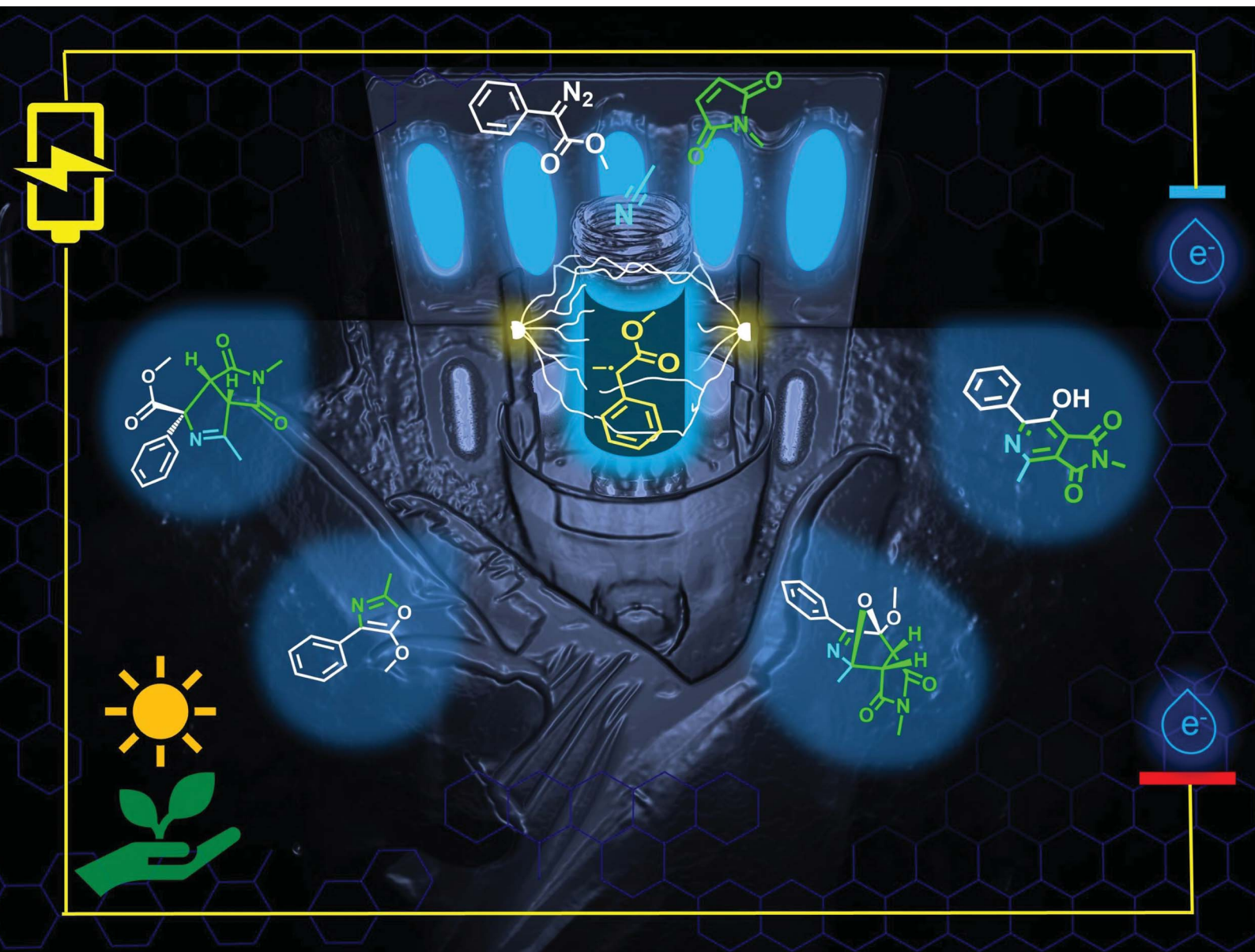


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EDGE ARTICLE

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Unveiling catalyst-free electro-photochemical reactivity of aryl diazoesters and facile synthesis of oxazoles, imide-fused pyrroles and tetrahydroepoxy-pyridines *via* carbene radical anions†

Debajit Maiti,^a Argha Saha,^b Srimanta Guin,^b Debabrata Maiti^b and Subhabrata Sen^{*a}

Herein, we report a reagent-less (devoid of catalyst, supporting electrolyte, oxidant and reductant) electro-photochemical (EPC) reaction [electricity (50 μ A) and blue LED (5 W)] of aryl diazoesters to generate radical anions which are subsequently reacted with acetonitrile or propionitrile and maleimides to generate diversely substituted oxazoles, diastereo-selective imide-fused pyrroles and tetrahydroepoxy-pyridines in good to excellent yield. Thorough mechanistic investigation including a 'biphasic e-cell' experiment supports the reaction mechanism involving a carbene radical anion. The tetrahydroepoxy-pyridines could be fluently converted to fused pyridines resembling vitamin B₆ derivatives. The source of the electric current in the EPC reaction could be a simple cell phone charger. The reaction was efficiently scaled up to the gram level. Crystal structure, 1D, 2D NMRs and HRMS data confirmed the product structures. This report demonstrates a unique generation of radical anions *via* electro-photochemistry and their direct applications in the synthesis of important heterocycles.

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Introduction

In recent years, electrochemistry has constituted a major pathway in steering numerous organic transformations.¹ By virtue of being generated *via* various renewable energy sources, it has successfully evolved as an ecologically sustainable and economical energy source to promote organic reactions.² Seminal reviews and perspective articles on electrochemistry have ignited the "electro-curiosity" of researchers to investigate electrochemical organic reactions.³ Similar to electrochemistry, photochemistry has been extensively utilized as an appropriate energy source for various organic transformations for many years. It has gained tremendous attention from the community of synthetic organic chemists, especially after the evolution of light-emitting diodes (LED) during the last decade.⁴

In recent years, these two apparently related but orthogonal techniques have been coupled together to facilitate and modulate organic transformations driven by single electron-redox pathways.⁵ As a concept, electro-photochemistry (EPC) was first reported by Moutet and Reverdy in 1979 through electrochemical generation of

phenothiazine radical cations and their subsequent photoexcitation.⁶ Immediately after that Rustling illustrated a photoexcited and electrochemically generated anthracene radical anion that reduced 4-chlorobiphenyl.⁷ Despite such ground-breaking disclosures it was not until 2019, that EPC was first used in facilitating an organic reaction.^{5,8}

In recent times, thermal and photochemical decomposition of diazoalkane and diazoester with and without metal catalysts have been extensively explored and widely used in synthetic organic chemistry.⁹ Among them, aryl diazoesters are one of the most unique carbene precursors where the electrophilicity of carbene can be tuned precisely through varying substitution in the donor as well as in the acceptor domain attached to it. Electrophilic carbenes generated from aryl and other diazoesters are employed in numerous chemical transformations including C–H, N–H, O–H insertions, cyclopropanation, ylide generation *etc.*¹⁰ However, electro-photochemical reactivity of aryl diazoesters remained unexplored so far. In one recent example, Huang *et al.* used diazoesters in an electrochemical reaction but the diazoester was not electrochemically activated or explored in that work.¹¹

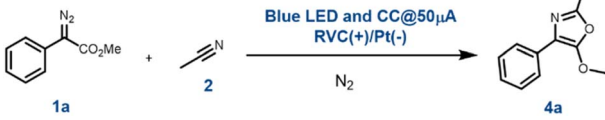
Careful curation of the literature revealed that there are only a few reports to date demonstrating the generation of carbene anion radicals. The McDonald research group (1986) and later Parker and Bethell *et al.* (1989) reported the electrochemical generation of the diazoalkane radical followed by thermal loss of dinitrogen to form the carbene anion radical.¹² Bierbaum *et al.* (2008) reported mechanistic insight for halogen substituted

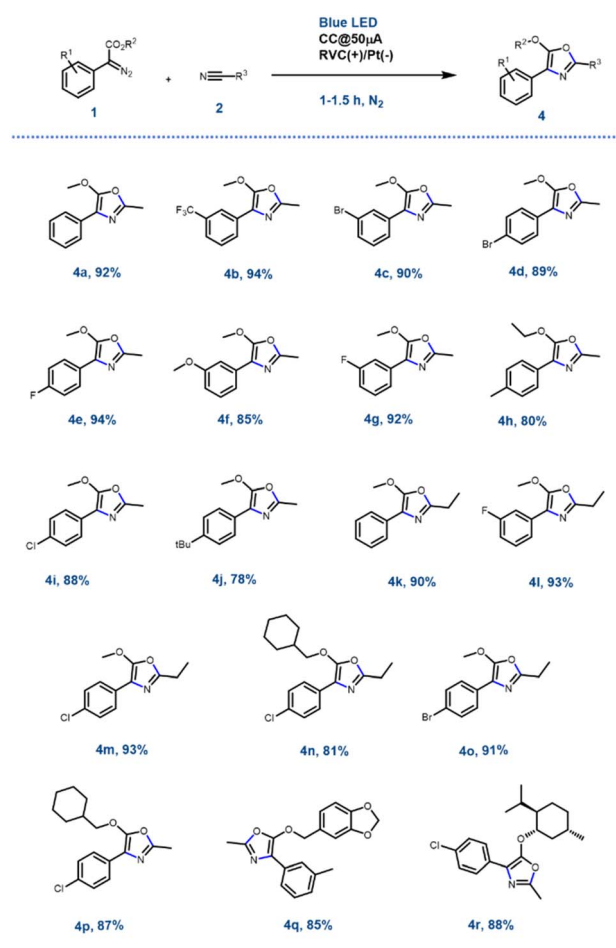
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† Electronic supplementary information (ESI) available. CCDC 2176481 and 2179729. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d3sc00089c>

Table 1 Optimization of the EPC reaction to generate oxazole, 4a^a

			
Entry	Deviation from the above conditions	Yield ^b	Comments
1	No deviation	92%	1.5 h reaction time
2	RVC (–), platinum (+)	74%	4.5 h reaction time
3	Graphite (+), platinum (–)	90%	4.5 h reaction time
4	Copper (–)	30%	1a decomposition prevalent
5	Graphite (–)	65%	6 h reaction time
6	Dark	0%	Partial 1a decomposition
7	No electricity	0%	1a decomposition after 3 h
8	NBu ₄ PF ₆ as supporting electrolyte	88%	4 h reaction time
9	Constant current @ 20 µA	90%	6 h reaction time
10	Constant current @ 100 µA	52%	In <1 h all 1a consumed
11	Constant voltage @ 1.5 V	88%	2.5 h reaction time
12	Constant voltage @ 2 V	78%	1.5 h reaction time

^a Reaction conducted with 50 mg of **1a**. ^b Isolated yield.

Scheme 2 different oxazoles through the EPC reaction.

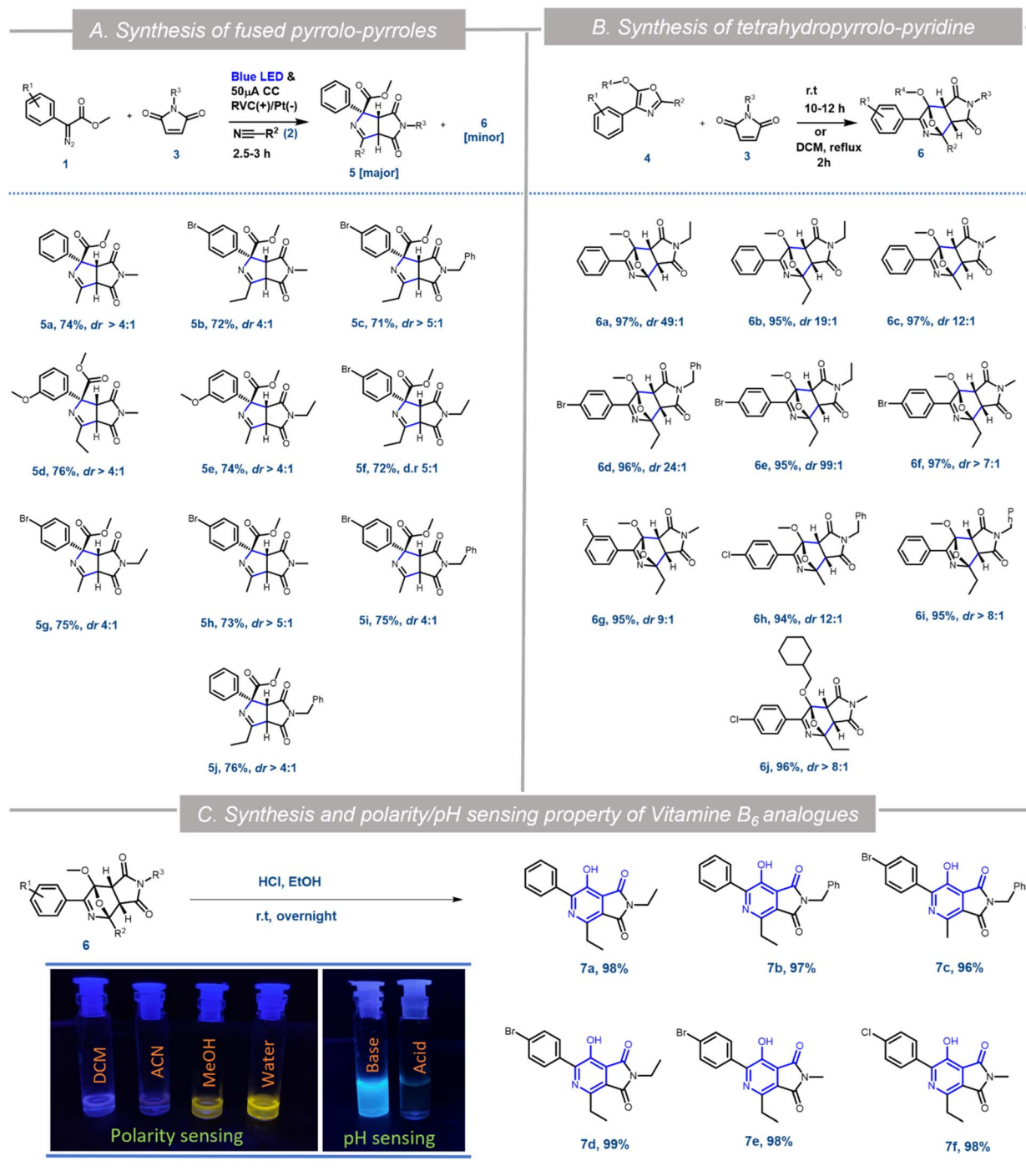
diazo esters, all the substitutions at the phenyl ring were tolerated affording the desired oxazoles **4a–r** in excellent yield (Scheme 2). However, the reaction with aryl diazo acetates containing electron donating substituents such as **1f**, **1h**, **1j**, **1l**, and **1n** occurred at a sluggish rate, thereby providing the desired compounds **4f**, **4h**, **4j**, **4n**, **4p**, **4r**, respectively, in a slightly lesser yield (80 to 90%) compared to their electron withdrawing counterparts (**1b**, **e** and **g** → **4b**, **4e**, **4g** and **4l**) (92 to 94%). This could be attributed to the formation of the radical anion **C** (Scheme 4) as a key intermediate in the reaction pathway, which was more stabilised by the electron withdrawing groups. This is discussed in the later part of the manuscript. The optimised reaction conditions were also amenable towards propionitrile **2b** and with different diazoesters such as **1a**, **e** and **l**, thereby affording the desired compounds **4k–o** in 81 to 93% yield (Scheme 2). It is noteworthy that with natural (–)-menthol derivative *p*-chlorophenyl diazo ester **1n**, the resulting oxazole **4r** was obtained in 88% yield. Reaction with 3-thiophene methyl diazo acetate [**1k**, Scheme S1 (ESI[†])] and **2a** failed to generate the desired product. Hence, the EPC reaction could successfully convert acetonitrile **2a** and propionitrile **2b** to various oxazoles when reacted with differently substituted aryl diazo esters **1a–o**. To demonstrate the scalability of this EPC reaction compound **4a** was synthesized on a 0.95 g scale from 1 g of **1a** and 5 ml of CH₃CN under the optimized conditions. The reaction went smoothly in 3.5 h to afford the desired product in 88% yield. A careful survey of the literature suggests that there are few protocols reported so far to synthesise oxazoles from diazo compounds; however, none of those had utilized the electro-photochemical reactivity of aryl-diazoesters as we have demonstrated here.¹⁶



Further synthetic application of the EPC reaction using N-protected maleimides

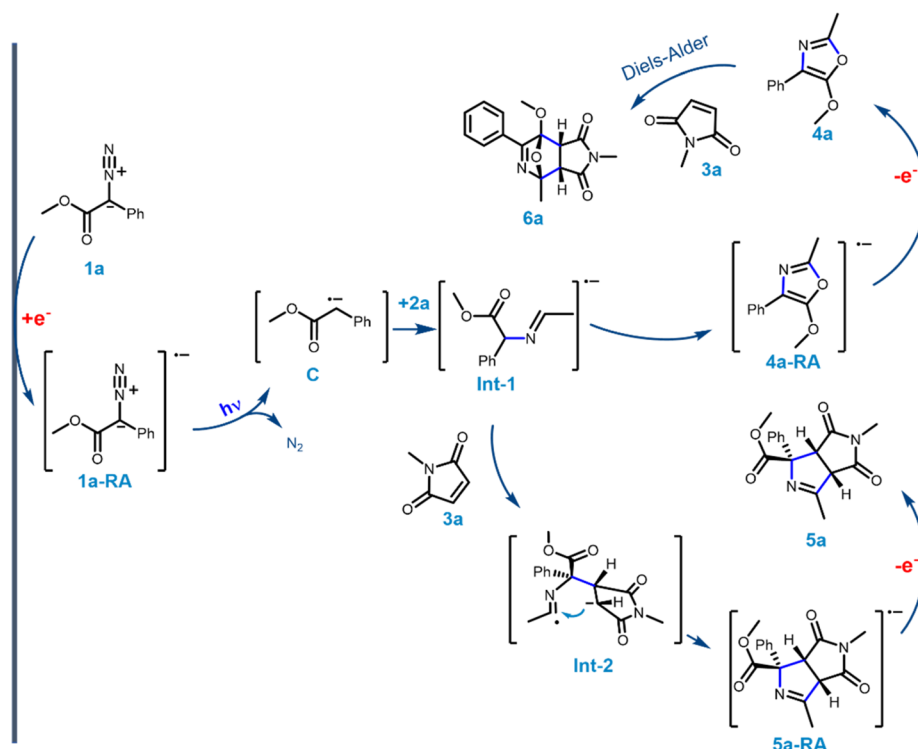
To demonstrate the further utility of the EPC strategy, *in situ* cycloaddition reactions of oxazole **4** with appropriate dipolarophiles were envisioned. The efficiency of *N*-substituted maleimides and acrylates as dipolarophiles in various [3 + 2]

cycloaddition reactions has been demonstrated.^{10f} Accordingly, when maleimide **3a** was added to the reaction mixture at the beginning of the electro-photochemical (EPC) reaction, two different maleimide adducts, **5a** and **6a** were obtained in ~75 : 25 ratio with nearly 100% conversion (Scheme 3). HRMS, NMR and single crystal XRD data (**5a** and **6h**) confirmed the structures of **5** and **6** (Scheme 1, Fig. S5 and S6 in ESI†). Hence as a generic



Scheme 3 Further application of the EPC reaction: (A) synthesis of pyrrolo-pyrroles through the EPC reaction, (B) synthesis of tetra-hydro-pyrrolo pyridine through the Diels–Alder reaction from oxazole; (C) synthesis and polarity and pH sensing properties of vitamin B₆ analogues [diastereomeric ratio (*dr*) determined through NMR analysis].





Scheme 4 Possible reaction mechanism based upon control experiments. Structure of the isomer obtained in the crystal structure used here as a representative entity.

reaction strategy, numerous aryl diazoacetates, **1a**, **d** and **f** were reacted with **2a/b** and **3a–c** to afford both **5a–j** as the major product with yields ranging from 71–76% (Scheme 3) and **6** as the minor products (enlisted in Scheme 4 separately). It was anticipated that maleimides **3** reacted with an intermediate as well as product **4** to afford **5** and **6**. This was clarified later while deciphering the mechanism of the reaction (Scheme 3A).

Since the single crystal X-ray of **6a** stipulated that it is the [4 + 2] cycloaddition reaction product between the oxazole **4a** and maleimide **3a**, in a bid to generate **6** exclusively, the *N*-methyl maleimide **3a** was added in the reaction mixture after the complete formation of **4a** in the EPC reaction of **1a** and **2a**. The blue LED and the electric current were turned off. Reaction **6a** was obtained as the exclusive product in 97% yield (Scheme 3). To further optimize the conditions for the formation of **6**, compound **4a** (isolated) and maleimide **3a** were reacted in dichloromethane under three different conditions: (i) under reflux conditions (ii) under a blue LED in an ice-bath and (iii) in the dark in an ice bath. We observed complete conversion and ~100% yield of **6a** under reflux within 2 h. However, under conditions (ii) and (iii) there was no product formation. The scope of the [4 + 2] cycloaddition reaction was demonstrated by generating ten derivatives **6a–j** (Scheme 3) by reacting **1a**, **1d**, **1g** and **1i** with **2a**, **2b** and **3a–c** (*N*-methyl/ethyl/benzyl maleimides respectively). By using either of the protocols *i.e.*, with *in situ* addition of **3** at r.t. after the formation of **4** or with isolated **4**

under reflux the yield of the reactions was nearly quantitative with excellent diastereoselectivity of up to 99% (Scheme 3B).

[4 + 2] Cycloaddition reactions between oxazoles and alkenes and their subsequent aromatization are one of the key strategies for the synthesis of pyridine derivatives. The pyridine derivatives are important because of their ubiquitous presence in natural products including Vitamin B₆ (pyridoxine) and its analogues.¹⁷ To demonstrate the synthetic application of **6** in the synthesis of fused pyridines (with the structural motif resembling vitamin B₆ derivatives), compounds **6b**, **6d–f**, **6i** and **6j** were treated with 1 N HCl in ethanol in r.t. overnight. To our expectation, **7a–f** were generated in excellent yield. Interestingly, these analogues as demonstrated by compound **7b**, displayed different fluorescence in different polar solvents (Scheme 3C). More interestingly, the aqueous basic solution of **7b** in 1 N NaOH exhibited bright fluorescence which was diminished in the aqueous acidic solution of **7b** in 1 N HCl (Scheme 3C). These observations indicated that such fused pyridines could potentially be utilised as polarity and pH sensing probes for biological studies. This would form the basis of a separate endeavour as further investigation is ongoing in our laboratory.

Mechanistic studies and the possible mechanism

To understand the possible mechanism of the EPC reaction, we performed several control experiments. Based on literature reports and our earlier observation, we initially could think of



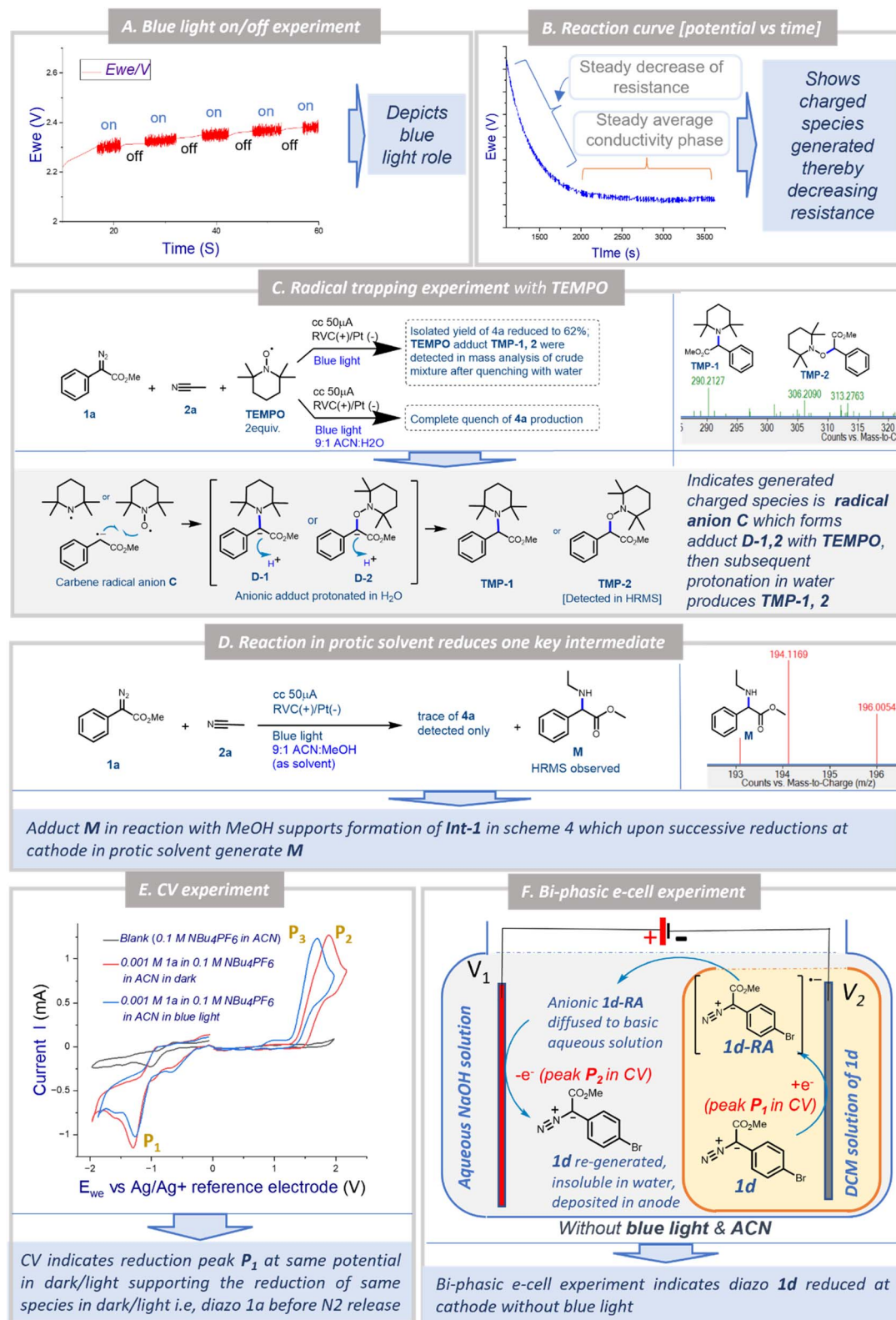


Fig. 1 Mechanistic investigation.

three possible mechanistic proposals for the transformation: Pathway [A]: under a blue LED, carbene was generated which could form the nitrogen ylide with acetonitrile followed by

cycloaddition to afford oxazole **4a** where electricity had no role to play; Pathway [B]: the aryl diazoester **1a** could be reduced at the cathode to generate the anion radical which could liberate

di-nitrogen under a blue LED to generate the carbene radical anion which could attack acetonitrile to generate **Int-1** (Scheme 4) and subsequent cyclisation and oxidation at the anode could lead to the formation of **4a**; Pathway [C]: at the outset the aryl diazoester could release dinitrogen under a blue LED to generate carbene and subsequently it is reduced at the cathode to generate the carbene radical anion which could attack acetonitrile to generate **Int-1** which then cyclise and get oxidised at the anode to generate **4a**.

To realise the possible mechanism, the observations from the optimisation experiments were analysed and several control experiments were performed. In the first place, it was observed that during the optimisation reaction of **1a** and acetonitrile **2a**, without the blue LED (with all the other parameters unchanged) there was no reaction (the reaction was monitored over a 3 h period) (Table 1, entry 6). Next, the blue LED was turned on and off at a regular interval of ~ 5 s and the potential was recorded against the time at a constant current. A distinct fluctuation of potential (E_{we}) was observed when the blue LED was 'on' and the plot was \sim linear when the blue LED was turned off (Fig. 1A). This indicated that during the reaction under the blue LED the electron flow to/from the potentiostat varied and that the reaction system could be experiencing a change in electron transfer from the cathode to the reaction solution and from the reaction solution to the anode. Since the reaction is free from any supporting electrolyte, additive and mediator, this change in electron transfer could be happening directly to/from the substrates. Again, in the optimisation study, the reaction under the blue LED and without any electricity failed to afford the formation of the desired product **4a** within 3 h of reaction time. Instead, partial diazo decomposition was observed (monitored through TLC) (Table 1, entry 7). Earlier Jurberg and Davies¹⁸ reported that the reaction of phenyl diazoester with acetonitrile under a 15 W blue LED and overnight formed a product which could be an oxazole (based on the characterisation data) possibly through nitrile ylide. There are also other reports of the formation of nitrile ylide under a blue LED in the reaction with nitrile and diazoesters.¹⁹ It is noteworthy that in all those cases higher intensity of the blue LED was used for a longer duration. But our EPC reaction protocol generated **4a** in 92% yield within 1.5 h reaction time and in the presence of a 5 W blue LED (Table 1, entry 1). As mentioned earlier, in this short time span and with a milder LED source no formation of oxazole was observed until electricity was applied (as mentioned in Table 1, entry 7). This observation and literature reports furthermore indicated that the mechanism in our case is not "Pathway [A]".

Next, when the reaction kinetics was explored through a potential vs. time plot (Fig. 1B), two distinct phases of the overall reaction were observed. In the initial phase of the reaction at a constant current, the potential (E_{we}) decreased steadily to a certain level and then in the remaining phase of the reaction it remained constant. This implicated that there must be a formation of charged species during the reaction which reduced the resistance of the solution. After reaching a certain concentration of the charged species (equilibrium), the reaction at a constant current behaved like that at a constant voltage. This continued until the completion of the reaction after which

the conductivity decreased and the potential increased to maintain the constant current possibly due to the consumption of all charged species towards the formation of a neutral product (Figs. 1B and S2 [ESI†]). These observations support two possibilities: (a) electricity is playing an important role during the reaction of oxazole **4a** formation and (b) there must be formation of a charged species which ultimately led to the formation of the product.

To understand the nature of the charged species and whether the reaction involved the radical mechanism, the EPC reaction of **1a** and **2a** was performed in the presence of TEMPO (2 equiv.) (Fig. 1C) in two different ways. In the first case, the reaction without water led to a decrease in the isolated yield of **4a** to 62%. The HRMS analysis of the reaction mixture after quenching with water whilst the reaction was still ongoing indicated the formation of TEMPO adducts **TMP-1** and **TMP-2**. Next, when the same reaction was performed with water (10% v/v), the formation of **4a** was completely quenched. This observation indicates that TEMPO formed anionic adducts **D-1** and **D-2** by reacting with anion radical **C** (Fig. 1C) which was then protonated in water to form **TMP-1** and **TMP-2**. Since the adducts **D-1** and **D-2** formed *via* reactions between **C** and TEMPO, the reaction towards the formation of **4a** was retarded. And that is why in the next case no formation of **4a** was observed when water was there to protonate both the anionic TEMPO adducts **D-1** and **D-2**, thereby driving the reaction more towards the formation of **TMP-1** and **TMP-2** as well as the direct quenching of **C** (Fig. 1C). These two complementary experiments outline the crucial formation of carbene radical anion **C** during the EPC reaction.

Furthermore, to identify any other possible intermediates, the experiment was performed using 9:1 $\text{CH}_3\text{CN}:\text{MeOH}$ as solvent (all other standard parameters unchanged). Interestingly, a trace of product **4a** and an adduct **M** was detected in HRMS analysis of the reaction mixture (Fig. 1D). This supported the formation of **Int-1** in the reaction between **C** and acetonitrile (in Scheme 4) which after protonation and successive reductions at the cathode might form **M** (unable to generate **4a** in the presence of methanol). In both TEMPO + water and ACN/MeOH experiments, no adduct of '-OH' or '-OMe' was observed which could eliminate the formation of any cationic intermediate.

Hitherto, the experiments and subsequent observations eliminated the possibility of mechanistic Pathway [A] (*i.e.* ylide mediated pathway) and supported the formation of carbene radical anion **C**. Now, **C** can be generated in two ways: (a) direct one-electron reduction of **1a** at the cathode generates diazo anion radical **1a-RA** which liberates di-nitrogen under blue light to generate **C**, or (b) carbene, after generation from **1a** under blue light undergoes one electron reduction at the cathode to generate **C**. In a bid to determine the immediate precursor of **C** we performed two experiments: cyclic voltammetry and the biphasic e-cell experiment. In cyclic voltammetry of **1a** in acetonitrile the reduction peak **P₁** was observed both in the dark and under a blue LED (Fig. 1E). However, under the blue LED oxidation peak **P₃** was observed instead of peak **P₂** in the dark. This indicated that the same reduction is happening both under LED and dark conditions which could possibly



correspond to the reduction of **1a** to generate **1a-RA** (Scheme 4). Peak **P₂** possibly corresponds to the oxidation of **1a-RA** to regenerate **1a** under dark conditions which had been further supported by the bi-phasic e-cell experiment explained below.

To demonstrate the reduction of methyl aryl diazoester in the dark as indicated by CV recording, a unique bi-phasic e-cell was devised in our lab (Figs. 1F, S3A and B†). The e-cell consisted of a 20 ml reaction vial, **V₁** containing 1 M NaOH solution, and a smaller 5 ml vial, **V₂** containing aryl diazoester **1d** as a solution in DCM. As DCM is immiscible with and heavier than water, **V₂** could be easily immersed in the aqueous solution without mixing the two solutions. Next, a RVC (as a cathode) was immersed in **V₂** and a RVC (as an anode) was immersed in **V₁**, and the electrolysis was performed at 2 V constant voltage in the absence of a blue LED. Interestingly, after some time yellow solid of **1d** was seen floating over the surface of the aqueous solution (Fig. S3C–E†). After about 60 minutes of electrolysis, the yellow deposit of **1d** was also observed over the anode (Fig. S3F†). This observation strongly stipulated the reduction of **1d** at the cathode (~corresponds to peak **P₁** @ –1.29 V, Fig. 1E) followed by the formation of a radical anion and oxidation at the anode (~corresponds to peak **P₂** @ +1.89 V, Fig. 1E) to regenerate aryl diazoester under standard electrochemical conditions in the absence of blue light. At the cathode, the reduction of **1d** initially generates radical anion **1d-RA**, which traversed through a basic aqueous solution to the anode, where it got oxidised to re-generate **1d**. Since **1d** is insoluble in water it is either deposited on the anode as a solid or floats over the surface of the aqueous layer after regenerating at the anode. It is noteworthy that there was no other way for **1d** to reach the anode from the DCM solution in **V₂** through an aqueous barrier except in the form of an anion (since it had originated at the cathodic chamber). There could be a possibility that in an aqueous solution the anion radical was protonated to an extent. This was anticipated and the basic aqueous solution was used to minimise it. Had an acidic solution or water been used then chances of protonation could have been higher and regeneration of diazo through oxidation could have been minimal or nothing. **1d** was considered for this experiment as it is a bright yellow coloured flaky solid at room temperature so that either buoyancy or deposition could be easily visible. Acetonitrile was not used in this experiment as the objective was to demonstrate the reduction of **1d** and not the formation of oxazole. Since acetonitrile is miscible with water the distinct two phases (water/DCM) could not have been constructed with acetonitrile.

In summary, the control experiments inferred that: (a) optimisation study and blue LED on/off experiments highlighted the necessity of blue LEDs for the transformation; (b) potential vs. time plot exhibited the generation of charged species during the EPC reaction; (c) the TEMPO experiment indicated that the charged species is carbene radical anion **C**; (d) the acetonitrile: MeOH experiment indicated the possible structure of **Int-1**; (e) CV and the bi-phasic e-cell experiment supported that aryl diazoester (**1a/1d**) was first reduced to generate **1a-RA/1d-RA**, subsequently nitrogen release under a blue LED generated the carbene radical anion **C**. All of these

observations supported possible mechanism Pathway [B] over [A] or [C] which has been depicted in Scheme 4.

Considering **1a**, **2a** and **3a** as the representative participants, the reaction could have begun with the formation of radical anion **1a-RA** (Scheme 4) which could be generated through single electron reduction at the cathode from **1a**. Radical anion **1a-RA** then released di-nitrogen under a blue LED to afford the carbene radical anion **C**. The anion radical or “radical anion” is unique chemical species where in general the LUMO (lowest unoccupied antibonding molecular orbital) of a neutral molecule becomes the SOMO (singly occupied molecular orbital) of the radical by addition of one electron to the neutral molecule.²⁰ Herein the anionic charge of **C** could have been delocalised to the adjacent ester carbonyl which could have made the SOMO lying over **C** (carbene carbon) to be electrophilic enough to attack the N-terminus of nitrile to generate **Int-1**. This could undergo cyclisation to afford the oxazole radical anion **4a-RA**. **4a-RA** was oxidised leaving an electron at the anode to form oxazole **4a** (possibly corresponds to peak **P₃** in CV). When the reaction occurred in the presence of **3a**, it was the intermediate **Int-1** and the product **4a** that participated in the reaction with maleimide **3a** to afford **5a** and **6a** as a mixture of ~75:25, respectively. When **3a** was added after the complete formation of **4a** and kept stirring overnight in r.t without electricity and blue light, **6a** was obtained as the exclusive [4 + 2] cycloaddition product as there was no **Int-1** left to react with **3a** (Scheme 4).

Manual set up

Finally, to demonstrate the simplicity of handling and cost-effectiveness of our photo-electrochemical reaction set-up, a customised apparatus was assembled in our lab with readily available electronic chips and components which included a 5V–1A (AC to DC) mobile adapter, 1 K ohm resistors, LEDs, connecting wires, a breadboard, 5 watt blue LED strip (430–450 nm) with 12 V AC to DC converter, a basic multimeter (to measure potential and current) (Fig. S4†). The total cost of all these components is ~1600 INR or 20 USD and could be purchased from a local electrical shop. A schematic of this setup is depicted in Fig. S4.† The reaction between **1a** and **2a** was performed using this set up and to our utmost gratification compound **4a** was obtained in 90% yield in 2.5 h.

Conclusion

In summary, herein we have unveiled a practical strategic amalgamation of electrochemistry and photochemistry to exploit aryl diazoesters in the generation of radical anions and their application in the synthesis of meaningful heterocycles like oxazoles **4**, imide-fused pyrroles **5** (from the anion radical) and tetrahydro-epoxypyrrolo-pyridines, **6** (from oxazole) from acetonitrile/propionitrile and maleimide. Compounds **6** could be easily transformed to diversely substituted fused pyridines **7** in excellent yield, resembling vitamin B₆ analogues. Compound **7** demonstrated fluorescence in various solvents and at different pH subject to further investigation. A plausible mechanism based on control experiments and a uniquely designed bi-



phasic e-cell experiment reveals a hitherto unexplored chemistry of carbene anion radicals generated from aryl-diazoesters under electro-photochemical conditions which facilitated the organic transformations. This EPC strategy devoid of any photoelectrodes, photo-redox catalysts, mediator and supporting electrolytes demonstrated a highly efficient organic transformation that could be scalable to the gram level. A cost-effective and practical reactor system was designed (Fig. S4†) using a simple cell phone charger as a source of electricity where the reaction occurred readily to generate the oxazole in excellent yield. Thus, this efficient synthetic process holds great promise to explore more organic transformations utilising the EPC protocol with diazoesters. Additionally, acetonitrile is a toxic solvent which gets metabolized to hydrogen cyanide (the source of its toxicity).²¹ Sustainable transformation of acetonitrile to useful heterocyclic compounds as demonstrated in this work is a value addition and could be envisioned as a strategy to utilise industry excess acetonitrile (as by-product) towards the synthesis of widely used pharmaceutical building blocks.²² Hence, it is worth mentioning, that our all-new EPC strategy could direct a new way to generate and utilize carbene anion radical in the field of electro-photochemistry.

Data availability

ESI† containing experimental and characterisation data are provided along with crystal data.

Author contributions

Mr DM conceptualized the project and synthesized the compounds. Mr AD and Mr SG assisted in the synthesis of compounds. Prof. DM and Prof. SBS managed the project. Prof. SBS supervised the project and wrote the manuscript with the help of all authors.

Conflicts of interest

There are no conflicts to declare.

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