an undivided cell having platinum electrodes as cathode and anode for 3 h. The progress of the reaction was monitored by thin-layer chromatography (TLC). Upon completion, the reaction mixture was extracted with ethyl acetate, and the organic layer was dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure using a rotary evaporator, and the resulting residue was purified by column chromatography on silica gel (60–120 mesh) using hexane/ethyl acetate as the eluent to obtain the desired product.

1.2 General procedure for the electro-biosynthesis of aza-Michael product (4a-4k). Firstly, the reaction vial containing magnetic bar was added with isatin isatin (**1**) (100 mg, 1 equiv.), hydroxyl amine hydrochloride (**2**) (71 mg, 1.5 equiv.), *n*Bu_4NI (376 mg, 1.5 equiv.) and base K_2CO_3 (95 mg, 1 equiv.) in 5 mL DMSO, and is stirred at 100 ℃ at constant current of 10 mA in an undivided cell having Platinum electrodes as cathode and anode for 3 h. As indicated by TLC regarding the completion of the reaction, the reaction was cooled to room temperature, and methyl vinyl ketone (150 µL, 2.5 equiv.), α-amylase from Aspergillus oryzae (4 mg/mL), and 10 mL of H_2O were added. The above reaction mixture was stirred at 50 ℃ for 12 h. The reaction was monitored using TLC. After the reaction was complete, the mixture was extracted with ethyl acetate, and the organic layer was dried over anhydrous sodium sulphate and concentrated using a rotavapor. The residual was purified using column chromatography using 60-120 mesh Silica Gel as the stationary phase and Hexane/ethyl acetate as the mobile phase.

Characterisation data of synthesized compounds

2-aminobenzonitrile (3a). δ ^1H NMR (500 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.35 – 7.30 (m, 1H), 6.76 – 6.70 (m, 2H), 4.41 (brs, 2H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.63, 134.06, 132.34, 118.02, 117.63, 115.14, 96.05 ppm. **HRMS (EI)** calculated for $C_7H_6N_2$ $[M+H]^+$ 119.0609, found 119.0597.

2-amino-4-methoxybenzonitrile (3b). ^1H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.7 Hz, 1H), 6.33 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.23 (d, *J* = 2.4 Hz, 1H), 4.43 (brs, 2H), 3.81 (s, 3H) ppm. ^{13}C NMR (76 MHz, $CDCl_3$) δ 164.21, 151.47, 133.88, 118.17, 105.83, 99.33, 88.68, 55.40 ppm. **HRMS (EI)** calculated for $C_8H_8N_2O$ $[M+H]^+$ 149.0715, found 149.0706.

2-amino-5-methylbenzonitrile (3c). ^1H NMR (300 MHz, $CDCl_3$) δ 7.24 – 7.06 (m, 2H), 6.68 (d, *J* = 8.3 Hz, 1H), 4.29 (s, 2H), 2.24 (s, 3H) ppm. ^{13}C NMR (76 MHz, $CDCl_3$) δ 147.48, 135.15, 131.94, 127.52, 117.85, 115.41, 95.99, 20.08 ppm. **HRMS (EI)** calculated for $C_8H_8N_2$ $[M+H]^+$ 133.0766, found 133.0756.

2-amino-3-methylbenzonitrile (3d). ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, *J* = 7.8 Hz, 1H), 7.23 (d, *J* = 7.4 Hz, 1H), 6.69 (t, *J* = 7.6 Hz, 1H), 4.41 (brs, 2H), 2.19 (s, 3H) ppm. ^{13}C NMR (76 MHz, $CDCl_3$) δ 148.03, 135.27, 130.11, 122.62, 118.13, 117.57, 95.67, 17.42 ppm. **HRMS (EI)** calculated for $C_8H_8N_2$ $[M+H]^+$ 133.0766, found 133.0756.

2-amino-5-nitrobenzonitrile (3e). ^1H NMR (500 MHz, DMSO) δ 8.37 (d, *J* = 2.7 Hz, 1H), 8.12 (d, *J* = 2.7 Hz, 1H), 8.10 (d, *J* = 2.7 Hz, 1H), 7.47 (brs, 2H), 6.85 (d, *J* = 9.5 Hz, 1H) ppm. ^{13}C NMR (126 MHz, DMSO) δ 135.75, 130.63, 129.39, 116.06, 114.97, 92.58 ppm. **HRMS (EI)** calculated for $C_7H_5N_3O_2$ $[M+H]^+$ 164.0460, found 164.0472.

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2-amino-5-fluorobenzonitrile (3f). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.09 (td, *J* = 7.6, 2.9 Hz, 2H), 6.74 – 6.66 (m, 1H), 4.32 (brs, 2H) ppm. ^{13}C NMR (76 MHz, CDCl$_3$) δ 156.15, 153.00, 146.51, 122.27 (d, $^2J_{C\text{-}F}$ = 22.8 Hz), 117.76 (d, $^2J_{C\text{-}F}$ = 25.1 Hz), 116.79 (d, $^3J_{C\text{-}F}$ = 7.34 Hz), 96.08 ppm. **HRMS (EI)** calculated for $C_7H_5FN_2$ [M+H]$^+$ 137.0515, found 137.0517.

2-amino-6-chlorobenzonitrile (3g). ^{1}H NMR (500 MHz, DMSO) δ 7.25 (t, *J* = 8.4 Hz, 16.4 Hz,1H), 6.74 (d, *J* = 7.6 Hz, 1H), 6.70 (s, 1H), 6.38 (brs, 2H) ppm. ^{13}C NMR (126 MHz, DMSO) δ 153.63, 134.98, 134.43, 115.83, 115.34, 113.80, 93.85 ppm. **HRMS (EI)** calculated for $C_7H_5ClN_2$ [M+H]$^+$ 153.0220, found 153.0212.

2-amino-5-chlorobenzonitrile (3h). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.36 (d, *J* = 2.5 Hz, 1H), 7.29 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.71 (d, *J* = 8.8 Hz, 1H), 4.49 (brs, 2H) ppm. ^{13}C NMR (76 MHz, CDCl$_3$) δ 148.32, 134.35, 131.29, 122.37, 116.57, 96.95 ppm. **HRMS (EI)** calculated for $C_7H_5ClN_2$ [M+H]$^+$ 153.0220, found 153.0217.

2-amino-6-bromobenzonitrile (3i). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.15 (t, *J* = 8.1 Hz, 1H), 6.94 (d, *J* = 7.9 Hz, 1H), 6.67 (d, *J* = 9.4 Hz, 1H), 4.56 (brs, 2H) ppm. ^{13}C NMR (76 MHz, CDCl$_3$) δ 151.53, 134.46, 125.08, 121.70, 116.28, 113.70, 99.59 ppm. **HRMS (EI)** calculated for $C_7H_5BrN_2$ [M+H]$^+$ 196.9714, found 196.9713.

2-amino-5-bromobenzonitrile (3j). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.49 (d, *J* = 2.4 Hz, 1H), 7.41 (dd, *J* = 8.8, 2.3 Hz, 1H), 6.66 (d, *J* = 8.8 Hz, 1H), 4.51 (brs, 2H) ppm. ^{13}C NMR (76 MHz, CDCl$_3$) δ 148.70, 137.04, 134.16, 116.85, 116.31, 108.73, 97.54 ppm. **HRMS (EI)** calculated for $C_7H_5BrN_2$ [M+H]$^+$ 196.9714, found 196.9709.

2-amino-4-bromobenzonitrile (3k). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.28 (d, *J* = 4.0 Hz, 1H), 6.96 (d, *J* = 1.8 Hz, 1H), 6.89 (dd, *J* = 8.3, 1.8 Hz, 1H), 4.50 (s, 2H) ppm. ^{13}C NMR (76 MHz, CDCl$_3$) δ 150.28, 133.40, 128.82, 121.39, 117.94, 116.98, 94.93 ppm. **HRMS (EI)** calculated for $C_7H_5BrN_2$ [M+H]$^+$ 196.9714, found 196.9710.

2-((3-oxobutyl)amino)benzonitrile (4a). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.40 – 7.34 (m, 2H), 6.71 – 6.60 (m, 2H), 4.82 (brs, 1H), 3.50 (q, *J* = 6.3 Hz, 2H), 2.80 (t, *J* = 6.5 Hz, 2H), 2.19 (s, 3H) ppm. ^{13}C NMR (126 MHz, CDCl$_3$) δ 206.85, 149.94, 134.36, 132.66, 117.76, 116.67, 96.12, 42.51, 37.71, 30.33 ppm. **HRMS (EI)** calculated for $C_{11}H_{12}N_2O$ 189.1028, found 189.1030.

5-methoxy-2-((3-oxobutyl)amino)benzonitrile (4b). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.04 (d, *J* = 11.2 Hz, 1H), 6.91 (s, 1H), 6.67 (d, *J* = 8.0 Hz, 1H), 4.47 (brs, 1H), 3.76 (s, 3H), 3.47 (s,

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2H), 2.81 (d, J = 7.1 Hz, 2H), 2.20 (s, 3H) ppm. ^{13}C NMR (76 MHz, $CDCl_3$) δ 207.06, 150.81, 145.05, 122.43, 117.69, 115.98, 112.61, 96.25, 55.95, 42.63, 38.46, 30.42 ppm. **HRMS (EI)** calculated for $C_{12}H_{14}N_2O_2$ 219.1134, found 219.1132.

5-methyl-2-((3-oxobutyl)amino)benzonitrile (4c). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, J = 9.7 Hz, 2H), 6.65 (d, J = 8.4 Hz, 1H), 4.65 (brs, 1H), 3.52 (d, J = 6.4 Hz, 2H), 2.89 – 2.72 (m, 2H), 2.25 (d, J = 4.5 Hz, 6H) ppm. ^{13}C NMR (76 MHz, $CDCl_3$) δ 206.99, 147.98, 135.28, 132.68, 126.24, 117.96, 110.82, 96.06, 42.56, 37.97, 30.42, 19.95 ppm. **HRMS (EI)** calculated for $C_{12}H_{14}N_2O$ 203.1184, found 203.1187.

5-fluoro-2-((3-oxobutyl)amino)benzonitrile (4d). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 – 7.02 (m, 2H), 6.67 – 6.55 (m, 1H), 4.69 (brs, 1H), 3.51 – 3.36 (m, 2H), 2.78 (td, J = 6.2, 2.4 Hz, 2H), 2.18 (s, 3H) ppm. ^{13}C NMR (76 MHz, $CDCl_3$) δ 206.94, 155.31, 147.07, 122.10 (d, $^2J_{C\text{-}F}$ = 21.9 Hz), 118.49 (d, $^2J_{C\text{-}F}$ = 26.2 Hz), 116.71, 111.99 (d, $^3J_{C\text{-}F}$ = 7.7 Hz), 95.98 (d, $^3J_{C\text{-}F}$ = 7.7 Hz), 42.37, 38.24, 30.39 ppm. **HRMS (EI)** calculated for $C_{11}H_{11}FN_2O$ 207.0934, found 207.0939.

2-chloro-6-((3-oxobutyl)amino)benzonitrile (4e). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 – 7.20 (m, 1H), 6.74 – 6.65 (m, 1H), 6.60 – 6.53 (m, 1H), 4.96 (brs, 1H), 3.53 – 3.44 (m, 2H), 2.80 (d, J = 6.3 Hz, 2H), 2.19 (s, 3H) ppm.^{13}C NMR (76 MHz, $CDCl_3$) δ 206.79, 151.53, 137.19, 134.47, 117.31, 115.25, 108.57, 97.12, 42.34, 37.92, 30.45 ppm. **HRMS (EI)** calculated for $C_{11}H_{11}ClN_2O$ 223.0638, found 223.0632.

5-chloro-2-((3-oxobutyl)amino)benzonitrile (4f). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 7.1 Hz, 2H), 6.65 (d, J = 9.5 Hz, 1H), 4.83 (brs, 1H), 3.50 (q, J = 6.3 Hz, 2H), 2.81 (t, J = 6.4 Hz, 2H), 2.22 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.62, 148.58, 134.47, 131.91, 121.16, 116.52, 111.90, 97.14, 42.29, 37.90, 30.38 ppm. **HRMS (EI)** calculated for $C_{11}H_{11}ClN_2O$ 223.0638, 223.0634.

2-bromo-6-((3-oxobutyl)amino)benzonitrile (4g). ^{1}H NMR (300 MHz, $CDCl_3$) ^{1}H NMR (300 MHz,) δ 7.37 – 7.23 (m, 2H), 6.96 (d, J = 7.7 Hz, 1H), 6.69 (d, J = 8.8 Hz, 1H), 4.99 (brs, 1H), 3.56 (td, J = 7.7, 3.5 Hz, 2H), 2.87 (dt, J = 8.7, 3.8 Hz, 2H), 2.29 (s, 3H) ppm. ^{13}C NMR (76 MHz, $CDCl_3$) δ 206.64, 151.77, 134.69, 125.75, 120.58, 116.43, 109.05, 99.59, 42.42, 37.96, 30.50 ppm. **HRMS (EI)** calculated for $C_{11}H_{11}BrN_2O$ $[M+H]^+$ 267.0133, found 267.0130.

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5-bromo-2-((3-oxobutyl)amino)benzonitrile (4h). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.53 – 7.41 (m, 2H), 6.60 (d, J = 13.6 Hz, 1H), 4.87 (brs, 1H), 3.49 (dt, J = 8.3, 4.1 Hz, 2H), 2.82 (d, J = 6.7 Hz, 2H), 2.22 (s, 3H) ppm. ^{13}C NMR (76 MHz, CDCl$_3$) δ 206.66, 148.93, 137.19, 134.74, 116.41, 112.24, 107.43, 97.67, 42.25, 37.83, 30.38 ppm. **HRMS (EI)** calculated for $C_{11}H_{11}BrN_2O$ [M+H]$^+$ 267.0133, 267.0135.

(R)-2-((3-oxocyclohexyl)amino)benzonitrile (4i). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.39 (dt, J = 10.1, 5.1 Hz, 2H), 6.74 – 6.57 (m, 2H), 4.50 (brs, 1H), 2.94 – 2.72 (m, 1H), 2.38 (tt, J = 26.1, 13.0 Hz, 4H), 2.13 (t, J = 7.4 Hz, 1H), 1.84 – 1.65 (m, 2H) ppm.^{13}C NMR (76 MHz, CDCl$_3$) δ 208.45, 148.49, 134.49, 133.15, 117.26, 111.13, 96.32, 51.91, 48.19, 40.93, 31.48, 22.24 ppm. **HRMS (EI)** calculated for $C_{13}H_{14}N_2O$ [M+H]$^+$ 215.1184, found 215.1181.

(R)-5-methoxy-2-((3-oxocyclohexyl)amino)benzonitrile (4j). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.08 – 6.80 (m, 2H), 6.66 (dd, J = 17.6, 9.1 Hz, 1H), 3.79 (brs, 1H), 3.72 (s, 3H), 2.83 – 2.76 (m, 1H), 2.44 – 2.27 (m, 2H), 2.10 – 1.96 (m, 3H), 1.72-1.59 (m, 3H) ppm. ^{13}C NMR (76 MHz, CDCl$_3$) δ 208.70, 151.66, 144.31, 122.77, 117.18, 116.02, 114.65, 113.35, 96.57, 55.99, 52.80, 48.36, 40.92, 31.56, 22.20 ppm. **HRMS (EI)** calculated for $C_{14}H_{16}N_2O_2$ [M+H]$^+$ 245.1290, found 245.1290.

(R)-5-fluoro-2-((3-oxocyclohexyl)amino)benzonitrile (4k). ^{1}H NMR (300 MHz, CDCl$_3$) ^{1}H δ 7.19 – 7.10 (m, 2H), 6.62 (dd, J = 9.0, 4.2 Hz, 1H), 4.36 (brs, 1H), 2.82 (ddt, J = 13.8, 4.0, 1.9 Hz, 1H), 2.67 – 2.12 (m, 4H), 2.28 – 2.01 (m, 2H), 1.82 – 1.34 (m, 2H) ppm. ^{13}C NMR (76 MHz, CDCl$_3$) δ 208.30, 152.42, 145.49, 122.34 (d, $^2J_{C\text{-}F}$ = 23.00 Hz), 118.77 (d, $^2J_{C\text{-}F}$ = 25.20 Hz), 112.59 (d, $^3J_{C\text{-}F}$ = 7.47 Hz), 96.37 (d, $^3J_{C\text{-}F}$ = 9.14Hz), 52.41, 48.18, 40.92, 31.56, 22.23 ppm. **HRMS (EI)** calculated for [M+H]$^+$ 233.1090, found 233.1088.

Conclusion

In summary, we have developed an electricity-mediated, sustainable protocol for the efficient synthesis of 2-aminobenzonitriles from isatins and hydroxylamine as starting materials. This strategy overcomes the limitations of previously reported methods that often require harsh reaction conditions, metal catalysts, or costly substrates. A range of substituted 2-aminobenzonitriles was obtained in good yields directly from corresponding substituted isatins. Furthermore, the electrochemically synthesized 2-aminobenzonitriles were successfully functionalized in a one-pot process by integrating electrochemical synthesis with α-amylase-catalyzed aza-Michael addition, affording clinically valuable β-amino carbonyl compounds. Furthermore, control experiments and cyclic voltammetry studies were conducted to gain mechanistic insight into the integrated protocol. Overall, this protocol highlights the potential of electrochemically driven C–C bond cleavage in isatin chemistry.

Credit Authorship contribution statement

Kirti Singh: Writing-original draft, Methodology, Investigation.

Shashi Pandey: Data characterisation and compilation of data

Vikas Tyagi: Writing-original draft, Project Administration, Investigation, Conceptualisation.

Conflicts of Interest

The authors declare no conflicts of interest.

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- The data supporting this article have been included as part of the Supplementary Information.

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