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eAmidation: An Electrochemical Amidation of Aldehydes via the Oxidation of N-Aryl Hydrazones

Luke Chen,[a,b] James D. F. Thompson,*[a] and Craig Jamieson*[b]

[a] Luke Chen, Dr. James D. F. Thompson
Medicinal Chemistry, GSK, Gunnels Wood Road, Stevenage, SG1 2NY, United Kingdom
E-mail: james.d.thompson@gsk.com

[b] Luke Chen, Prof. Craig Jamieson
Pure & Applied Chemistry, University of Strathclyde Glasgow, G1 1XL, United Kingdom
E-Mail: craig.jamieson@strath.ac.uk

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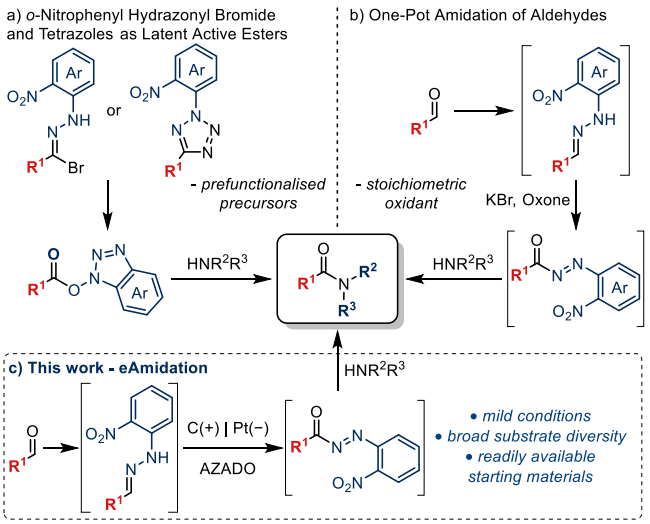
Abstract: In recent years, the use of electrochemistry has emerged as a powerful yet sustainable means of enabling key transformations. Amidation is one of the most frequently executed transformations in synthetic chemistry, and using an electrochemical approach, the current study has demonstrated the synthesis of amides from aldehydes and amines. Mechanistic work indicates that the reaction proceeds *via* the oxidation of an intermediate hydrazone to generate an acyl diazene as the acylating species. The protocol developed has enabled the synthesis of a broad range of amides, including access to pharmaceutically relevant products, directly from aldehydes without recourse for hazardous chemical oxidants and activating agents.

Introduction

The amide bond is found ubiquitously in drugs and biomolecules, as well as in materials such as nylon. Owing to its biological significance, prevalence in bioactive molecules, and utility in materials chemistry, amide bond forming reactions are one of the most regularly performed in synthetic chemistry.[1–6] The traditional approach involves the activation of carboxylic acids with an exogenous coupling reagent to generate a reactive, electrophilic acyl component.[7,8] Despite the ease of amide synthesis using these activating agents, there are several limitations associated with these species, including toxicity, chemical stability, cost, and atom economy.[9–13] As a result, there has been a pressing need to develop more efficient amidation processes, including the use of alternative precursors such as aldehydes.[14–20]

The application of nitrile imines in the synthesis of amides has previously been a topic of interest to our laboratories. In our previous reports, this involved the 1,7-rearrangement of a nitrile imine bearing an *N*-2-nitrophenyl substituent to generate an *N*-hydroxybenzotriazole activated ester which can then react with amines (Scheme 1a).[21,22] These reports demonstrated that hydrazonyl bromides and tetrazoles, precursors to nitrile imines, could serve as masked, latent active esters. To further exploit this reactivity, it was of interest to identify novel methods to access the nitrile imine from more readily available starting materials. Recently, our laboratories have demonstrated the oxidative amidation of aldehydes, *via* an *in situ*-generated hydrazone (Scheme 1b).[23] The original reaction design sought to utilise the 1,7-electrocyclisation of nitrile imines, however, subsequent studies revealed that this followed a distinct reaction pathway. Using a mixture of KBr and Oxone®, the oxidation of the intermediate hydrazone resulted in the formation of an alternative active ester species, the acyl diazene, which has enabled the direct synthesis of amides from aldehydes.



Scheme 1. a) *o*-Nitrophenyl hydrazonyl bromide and tetrazoles as latent active esters. b) One-pot amidation of aldehydes. c) This work: eAmidation of aldehydes.

Additionally, our laboratories and other research groups have independently reported the electrochemical oxidation of hydrazones in the synthesis of various heterocycles, including oxadiazoles, pyrazoles, and pyrazolines.[24,25] On this basis, it was reasoned that a more sustainable amide coupling reaction may be possible by generating the reactive nitrile imine species through an electrochemical manifold. This would benefit from environmentally benign conditions and obviate the use of stoichiometric oxidants.[26–29] Given that amines are susceptible towards oxidation, this was considered to be a major challenge for an electrochemical amidation (eAmidation) reaction at the outset of this work.[30–32] To mitigate the potential for poor functional group compatibility, redox mediators have commonly been utilised in the literature.[33,34] This enables lower electrode

potentials to furnish mild reaction conditions. An indirect electrolysis was, therefore, proposed for the current study to convert aldehydes into amides, either through the formation of the HOBt ester or the acyl diazene (Scheme 1). Accordingly, a protocol for a one-pot eAmidation of aldehydes and the investigations into its reaction mechanism are described herein.

Results and Discussion

Reaction Optimisation

The development of the eAmidation began by adapting the reaction conditions of our previous work in oxadiazole synthesis and applying those conditions on the 2-nitrophenyl hydrazone **1a** (Figure 1a).[25] Using the ElectraSyn 2.0, these initial conditions gave limited amide formation and attempts to improve the reaction with minor changes in the reaction parameters, such as electrode and solvent, were unsuccessful. Despite the low yields, the formation of product was promising and confirmed that the proposed electrochemical approach to amide bond formation was feasible. During these initial studies, it was found that the reaction temperature influenced the variability of the results. Higher temperatures provided greater consistency and further optimisation was performed at an elevated temperature of 40 °C, which was achieved using the IKA ElectraSyn GOGO Module and a heating block.

Given the limited success with DABCO as the redox mediator, subsequent efforts were focussed on the identification of an alternative (Figure 1b). The majority of mediators screened were incompatible, however, the use of the less sterically hindered *N*-oxyl radicals ABNO (9-azabicyclo[3.3.1]nonane *N*-oxyl) and AZADO (2-azaadamantane *N*-oxyl) gave a substantial increase in yield, with the latter affording the best conversion.[35–38] Furthermore, doubling the stoichiometry of the AZADO mediator led to an isolated yield of 90%. With the increase in the amount of mediator employed, a greater total charge of 8 F mol^{-1} was required to achieve complete reaction.

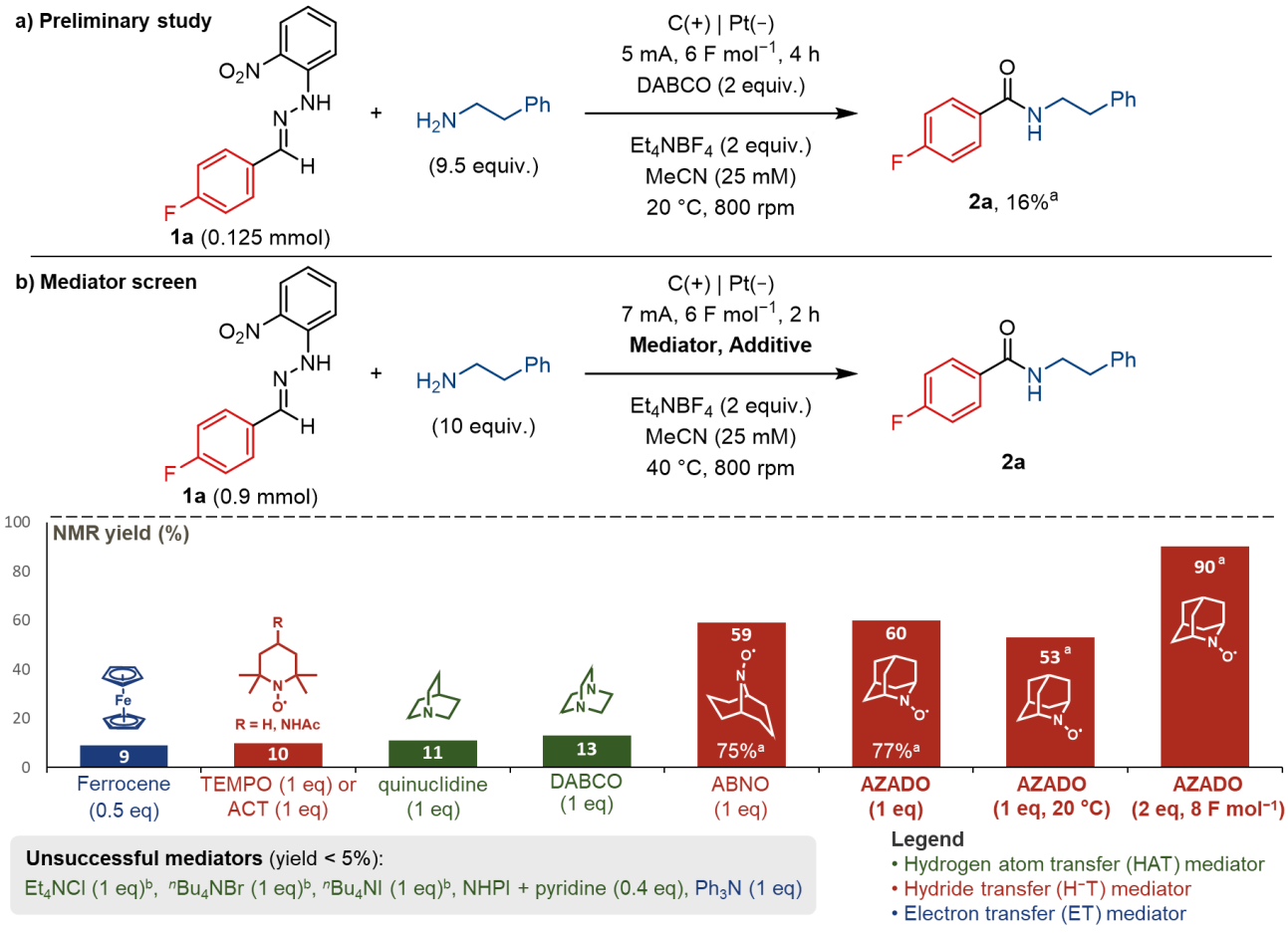
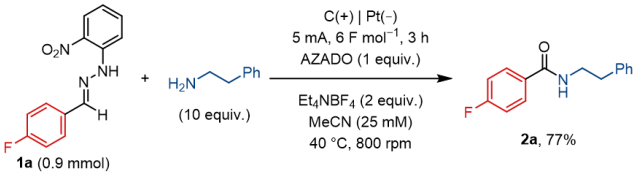


Figure 1. a) Preliminary study into the eAmidation. b) Mediator screen for the optimisation of eAmidation. Yields determined by ^{19}F NMR spectroscopy. [a] isolated yield [b] Instead of Et_4NBF_4. C = graphite, NHPI = *N*-hydroxyphthalimide.

A reduction in the amine stoichiometry unfortunately led to a drop in the yield (Table 1, Entries 1 and 2). This may be due to the low oxidation potential of amines, resulting in a competing oxidation process which depletes the nucleophile.[29,33,39] It is possible that the amine may be acting as both a reactant and a base, therefore, the use of base additives was examined. Of these, only DABCO gave comparable yields, and the reaction did not tolerate the addition of pyridine, DMAP, triethylamine, nor sodium carbonate. The addition of DABCO enabled higher yields when using lower amine stoichiometries (Table 1, Entries 3–5), however, this did not give further improvement with larger excesses of amine. Nonetheless, it was useful to have identified a suitable base for free basing amines supplied as an ammonium salt.

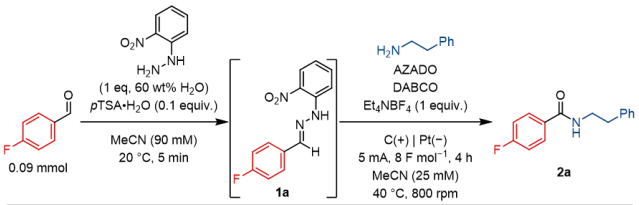
Table 1. Investigation of amine stoichiometry and base additives. Yields refer to isolated yields.



Entry	Deviation from above conditions	Yield (%)
1	Amine (5 equiv.)	61
2	Amine (1.5 equiv.)	37
3	Amine (10 equiv.), addition of DABCO (1 equiv.)	70
4	Amine (5 equiv.), addition of DABCO (1 equiv.)	71
5	Amine (1.5 equiv.), addition of DABCO (1 equiv.)	58

It was of interest to employ aldehydes rather than hydrazones as the starting material, thus, having identified conditions for the electrolysis, a one-pot protocol was next investigated. The initial hydrazone formation step between the aldehyde and 2-nitrophenyl hydrazine was found to be slow and as such, an acid catalyst may be beneficial to improve the rate of reaction. Unfortunately, the mild acetic acid did not have a significant effect on the rate of hydrazone formation and thus, a strong acid was required. The solid *p*-toluene sulfonic acid (*p*TSA) was chosen for practical reasons, however, other strong acids, such as HCl and trifluoroacetic acid (TFA), were also competent to rapidly convert the aldehyde to the hydrazone. This intermediate was then electrolysed without isolation and pleasingly, the amide product could be afforded in almost quantitative yields (Table 2, Entry 1). It was also found that the stoichiometry of AZADO and the electrolyte could be lowered, without detriment to the reaction outcome (Table 2, Entry 2). In addition, preliminary studies on the scope showed that DABCO did not have a significant effect on the yield for more challenging substrates, nor when less amine coupling partner was used (Table 2, Entries 3 and 4). As high yields could still be achieved in the absence of DABCO, this additive was, therefore, not included as part of the general procedure when exploring the substrate scope.

Table 2. Investigations into a one-pot eAmidation. Yields refer to isolated yields.



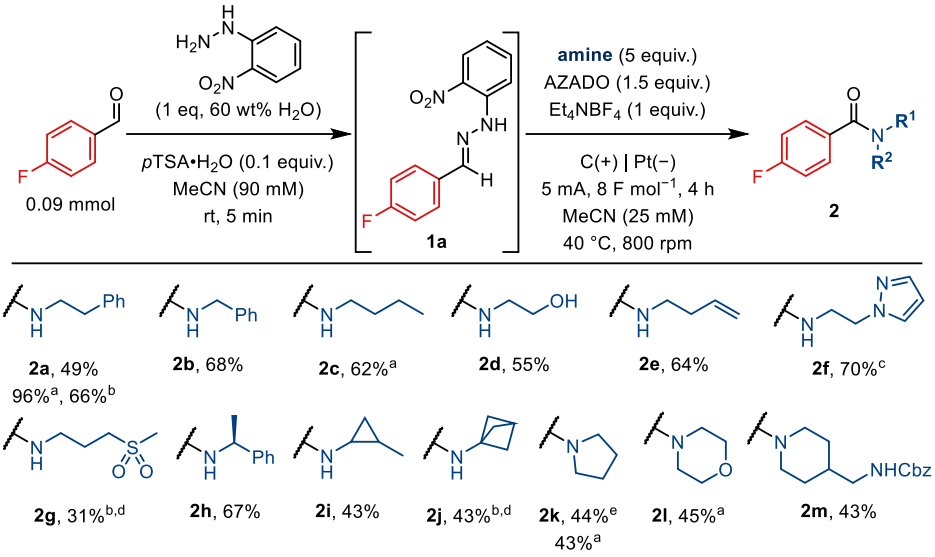
Entry	Deviation from above conditions	Yield (%)
1	Amine (10 equiv.), AZADO (2 equiv.), DABCO (1 equiv.)	98
2	Amine (10 equiv.), AZADO (1.5 equiv.), no DABCO	96
3	Amine (5 equiv.), AZADO (1.5 equiv.), DABCO (1 equiv.)	74
4	Amine (5 equiv.), AZADO (1.5 equiv.), no DABCO	49

Substrate Scope

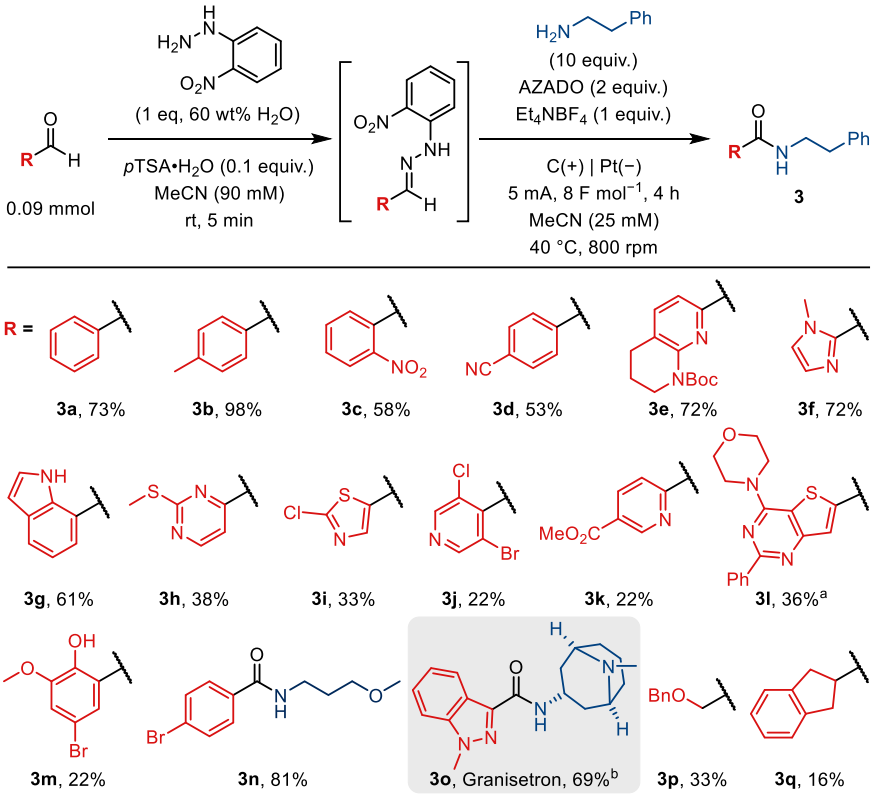
With a robust set of reaction conditions established, the scope of the emerging eAmidation process was examined, and a broad selection of alkyl amines were shown to be compatible (Scheme 2). In the case of **2a**, a larger excess of amine afforded a higher yield, however, many other amides could be synthesised with moderate to good yields using a lower stoichiometry of 5 equivalents of the amine nucleophile. Primary amines generally gave greater success, although several secondary amines (**2k**, **2m**) as well as the more sterically hindered α-secondary and tertiary alkyl amines (**2i**, **2j**) were also tolerated. A diverse range of functionalities were compatible including groups that may be more susceptible towards oxidation, such as unprotected alcohols (**2d**), benzylic systems (**2b**, **2h**), and pyrazole (**2f**). Additionally, amides containing an alkene (**2e**), ether (**2l**), and alky sulfone (**2g**) could also be accessed using this eAmidation approach. Aniline derived species were not competent substrates in the reaction, presumably due to their reduced nucleophilicity and propensity towards oxidation.

In relation to the aldehyde scope, a raft of aryl aldehydes could be converted to the corresponding amides with good to excellent yields (Scheme 3). This ranged from simple phenyl groups (**3a**, **3b**) to those with electron-withdrawing substituents, such as the nitro (**3c**), nitrile (**3d**), and ester (**3k**) groups. Despite the increased susceptibility of electron-rich functionalities towards oxidation, it was pleasing to note that phenol **3m** was tolerated in the reaction. A variety of heterocycles were also compatible, including the electron-deficient naphthyridine (**3e**), as well as more electron-rich heteroarenes, such as imidazole (**3f**) and indole (**3g**). This extended to more complex heteroaromatic systems including the pyrimidine (**3h**) and thienopyrimidine (**3l**). In a number of cases, the comparatively low yields observed are believed to be attributed to the limited solubility of the hydrazone intermediates in the reaction milieu.

Halide substituents were shown to be tolerated as well, with the successful synthesis of amides with the chloro-thiazole (**3i**) and bromophenyl (**3n**) substituents. In the case of *ortho*-substituted aryl halides (**3j**), these generally saw reduced yields. As the aryl bromide **3n** was obtained with a high yield of 81%, the diminished yields for the *ortho*-halides may result from the increased sterics of this position around the reactive site.



Scheme 2. Amine Scope. Yields refer to isolated yields. [a] 10 equiv. amine; [b] Where amine was used as a HCl salt, DABCO (5 equiv.) was also added; [c] 7 F mol^{-1}; [d] 12 F mol^{-1}; [e] 6 F mol^{-1}.



Scheme 3. Aldehyde Scope. Yields refer to isolated yields. [a] 24 F mol^{-1}; [b] amine (5 equiv.).

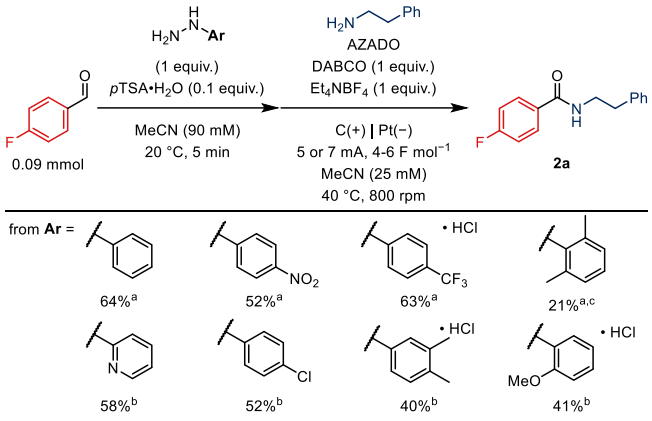
Similarly, alkyl aldehydes were comparatively poorer performing substrates and typically gave lower product yields (**3p**, **3q**). In the case of enolisable aldehyde substrates, the formation of the desired hydrazone intermediate was not straightforward. Under the acid catalysed conditions, it is conceivable that the hydrazones could undergo rapid tautomerisation to their enamine-derived counterparts. These electron rich species may then be susceptible to undesired oxidation. In addition, some of

these substrates were observed to undergo an aldol-type coupling with unreacted aldehyde.

Overall, the substrate scope examined suggests that the methodology exhibits broad compatibility with a diverse range of functional groups. In particular, the eAmidation approach was applied to the synthesis of the 5-HT_3 antagonist granisetron (**3o**).[40,41] This product was obtained with a good yield, which compares favourably with the yield of that in the original report (65%), where the amide was synthesised *via* the acid chloride.[42] The tolerance for the electron-rich indazole and the presence of multiple amines that may be oxidatively labile serve to further underline the mild nature of the method. Together with the wide functional group tolerance, the synthesis of this biologically active exemplar demonstrates the utility of the methodology, especially in a medicinal chemistry setting.

Control Experiments and Mechanistic Analysis

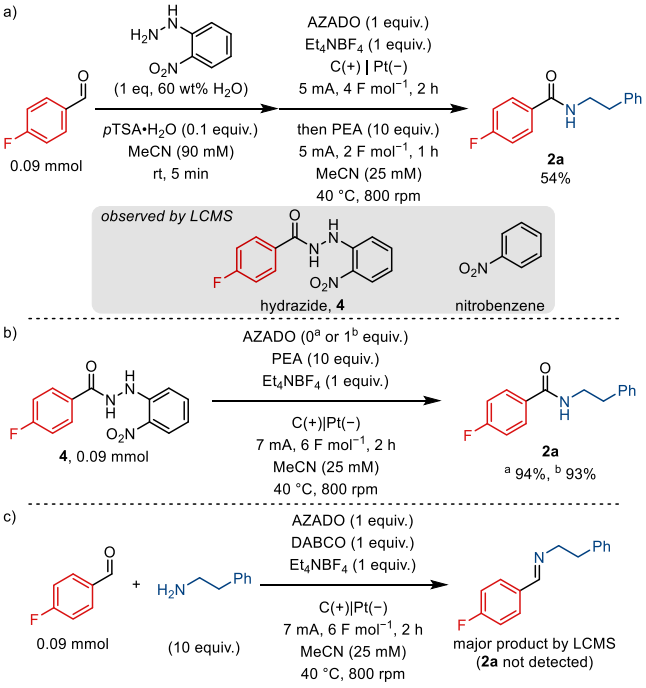
Based on the known reactivity of nitrile imines, two potential reaction pathways in which the eAmidation can proceed include the formation of a HOBt ester *via* a 1,7-rearrangement or formation of the acyl diazene.[21–23] As the 1,7-rearrangement cannot take place without the 2-nitro substituent, to probe this a negative control experiment was conducted by exploration of the *N*-aryl substituents of the hydrazone (Scheme 4). This study showed that amide formation still occurs even in the absence of the *ortho*-nitro group, albeit with reduced yield, which would suggest the reaction proceeds through an alternative mechanism distinct from the initially established rearrangement process.



Scheme 4. Effect of different *N*-aryl substituents on the eAmidation. Yields refer to isolated yields of **2a**. [a] From isolated hydrazone, AZADO (1 eq), amine (10 eq); [b] AZADO (1.5 eq), amine (2.5 eq). [c] 10 mA, 8 F mol^{-1}.

The reaction was performed with the delayed addition of phenethylamine (PEA) to examine how the hydrazone changes upon electrolysis (Scheme 5a). This resulted in a complex reaction profile as determined by LCMS. Within this mixture, hydrazide **4** was identified as one of the components, likely formed from the oxidation of the incipient nitrile imine which is generated electrochemically from the hydrazone as demonstrated recently by Waldvogel and co-workers.[24] When PEA was subsequently added to this reaction mixture, amide formation was observed, however, the yield was lower compared to reactions where amine was added prior to electrolysis. This may suggest that key intermediates readily decompose under the electrochemical conditions and require trapping with an amine as the reaction progresses. In addition to the observed hydrazide, nitrobenzene was found to be a consistent by-product for the reactions that afforded amide. The presence of both hydrazide and nitrobenzene supports a reaction pathway that involves the formation of an intermediate acyl diazene. This reaction mechanism is consistent with the previous report from our laboratories concerning aldehyde amidation using Oxone®.[23]

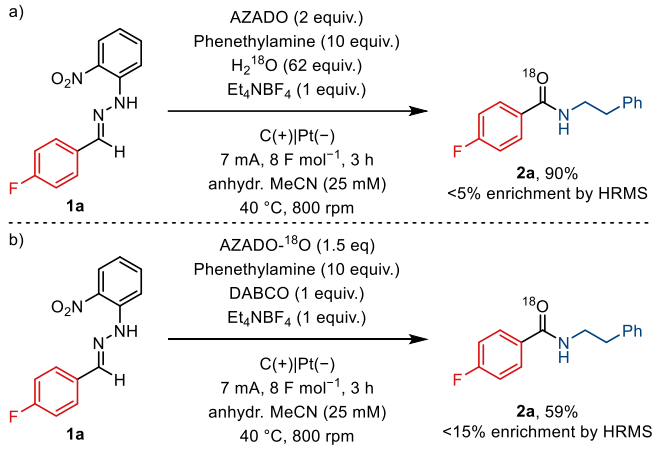
Consequently, the electrolysis of hydrazide **4** was conducted to validate its role as an intermediate (Scheme 5b). This experiment demonstrated that the hydrazide is a competent intermediary species in the formation of amide, as near quantitative yields were obtained. Interestingly, similar yields were obtained both in the presence and absence of AZADO, suggesting that the hydrazide can likely undergo direct oxidation to the acyl diazene at the anode. In addition, the amidation reaction was attempted directly from the aldehyde in the absence of the arylhydrazine component (Scheme 5c). For this reaction, LCMS analysis showed that the corresponding imine was the major product, and no amide formation was observed. As the reaction does not appear to proceed *via* the oxidation of a hemiaminal or imine intermediate, this confirms the need for the hydrazone to serve as an auxiliary. Although various arylhydrazines could be used to form the hydrazone, the hydrazine of choice was 2-nitrophenylhydrazine which afforded higher yields. As the addition of the amine to the acyl diazene generates an aryl anion, the improved yield may be due to the stabilisation of the anion by the *ortho*-electron withdrawing group.



Scheme 5. Mechanistic studies to elucidate reaction intermediates: a) delayed addition of amine after 4 F mol^{-1} had been passed; b) from hydrazide **4** in the

presence or absence of AZADO; c) from the aldehyde in the absence of hydrazine or hydrazone.

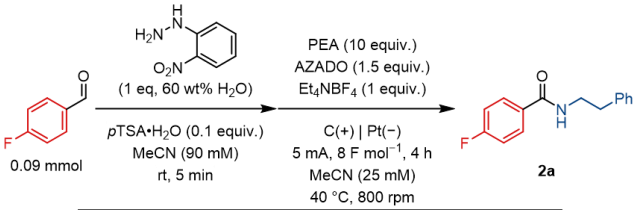
As it is postulated that the hydrazone is converted into a nitrile imine, the hydrolysis of this intermediate is a possible mechanism for the formation of the hydrazide. To verify this, the reaction mixture was doped with $H_2{}^{18}O$, however, limited isotopic labelling was observed (Scheme 6a). Other potential sources of the carbonyl oxygen include the mediator and molecular oxygen. When the reaction was performed using oxygen-18 enriched AZADO, minimal ^{18}O-incorporation was again observed (Scheme 6b).



Scheme 6. Isotopic labelling experiments with a) water-^{18}O and b) AZADO-^{18}O.

Conversely, conducting the electrolysis under a nitrogen atmosphere resulted in a reduced yield, which suggests that oxygen plays a role in the reaction (Table 3, Entry 3). Given that the carbonyl oxygen is not derived from water or AZADO, it is possible that molecular oxygen facilitates the oxidation of the nitrile imine. Although the exact role that this plays requires further investigation, examples of the autooxidation of hydrazone under oxygen atmospheres have previously been reported.[43–46] It was determined, however, that for the eAmidation reaction, oxygen in air alone is insufficient to initiate the oxidation of the *N*-nitrophenyl hydrazone. This was evidenced by additional control experiments which confirm that the reaction is driven through an electrolytic process, as no reaction occurs in the absence of a current (Table 3, Entry 1). Similarly, although direct oxidation can still occur, the removal of the mediator leads to a diminished yield demonstrating the poor efficiency compared to the mediated reaction (Table 3, Entry 2).

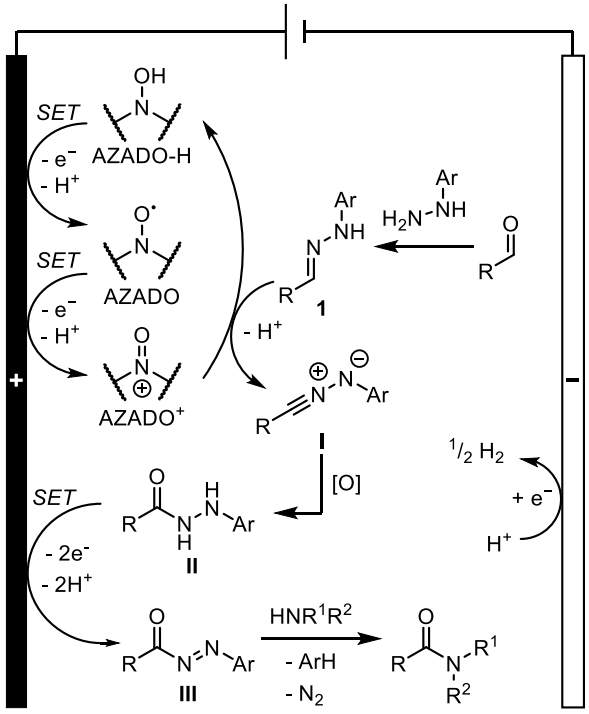
Table 3. Control experiments.



Entry	Control experiments	Yield (%)
1	No current	0
2	No AZADO	14[a]
3	Under N_2	3[b]

[a] From isolated hydrazone; isolated yield; [b] AZADO (1 equiv.), LCMS area %.

Based on these observations a potential mechanism has been proposed (Scheme 7). Starting with the aldehyde, condensation with the arylhydrazine forms the corresponding hydrazone. Next, AZADO is oxidised at the anode to the oxoammonium (AZADO$^+$) which can subsequently react with the hydrazone to give a nitrile imine (**I**) in a hydride transfer step. The nitrile imine is then converted to the hydrazide (**II**) *via* a process in which an oxygen-derived species is presumed to be involved. Intermediate **II** can then undergo an anodic oxidation to form the acyl diazene (**III**). This acylating species is then trapped by the amine to afford the amide product. The hydroxylamine AZADO-H can be oxidised at the anode back to the *N*-oxyl radical and oxoammonium ion. This proposed mechanism aligns with our previously reported aldehyde amidation,[23] as well as other related studies involving the oxidative cleavage of aryl hydrazides.[47–52]



Scheme 7. Proposed mechanism for the eAmidation.

Conclusion

In conclusion, a method to convert aldehydes to amides has been developed using a one-pot, indirect electrolysis which has wide substrate compatibility. The reaction proceeds *via* the *in situ* formation of an intermediate hydrazone which can undergo a mediator-assisted electrochemical oxidation. Mechanistic analysis suggests that the reaction proceeds through the formation of a hydrazide and its subsequent oxidation to the acyl diazene which acts as the acylating species. The eAmidation makes use of mediated electrolysis to achieve mild reaction conditions and greater functional group compatibility, enabling the synthesis of a selection of amides bearing pharmacologically relevant functional groups, including the marketed drug product granisetron (**3o**).

Experimental

The general procedure for the amide synthesis is given below. For full details and characterisation data, see Supporting Information.

General Procedure for Amide Synthesis:

To a 5 mL ElectraSyn 2.0 reaction vessel containing a stirrer bar, (2-nitrophenyl)hydrazine (60% wt, 23.2 mg, 90 µmol, 1 equiv.), aldehyde (90 µmol, 1 equiv.), and *p*-toluenesulfonic acid monohydrate (1.7 mg, 9 µmol, 0.1 equiv.) were added, followed by acetonitrile (1 mL). The reaction mixture was stirred at room temperature for 5 min or until hydrazone formation was complete. AZADO (20.5 mg, 135 µmol, 1.5 equiv.), tetraethylammonium tetrafluoroborate (19.6 mg, 90 µmol, 1 equiv.), and amine (5 or 10 equiv.) were added to the reaction mixture, followed by acetonitrile (2.6 mL). For amines used as a hydrochloride salt, DABCO (50.5 mg, 450 µmol, 5 equiv.) was also added at this stage. The reaction mixture was electrolysed under a constant current of 5 mA at 40 °C with a graphite anode and a platinum foil cathode, stirring at 800 rpm until a total charge of 8 F mol^{-1} had been passed. The electrodes were rinsed with MeOH (~2 mL) into the reaction mixture and the reaction mixture was concentrated *in vacuo* and purified by column chromatography.

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Keywords: Amides • Electrochemistry • Hydrazones • Indirect Electrolysis • Oxidation

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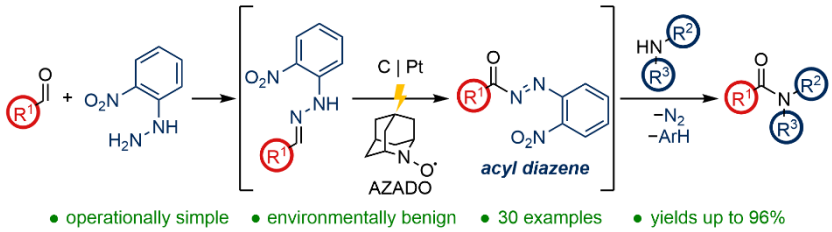

The indirect electrochemical oxidation of *N*-aryl hydrazones offers an efficient approach to access amides from aldehydes and amines. The AZADO-mediated reaction enables the selective synthesis of a broad range of valuable amides using readily available aldehydes.

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