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Electrochemical synthesis of isobenzofuran-1-imines using oxidative halocyclization of *o*-alkynylbenzamides†

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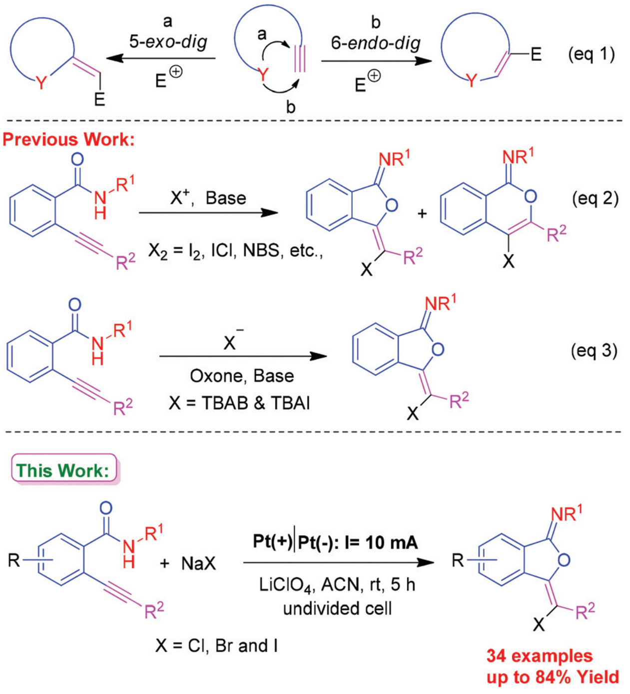
Electrochemical oxidative 5-*exo*-*dig*-oxo-halocyclization of *o*-alkynylbenzamides was achieved using readily available NaX (X = Cl, Br and I) salts under mild reaction conditions. The use of a cheap and highly stable sodium halide as a halide ion source is impressive for the synthesis of a variety of halogenated isobenzofuran-1-imines. This electrochemical protocol shows regioselectivity and excellent conversion to isobenzofuran-1-imines in good yields without the use of stoichiometric amounts of oxidants and transition metal catalysts.

Introduction

The halocyclization of functionalized alkynes has been a versatile tool for the synthesis of several important heterocyclic and carbocyclic compounds.[1–5] In general, this kind of cyclization reaction is achieved by the reaction of alkynes with an electrophile followed by an intramolecular *N*- and *O*-nucleophilic attack on the cationic intermediate *via* 5-*exo*- or 6-*endo*-*dig* cyclization (Scheme 1, eqn (1)).[6–13] Over the past decade, a variety of halogenated oxo-cyclization reactions of *o*-alkynylbenzamides have been reported using electrophilic halogen sources such as I_2, ICl, and NBS, leading to both halogenated isobenzofuran-1-imines (5-*exo*-*dig*) and isochromen-1-imines (6-*endo*-*dig*) (eqn (2)).[14,15] In recent years, the use of cheap and highly stable halide salts as a halogen source has gained significant attention in the cyclization reactions[16] and also owing to the structural importance of isobenzofuran-1-imines.[5,17] Interestingly, Wang *et al.* have reported a regioselective 5-*exo*-*dig*-*oxy* cyclization of *o*-alkynylbenzamides using TBAB and TBAI with a stoichiometric amount of oxidant and base (eqn (3)).[18,19] To avoid the use of a stoichiometric amount of oxidant and base, the development of a simple, mild and alternative method for the halogenated 5-*exo*-*dig*-*oxy*-cyclization of *o*-alkynylbenzamides with high atom economy is highly desirable.

Electrochemical synthesis has attracted significant attention in organic synthesis because it is environment friendly, shows excellent atom economy and replaces oxidants, transition metals, and ligands.[20–22] In particular, halogen-mediated electrochemical synthesis is an emerging area as it involves the anodic oxidation of the halide anion into X^+, $X^\bullet$ and X_2 and the cathodic reduction of protons to hydrogen.[23,24] Moreover, these halogen species are believed to play a key role in the selective formation of C–C, C–N, C–O, and C–S bonds in



Scheme 1 5-*exo*-*dig*-oxo-cyclization of *o*-alkynylbenzamides.

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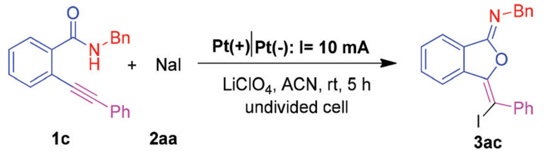
electrochemical processes and dehydrogenation in atom economical and sustainable methods.[25–32] Recently, our group has developed visible light initiated cyclization reactions *via* a radical pathway.[33–35] To the best of our knowledge, there is no report on the synthesis of these target molecules *via* dehydrogenative cyclization under electrochemical conditions. We wish to report an oxidative 5-*exo-dig-oxy*-cyclization of *o*-akynylbenzamides for the synthesis of isobenzofuran-1-imines using NaX salts under electrochemical conditions (Scheme 1).

Results and discussion

We chose *N*-benzyl-2-(phenylethynyl)benzamide (**1c**) and NaI (**2aa**) as the model substrates to explore the electrochemical conditions in an undivided cell (Table 1). Initially, the reaction was performed in an undivided cell at a constant current of 10 mA in the presence of $LiClO_4$ as the electrolyte and CH_3CN as a solvent. After 5 h, the desired product halogenated isobenzofuran-1-imine **3ac** was obtained with 84% yield (Table 1, entry 1). Other iodide salts, such as KI and ^{n}Bu$_4$NI, were found to be less efficient than NaI (Table 1, entries 2 and 3). Also, the effect of solvents including THF, ACN : H_2O, and MeOH was tested under the optimized conditions, affording a moderate yield of **3ac** (Table 1, entries 4–6). Furthermore, on replacing the electrolyte $LiClO_4$ with ^{n}Bu$_4$NClO$_4$, **3ac** was obtained in 44% yield. However, the absence of electrolytes also afforded product **3ac** in 34% yield. Changing the current was found to reduce the reaction performance (Table 1, entries 9–11). There is no significant improvement in the yield of **3ac** when replacing the electrodes, C(+)|Pt(−), RVC(+)|Pt(−) and C(+)|C(−) (Table 1, entries 12–14). Notably, no product was observed without an electric current. The result indicates the need for a constant current in the reaction.

Table 1 Optimization table for the synthesis of isobenzofuran-1-imines from *o*-alkynylbenzamides[a,b]



Entry	Variation from the standard conditions	Yield[b] (%)
1	None	84[c]
2	KI instead of NaI	81
3	^{n}Bu$_4$NI instead of NaI	78
4	THF instead of ACN	45
5	ACN : H_2O (1 : 1) instead of ACN	31
6	MeOH instead of ACN	Trace
7	^{n}Bu$_4$NClO$_4$ instead of $LiClO_4$	44
8	Absence of $LiClO_4$	34
9	5 mA instead of 10 mA	55
10	8 mA instead of 10 mA	71
11	12 mA instead of 10 mA	84
12	C(+)|Pt(−) instead of Pt(+)|Pt(−)	46
13	RVC(+)|Pt(−) instead of Pt(+)|Pt(−)	44
14	C(+)|C(−) instead of Pt(+)|Pt(−)	38
15	Without an electric current	n.r.

[a] Reaction conditions: 0.15 mmol (**1c**), 0.22 mmol (**2aa**), $LiClO_4$ (0.3 M), ACN (8.0 mL), a Pt disk (80 mm × 6.3 mm × 2 mm) anode, a Pt wire (70 mm × 6.3 mm × 0.5 mm) cathode, rt, 10 mA, 12 F mol^{-1}. [b] Yields were determined after the purification of the compound. [c] Current efficiency η = 27%. n.r. = no reaction.

Encouraged by these promising results, a diverse array of 3-iodo-isobenzofuran-1-imine derivatives were explored using different substituted *o*-alkynylbenzamides with NaI **2aa** under the optimized conditions as shown in Table 2. The substrate scope of various *N*-substituted (**R^1**) derivatives was examined. A variety of aliphatic (**1a–1e**) *N*-substituted *o*-alkynylbenzamides smoothly underwent intramolecular cyclization with NaI **2aa**, affording the corresponding products **3aa–3ae** in 79–84% yields. Different aryl group *N*-substituted *o*-alkynylbenzamides (**1f–1l**) also reacted smoothly to furnish the corresponding products **3af–3al** in 66–74% yields. Furthermore, we studied the substituent effect of the alkyne (**R^2**) group in *o*-alkynylbenzamides; both aliphatic (**1m–1p**) and aromatic (**1q–1s**) alkynes were reacted with NaI to afford the corresponding 3-iodo-isobenzofuran-1-iminines **3am–3as** in 68–78% yields. Bromo substituted *o*-alkynylbenzamide **1t** also gave the product **3at** in 69% yield. In contrast, *o*-alkynylbenzamide **1au** and *N*,*N*′-disubstituted *o*-alkynylbenzamide **1av** failed to produce **3au** and **3av**, respectively.

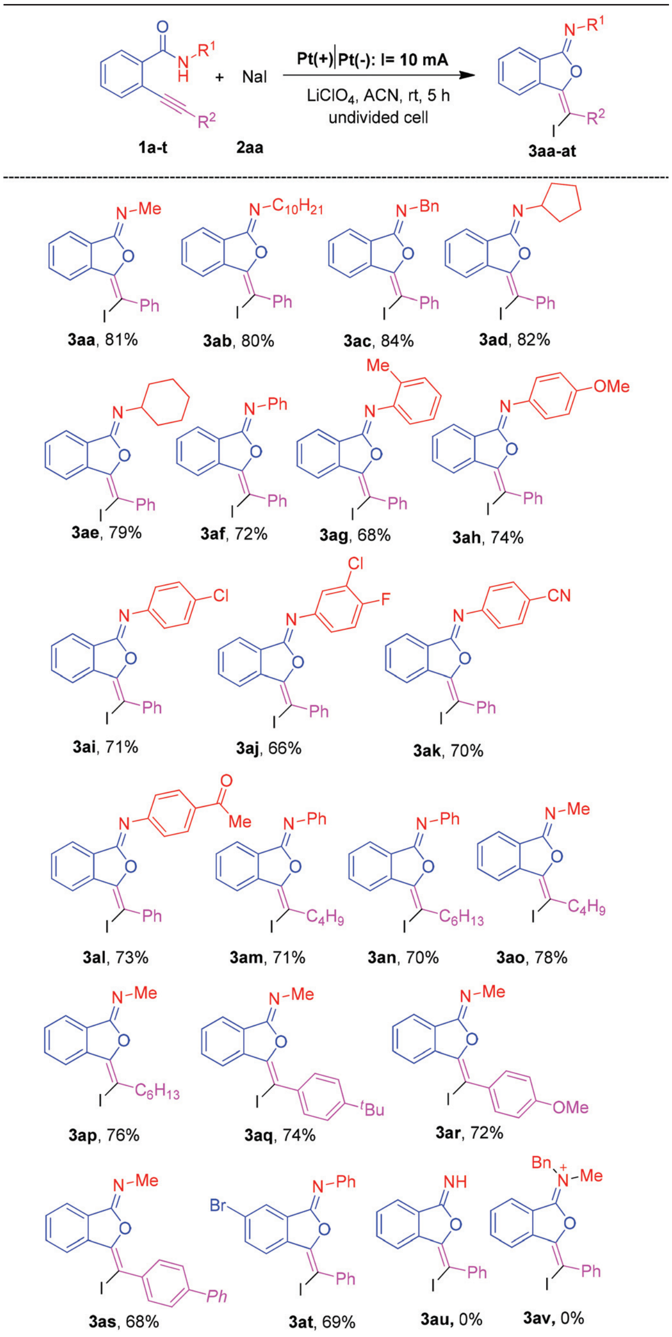
Next, we investigated the scope of different *o*-alkynylbenzamides with NaBr **2ba** for the synthesis of 3-bromo-isobenzofuran-1-imines and the results are shown in Table 3. The various *N*-substituted (**R^1**) *o*-alkynylbenzamides (**1a–1g**) were successfully tested with NaBr **2ba** under electrolytic conditions, affording the corresponding 3-bromo-isobenzofuran-1-iminines **3ba–3dg** in 61–77% yields. Furthermore, different alkyne (**R^2**) substituted *o*-alkynylbenzamides also smoothly reacted with NaBr **2ba** to yield the corresponding products **3bh–3bk** in 66–71% yields. Furthermore, we screened halogen substituted *o*-alkynylbenzamides in this electrochemical cyclization to afford the corresponding products **3bl** and **3bm** with good yields. Notably, NaBr **2ba** shows less efficiency for halocyclization under the optimized conditions and also produced slightly lower yields than NaI **2aa**.

The synthetic utility of 3-halo-isobenzofuran-1-imines **3ae** and **3be** was studied by coupling them with phenylacetylene in a palladium-catalyzed Sonogashira cross-coupling reaction, which afforded the coupled product **4** in good yields, respectively. The acid hydrolysis of **3ae** and **3be** afforded the corresponding isobenzofuran products **5** and **6** with good yields (Scheme 2).

The scale-up reaction was performed for the halogen mediated electrochemical halocyclization reaction. Under the optimized conditions, 1.24 g of **1c** (4.0 mmol) afforded the product **3ac** in 71% (1.23 g) yield (Scheme 3).

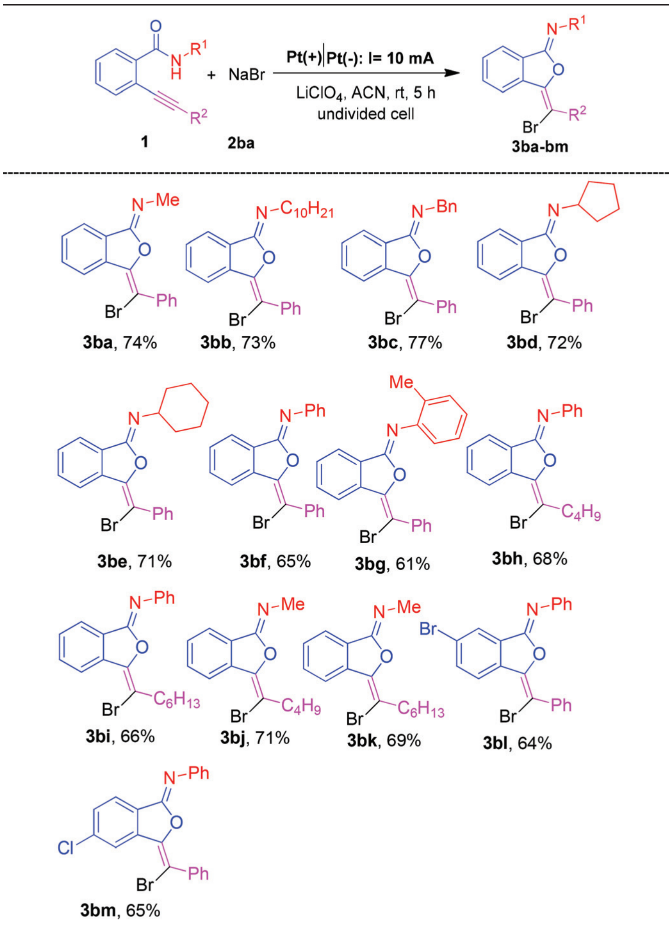
The control experiments were carried out to study the reaction mechanism as shown in Scheme 4. First, the optimized reaction was performed with the addition of 2,2,6,6-tetramethylpiperidinooxy (TEMPO) as a radical scavenger, which afforded the product **3ac** in 0% yield (Scheme 4a). The results imply that

Table 2 Substrate scope of *o*-alkynylbenzamides for the synthesis of 3-iodo-isobenzofuran-1-imines[a,b]

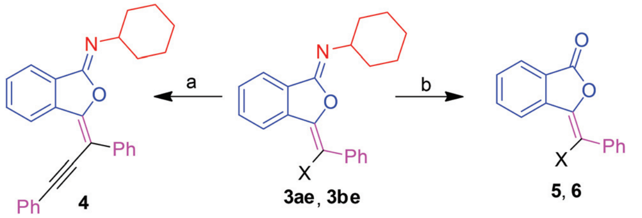


[a] All reactions were carried out with 0.15 mmol (**1**), 0.22 mmol (**2aa**), $LiClO_4$ (0.3 M), ACN (8.0 mL), Pt(+)|Pt(−), rt, 5h. [b] Yields were determined after the purification of the compound.

Table 3 Substrate scope of *o*-alkynylbenzamides for the synthesis of 3-bromo-isobenzofuran-1-imines[a,b]



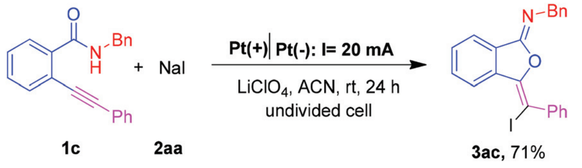
[a] All reactions were carried out with 0.15 mmol (**1**), 0.22 mmol (**2ba**), $LiClO_4$ (0.3 M), ACN (8.0 mL), Pt(+)|Pt(−), rt, 5 h. [b] Yields were determined after the purification of the compound.



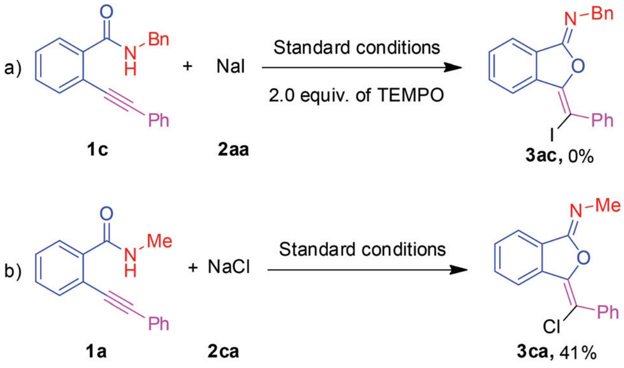
Scheme 2 Synthetic transformations of 3-halo-isobenzofuran-1-imines. Reagents and conditions: (a) Phenyl acetylene (1.2 equiv.), $PdCl_2(PPh_3)_2$ (5 mol%), CuI (2 mol%), Et_3N, 6 h, 70 °C, **4**, X = I, 89% and **4**, X = Br, 78%; (b) HCl (37% aq, 0.5 ml), THF : H_2O (1 : 1), 2 h, rt, **5**, X = I, 82% and **6**, X = Br, 81%.

the reaction might have proceeded *via* a radical pathway. Interestingly, NaCl **2ca** also reacted with **1a**, affording the corresponding cyclized product **3ca** in 41% yield (Scheme 4b).

Cyclic voltammetry (CV) experiments were performed to investigate the reaction mechanism using the attained redox potentials and the possible iodine-related active species (Fig. 1). All the experiments were conducted using a Pt(+)|Pt(−) electrode system with Ag/AgCl (in saturated KCl solution) as a reference electrode. Curve b, **1c** (in the absence of **2aa**) showed no oxidation and redox peaks. The CV of **2aa** alone had two oxidation peaks (curve c). The first peak at +0.365 mV corresponds to the conversion of iodide to triiodide and the second peak at +0.695 mV corresponds to the oxidation of



Scheme 3 Gram-scale synthesis of isobenzofuran-1-imines.



Scheme 4 Control experiments.

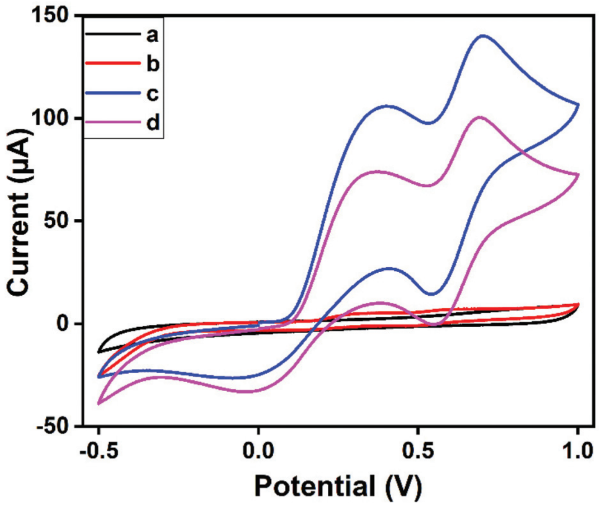
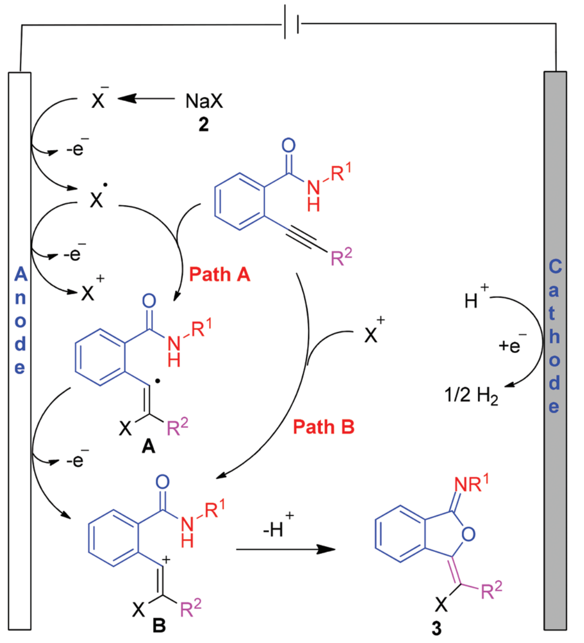


Fig. 1 Cyclic voltammograms of a mixture in 0.03 M $LiClO_4/CH_3CN$ using a Pt disk (80 mm × 6.3 mm × 2 mm) working electrode, Pt wire (70 mm × 6.3 mm × 0.5 mm) and Ag/AgCl (in saturated KCl solution) as counter and reference electrodes at a scan rate of 100 mV s^{-1}: (a) background, 0.3 M $LiClO_4$; (b) **1c** (0.15 mmol); (c) **2aa** (0.22 mmol); (d) **1c** (0.15 mmol) + NaI (0.22 mmol).

triiodide to iodine.[22,27] Notably, the CV of a mixture of **1c** and **2aa** (curve d) showed similar oxidation peaks with slightly lower potentials (+0.352 mV and +0.680 mV). Therefore, the CV studies clearly showed that NaI was oxidized by an electric current acting as an iodine source.

Based on all the aforementioned experimental studies, CV measurements, and literature reports, a plausible mechanism is proposed in Scheme 5.[20,36] On the surface of the anode, X^- is oxidized to $X^•$ by the loss of a single electron, which is further oxidized to X^+ by one more loss of a single electron. Then, *o*-alkynylbenzamide reacted with the *in situ* generated X^+ by electrophilic addition to afford alkenyl cation **B** (path B). At the same time, *o*-alkynylbenzamide reacted with the *in situ* generated $X^•$ by radical addition to form alkene radical **A** (path A), which on further oxidation reaction on the anodic surface afforded alkenyl cation **B** by the loss of a single electron. Finally, alkenyl cation **B** undergoes intramolecular cyclization *via O*-nucleophilic attack, affording products **3** by the loss of a proton. Meanwhile, the cathodic reduction of the proton led to the formation of hydrogen.



Scheme 5 Plausible mechanism pathway for the electrochemical halo-cyclization reaction.

Conclusions

In conclusion, we have developed an electrochemical oxidative 5-*exo*-*dig*-oxo-halocyclization of *o*-alkynylbenzamides for the synthesis of isobenzofuran-1-imines using readily available NaX salts. A simple and cheaper NaX (X = Cl, Br and I) salt acts as the halogen source under an applied current. This electrochemical protocol replaces the use of a stoichiometric amount of oxidants and transition metals. Owing to its simple operation, high atom economy, and excellent regioselectivity, this electrochemical protocol is an efficient approach and it can be an alternative method to avoid the use of oxidants and transition metals.

Conflicts of interest

There are no conflicts to declare.

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