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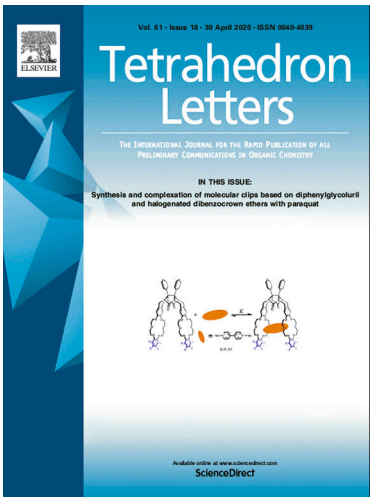

$CuCl_2$-catalyzed N-O bond cleavage of oxime esters: approach to imidazoheterocycles and furo[3,2–c]chromenyl fused imidazoles

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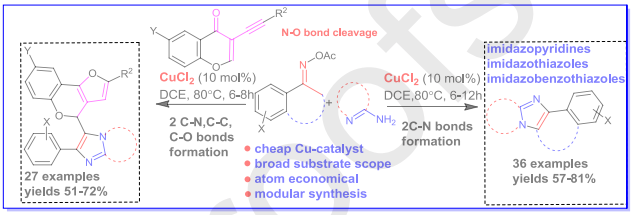

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ABSTRACT

An articulate approach to a diverse set of imidazoheterocycles in good to high yields via a copper-catalyzed aza-annulation of several oxime esters with a group of 2-amino-azaarenes was developed. The above cyclization reaction probably proceeds via a single electron transfer process which embodies a new technique for creating two new C-N bonds for imidazole ring synthesis. Gratifyingly, the implementation of this chemistry could be further stretched to the synthesis of a novel class of fused imidazoles bearing a furo[3,2-*c*]chromene moiety via a sequential C-N bond formation, followed by $C(sp^2)$-H functionalization/5-endo-dig-oxacyclization (C-C and C-O bonds) of in situ produced fused imidazoles with cyclic enynones in the presence of copper(II) as a π-electrophilic Lewis acid catalyst.

The imidazo[1,2-*a*]pyridines (IPs) are one of the most fascinating classes of N-fused bicyclic molecules.[1] Because these pivotal cores are commonly found in many bioactive natural products[2] and biologically active substances.[3] In addition, these moieties have great applications in material science[4] and organometallic chemistry.[5] Most importantly, they constitute a number of best-selling marketable medicines (Figure 1) such as anxiolytic drug alpidem, osteoporosis drug minodronic acid, GSK 812397 (treatment for infection) etc.[6] Owing to their wide ranging bioactivities, a variety of modern tools have been developed for substituted IPs (Scheme 1).[7-19] For example, the traditional route follows the condensation-cyclization reaction involving 2-aminopyridines as 2N1C synthons and 2-haloketones in the presence of base or catalyst-free conditions was established, offering a powerful tactic for the rapid access to IPs (Route A, Scheme 1).[8] Besides, several research groups have developed one of the most modern approaches for the synthesis of substituted IPs via copper-catalyzed [CuI, Cu(II)-nanoTiO_2 or Cu(II)-ZnI_2] oxidative coupling reaction between 2-aminopyridines with unactivated methyl ketones triggered by several ligands or additives under O_2 atmosphere.[9-13] Excitingly, replacing ketones by N-tosylhydrazones, the aerobic oxidative coupling reaction also proceeded nicely with 2-aminopyridines using Au(I)

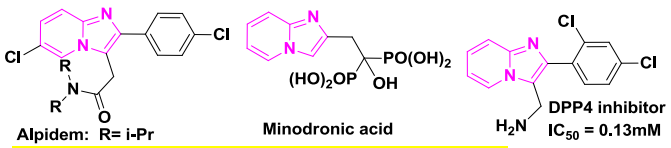
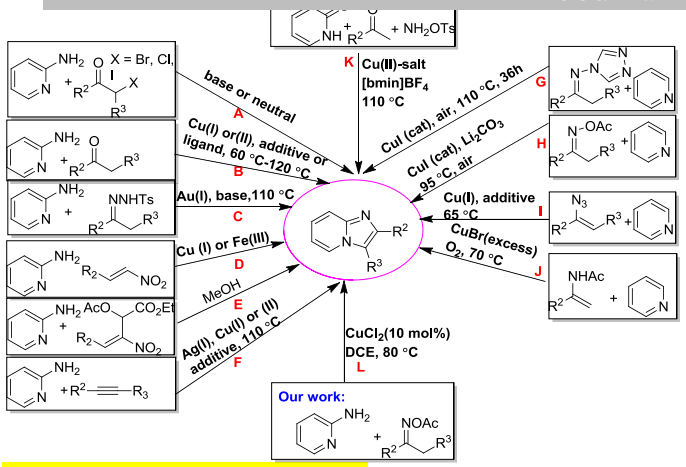


Figure 1. Selective examples of IP-based drug molecules.

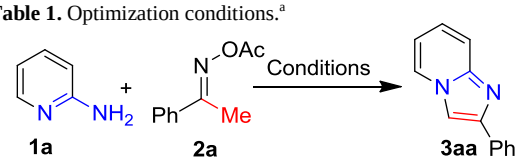
and CsOAc as a combined catalytic system at 110 ˚C (Route C).[14] Similarly, by using different kinds of 2C coupling partners, many attractive methods documented which include Cu(I) or Fe(III)-catalyzed [3+2] cyclization reaction involving nitroalkenes as 2C sources (Route D),[15] a catalyst-free Michael-*5-exo-trig*-azacyclization of MBH acetates with 2-aminopyridines (Route E),[16] silver-or copper-catalyzed direct oxidative coupling/cyclization reaction of both terminal and internal alkynes with 2-aminopyridines.[17] Intriguingly, suppressing the use of 2-aminopyridines by pyridines (1N1C systems), Jiang, Fu and Adimurthy groups brilliantly synthesized mainly C2-substituted IPs via a copper-catalyzed oxidative C-H functionalization of pyridines with several 1N2C synthons namely N-(1-arylethylidene)-4*H*-1,2,4-triazol-4-amines (Route G), oxime esters (Route H), vinyl azides (Route I) and enamides (Route J) promoted by Li_2CO_3 or molecular sieves. [18] Moreover, Meshram et al. also established a convenient three-component reaction for accessing to 3-unsubstituted IPs via a C-H functionalization/cyclization process using Cu(II)-salt in $[bmin]BF_4$ as a reusable ionic liquid (Route K).[19] Even though, the great achievements have been made for the synthesis of substituted IPs. However, most of the reported methods are linked with several issues such as use of co-catalyst, additive or ligand, need of high temperature, unsatisfactory yields, longer reaction time, limited substrate scope etc. Therefore, we are interested to devise an alternative, catalytic, additive-free method for accessing both C2-and C3-substituted imidazoheterocycles from simple substances.



Scheme 1. Various routes to IPs synthesis.

As part of our research works related to the development of new domino methods for making a biologically relevant N-containing heterocycles including alpidem derivative,[20] here in, we further disclose a novel $CuCl_2$-catalyzed aza-annulation method for the modular synthesis of imidazoheterocycles from 2-aminopyridines and oxime esters without using any co-catalyst and additive (Route **L**, Scheme **1**).

Table 1. Optimization conditions.[a]

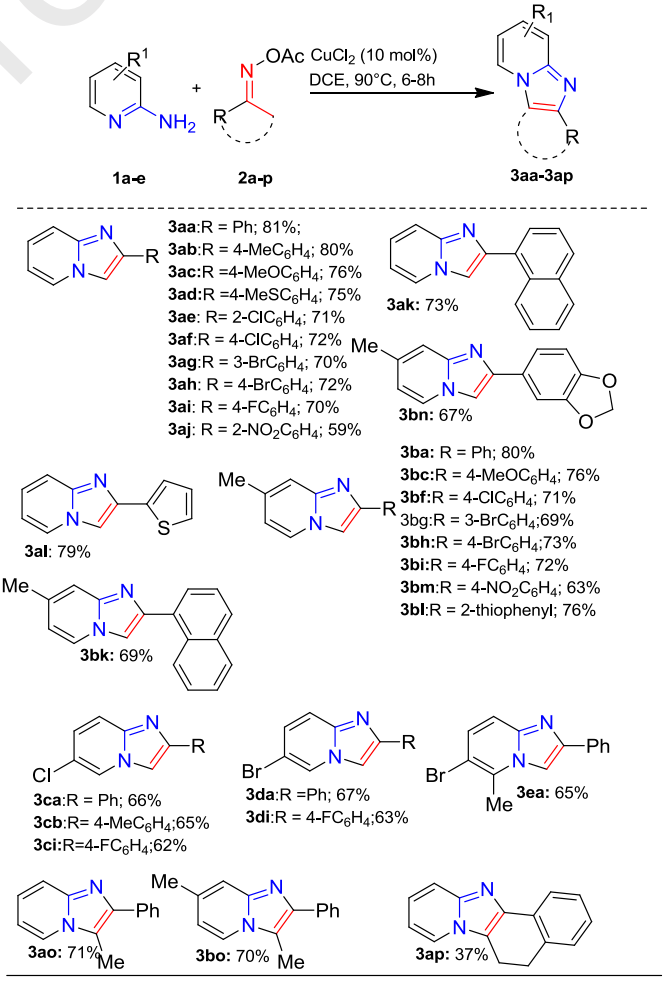


Entry	Catalyst	Solvent	T °C	T (h)	Yield[b](%)
1	-	Dioxane	80	12	nd[e]
2	$CuCl_2$	Dioxane	80	6	55
3	$CuCl_2$	Dioxane	90	6	76
4	$CuCl_2$	Dioxane	100	6	74
5	$CuCl_2$	DCE	90	6	81
6	$CuCl_2$	Toluene	90	6	66
7	$CuCl_2$	DMF	90	6	25
8	$CuCl_2$	MeCN	90	6	69
9	$CuBr_2$	DCE	90	6	71
10[c]	$Cu(OAc)_2.H_2O$	DCE	90	6	67
11[c]	$CuCl_2.2H_2O$	DCE	90	6	72
12	$Cu(OTf)_2$	DCE	90	6	36
13	CuI	DCE	90	12	>10
14	CuBr	DCE	90	12	>10
15	$FeCl_3$	DCE	90	12	>5
16	$AuBr_3$	DCE	90	12	nd[e]
17	AgOAc	DCE	90	12	nd[e]
18	AgOTf	DCE	90	12	nd[e]
19	AgTFA	DCE	90	12	nd[e]
20[d]	$CuCl_2$	DCE	90	12	61

[a]All the reactions were carried out with 2-aminopyridine (0.2 mmol), oxime ester (**2a**, 0.24 mmol) and catalyst (0.02 mmol, 10.0 mol%) in specified dry solvent (1.5 mL) under N_2 atmosphere and temperature. [b]Isolated yield after mol% $CuCl_2$ was used. [e]nd= not detected

The study was commenced by examining the reaction between 2-aminopyridine (**1a)** and oxime acetate **2a** in 1,4-dioxane using 10 mol% of anhydrous $CuCl_2$ as a catalyst at 80 °C (entry 2, Table 1). To our delight, after 6h, the expected imidazo[1,2-*a*]pyridine **3aa** was isolated in a moderate yield (55%). Interestingly, upon rising the temperature to 90 °C, the reaction yielded to 76% of **3aa**. To improve the yield further, several common solvents namely 1,2-dichloro ethane (DCE), toluene, DMF and MeCN were tested for this annulation reaction. Results indicated that DCE provided a better yield (81%, entry 5) than other solvents (yields up to ≤ 69%, entries 6-8). Next, we screened other catalysts such as $CuBr_2$, $Cu(OAc)_2.H_2O$, $CuCl_2.2H_2O$, $Cu(OTf)_2$, CuI, CuBr, $FeCl_3$, $AuBr_3$ and Ag-salts (entries 17-19). It was found that Cu(I), Fe(III), Au(III) and Ag(I)-catalysts did not promote the reaction effectively. However, hydrated Cu(II)-salts (entries10 and 11) afforded good yields of **3aa** (67-72%) along with a small amount of acetophenone (10-15% yields). Furthermore, 71% and 36% yields of **3aa** were obtained by using $CuBr_2$ and $Cu(OTf)_2$ as catalysts respectively. Therefore, taking into the consideration of the yield**,** $CuCl_2$ was found to be a superior catalyst as compared to other Cu-salts, selecting the best catalyst for this aza-annulation reaction.

With optimal catalytic conditions in hand, we demonstrated the scope and limitation of the [3+2] annulation reaction by

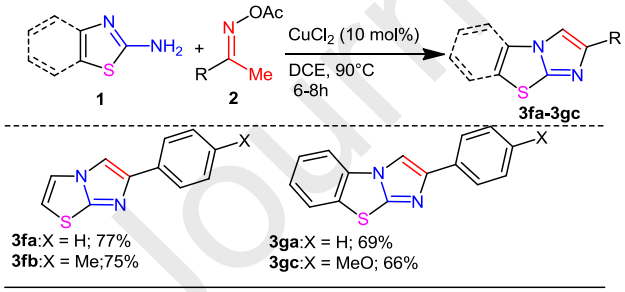


Sche

1a-e (0.2 mmol), **2a-p** (0.24 mmol) and $CuCl_2$ (0.02 mmol) in DCE (1.5 mL) under N_2 atmosphere at 90 °C for 6-8h.[26]

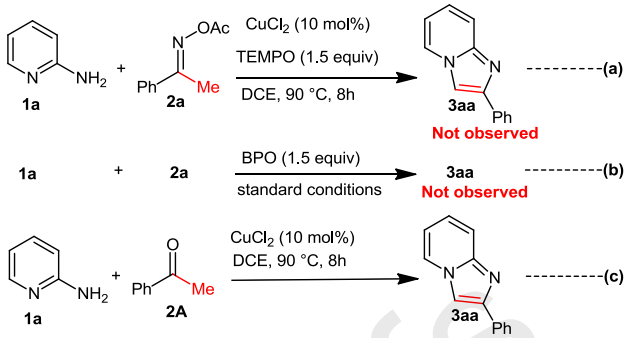
taking several 2-aminopyridines and a wide range of oxime esters as 2C sources under established conditions. The obtained results are included in Scheme 2. It was found that oxime esters **(2b-d)** bearing electron-donating (Me, MeO and MeS) substituents on the aryl rings provided better yields (75-80%) of the corresponding C2-substituted IPs (**3ab-3ad**) than electron-withdrawing ones (Cl, Br, F, NO_2; **3ae-3aj** for 59-72% yields). It is noteworthy to mention that zolimidine as a gastroprotective drug could be synthesised from compound **3ad** through a one-step operation. Interestingly, oxime esters **2k** and **2l** derived from an either bulky naphthyl or heteroaryl group ran nicely with **1a** to give the targeted heterocycles **3ak** and **3al** in promising yields in 73% and 79% yields respectively. Moreover, several functionalities namely Me, Cl and Br attached to the aza-rings were subjected to the radical cyclization reaction with a series of oxime esters (**2a-n**) via a N-O bond cleavage, leading to the expected 2-aryl/heteroaryl-substituted IPs (**3ba-3ea**) in good to high yields (63-80%). Notably, the presence of electron withdrawing functionalities of starting materials (2-aminopyridines or oxime esters) had reduced the rate of the reaction, resulting in slightly lower yields. Notably, the completion of cyclization process also required extra time. To our great pleasure, oxime esters (**2o** and **2p**) derived from propiophenone and α-tetralone were also productive, leading to the 71%, 70% and 37% yields of 2,3-disubstituted fused imidazoles **3ao, 3bo** and **3ap** respectively.

To explore a more challenging substrates, we employed 2-aminothiazole (**1f**) and 2-aminobenzothiazole (**1g**) in this aza-annulation process. As can be seen in Scheme 3, oxime esters (**2a, 2b** and **2c**) derived from acetophenones provided 77%, 75%, 69% and 66% yields of the corresponding imidazo[2,1-*b*]thiazoles **3fa, 3fb, 3ga and 3gc** respectively, while reacting with **1f** and **1g**.



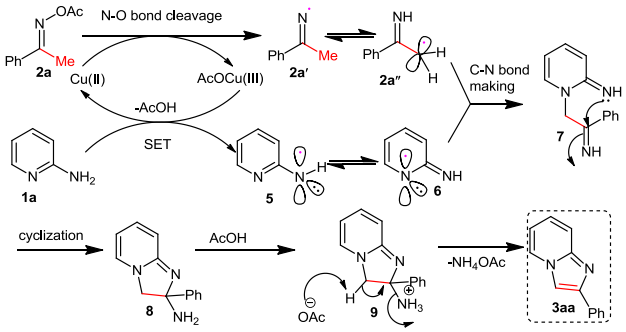
Scheme 3. One-Pot synthesis of imidazoheterocycles**.** Reaction conditions: compound **1** (0.2 mmol), **2**(0.24 mmol) and $CuCl_2$ (0.02 mmol) in DCE (1.5 mL) under N_2 atmosphere at 90 °C for 6-8h.

To gain mechanistic insight, the control experiments were conducted. By using a strong radical scavenger TEMPO or BPO, the reaction was completely inhibited by radical scavenger and did not provide **3aa** (Scheme **4a** and **4b**). Thus, the results suggested that annulation reaction proceeded through a radical pathway. Moreover, under optimal conditions, it was found that the product **3aa** did not generate form acetophenone (**2A**) and **1a** in the presence of $CuCl_2$.



Scheme 4. Control experiments.

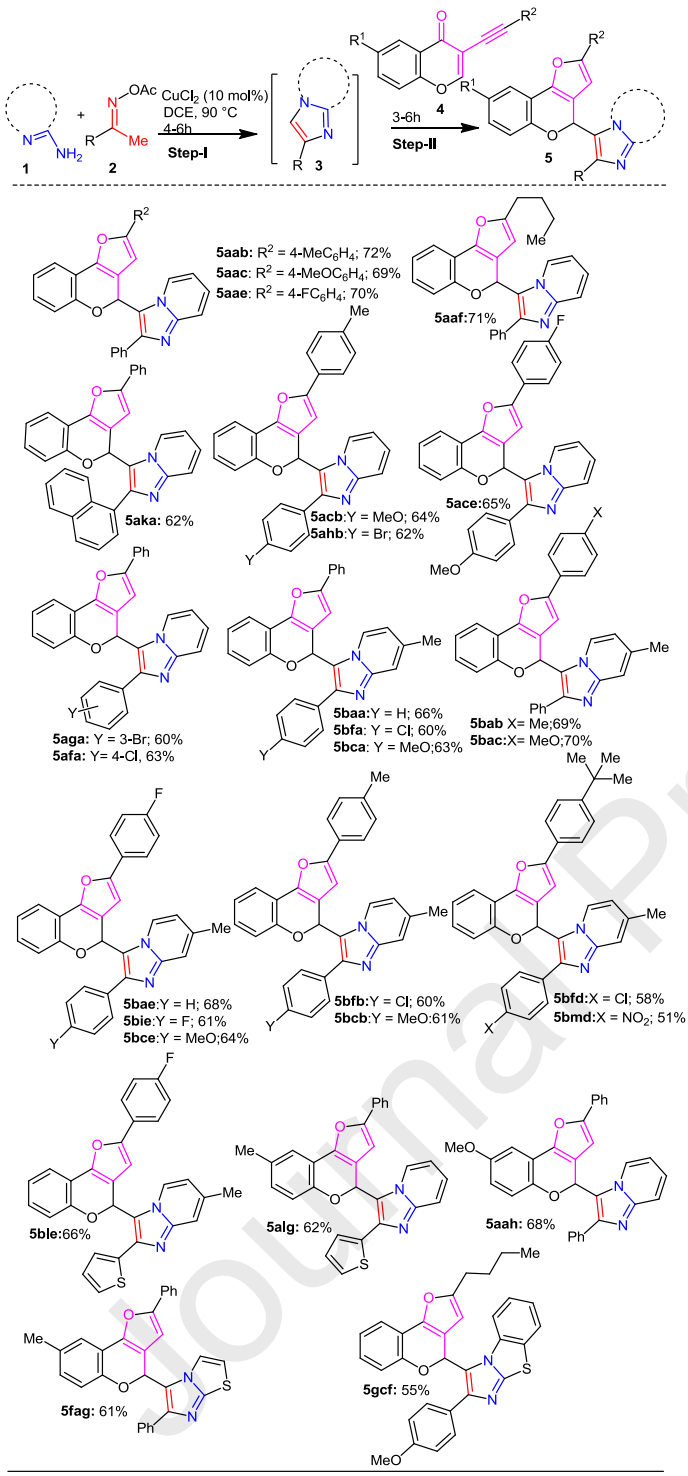
Based on the above control experiments as well as literature report,[21] we propose a tentative mechanism of the reaction as depicted in Scheme 5. Firstly, the oxidative addition of Cu (II) to **2a** generates iminium radical **2a′** along with AcOCu(III) via a N-O bond cleavage. This radical undergoes tautomerization to **2a″**. On the other hand, a single-electron-transfer (SET) process may take place between **1a** and AcOCu(III) to form a stable pyridinium radical **6** via a tautomerization of aminyl radical **5.** The intermediate **6** may stabilize by delocalizing the π-type of N-center radical via a resonance or a captodative effect**.** It should be noted that AcOH and Cu(II)-catalyst are generated during this SET process. It requires for next catalytic cycle. Next, the radical coupling between **2a″** and **6** may proceed via a C-N bond formation, resulting in intermediate **7** which in turn cyclizes to give intermediate **8.** The latter subsequent eliminates NH_4OAc triggered by AcOH, leading to the **3aa.**



Scheme 5. Possible mechanism.

Presently, the direct C(sp^2)-H bond functionalization of IPs has been given special importance in synthetic and medicinal chemistry community.[22] Since, this novel technique serves efficiently C3-substituted IPs with elusive substitutions patterns in an atom-economical way. Literature study showed that all the reported methods are based on the use of isolated IPs. Therefore, it is meaningful to develop a new catalytic one-pot strategy for the direct synthesis as well as functionalization of IPs. On the other hand, we previously reported $AgSbF_6$-catalyzed a tandem cyclization reaction of cyclic enynones with 2-alkynyl anilines to afford 2,3-disubstituted indole scaffolds.[23] Thus, we planned to extend our current annulation reaction for the installation of a

valu ed a tandem C(sp^2)-H bond functionalization of in situ generated IPs with 3-alkynyl-4*H*-chromen-4-ones as appropriate electrophiles under present conditions.[25] Results in Scheme 6 showed that efficiently in the Friedel-Crafts/*5-endo-dig*-oxacyclization reaction with a group of 3-(1-alkynyl)-4*H*-chromen-4-ones (**4a-f**) catalyzed by $CuCl_2$ as a π-electrophilic Lewis acid. Consequently, all the reactions produced promising yields (51-72%, overall) of an impressive array of furo[3,2-*c*]chromenyl-substituted IPs (**5aab**-**5ble**) via a selective two C-N, C-C and C-O bonds formation. It is noteworthy to mention that the attaching electron withdrawing (F, Cl, Br and NO_2) substituents on the pyridine rings of IPs reduced their nucleophilicities, resulting in slightly lower yields of corresponding furo[3,2-*c*]chromene adducts. Pleasantly, incorporation of Me and MeO groups on the aryl rings of cyclic enynones did not hamper the reactivities, providing 62% and 68% yields of **5ajg** and **5aah** respectively. Gratifyingly, imidazo[2,1-*b*]thiazole (**3fa**) and benzo[*d*]imidazo[2,1-*b*]thiazole (**3gb**) were well tolerated in this sequential process to deliver the targeted furo[3,2-*c*]chromenyl fused imidazoles (**5fag** for 61% yield and **5gcf** for 55% yield).



Scheme 6. Sequential one-pot synthesis of furo[3,2-*c*]chromenyl imidazoheterocycles**.** Reaction conditions: All the reactions were carried out with 2-aminopyridine **1** (0.2 mmol), oxime ester **2** (0.24 mmol) and $CuCl_2$(0.02 mmol, 10.0 mol%) in DCE (1.5 mL) under N_2 atmosphere at 90 °C for 4-6h, afterwards, cyclic enyone **4** (0.24 mmol) in (0.5 mL) was added to the above reaction mixture at same temperature for 3-6h. [27]

In summary, we have demonstrated an efficient copper-catalyzed one-pot modular synthesis of a series of medicinally well-recognized imidazoheterocycles via an aza-annulation reaction of 2-amino-azaarenes with several oxime esters. This cyclization process provides good to high yields of aforesaid scaffolds via a N-O bond cleavage/two C-N bonds formation, thus it guarantees a wide substrate scope. Moreover, the radical trapping experiment suggests that the reaction possibly initiates via a single electron transfer process. In addition, this flexible catalytic approach can be further extended towards the synthesis of an important class of furo[3,2-*c*]chromenyl fused imidazoles in satisfactory yields via a π-electrophilic $CuCl_2$-catalyzed direct C(sp^2)-H bond functionalization of IPs, capable of making C-N, C-C and C-O bonds in a one-pot manner with high efficiency. Further efforts towards the more substrates and their biological study are in progress which will be published in due course of time.

Acknowledgments

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Supporting Information

Experimental details, characteristic data, ^{1}H and ^{13}C NMR spectra of products are included, which can be found in the online version

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26. **Representative procedure for the synthesis of imidazo[1,2-*a*]pyridines:** A mixture of 2-aminopyridines **1 (**0.2 mmol), oxime esters **2** (0.24 mmol) and anhydrous $CuCl_2$ (2.7 mg, 0.02 mmol) in dry DCE (1.5 mL) under nitrogen atmosphere was heated in oil bath at 90 °C. The reaction was monitored by TLC. After reaction was finished, it was quenched with water, extracted with ethyl acetate (3 ×10 mL) and dried over Na_2SO_4. The combined filtrate was concentrated under reduced pressure to leave the crude mass. Finally, it was purified by silica-gel column chromatography technique (hexane/ethyl acetate = 70:30**)** to afford the desired imidazo[1,2-*a*]pyridine **3. Compound 3aa:** pale yellow solid; mp 133-135 °C; yield 81% (31.4 mg); R_f = 0.60 (ethyl acetate/hexane = 3:7); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 6.4 Hz, 1H), 7.96 (d, *J* = 7.4 Hz, 2H), 7.86 (s, 1H), 7.66 (d, *J* = 9.0 Hz, 1H), 7.44 (t, *J* = 7.3 Hz, 2H), 7.33 (t, *J* = 7.1 Hz, 1H), 7.18 (t, *J* = 7.7 Hz, 1H), 6.78 (t, *J* = 6.4 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.6, 145.5, 133.5, 128.7, 128.0, 126.1, 125.6, 124.8, 117.5, 112.6, 108.1 ppm; HRMS-ESI: *m/z* calcd for $C_{13}H_{11}N_2$ $[M+H]^+$: 195.0917, found: 195.0914.

    Reported data for compound 3aa:[13a] Light yellow solid, mp =135-137 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 6.8 Hz, 1H), 7.95 (d, *J* = 7.2 Hz, 2H), 7.83 (s, 1H), 7.63 (d, *J* = 9.0 Hz, 1H), 7.43 (t, *J* = 7.6 Hz,2H), 7.32 (t, *J* = 7.4 Hz, 1H), 7.19 – 7.11 (m, 1H), 6.75 (t, *J* = 6.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.70, 145.61, 133.64, 128.68, 127.95, 126.02, 125.54, 124.65, 117.47, 112.41, 108.08.
27. **General experimental procedure for the synthesis of 4*H*-furo[3,2-*c*]chromen-4-yl)imidazo[1,2-*a*]pyridines:** To a stirred solution of 2-aminopyridines **1 (**0.2 mmol), oxime esters **2** (0.24 mmol) and anhydrous $CuCl_2$ (2.7 mg, 0.02 mmol) in dry DCE (1.5 mL) under nitrogen atmosphere was heated at 90 °C for 4-6h (monitored by TLC). Afterwards, cyclic enynones **4** (0.24 mmol) in DCE (0.5 mL) was added to the above reaction mixture at same temperature for another 3-6h. The reaction was monitored by TLC. Afterwards, the reaction mixture was extracted with ethyl acetate (3 ×10 mL), washed with water and dried over Na_2SO_4. The combined organic solvents were concentrated under reduced pressure to give the crude product which was purified by silica-gel column chromatography technique (hexane/ethyl acetate = 70:30) to give the product **5.**

    Compound 5aga: pale yellow solid; mp 178-180 °C; yield 60% (62.3 mg); R_f = 0.70 (ethyl acetate/hexane = 3:7); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 6.9 Hz, 1H), 7.98 (s, 1H), 7.62-7.70 (m, 5H), 7.53 (d, *J* = 8.5 Hz, 1H), 7.31 – 7.43 (m, 3H), 7.24 – 7.30 (m, 2H), 7.15 – 7.23 (m, 2H), 7.08 (t, *J* = 7.2 Hz, 1H), 6.96 (d, *J* = 8.0 Hz, 1H), 6.71 (t, *J* = 6.5 Hz, 1H), 6.20 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 153.0, 146.3, 146.2, 145.1, 135.8, 132.0, 131.4, 130.1, 129.8, 129.1, 128.8, 128.0, 127.5, 126.2, 125.9, 123.7, 122.8, 122.2, 119.8, 117.8, 116.9, 116.7, 116.0, 115.5, 112.6, 103.0, 70.6 ppm; HRMS-ESI: *m/z* calcd for $C_{30}H_{20}BrN_2O_2[M + H]^+$: 519.0703, found: 519.0674.

    Compound 5afa: pale yellow solid; mp 224-226 °C; yield 63% (59.8 mg); R_f = 0.70 (ethyl acetate/hexane = 3:7); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.72 (s, 3H), 7.62 (t, *J* = 7.6 Hz, 3H), 7.46 (d, *J* = 6.8 Hz, 2H), 7.37 (t, *J* = 7.4 Hz, 2H), 7.27 (d, *J* = 11.0 Hz, 2H), 7.13 – 7.23 (m, 2H), 7.08 (t, *J* = 7.4 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.71 (t, *J* = 6.5 Hz, 1H), 6.20 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 153.0, 146.3, 145.5, 134.5, 132.2, 130.2, 129.8, 129.1, 128.9, 128.8, 128.0, 126.3, 125.8, 123.7, 122.2, 119.8, 117.7, 116.7, 116.0, 115.6, 112.6, 103.0, 70.7 ppm; HRMS-ESI: *m/z* calcd for $C_{30}H_{20}ClN_2O_2$ $[M + H]^+$: 475.1208, found 475.1214.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Highlights

- Copper(II)-catalyzed one-pot approach to imidazoheterocycles in good to high yields.
- The reaction has been proceeded via a N-O bond cleavage of oxime esters.
- One-pot two-step sequential synthesis of furo[3,2-*c*]chromenyl fused imidazoles in

Dear Sir/Madam
We declared the following items.

1. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.
2. The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Sampak Samanta (on behalf of all the authors)