Novel synthesis of divergent aryl imidazoles from ketones involving copper-catalyzed $\alpha$-amination and oxidative C–C bond cleavage†

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A one-pot synthesis, initiated by a copper salt with inorganic (NH$_4$)$_2$CO$_3$ as the nitrogen source, forms divergent aryl imidazole derivatives from ketones via $\alpha$-amination and oxidative C–C bond cleavage reactions. The approach provides a simple and rapid synthesis of imidazole derivatives and has certain versatility.

The aryl imidazole is a core skeleton for chiral ligands widely used in asymmetric synthesis, as well as many drug molecules and natural products that possess anti-cancer, anti-infection, anti-histamine, anti-ulcer, antihypertensive, and anti-malarial activities (Fig. 1). Therefore, how to construct an aryl imidazole core is of great significance and has been extensively studied for the development of different synthetic methods.

As early as 1858, imidazoles were first synthesized by Heinrich Debus’ research group, and many other synthetic methods have been reported since then. These include the Bredereck synthetic method, the Leusen reaction, the Debus-Radziszewski reaction, the Claisen rearrangement reaction, the Phillips method, the isonitrile synthesis, and the ketones method (Scheme 1a). These methods mostly involved the traditional amination process which typically employs indirect sources including iodoimines, chloramines T, organic azides, hydroxylamines, NFSI, aromatic nitroso derivatives, and other organic nitrogen-containing compounds. Furthermore, it is surprising that the catalytic $\alpha$-amination of the ketone results in a small amount of amide. Herein, we report a novel approach for the synthesis of imidazole derivatives.

Following our interest in tandem metal-catalyzed transformation for the heterocyclic synthesis, especially the $\alpha$-amination catalyzed by transition metal complexes, which is an attractive reaction for the synthesis of amine derivatives and amino-functionalized heterocycles, we explored the metal-catalyzed $\alpha$-amination reaction of ketones using ammonia released from ammonium carbonate. In transition metal-catalyzed amination, the simple inorganic ammonium salts as the nitrogen source is a change from the conventional nitrogen sources including iodoamines, chloramines T, organic azides, hydroxylamines, NFSI, aromatic nitroso derivatives, and other organic nitrogen-containing compounds. Furthermore, it is surprising that the catalytic $\alpha$-amination of the ketone results in the tandem reactions for the synthesis of imidazole while producing a small amount of amide. Herein, we report a novel approach for the synthesis of imidazole derivatives.

Fig. 1 Bioactive molecules containing aryl imidazole.
approach of imidazole formation involving $\alpha$-amination and C–C bond cleavage reaction with an excellent substrate scope.

Firstly, using propiophenone as the substrate, we investigated the effect of different reaction conditions on the reaction. As shown in ESI Table 1.† The use of inexpensive ammonium carbonate as a nitrogen source and copper iodide as a catalyst and readily available starting materials makes this protocol economically visible.

Under the optimal reaction conditions, we explored the substrate scope of the reaction (Scheme 2). In this investigation, the corresponding imidazole derivatives (2a–2p) were obtained from the reaction of a series of aromatic ketones. The results show that the substrates with electron-withdrawing groups on the aromatic ring have higher reactivity than the substrates with electron-donating substituents on the aromatic ring with the exception of 2k. The substrates containing electron-withdrawing groups on the aromatic ring afforded moderate to high yield of the imidazole products (2b–2g). In addition, the alkyl chain length of the aryl alkyl ketones also affected the yields of the reaction, and the longer the chain length, the lower the reactivity (2n, 2o). The $\alpha$-aryl substituted aromatic ketones also can afford the corresponding imidazole product (2p).

To understand the reaction for novel imidazole synthesis well, we designed a series of experiments to observe the special effects of some conditions on the imidazole synthesis (see ESI†). The effect of the nitrogen source on the reaction was first investigated. No reaction occurred in the absence of (NH$_4$)$_2$CO$_3$. This result indicates that (NH$_4$)$_2$CO$_3$ is really a nitrogen source for the reaction and it may decompose into ammonia to form a complex with copper and participates in the catalytic cycle. To confirm this point, ammonia-saturated methanol was used as the reaction solvent. The reaction occurred, but the yield of the corresponding product was only 46%. This lower yield may be due to the fact that only a limited amount of ammonia dissolved in methanol. Subsequently, the copper–ammonia complex (Cu[NH$_3$]$_4$SO$_4$) was prepared by the reaction of the copper salt with excess ammonia water and was used in the reaction. The result shows that the product was obtained in 72% yield, which confirmed that the copper–ammonia complex was not only the catalyst of the reaction, but also the nitrogen source. In addition, the effects of air and water on the reaction were also investigated. In the absence of water (anhydrous methanol) or air, no target product was obtained, indicating that water and air play an important role in the cleavage of C–C bond of propiophenone. Further, to confirm the $\alpha$-C–H activation and $\alpha$-amination in the imidazole formation, $\alpha$-perdeuterated propiophenone was used as the substrate using deuterated methanol as a solvent in the presence of dry air and D$_2$O, the product was obtained in only 11% yield. The results show that C–H activation is a prerequisite for the reaction process.

In addition, referring to the C–C bond cleavage reaction, during the formation of imidazoles, we speculated that a portion of propiophenone may undergo cleavage of the C–C bond to produce an aldehyde. In order to confirm this, benzaldehyde was added to the reaction system, and only trace amount of original product 2a was found. In contrast, the corresponding aldehyde condensation products was obtained in yields of 66%, respectively. If 4 equivalents of benzaldehyde are added, the formation of 2a can also be completely inhibited. The results indicate that a competitive reaction occurs when an excess of other aldehyde is present, and the root cause is related to more rapidly $\alpha$-amination than the cleavage of the C–C bond of propiophenone during the reaction. The experimental results

![Scheme 1](image-url)
make us to use other aldehydes and ketones in the synthesis of divergent aryl imidazoles. As shown in Scheme 3, divergent imidazoles were obtained in excellent yield by adding four equivalents of the aldehyde to the reaction system. Both aliphatic and aromatic aldehydes yield the ideal results, but ketones failed to afford pure corresponding products, the reaction is messy and complicated. It is interesting that when 1,2-diarylethan-1-one replaces propiophenone 1a, the addition of ketones resulted in the formation of corresponding 2H-imidazoles (Scheme 4). Meanwhile, the formation of 4j further indicates that the reaction rate of \( \alpha \)-amination is faster than that of C–C bond cleavage. The structures of 2d and 3m, 4a were further confirmed by the X-ray single crystal analysis (the detailed crystal data are provided in the ESI†).

At the same time, ethylamine was used as a nitrogen source and phenylacetone as a substrate to react under the same reaction conditions. The intermediates \( \alpha \)-ethylphenylacetone, (E)-ethylacetone-1-(ethylimino)-1-phenyl-propan-2-amine and...
\(N\)-ethylbenzamide and their products 1,3-diethyl-4-methyl-1-phenyl-2,3-dihydro-1H-imidazole were found by LC-MS (see ES1).

On the basis of experimental results and the previously proposed mechanisms, a reaction pathway for aryl imidazole synthesis was proposed (Scheme 5). First, \(\text{Cu}(I)\) is oxidized to \(\text{Cu}(II)\) under an oxygen atmosphere. The \(\text{Cu}(II)\) species then forms a complex with ammonia (released from ammonium carbonate). Subsequently, the copper-ammonia complex reacts with the substrate to give intermediate A. A is converted into intermediate B after loss of a proton. B then undergoes a disproportionation reaction with \(\text{NH}_2\) insertion to afford intermediate C. Intermediate D occurs via cleavage of C-C bond. Intermediate E forms via ammonia 1,2-addition to species D. The intermediate E is then dehydrated to form compound F. Simultaneously, \(\text{O}_2\) insertion into the C-Cu bond of intermediate A results in intermediate G. Addition of water then forms intermediate H. An aldehyde is then formed by electron transfer and cleavage of the C-C bond. Finally, the nucleophilic addition reaction of the aldehyde with intermediate F occurs to obtain the imidazole product by further dehydration and loss of a proton.

In conclusion, under copper catalysis, the aryl alkyl ketones were reacted with an inorganic salt \((\text{NH}_4)_2\text{CO}_3\) in one-pot to form the imidazole derivatives by C-H activatedamination and C-C oxidative cleavage. We speculate that in the imidazole synthesis, a portion of aryl alkyl ketones underwent the C-C bond cleavage, and the cleavage fragment is further subjected to a multicomponent cascade reaction with other reaction intermediates to form imidazole derivatives. The approach provides a simple and rapid synthesis for imidazole derivatives and has certain versatility. When the applicability of the reaction was further explored, it was found that the addition of other aldehydes in the reaction of the arylalkyl ketone inhibited the formation of the original product, but produced a new imidazole derivative formed by condensation with the aldehydes. In the aryl alkyl ketone reaction, the addition of other aldehydes and ketones can produce more diverse imidazole derivatives.

Conflicts of interest

There are no conflicts to declare.

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