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Electrochemical C–H functionalization reaction of N-heterocycles with alkyl iodides†

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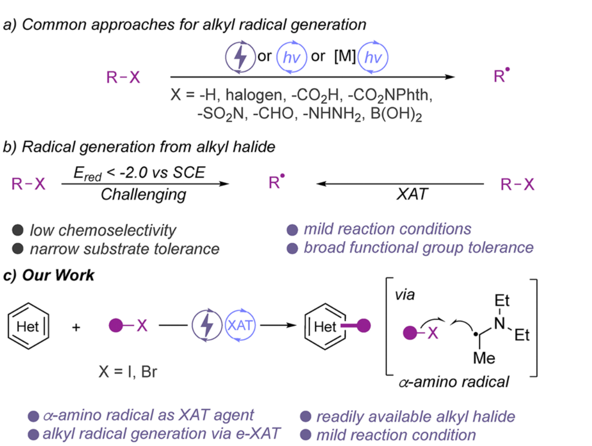
Herein, we report on an electrochemical protocol for the C–H alkylation of N-heterocycles with easily accessible alkyl halides. A wide range of azauracil derivatives including bioactive tethered azauracil, pyrazinone and quinoxalinone were well accommodated and delivered the alkylated products in good to excellent yield.

The direct functionalization of C–H bonds is one of the most straight-forward approaches to increase molecular complexity and to introduce new functional groups onto an existing molecular framework. In this context, C–H functionalization reactions of N-heterocycles are of particular interest owing to the widespread use of such building blocks in modern drugs and agrochemicals.[1] Current methods for the direct functionalization of N-heterocycles often proceed through the use of highly reactive intermediates, such as low-valent carbene or radical intermediates for the construction of new C–C bonds.[2–8] Such radical C–H functionalization reactions have recently attracted significant interest and today a range of different approaches to access the pivotal alkyl radical intermediate have been described.[2] Common approaches involve the utilization of suitable radical precursors, such as *N*-hydroxyphthalimide esters,[3] carboxylic acids,[4] or alkyl halides.[5] Besides these substrates, aliphatic aldehyde,[6] boronic acids,[7] or alkyl hydrazines[8] have also been documented for radical functionalization of N-heterocycles (Scheme 1a). Although these molecules have been utilized for alkylation reaction, the development of more sustainable and mild protocols by using more easily accessible radical precursor feed-stocks are highly desirable.

Among the radical precursors, alkyl halides dominate as one of the most readily accessible substrates that are commercially available or can be easily prepared from the corresponding alcohols. However, due to the low reduction potential ($E_{red} < -2$ V *versus* SCE) of alkyl halides, their application as radical precursors in chemical transformation poses a challenge in terms of compatibility with reacting partners.[9] This challenge could be overcome by employing halogen-atom transfer (XAT)[10] agents under mild reaction conditions, and the generation of alkyl radicals *via* SET[11] has been reported (Scheme 1b). In contrast, very recently, photoinduced palladium catalysis has been explored to activate alkyl halides for various alkylation reactions.[12] In this context, our group has demonstrated the radical C–H alkylation of N/O heterocycles using photoinduced metal catalysis.[13] Similarly, electrochemistry has recently opened a window to generate alkyl radicals from alkyl halides through an electrochemical halogen-atom transfer (e-XAT) strategy without compromising its efficiency and substrate compatibility.[14,15] To the best of our knowledge, this strategy has not been applied for the alkylation of heterocycles (Scheme 1c). Due to the mild and sustainable nature, we anticipated that the e-XAT strategy could be applied for the alkylation of N-heterocycles.

In the initial experiment, we performed the reaction of azauracil derivative **1a** with cyclohexyl iodide (**2a**) and triethyl



Scheme 1 Approaches for the radical C–H functionalization of heterocycles with alkyl halides.

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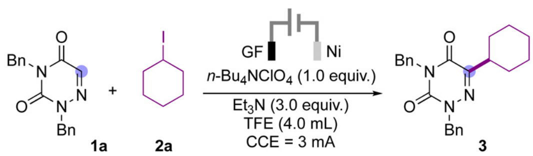
Table 1 Optimization of the reaction conditions[a]

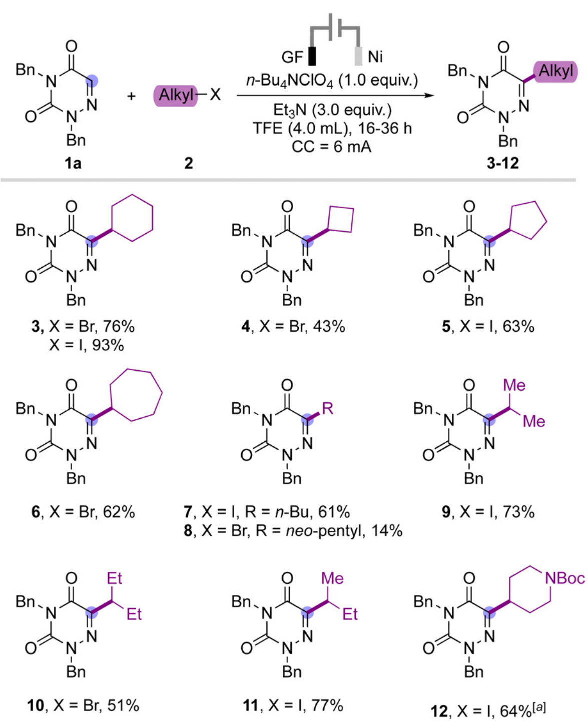


Entry	Deviation from the reaction conditions	Time (h)	Yield [%] of **3**
1	TBAI, graphite electrodes and MeCN as solvent	30	13
2	TBAI as electrolyte, and MeCN/CH_2Cl_2/THF/HFIP/TFE/MeOH/DMF as solvent	17–30	33/61/31/77/86/18/traces
3	None	30	90
4	$TBAPF_6$ instead of $TBAClO_4$	50	13
5	TBABr instead of $TBAClO_4$	30	69
6	DIPEA instead of Et_3N	42	53
7	Et_3N (1.0 equiv.) was used	42	82
8	**2a** (1.0 equiv.) was used	42	69
9	CCE at 6.0 mA	22	93(76)[b]
10	CCE at 9.0 mA	17	86

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (2.0 equiv.), n-Bu_4NClO_4 (1.0 equiv.) and Et_3N (3.0 equiv.) in TFE (4.0 mL) at rt under CCE of 3 mA. TFE (trifluoroethanol). TBA (tetrabutylammonium). [b] The yield in parentheses is with bromocyclohexane.

amine as an XAT agent under electrochemical conditions using graphite as the electrodes in acetonitrile solvent (Table 1, entry 1). To our delight we obtained the desired alkylation product **3** in 13% yield. With this positive result we exchanged the graphite cathode with a nickel electrode and the product yield was increased to 33% (Table 1, entry 2). We further evaluated various solvents using Ni-foam as the cathode and observed that trifluoroethanol proved to be the best solvent for this transformation to give the desired product in a yield of 86% (Table 1, entry 2). When the reaction was carried out in DMF, only trace amounts of the desired product were observed. Further screening of the electrolytes (Table 1, entries 3–5) for this transformation was carried out and revealed that n-tetrabutylammonium perchlorate ($TBAClO_4$) was superior to other electrolytes to afford the desired product in 90% yield (Table 1, entry 3). When using Hunig's base as an XAT agent, a reduced yield of the product was observed (Table 1, entry 6). Similarly, lowering the equivalents of triethyl amine provided a lower yield of the product (Table 1, entry 7). A sharp decrease in the yield of product **3** was observed on reducing the equivalents of alkyl iodide **2a** (Table 1, entry 8). Further increasing the current to 6 mA improved the yield and the product was isolated in 93% yield (Table 1, entry 10). However, at 9 mA current, the product was obtained in a lower yield (Table 1, entry 10).

After obtaining the optimized reaction conditions, we proceeded with the evaluation of the substrate scope by varying the alkyl halide component (Scheme 2). Both cyclic and acyclic alkyl bromide or –iodide were well accommodated in this transformation to provide the products **3–11** in moderate to good yield. The ring size of the cycloalkane shows a moderate effect on the yield as the cyclobutyl bromide provided the product **4** in lower yield compared to product **3** obtained from cyclohexyl bromide. Similarly, iodocycloalkanes provided the desired product in higher yield than the bromo analogue probably due to the lower bond dissociation energy of alkyl iodides. Cyclopentyl iodide gave the desired product **5** in 63% yield and cycloheptyl bromide also underwent a smooth transformation to provide product **6** in 62% yield. Also, acyclic primary and secondary alkyl bromides and iodides were well suited for this transformation and provided the products **7–11** in good yield. However, neopentyl bromide only gave the product **8** in 14% yield, which may be related to undesired side reactions of putative alkyl radical intermediates. Additionally, Boc-protected 4-iodopiperidyl was also tested under a slightly modified reaction condition to provide the product **12** in good yield. Limitations lie within the use of tertiary alkyl halides, which proved incompatible with the reaction conditions.



Scheme 2 Substrate scope with various alkyl halides. [a] The reaction was carried out at 3 mA for 72 h.

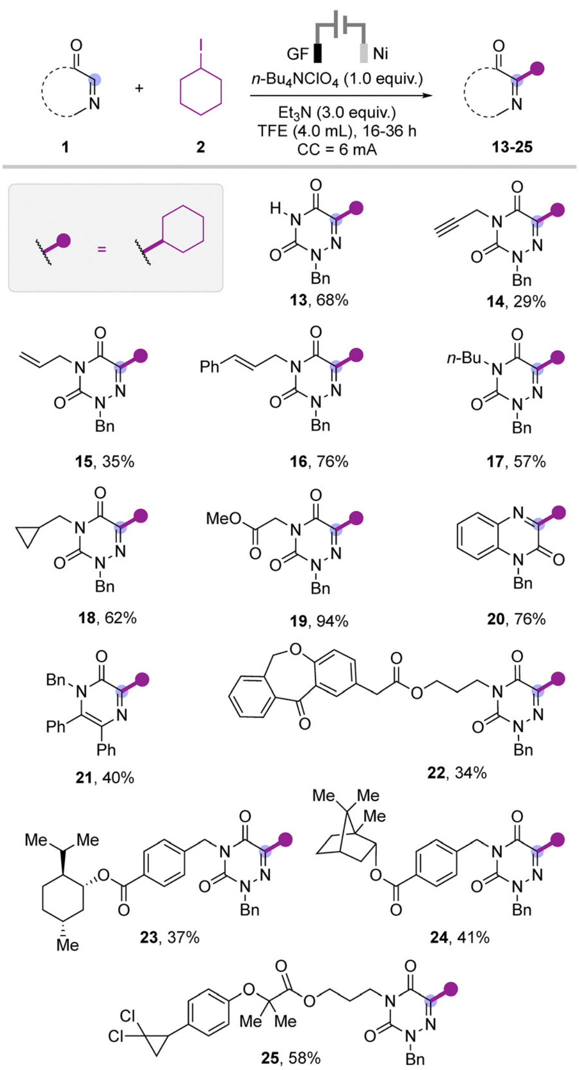
We then proceeded with the evaluation of the scope by changing the substituents on the heterocycle **1** (Scheme 3). The reaction of mono substituted azauracil also worked smoothly to deliver the product **13** in 68% yield. Furthermore, we varied the substitution on the *N*-benzyl azauracil such as propargyl, allyl, alkyl, cinnamyl, cyclopropyl and acetate that were well tolerated under the standard reaction conditions to provide the corresponding products **14–19** in moderate to excellent yield. In the case of propargyl and allyl bearing azauracil, the desired products **14** and **15** were isolated in moderate yields. In addition, quinoxaline and the pyrazine heterocycle were also well accommodated to deliver the corresponding products **20** and **21** in 76% and 40% yields, respectively. Furthermore, azauracil with *N*-bioactive tethered scaffolds such as isozepac, menthol, borneol and ciprofibrate were also tested under the optimized reaction conditions to afford the respective products **22–25** in moderate yields.

To demonstrate the applicability of the developed protocol, the reaction was performed at 1 mmol scale and the product was obtained in 54% yield (Scheme 4a). Additionally, aza-Michael addition of **13** with maleimide **26** under electrochemical conditions provided the product **27** in 72% yield (Scheme 4b). Furthermore, the NH insertion reaction of **13** with phenyl diazoacetate **28** was also performed under photochemical conditions[16] and the insertion product **29** was isolated in 67% yield (Scheme 4c).

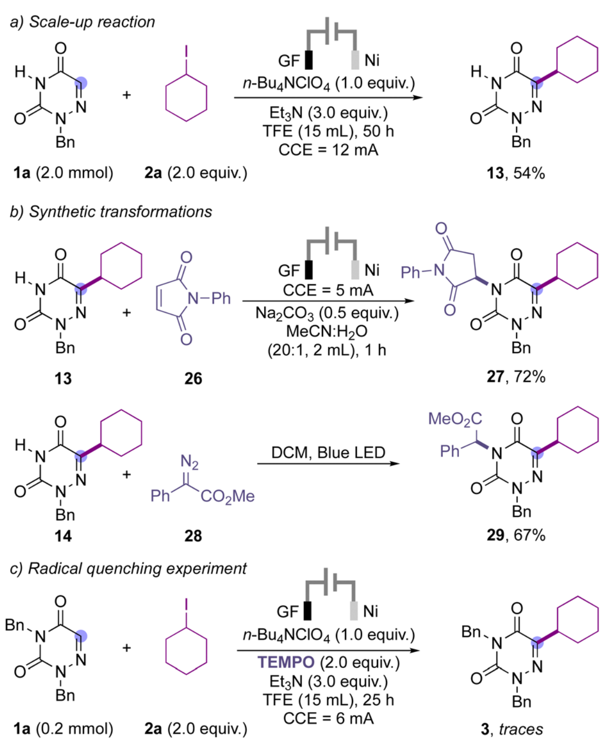
From the previously reported literature,[15] it is evident that triethyl amine acts as an XAT agent to generate the alkyl radical from the corresponding alkyl halide. This alkyl radical then adds onto the imine carbon, which upon subsequent oxidation delivers the alkylated product. To prove the radical nature of the electrochemical reaction, a radical quenching experiment was performed using TEMPO as a radical quencher, which resulted in complete suppression of the formation of product **3**, suggesting the radical nature of the reaction (Scheme 4c).

We consider that the reaction proceeds by initial oxidation of triethylamine under electrochemical conditions, followed by deprotonation to α-amino radical intermediate **Int-A**. Then, the radical intermediate abstracts a halogen atom from the alkyl halide to generate the alkyl radical **Int-B** and α-halo amine. Finally, the intermediate **Int-B** adds onto the imine carbon followed by deprotonation and subsequent oxidation to provide **3** (Scheme 5).

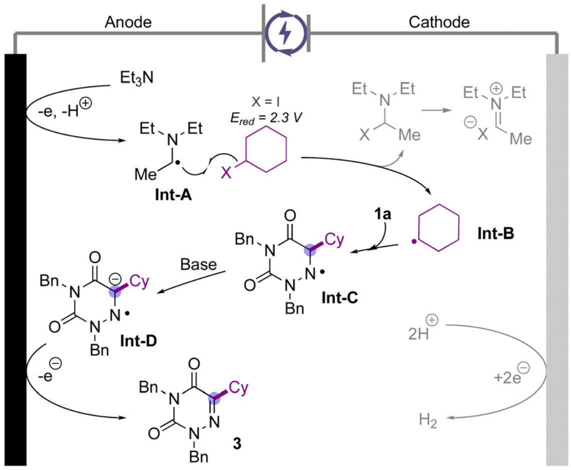
In conclusion, we have developed an electro-catalyzed alkylation of heterocycles with alkyl halide through an XAT strategy. A wide range of alkyl halides (Br, I) were tolerated to deliver the alkylated heterocycles. Furthermore, azauracil bearing various functionalities and bioactive molecules *viz.* isozepac, borneol, menthol *etc.* also delivered the corresponding alkylated products in an acceptable yield.



Scheme 3 Substrate scope with *N*-substituted uracil and various heterocycles.



Scheme 4 (a) Scale-up reaction, (b) post synthetic transformations, and (c) radical quenching experiment.



Scheme 5 Putative reaction mechanism.

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Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There is no conflict to declare.

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