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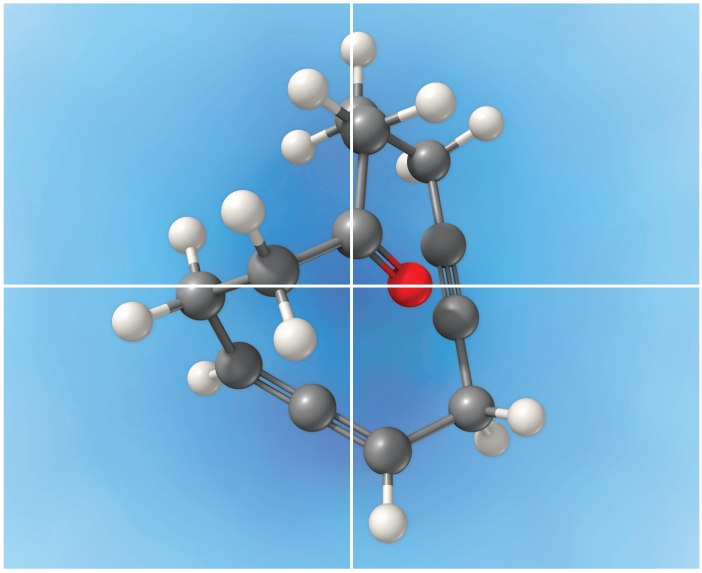

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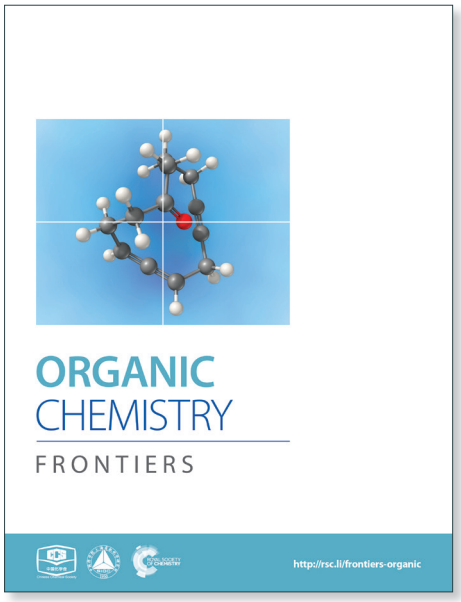

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COMMUNICATION

Selective formation of C-N and C=N bonds *via* C(sp^3)−H activation of isochroman in the presence of DTBP

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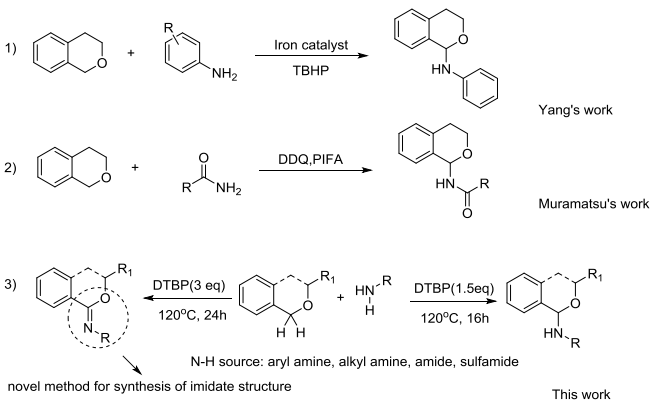
An approach for synthesis of isochroman derivatives *via* direct C(sp^3)−H bond and N-H bond coupling was described. The C-N (amine or amide) and C=N (imidate) products can be selectively achieved by controlling the amount of oxidants. Moreover, this metal- and base-free protocol is simple, easy-to-handle, and atom-economic which may have potential application in drug synthesis.

Over the past few decades, significant progress has been made in direct C−H functionalization reactions.[1] In particular, C−H bond activation reaction such as cross-dehydrogenative coupling (CDC) reaction is of immense importance because of its atom-economic and the environmental sustainability. CDC protocols have been successfully employed to access a diverse array of C-C and C-heteroatom bonds, by functionalizing C−H bonds of all types (sp, sp^2, sp^3).[2] Among them, the functionalization of inert C(sp^3)−H bond has received special attention in recent years.[3] The existing reports in this area mainly focus on the C(sp^3)–H bond functionalization of cycloalkanes or benzylic arenes,[4] chelating group assisted C(sp^3)–H bond functionalization[5] and the functionalization of C(sp^3)–H bond adjacent to heteroatoms.[6]

Isochroman derivatives are a class of important compounds which exhibit various potential bioactivities[7] and serve as important building blocks in synthetic chemistry and drug design.[8] Typically, isochroman derivatives have been prepared by different methods such as reduction of corresponding esters[9], intramolecular or intermolecular cyclization reactions[10] and decorations of isochroman.[11] Recently guided by powerful C−H activation technology, direct C-H bond functionalization of isochroman derivatives have appeared., and the direct C-C bond formations at the C(1) position of isochroman have been widely studied.[12] However only a few methods for the catalytic carbon-heteroatom formation, especially the C-N formation, were reported (Scheme 1, eq. 1). In 2013, Yang and co-workers reported the Iron-catalyzed direct C(sp^3)–H amination reactions of isochroman derivatives.[13] Subsequently, Muramatsu and co-workers succeeded in the amidation of isochroman utilizing DDQ and PIFA as the oxidant (Scheme 1 eq. 2).[14]

While acknowledging the pioneering work in this area, some issues such as the use of toxic reagents, limited substrate scopes (only two examples were reported in Muramatsu's work; the substrates of Yang's work were limited to aryl amines) and complex experimental procedures (separation of the iron mud from the products etc.) still need to be addressed. Moreover, the reactions under metal-free conditions are more appreciable in the nitrogen-containing pharmaceutical synthesis. In this regard, studies on the C-N coupling of isochroman derivatives and amines are still the cherished target.



Scheme 1. C-N couplings of isochroman.

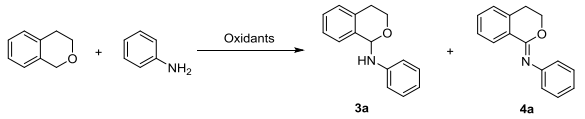
During our previous research, DTBP was found to be a suitable oxidant to promote the C-N formation between isochroman and aniline. Surprisingly, isochroman-1-imine was also detected by variation of reaction conditions. Screening of the references revealed that there lacks efficient method for synthesis of imidate structure[15], especially isochroman-1-imine derivatives. Herein, we wish to report a straightforward, convenient and selective CDC protocols for the sp^3 C-H amination, amidation and further imidization of isochroman in metal-free conditions (Scheme 1 eq. 3) .

Initially, the coupling of isochroman and aniline was selected to optimize the reaction conditions. As shown from Table 1, the oxidant was crucial for this reaction. The reaction could not occur

without an oxidant (entry 1), while the yield of **3a** was increased to 82% in the presence of 1.5 equivalents of DTBP (entry 2). Other oxidants or oxidation systems were then screened, and the results revealed that DTBP was still the best choice (entries 2-7). Next, the reaction temperature was examined, and 120 ^{o}C was found to be the most appropriate temperature (entries 2, 10-11).

Accompany with the C-N coupling product **3a**, trace amount of imidate product **4a** was also observed at 120 ^{o}C for 16 h (entry 2). Encouraged by the formation of unexpected product **4a**, the oxidant equivalents and reaction time were then checked respectively to seek the possibility for selectively synthesis of product **3a** or **4a**. To our delight, moderate yield of product **4a** was obtained when DTBP was added to 3 equivalents (entry 13). Further extension of reaction time afforded the product **4a** in a satisfactory yield (entry 14). However adding more DTBP (4 equivalents) or prolonging reaction time to 36 h did not give any significant improvement (entries 15, 16).

Table 1. Optimizations for the C-N coupling of isochroman[a]

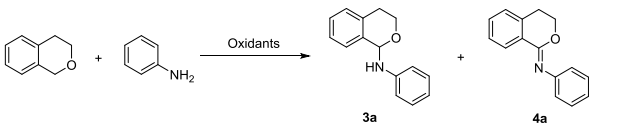


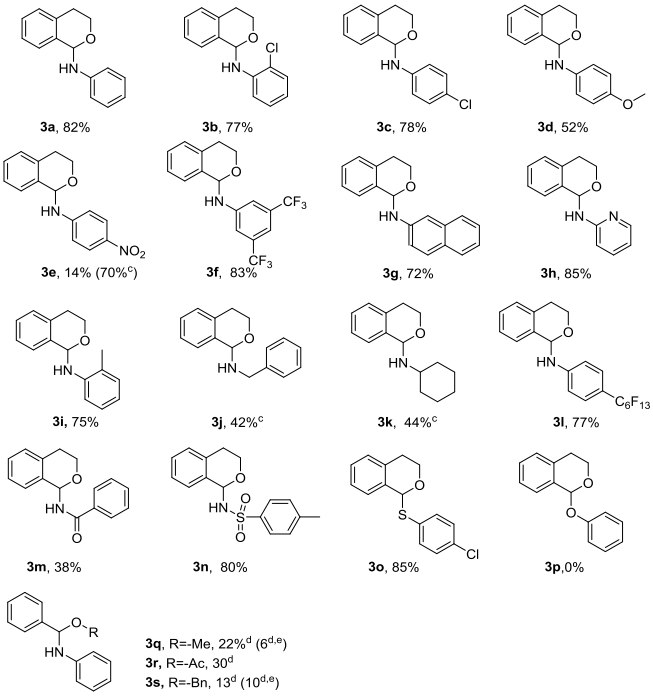
Entry	Oxidants	Time h	Temp ^{o}C	Yield of **3a** %[b]	Yield of **4a** %[b]
1		16	120	0	0
2	DTBP (1.5eq)	16	120	82	trace
3	TBHP(1.5eq)	16	120	7	0
4	BPO (1.5eq)	16	120	0	0
5	DDQ (2eq)	16	120	10	0
6	$FeCl_2$ (0.1eq) /TBHP(2eq)	16	120	55	0
7	CuBr (0.1eq) / TBHP(2eq)	16	120	26	0
8	DTBP (1.5eq)	4	120	22	0
9	DTBP (1.5eq)	24	120	79	8
10	DTBP (1.5eq)	16	100	43	0
11	DTBP (1.5eq)	16	140	62	8
12	DTBP (2eq)	16	120	77	11
13	DTBP (3eq)	16	120	28	62
14	DTBP (3eq)	24	120	8	76
15	DTBP (5eq)	24	120	7	76
16	DTBP (3eq)	36	120	5	77

[a] Reaction conditions: aniline (1.3 mmol), isochroman (1 mmol), oxidant (1.5 mmol), neat. [b] The yield was determined by LC.

With the optimized conditions in hand, a series of aromatic amines, aliphatic amines and amides were chosen to establish the scope and generality of the C-N couplings (Table 2). As can be seen from Table 2, the present methodology was applicable to diverse aryl amines (**3a**-**3i**). The position of the substituent such as chloro had no significant influence on this reaction with comparable results obtained (**3b** ***vs*** **3c**). The electronic effect played an important role, aryl amines bearing electron-withdrawing substituents coupled with isochroman smoothly to afford the corresponding products in better yields than those with electron-donating groups. As for 4-nitroaniline, the C-N product **3e** and the C=N product **4b** existed simultaneously even at the starting of the coupling. Product **4b** could be obtained in the yield of 70%, compared to 14% of product **3e**, in 16 hours. It is worth noting that 1-aphthylamine and 2-aminopyridine were well tolerated under the reaction conditions, giving the corresponding products in 72% and 85% yield, respectively (**3g**, **3h**). This protocol was also suitable to aniline bearing a fluorous tail which may have potential use in fluorine chemistry. Benzyl amine and alkyl amine were also examined. Unfortunately, along with the target products in moderate yields, some byproducts were also formed which could hardly be separated (**3j**, **3k**). These byproducts may come from the C-H functionalization of the corresponding amine substrates **3**. Examples using amides as the substrates were also investigated. Benzenesulfonamide underwent the coupling smoothly with a 80% yield of product (**3n**), while benzoic amide was less reactive (**3m**). Next, linear benzylic ether was tried to replace isochroman. However, the reaction didn't show significant selectivity, producing *N*-(methoxy(phenyl)methyl) aniline, methyl-*N*-phenyl benzimidate and *N*-phenylbenzamide as a mixture (**3q**-**3r**).

Table 2. Substrate scopes for the C-N coupling [a, b]

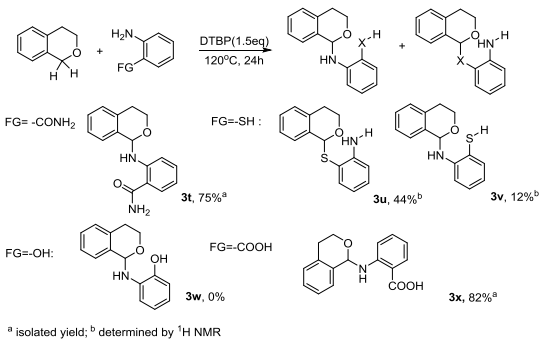




[a] Reaction conditions: aniline (1.3 mmol), isochroman (1 mmol), DTBP (1.5 mmol), neat, 120^{o}C, 16h. [b] Isolated yield.[c] the yield of product **4b** in Table 3. [d] by GC-Ms. [e] the yield of N-phenylbenzamide.

To further broaden the scope of our methodology, *ortho*-bifunctionalized substrates were then applied for the C-N coupling (Scheme 2). Interestingly, 2-aminobenzamide afforded **3t** as the only product. Likewise, 2-aminobenzoic acid afforded **3x** in the yield of 82%. However, two main products were obtained with 2-aminobenzenethiol. The ratio of C-S coupling product and C-N coupling product is nearly 3:1 (Scheme 2, **3u**, **3v**). 2-Aminophenol failed to this reaction may due to the instability of the substrate. From the results above, it may briefly concluded that, in this DTBP

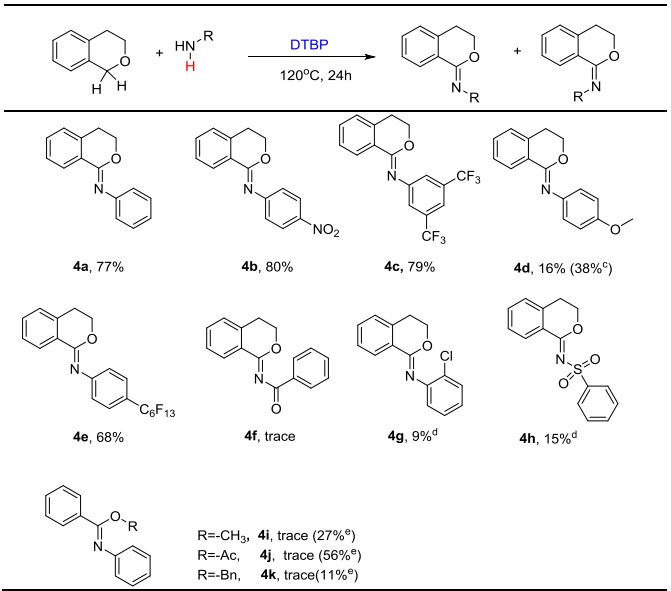
mediated CDC coupling, the reactivity order is -SH > -NH_2> -$CONH_2$, -COOH.



Scheme 2. The C-N coupling of isochroman and *ortho*-bifunctionalized amines.

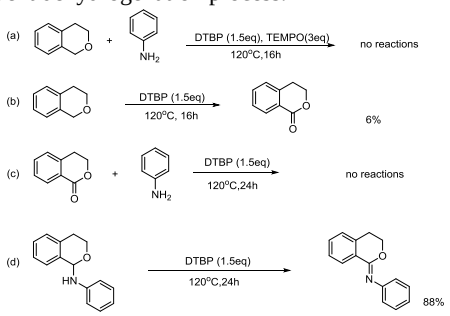
As mentioned above, the unexpected *N*-phenylisochroman-1-imine could be obtained under relatively harsher conditions. To explore the generality for the formation of imidate compounds, some representative amine or amide substrates were screened (Table 3). Aryl amines were found to be suitable for this transformation. Particularly, anilines substituted with electron-withdrawing groups such as $–CF_3$, $-NO_2$ smoothly coupled with isochroman to deliver the imidate in good yields (**4b**, **4c**). In contrast, substrate bearing methoxyl group was less reactive with *N*-(4-methoxyphenyl)isochroman-1-imine and *N*-(4-methoxyphenyl) isochroman- 1-amine obtained as a mixture in the yield of 16% and 38%, respectively (**4d**). The fluorous tail substituted aniline was also applied to the optimized conditions, giving the product **4e** in 68% yield. In regard to the benzamide and sulfamide, only trace of the product was formed due to its low reactivity (**4f**, **4h**). Linear benzylic ether (or ester) was also tried; N-phenylbenzamide instead of the desired imidate product was produced in moderate yield. Comparatively, benzyl acetate showed higher yields.

Table 3. Substrate scopes for the formation of imidate products



a Reaction conditions: aniline (1.3 mmol), isochroman (1 mmol), DTBP (3 mmol), neat, 120°C, 24h. b Isolated yield. c The yield of **3d**. d GC yield. e The yield of N-phenylbenzamide

A series of controlled experiments were then carried out to investigate the details of the mechanism for the C-N and C=N formation protocols (Scheme 3). Excess TEMPO was initially added as a radical inhibitor. As expected, no desired product was observed, indicating that the present reaction may follow a radical mechanism. Then we further tried to clarify the unexpected C=N formation process. Small amount of isochroman-1-one could be observed in the presence of DTBP without adding any coupling partners. It is possible that aniline reacted with the isochroman-1-one to afford the N-phenylisochroman-1-imine. However, the negative result of the reaction between isochroman-1-one and aniline excluded the possibility. In the course of the C=N formation process, *N*-phenylisochroman-1-amine may work as the intermediate and subsequent tracking of the reaction process have proved this point (Fig 1). In the reaction process, the C-N bond and C=N was formed successively by variation of time. Remarkably, the C-N formation and C=N formation could be selectively achieved because of the reactivity difference in the first C-H functionalization process and the subsequent dehydrogenation process.



Scheme 3 Controlled experiments

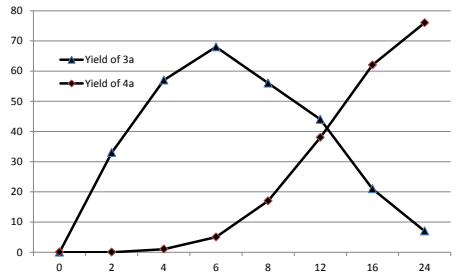
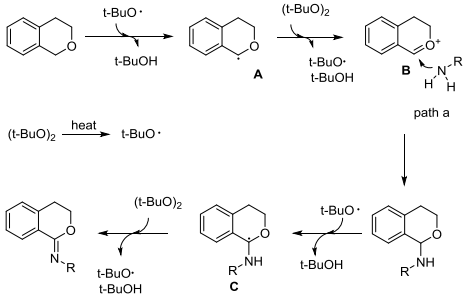


Fig 1 tracking of reaction process by variation of time

Based on the above experiments and the reported literatures[3e], a plausible reaction mechanism was proposed in Scheme 4. DTBP decomposed into the *tert*-butoxyl radical under heating. A hydrogen abstraction of the C–H bond adjacent to an oxygen atom produced intermediate **A**, which was further oxidized to intermediate **B**. Aniline then coupled with **B** giving the C-N formation product **3a**. When excess DTBP existed, the C-H bond of product **3a** could be further activated. Similarly, the hydrogen abstraction of the C–H bond adjacent to an oxygen atom produced intermediate **C**, which could finally lead to the imidate product **4a.**



Scheme 4 Proposed mechanism.

Conclusions

In summary, an unprecedented C−N formation *via* the direct oxidative cross-couplings of isochroman with amines (or amides) in the metal-free conditions has been developed. This protocol can also afford the unexpected C=N formation products in the excess amount of oxidant. Moreover, simple, metal- and base-free conditions, and atom-economic make this protocol more environmental friendly.

Notes and references

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Electronic Supplementary Information (ESI) available: [Experimental procedures; spectral data for all reported compounds. See DOI: 10.1039/b000000x/

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