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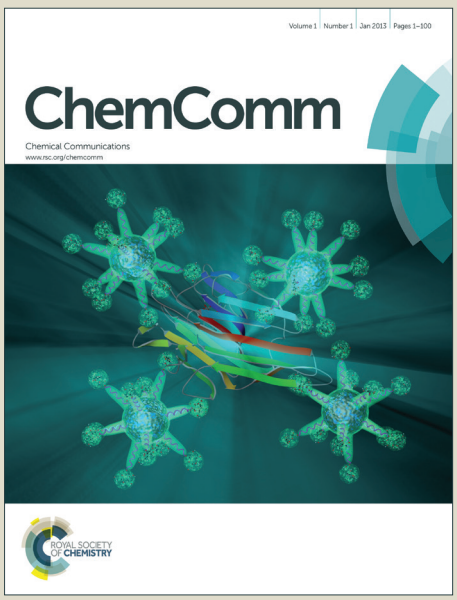

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ARTICLE TYPE

n-Bu_4NI-catalyzed selective dual amination of sp^3 C–H bonds: oxidative domino synthesis of imidazo[1,5-*c*]quinazolines on a gram-scale

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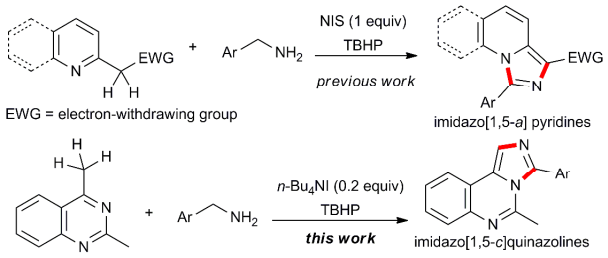
An *n*-Bu_4NI catalyzed domino reaction that involves selective dual amination of sp^3 C–H bonds has been developed. The protocol affords a facile and efficient approach to the synthesis of imidazo[1,5-*c*]quinazolines under mild conditions.

In recent years, considerable achievements have been made in transition-metal-catalyzed C–H bond activation. Direct C–N bond formation via C–H bond activation is more preferable than traditional synthetic strategies in the construction of nitrogen-containing molecules.[1] Despite the major advances achieved in transition-metal-catalyzed C–H amination, the cost effectiveness as well as the presence of heavy transition metal impurities in the final products is a major problem regarding their practical applicability, especially in preparing pharmaceutical agents. Thus, the alternative metal-free direct C–H amination is highly desirable. Recently, iodine-based catalytic systems in C–H bond activation have been established and received much attention.[2] Furthermore, these efficient and environmentally friendly strategies also availably promote the more challenging sp^3 C–H amination.[3] For example, iodine promoted benzylic C–H amination has been developed by Chang[4a] and Zhu[4b]. However, nitrogen sources were limited to sulphonamides and benzoazoles. Therefore, benzylic C–H bond, especially the more challenging primary C–H oxidative amination with primary amine remains highly desirable.

Domino strategy has been widely applied for the synthesis of organic compounds due to its high atom and synthetic efficiency.[5] A variety of iodine promoted oxidative domino reactions that involve C–N bond formation have been demonstrated to date, while the catalytic variants of iodine-initiated domino reactions are still rarely documented.[2c] Thus, we focused our attention on iodine catalyzed domino sp^3 C–H amination.

Nitrogen-containing fused heterocycles constitute an important class of biologically active agents and play an important role in medicinal chemistry. Imidazoquinazoline is the critical skeleton in drug molecules, such as those are used clinically as anti-thrombotic and cardiotonic agents.[6] Structural variants of imidazoquinazoline show a wide range of biological activities, including anticonvulsants[7a], antitumor[7b] and antihypertensive[7c-d] effects. Despite the high interest, synthetic routes available for these molecules often suffer from some disadvantages, such as strict reaction conditions, complex manipulations and inaccessible starting materials.[8] Therefore, alternative synthetic approaches for imidazoquinazoline derivatives under mild conditions are desired. Very recently, the analogous imidazo-*N*-heterocycle, imidazo[1,5-*a*]pyridines were synthesized from electron-withdrawing group substituted 2-methylpyridines and benzylamines via iodine-mediated benzylic secondary C–H amination.[9] Encouraged by above results, and in the continuation of our research on quinazoline derivatives,[10] we herein report a direct approach for the synthesis of imidazo[1,5-*c*]quinazolines from readily available 4-methylquinazolines and benzylamines. To the best of our knowledge, imidazo[1,5-*c*]quinazolines possess a novel heterocyclic skeleton to date. Besides, benzylic primary C–H oxidative amination with primary amines has been scarce until now.



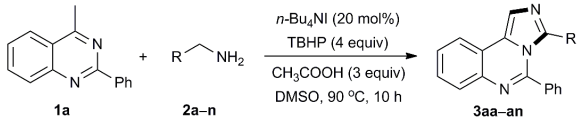
Scheme 1 Synthesis of imidazo-*N*-heterocycles via iodine promoted dual benzylic C–H aminations.

Initially, our studies began from an exploration of the reaction conditions on 4-methyl-2-phenylquinazoline (**1a**) and benzylamine (**2a**) (Table S1, see ESI). In the presence of 20 mol% *n*-Bu_4NI, the desired product **3aa** was afforded in 36% yield when 4 equiv. of TBHP was used as an oxidant (entry 1). In the absence of catalyst, no **3aa** was detected (entry 2). Next, various iodine reagents were investigated, but no further improvement in the yield was observed (entries 3–6). Among the examination of various oxidants, gratifyingly, 70% aqueous TBHP gave a yield similar to a decane solution of TBHP, which indicated a small amount of water would not inhibit this reaction (entries 7–11). Further experimental data suggested that both organic and inorganic acids could facilitate this reaction and acetic acid improved the yield significantly (entries 12–20). Performing the reaction in other organic solvents instead of DMSO did not enhance the yield (entries 21–28). In addition, the amount of TBHP as well as acetic acid was also optimized and the results were listed in Table S1 (entries 29–31 and 37). The

investigations on reaction temperature and time showed that reacting at 90 °C for 10 h was optimal for the process. Finally, the optimal conditions were 20 mol% *n*-Bu_4NI with 4 equiv. TBHP and 3 equiv. acetic acid in DMSO under air.

With the optimized conditions in hand, various benzylamines were reacted with 4-methyl-2-phenylquinazoline (**1a**) to give the corresponding imidazo[1,5-*c*]quinazolines (**3aa**–**an**) (Table 1). We found that the steric hindrance had little influence on the reaction (entries 2–4). In all cases, both electron-donating and withdrawing substituents in the phenyl ring were well tolerated, and gave good yields (entries 5–10). Notably, functional groups such as F, Cl and Br were also compatible with the reaction conditions, which providing an additional handle for further functionalization of the products. Moreover, naphthalen-1-ylmethanamine and several heterocyclic benzylamines were also proved applicable, giving the desired products in good yields (entries 11–13). However, pyridin-2-ylmethanamine (**2n**) failed to yield the desired product, but gave an unexpected byproduct via self-condensation and cyclization (for details, see ESI).

Table 1 Substrate scope of benzylamines[a]

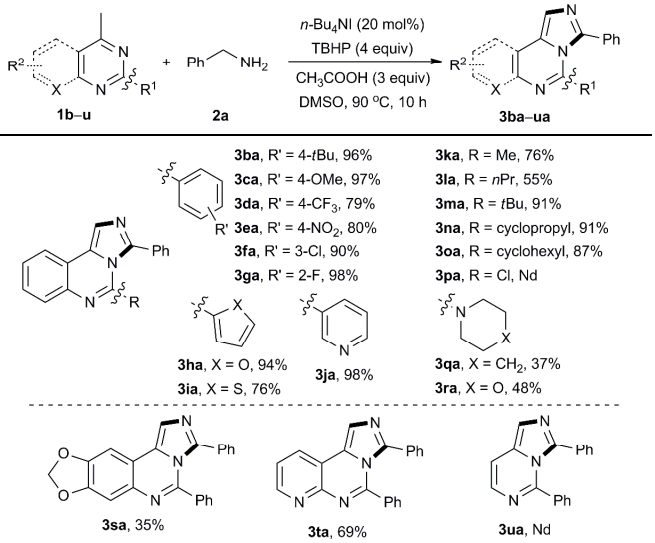


Entry	R	Product	Yield[b] (%)
1	Ph (**2a**)	**3aa**	88
2	2-Me-Ph (**2b**)	**3ab**	83
3	3-Me-Ph (**2c**)	**3ac**	75
4	4-Me-Ph (**2d**)	**3ad**	71
5	4-*t*Bu-Ph (**2e**)	**3ae**	76
6	4-OMe-Ph (**2f**)	**3af**	75
7	4-F-Ph (**2g**)	**3ag**	85
8	4-Cl-Ph (**2h**)	**3ah**	76
9	4-Br-Ph (**2i**)	**3ai**	80
10	4-CF_3-Ph (**2j**)	**3aj**	77
11	1-naphthyl (**2k**)	**3ak**	90
12	2-furyl (**2l**)	**3al**	62
13	2-thienyl (**2m**)	**3am**	76
14	2-pyridyl (**2n**)	**3an**	Nd[c]

[a] Reaction conditions: **1a** (0.3 mmol), **2** (0.6 mmol), *n*-Bu_4NI (0.06 mmol), 70% Aq. TBHP (1.2 mmol), CH_3COOH (0.9 mmol), DMSO (2 mL), 90 °C, 10 h. [b] Isolated yield. [c] Nd = Not detected.

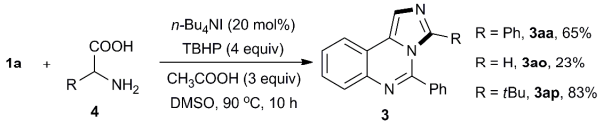
To evaluate the generality of this reaction, a variety of quinazolines and benzylamine were further tested. As shown in Table 2, 2-position substituted quinazolines with benzene ring bearing alkyl, methoxy, fluoro and chloro group were well tolerated to give excellent yields, and those with strong electron-withdrawing groups, such as trifluoromethyl and nitro group still gave target products in good yields (**3ba**–**ga**). 4-Methylquinazoline with other aryl substituents such as furyl, thienyl and pyridyl groups also underwent the reaction efficiently (**3ha**–**ja**). The 2,4-dimethylquinazoline (**1k**) was successfully transformed in 76% yield with excellent regioselectivity probably due in part to the weaker C–H bond of 4-methyl substituent.[11] Moreover, exclusive selectivity was also observed for amination at methyl over methylene sp^3 C–H bond (**3la**). Other alkyl substituents, such as branched and cycloalkyl groups were also suitable for the present transformation (**3ma**–**oa**). 2-Cl substituted quinazoline failed to yield the product, but gave a byproduct (**3pa'**, for details, see ESI). Substituted 2-aminoquinazolines (**1q** and **1r**), substituted phenylquinazoline (**1s**) and pyridopyrimidine (**1t**) were also tested and the corresponding products were afforded in moderate to good yields. However, 4-methylpyrimidine showed no reactivity in current conditions.

Table 2 Substrate scope of 4-methylquinazolines[a]



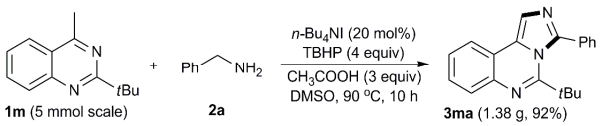
[a] Reaction conditions: **1** (0.3 mmol), **2a** (0.6 mmol), *n*-Bu_4NI (0.06 mmol), 70% Aq. TBHP (1.2 mmol), CH_3COOH (0.9 mmol), DMSO (2 mL), 90 °C, 10 h. [b] Isolated yield. Nd = Not detected.

Recently, α-amino acids have been applied in the preparation of nitrogen-containing heterocycles via decarboxylative reaction under metal-free conditions.[12] The success of benzylamines gives us a hint to further test the scope of this reaction with α-amino acids (Scheme 2). To our delight, when an aryl or alkyl group was connected to the α-carbon atom of the amino acid, the corresponding products were obtained with satisfactory yields. When glycine was employed as the substrate, the reaction also worked although gave a low yield. We believe the wide tolerance of various functional groups in imidazolyl ring make this reaction highly practical and reliable.



Scheme 2 Synthesis of imidazo[1,5-*c*]quinazolines from amino acids.

The scalability of the method was verified by running the reaction of **1m** with **2a** on 5 mmol scale (Scheme 3), and the product was isolated in identical high yield.



Scheme 3 Large scale synthesis of **3ma**.

Further control experiments have been performed to obtain insights into the mechanism (Scheme S1, see ESI). It was thought

that iodo product **5** may be the key reaction intermediate derived from **1a**. However, **1a** under standard conditions in the absence of **2a** and acetic acid did not afford **5** (Scheme S1, A), suggesting an '*in situ* iodination' based oxidative coupling pathway[2c] could be excluded. When 20 mol% $PhI(OAc)_2$ was employed, the reaction did not work (Scheme S1, B). This result indicated hypervalent iodine reagents might not be involved in the transformation. Adding a radical inhibitor BHT (2,6-di-*tert*-butyl-4-methylphenol) or TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl) to the reaction system, a negative influence on the yield was observed (Scheme S1, C). This result suggested that reaction probably proceeded via a free radical process. When **1a** was used as a substrate under standard conditions in the absence of benzylamines, an unexpected benzylic acetate **6** was obtained (Scheme S1, D). To help ascertain whether **6** is a potential intermediate, we explored the coupling of **6** with **2a** under standard conditions (Scheme S1, E). The desired product was obtained in 76% yield within 5 h, suggesting **6** was most likely a possible intermediate for the present transformation. Additionally, no reaction occurred in the absence of *n*-Bu_4NI or TBHP, indicating proper oxidation state of the iodine catalyst was an important requirement for reactivity. When sodium acetate was subjected to the reaction conditions, no benzylic acetate was detected (Scheme S1, F). Thus, a benzyl cation is not involved in this reaction.

On the basis of the above evidences and previously reported results,[9,13] a possible mechanism is proposed as shown in Scheme S2 (see ESI). Initially, TBHP decomposes to generate the *tert*-butoxyl and *tert*-butylperoxy radicals in the presence of iodide ion (I^-). These radicals subsequently abstract hydrogen atoms from the acetic acid and **1** to provide both the acyloxy and benzylic radical **A**, respectively. Then the coupling of these two radicals forms the intermediate **6**. **B** is generated via amination of **6** under current conditions,[14] followed by oxidation to give **C** or **C'**. Subsequently, **C** or **C'** is oxidized to **E** via sp^3 C–H functionalization under iodine-catalyzed reaction conditions. Then **E** is converted to the product after intramolecular amination/cyclization and rearrangement in tandem process.

In summary, a facile and efficient approach to the synthesis of imidazo[1,5-*c*]quinazolines was developed via a tandem reaction following sp^3 C–H functionalization under metal-free conditions. Moreover, the reaction showed a broad scope of substrates including the common commercially available benzylamines and α-amino acids. The new protocol serves not only as a method to construct a new class of imidazo-*N*-heterocycles but also as a rare example of benzylic primary C–H oxidative amination with primary amines. The investigation of mechanism indicated that benzylic acetate as a possible intermediate was involved in the reaction. Ongoing research involves further application of the methodology in other heterocycles synthesis and bioactive evaluation of imidazo[1,5-*c*]quinazolines is currently underway in our laboratory.

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Notes and references

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