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COMMUNICATION

Electrochemical Access to Benzimidazolone and Quinazolinone Derivatives via *in situ* Generation of Isocyanates

Debarshi Saha,[a] Irshad Maajid Taily,[a] Sumitra Naik [a] and Prabal Banerjee [a]*

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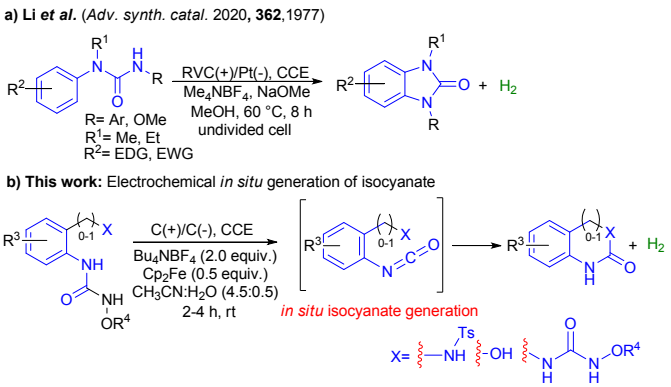
Isocyanates are the key intermediates for several organic transformations towards the synthesis of diverse pharmaceutical targets. Herein, we report the development of an oxidant-free protocol for electrochemical *in situ* generation of isocyanates. The strategy highlights expedient access to benzimidazolones and quinazolinones and eliminates the need for exogenous oxidants. Furthermore, detailed mechanistic studies provide strong support towards our hypothesis of *in situ* isocyanate generation.

Isocyanates, discovered in 1848 by Wurtz, are one of the most prevalent intermediates in organic chemistry.[1] Currently, the global isocyanate market surge of more than 5% per year underlines its importance towards the synthesis of structural scaffolds like biurets, allophanate, and most widespread polyurethanes.[2a] Notably, isocyanates are often derived from the reaction of toxic phosgene with amines.[2a] Phosgene, being hazardous to health, difficult to store, and handling issues, has made the synthetic community to think about its alternative. In 2018, Rousseaux and co-workers turned up with a phosgene and metal free synthesis of unsymmetrical ureas and carbamates where they employed isocyanate as an intermediate.[2b] Despite the importance and significant research efforts, isocyanate intermediates still suffer from one of the most significant challenges, i.e., sensitivity towards moisture.[2b] To overcome this, blocked isocyanates,[3] which contains a protected isocyanate, were introduced. Manoeuvring these isocyanates, many groups have demonstrated their utility towards the synthesis of many nitrogen containing biologically active heterocycles. Being highly valuable and pivotal intermediate, chemists persuade their *in situ* generation. An example of this was demonstrated by Beauchemin *et al.*, whereby engaging an *N*-substituted isocyanate, cascade synthesis of aminohydantoin was conducted.[4a] Among the nitrogen heterocycles, quinazolinones and benzimidazolones are extensively studied for their antitumor, anticancer, anti-inflammatory, anti-HIV, and other multifarious biological activities.[4b] Hence, many efficacious protocols have been disclosed for their construction.[8] In spite of the landmark advancement in the synthesis of these vital structural scaffolds, modern methodologies which are green and environmentally benign has always fascinated the scientific community. In recent times, electroorganic chemistry has bestowed us an appealing tool for various redox transformations.[5] Employing electrons as the reagent makes this methodology green and sustainable[6] and has intrigued the organic chemists to adopt this promising technology.[7a] Allured by this elegant technology, recently, Xu *et al.* established an electrosynthetic procedure for the construction of benzimidazolones and benzoxazoles.[9a]



Scheme 1. Electrochemical synthesis of benzimidazolones and quinazolinones.

In continuation of the endeavour, very recently, Li's group achieved an electrochemical intramolecular oxidative C-N coupling from simple aryl ureas towards the synthesis of benzimidazolones[9b] (**Scheme 1a**). Motivated by the incredible utility of this chemistry towards C-C[7b,7c], C-X[7d-7g] bond formation, we envisaged that this process can be exploited towards *in situ* generation of isocyanates and the same could be further exploited towards the sustainable synthesis of benzimidazolones and quinazolinones (**Scheme 1b**). In line with

[a] Department of Chemistry, Indian Institute of Technology Ropar, Nangal Road, Rupnagar, Punjab-140001, India. E-mail: prabal@iitrpr.ac.in.
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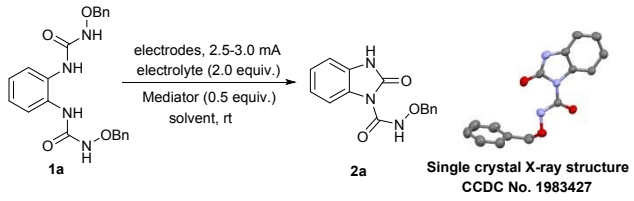
our thought, we found, in 2014, seminal work by Jeffrey *et al*. encountered an isocyanate intermediate in the presence of iodobenzene diacetate ($PhI(OAc)_2$), while attempting [4+3] cycloaddition reaction via diazaoxy-allylic cation.[10] Although hypervalent iodine reagents are used in various transformations, and suffer from several limitations such as the stoichiometric generation of waste, large scale preparation, etc.[11] We contend that electrochemical *in situ* generation of isocyanate remains fully unexplored. In this particular context, herein, we report an unprecedented *in situ* electrochemical generation of isocyanate pathway for the synthesis of benzimidazolone and quinazolinones.

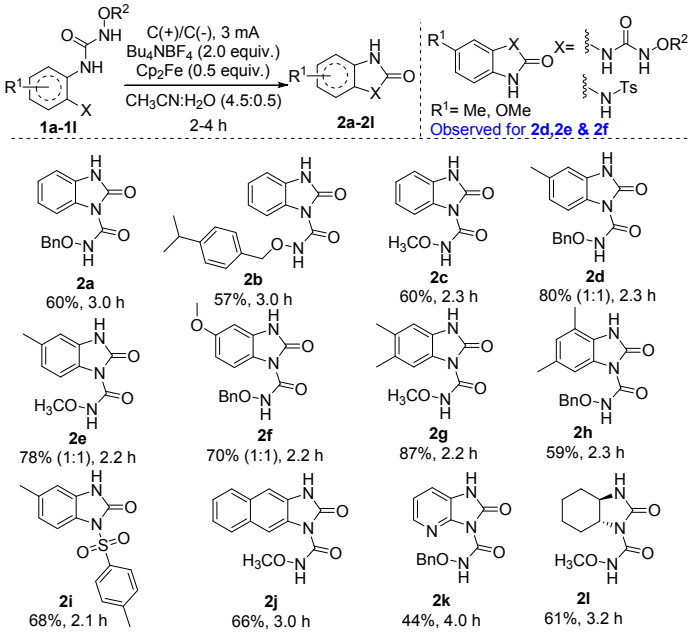
Table 1: Optimization of reaction conditions



Entry	Variation from standard conditions[a]	Yield[b]
1	None	60
2	Bu_4NPF_6 instead of Bu_4NBF_4	15
3	Bu_4NBr instead of Bu_4NBF_4	14
4	Bu_4NClO_4 instead of Bu_4NBF_4	17
5	Et_4NBF_4 instead of Bu_4NBF_4	45
6	Dry CH_3CN instead of CH_3CN:H_2O	44
7	DCM, CH_3OH and DMF instead of CH_3CN:H_2O	n.r.
8	TEMPO instead of Cp_2Fe	58
9	Pt cathode instead of Carbon	56
10	Pt anode instead of Carbon	trace
11	At constant current of 5.0 mA	trace
12	At constant current of 1.5-2.0 mA	24
13	Without electricity or Cp_2Fe	n.r.
14	Without electricity in the presence of NaH, NaOH and K_2CO_3	n.r.

[a]Unless otherwise stated, all the reactions were performed at a constant current of 3.0 mA with carbon as both anode and cathode, Cp_2Fe as a mediator, Bu_4NBF_4 as supporting electrolyte, and CH_3CN:H_2O as a solvent with **1a** (0.1 mmol). [b]isolated yield. n.r. = no reaction.

To test our hypothesis, we initially took 1,1'-(1,2-phenylene)bis(3-(benzyloxy)urea) **1a** as a model substrate, Cp_2Fe **(0.5 equiv.)** as a mediator, and Bu_4NPF_6 **(2.0 equiv.)** as a supporting electrolyte in an undivided cell equipped with graphite electrodes. The electrolysis was performed at a constant current of 3.0 mA (cell potential during the reaction lies in the range of 2.23-2.90 V), and gratifyingly *N*-(benzyloxy)-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazole-1-carboxamide **2a** was obtained in low yields. The structure of **2a** was confirmed by single-crystal X-ray structure analysis. Encouraged by this result, we screened the reaction conditions for the following transformation which are summarized in **Table 1**. Initially, supporting electrolytes like Et_4NBF_4, Bu_4NClO_4, Bu_4NBr, and Bu_4NBF_4 were varied (entry 2-5). We found that Bu_4NBF_4 **(2.0 equiv.)** served as a better supporting electrolyte. Among others, Et_4NBF_4 proved equally efficient, whereas Bu_4NClO_4 and Bu_4NBr resulted in diminished yields. Although the reaction worked well with the dry CH_3CN (entry 6) but incorporating a trace amount of H_2O enhanced the yield to 60% (entry 1). Further, replacement of CH_3CN with DCM, MeOH, DMF (entry 7) was found fatal. Usage of TEMPO (entry 8) instead of Cp_2Fe furnished a decent yield. The choice of the electrode materials was found critical because replacing the graphite anode with the platinum anode (entry 10) showed lower efficiency. However, the usage of Pt cathode has no profound effect on the yield (entry 9). Furthermore, increasing or decreasing the current from 3.0 mA (entry 11-12) resulted in compromised yield. Control experiments demonstrated electricity and Cp_2Fe as (entry 13) crucial parameters for the electrolysis. Moreover, to ascertain the role of electricity, the reaction (in the absence of electricity) was also performed in the presence of stoichiometric amount of bases like NaH, NaOH, and K_2CO_3 (entry 14), but no product formation was observed.

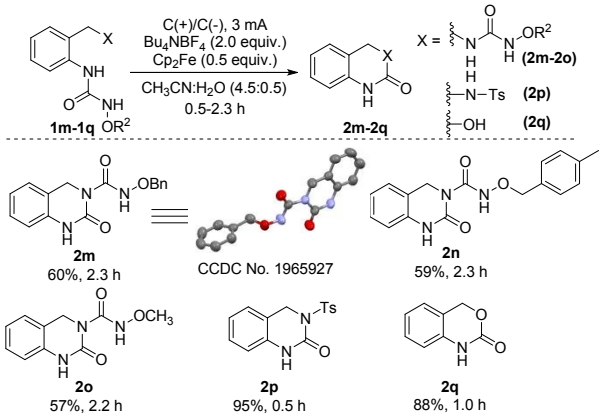


Scheme 2. Substrate scope of benzimidazolone derivatives.

Once the optimized conditions were established, the substrate scope was investigated. Initially, the effect of (un)substituted benzyloxy group was screened **(2a** and **2b)**. To our delight, *para*-isopropylbenzyloxy derivative **(2b)** furnished moderate yield. Further, no profound effect on the yield was observed on replacing the benzyloxy group with the methoxy group **(2c)**. Next, substituted *ortho*-phenylene diamines having electron donating groups delivered the product in moderate yields **(2d-2h)**. In the case of *para*-methyl **(2d** and **2e)** and *para*-methoxy phenylene diamines **(2f)**, NMR data revealed the formation of two inseparable regioisomers (1:1). Although the dimethyl substituents **(2g** and **2h)**, irrespective of their position, rendered the single regioisomers in good yields. To resolve the issue of regioselectivity, the reaction of the unsymmetrical substrate

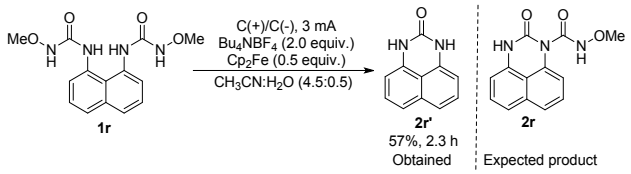
(2i) evinced the formation of a single regioisomer. However, electron withdrawing substituents on the aryl ring of the corresponding diamines proved incompatible, possibly due to compromised nucleophilicity. On the other hand, the replacement of the aryl group with naphthalene moiety **(2j)** proved compatible. Heterocyclic motif, like pyridine-2,3-diamine **(2k)**, gave the single regioisomer with slightly inferior yield due to the decreased nucleophilicity of the amine group. Pleasingly, when the phenylene diamine was replaced by *rac*-cyclohexane-1,2-diamine our protocol furnished *rac*-*N*-methoxy-2-oxooctahydro-1*H*-benzo[*d*]imidazole-1-carboxamide **(2l)** with 61% yield.

To extend the generality of our concept, the synthesis of quinazolinone derivatives was also attempted, and four different derivatives were obtained **(Scheme 3)**. Similar yields were observed when the benzyl substituents were varied (**2m-2q**). The structure of *N*-(benzyloxy)-2-oxo-1,2-dihydroquinazoline-3(4*H*)-carboxamide **(2m)** was confirmed by single-crystal X-ray structure analysis. Next, the protocol was attempted with unsymmetrical substrates **(2p** and **2q),** which resulted in significant improvement of the yield. Pleasingly, the synthesis of diverse heterocyclic scaffolds like *N*-tosylated quinazolinones **(2p)** and oxazinone **(2q)** was accomplished by employing this methodology.



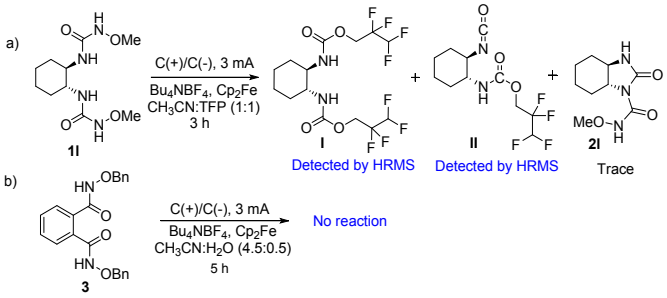
Scheme 3. Formation of quinazolinones and oxazinone.

Salubrious with the above result, we attempted the synthesis of *N*-methoxy-2-oxo-2,3-dihydro-1*H*-perimidine-1-carboxamide (**2r**). Surprisingly, the *N*-methoxy amide group got hydrolyzed during the reaction, and we obtained perimidinone (**2r'**) as a product **(Scheme 4)**, which has been reported for anxiolytic effects.[11]



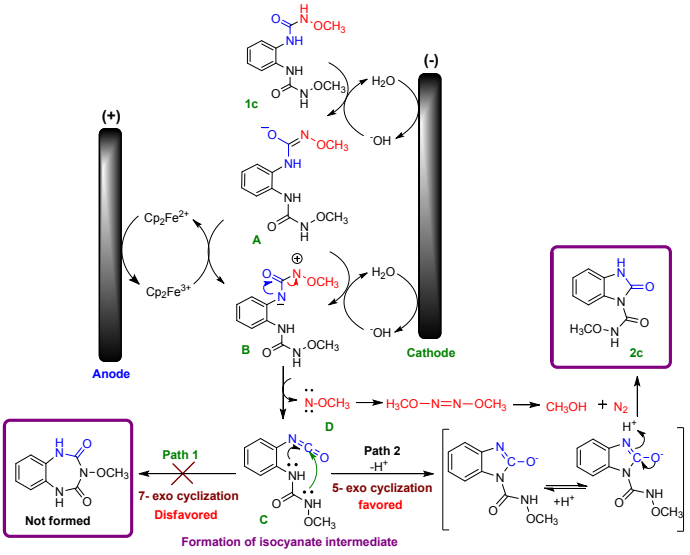
Scheme 4. Formation of perimidinone.

To investigate the reaction pathway, the reaction was performed in the presence of a stoichiometric amount of TFP (2,2,3,3-tetrafluoro-1-propanol).[10] The substrate **1l** initially undergoes anodic oxidation followed by a nucleophilic attack of TFP to form adducts **I** and **II** with a trace amount of product formation. The adduct **I** and **II** (detected by HRMS) describe the *in situ* generation of isocyanate intermediate **(Scheme 5a)**. Moreover, the electrolysis failed in the absence of nitrogen of diamines **(Scheme 5b)**.



Scheme 5. Mechanistic studies.

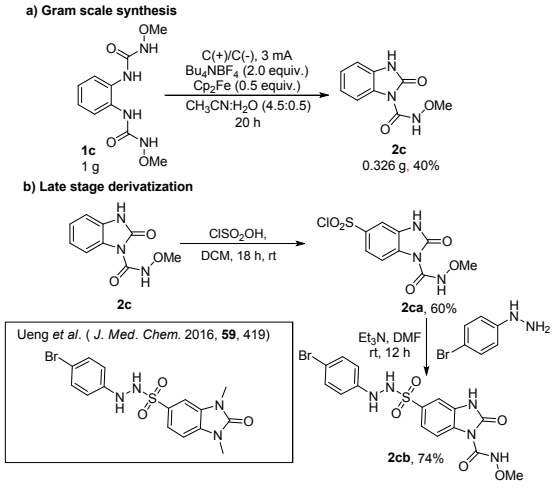
Furthermore, cyclic voltammetry experiments (see supporting information) could figure out the role of Cp_2Fe in lowering the oxidation peak of **1c** (2.53 V v/s Ag/AgCl) to 2.27 V, indicating that Cp_2Fe acts as a mediator. Also, to determine the role of water the experiment was performed in the presence of 0.1 M NaOH, which enhanced the catalytic current between $[Cp_2Fe]^+$ and **1c**. Henceforth, the generation of ^-OH is one of the key steps for this protocol. Based on the experimental results and literature reports, we proposed a plausible mechanism **(Scheme 6)**. The process gets initiated with the synergistically paired electrolytic cycles as suggested by Luo *et al*.[12] These two processes further facilitate the oxidation of **1c** to generate nitrenium intermediate **B** via the formation of intermediate **A**. Subsequently, nitrenium intermediate **B** underwent the formation of isocyanate **C** and eliminates nitrene intermediate **D**, which is followed by 5-*exo* cyclization instead of 7-*exo* cyclization which leads to the formation of **2c**.



Scheme 6. Plausible Mechanism.

Further, the nitrene intermediate **D** dimerizes to an unstable hyponitrite ester, subsequently loses nitrogen, and forms methanol.[13] Although among the two nitrogen functionality, the one having aryl/alkyloxy group is more nucleophilic, as demonstrated by our group.[14] But in this case, the one which is less nucleophilic attacks, i.e., path 2 is preferred over path 1, suggesting that the nitrogen which is in close proximity with isocyanate could attack easily in comparison to the more nucleophilic one, in addition to the fact that 5-membered ring is thermodynamically more stable.

To evaluate the practicality of our protocol, the electrolysis was performed at a gram-scale, and the reaction demonstrated scalability with a moderate yield of 40% **(Scheme 7a)**. Furthermore, derivatization of **2c** was performed by reaction with chlorosulfonic acid to obtain **2ca**, which was further treated with (4-bromophenyl)hydrazine to furnish 5-((2-(4-bromophenyl)hydrazinyl) sulfonyl)-*N*- methoxy-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazole-1-carboxamide **(2cb) (Scheme 7b)**. Delightfully, the synthesized molecule bears structural similarity to the molecule which is reported to have antitumor activity.[15]



Scheme 7. Synthetic Application.

Conclusions

In summary, we disclosed an electrochemical pathway for *in situ* generations of isocyanate under oxidant-free conditions. It involves a straightforward, general protocol towards the construction of benzimidazolones, quinazolinones, perimidinone, and oxazinones. This methodology demonstrates an inexpensive Cp_2Fe as a redox catalyst with the release of H_2 gas, thereby eliminating the need for expensive transition/noble metal catalyst and hypervalent iodine reagents. Furthermore, the synthetic applications of this work highlight scalability and also involves the synthesis of a drug-like molecule.

Conflicts of interest

There is no conflict of interest to declare

Notes and references

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