Iron-Catalyzed Acceptorless Dehydrogenative Coupling of Alcohols With Aromatic Diamines: Selective Synthesis of 1,2-Disubstituted Benzimidazoles

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Benzimidazoles are important N-heteroaromatic compounds with various biological activities and pharmacological applications. Herein, we present the first iron-catalyzed selective synthesis of 1,2-disubstituted benzimidazoles via acceptorless dehydrogenative coupling of primary alcohols with aromatic diamines. The tricarbonyl (η⁴-cyclopentadienone) iron complex catalyzed dehydrogenative cyclization, releasing water and hydrogen gas as by-products. The earth abundance and low toxicity of iron metal enable the provision of an eco-friendly and efficient catalytic method for the synthesis of benzimidazoles.

Keywords: iron catalysis, dehydrogenative coupling, borrowing hydrogen, alcohol, benzimidazoles

INTRODUCTION

Benzimidazoles, which have been found in pharmaceuticals and natural products, are important N-heteroaromatic structural motifs because of their biological activities (Bansal and Silakari, 2012; Chandrika et al., 2016; Suk et al., 2019). Of these, the 1,2-disubstituted benzimidazole is considered a privileged scaffold in drug discovery. As shown in Figure 1, many drugs contain this moiety in their structures, for example, maribavir (antiviral), mizolastine (antihistamine), and telmisartan and candesartan (antihypertensive). Furthermore, 1,2-disubstituted benzimidazoles show various biological activities, such as anticancer (Zimmermann et al., 2013, 2014) antibacterial (Bandyopadhyay et al., 2011; Göker et al., 2016), antiallergic (Nakano et al., 2000), and anti-HIV (Morningstar et al., 2007) traits along with cannabinoid-1 (CB1) and cannabinoid-2 (CB2) receptors (Watson et al., 2011; Nanda et al., 2014). Based on their attractive biological profiles, the synthesis of 1,2-disubstituted benzimidazoles has gained the interest of synthetic chemists.

Diverse synthetic approaches have been reported for the synthesis of 1,2-disubstituted benzimidazoles (Scheme 1). The first is the respective substitution on the C-1 or N-2 position of the preformed benzimidazoles, (i) N-alkylation of 2-substituted benzimidazoles (Ramla et al., 2007; Martin et al., 2015) and (ii) Suzuki coupling of aryl boronic acids with 1-halo-2-alkylbenzimidazoles (Wang and Smith, 2003; Martin et al., 2015). Another approach is the classic cyclocondensation of (iii) N-alkyl-N-acyl-1,2-diaminobenzene (Smith and Krchnák, 1999; Takeuchi et al., 2000) or (iv) N-alkyl-1,2-diaminobenzene with aldehyde (Smith and Krchnák, 1999; Özden et al., 2005).
In addition, a large number of (v) direct one-pot
cyclocondensations of 1,2-diaminobenzene with aldehydes
have been reported (Chebolu et al., 2012; Girish et al., 2015;
Sharma et al., 2015). This appears to be a straightforward
approach; however, selectivity control between 2-substituted and
1,2-disubstituted benzimidazoles is often problematic.

During the past decade, the borrowing hydrogen (BH)
strategy has become a powerful tool for the benign and
sustainable construction of C–N bonds using abundant alcohols
as coupling reagents (Mutti et al., 2015; Yang et al., 2015).
C–N bond couplings through BH usually proceed in the
following sequence (Figure 2, blue): dehydrogenation of an
alcohol to the corresponding carbonyl compound, followed by
condensation and reduction of imine using the borrowed H₂
from the alcohol. If the imine participates in the aromatic system,
the last hydrogenation step is suppressed, and the hydrogen
gas is liberated (Figure 2, red), so it is called acceptorless
derehydrogenative coupling (ADC). ADCs are highly efficient and
environmentally benign methods to construct N-heteroaromatic
structures since water and hydrogen gas are the only valuable
by-products (Gunanathan and Milstein, 2013; Michlik and
Kempe, 2013; Nandakumar et al., 2015). In recent years,
considerable progress has been directed toward the synthesis of
benzimidazole involving dehydrogenative coupling (Scheme 2);
however, most of these methods use precious noble metals, such
as Ru- (Blacker et al., 2009; Li et al., 2018), Ir- (Hille et al.,
2014; Sharma et al., 2017), and Pd-based catalysts (Mori et al.,
2019). The replacement of noble-metal catalysts by inexpensive
and environmentally friendly earth-abundant base metals is an
important task for organic chemists. Among the base metals,
Cu- (Xu et al., 2017, 2018), Co- (Daw et al., 2017), Ni-
(Bera et al., 2019), and Mn-based catalysts (Das et al., 2018; Zhang et al., 2019) have been well-applied in the condensation of alcohols with 1,2-diaminobenzene to benzimidazoles. However, many of these metal complexes utilize quite expensive or labile ligands to achieve higher product yields, which is a major concern in comparison to the advantages of base metals. Iron is the second most earth-abundant and highly desirable metal catalyst in the synthesis of pharmaceuticals due to its low toxicity (Bauer and Knölker, 2015; Fürstner, 2016). The tricarbonyl (η4-cyclopentadienone) iron complexes were initially described by Knölker (Knölker et al., 1999), and they have a core bifunctional structure to mediate the BH process consisting of both a proton-donor site (ligand) and a hydride-donor site (metal center) (Ikariya and Blacker, 2007). Since it was first developed, Knölker’s complex has been widely applied in C–N or C–C bond formation through a BH strategy (Yang et al., 2014; Brown et al., 2017; Reed-Berendt et al., 2019). Based on the previous results, we envisioned the possibility of iron-catalyzed direct benzimidazole formation starting from 1,2-diaminobenzene and alcohol via the ADC strategy. To the best of our knowledge, the synthesis of benzimidazoles directly from 1,2-diaminobenzene and alcohol catalyzed by iron has not been reported. Herein, we describe a selective method to synthesize 1,2-disubstituted benzimidazoles using Knölker-type iron complexes as a catalyst.

**MATERIALS AND METHODS**

All catalytic reactions were carried out under nitrogen atmosphere using a Schlenk flask. Fe complexes cat. I–V (Moulin et al., 2013) and cat. VI (Dambatta et al., 2019) were prepared according to the literature. All commercially available reagents and solvents (purchased from Sigma-Aldrich, TCI, Alfa-Aesar and Acros) were used without further purification unless otherwise noted. Reactions were monitored by thin-layer chromatography on silica gel 60 F254 plate using UV illumination at 254 nm. Column chromatography was performed on silica gel (230–400 mesh), using a mixture of hexane and ethyl acetate as eluents. Nuclear magnetic resonance (1H-NMR 400 MHz (1H), 100 MHz (13C)), using CDCl3 as solvent. It was reported in ppm relative to CDCl3 (δ 7.26) for 1H-NMR and relative to the central CDCl3 (δ 77.16) for 13C-NMR. Coupling constants (J) in 1H-NMR and 13C-NMR are in hertz. All high-resolution mass spectra (HR-MS) were acquired under fast atom bombardment (FAB) condition on a JMS-700 MStation mass spectrometer. Melting points were measured on a Büchi B-540 melting point apparatus and were not corrected. X-ray diffraction studies were carried out in a Super Nova, Dual, Mo at home/near, Atlas S2 diffractometer.

**General Procedure for the Synthesis of 1-Benzyl-2-aryl-1H-benzo[d]imidazoles (3)**

In a 15-ml Schlenk flask, a mixture of 1,2-diaminobenzene (1a, 54.05 mg, 0.5 mmol), alcohol (2, 1.5 mmol), 1BuOK (84.16 mg, 0.75 mmol), cat. I (8.36 mg, 0.02 mmol), and TMAO (3.0 mg, 0.04 mmol) was stirred at 150°C in xylene (2 mL) for 24 h under a nitrogen atmosphere. Then, the reaction mixture was cooled to room temperature and diluted with dichloromethane. After removing the solvent, the resulting residue was further purified by column chromatography on silica gel using 10–30% ethyl acetate in hexane as an eluent to obtain the desired benzimidazoles.

**RESULTS AND DISCUSSION**

In a preliminary study, we explored the feasibility of benzimidazole formation between 1,2-diaminobenzene 1a and benzyl alcohol 2a using standard Knölker complex cat. I (Table 1). The reaction was carried out in toluene, and trimethylamine N-oxide (TMAO) was used to activate cat. I and liberate a vacant site in situ. In the first trial, no benzimidazole products were formed in the absence of a base (entry 1). Based on previous reports (Xu et al., 2017; Das et al., 2018), we expected that a stoichiometric amount of base is required for benzimidazole formation. Various kinds of bases were screened in the reaction system, and 1BuOK was found to be a more effective base than KOH and K2CO3 for the formation of 1,2-disubstituted benzimidazoles 3a (entries 2–4). Surprisingly, we could not detect any 2-mono-substituted benzimidazole product in the reaction. Higher conversion was achieved when

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Putta et al. Benzimidazole Synthesis via Dehydrogenative Coupling

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**Scheme 2** | Transition metal catalyzed 1,2-disubstituted benzimidazole synthesis via dehydrogenative coupling of alcohol.
the reaction temperature was increased from 130 to 150°C (entries 4 and 5). Next, we examined the efficacy of different solvents and neat conditions, and the best yield of 3a (85%) was obtained in xylene (entries 5–8). The control experiment was also performed, and it was revealed that no desired product was obtained in the absence of a catalyst, demonstrating a crucial role of iron complex in the dehydrogenative coupling (entry 9). Additionally, we tried to reduce the amount of alcohol 2a and base in the reaction; however, slightly lower yields were observed (entries 10 and 11). To investigate a feasibility for the selective synthesis of 2-mono-substituted benzimidazole, 1.0 equivalent of 2a was reacted with 1a. Unfortunately, 1,2-disubstituted and 2-substituted benzimidazoles were obtained in 17 and 6% yields, respectively (entry 12).

As we were optimizing the reaction conditions, the effect of the amount of catalyst was also investigated (Table 2). Decreasing the loading of catalyst from 4 to 3 mol% resulted in 80% yield of desired product 3a, and a small amount of dime al substrate 1a remained. Interestingly, when we increased the catalyst loading to 5 mol%, a significantly decreased yield of 3a and increased formation of N,N-dibenzylbenzene-1,2-diamine 4 were observed. We supposed that a large amount of catalyst accelerated imine reduction competitively with the annulation process. Various Knölker-type complexes were also explored to estimate their activity in the reaction, and the results are shown in Table 2. The cat. VI gave desired product 3a in good yield (80%), similar to that of cat. I. However, the cat. II and IV showed moderate efficiency and cat. III and V resulted in low efficiency. Based on the above results, we choose the optimal dehydrogenative coupling conditions as diamine 1 (1.0 equiv.), alcohol 2 (3.0 equiv.), cat. I (4 mol%), TMAO (8 mol%), and BuOK (1.5 equiv.) in xylene (2 ml) at 150°C under N₂ for 24 h.

We applied the optimized conditions on a variety of diamines 1 and alcohols 2 to explore the reaction scope. First, a wide range of alcohol 2 was employed for annulation with 1a (Table 3). Benzyl alcohols containing electron-donating groups in the phenyl ring showed good yields (3b–f, 75–83%). The steric effect slightly influenced the formation of the desired product, depending on the position of the substituent. Substrates with substituents at the ortho position showed slightly lower yields than those of meta- and para-substituted analogs (yield sequence order: para > meta > ortho). 4-Chlorobenzyl alcohol afforded excellent yield for the corresponding product (3g, 92%), whereas low yield was obtained in the case of bromo- and iodo-substituted analogs with loss of one halogen atom (3h and 3i, 52–59%). This partial dehalogenation might be involved in the hydrogenative activity of the hydrogenated iron complex, which could be formed in situ. The molecular structure of 3i was confirmed by X-ray crystal structure as shown in Table 3. XRD data showed that the N-substituted benzyl group has iodine and C-2-substituted phenyl ring loose iodine. A series of alcohols containing heterocycles, such as furan, thiophene, and pyridine, were well-applied and afforded the desired products in good yields (3j–l, 72–82%). In the case of 1,3-benzodioxole-5-methanol and 4-trifluoromethyl benzyl alcohol, the desired products were obtained in moderate yield even if a longer reaction time is needed for full conversion (3m and 3n, 67–68%). Additionally, 1-naphthalene methanol was also applied in the reaction system and gave the corresponding product in high yield (3o, 85%). For further expansion of the alcohol scope, aliphatic alcohols such as 1-hexanol and 3-phenyl propanol were also investigated. Aliphatic alcohols could participate in dehydrogenative coupling; however, desired products were obtained in low yields (3p–q, 38–40%). After the screening of alcohols, the scope of diamine 1 was

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**Table 1** | Optimization of the reaction conditions.

| Entry | Alcohol (eq) | base (eq) | Solvent | T (°C) | Yield (%) |
|-------|--------------|-----------|---------|--------|-----------|
| 1     | 3            | –         | Toluene | 130    | –         |
| 2     | 3            | K₂CO₃ (1.5)| Toluene | 130    | Trace     |
| 3     | 3            | KOH (1.5) | Toluene | 130    | 21        |
| 4     | 3            | ¹BuOK (1.5)| Toluene | 130    | 42        |
| 5     | 3            | ¹BuOK (1.5)| Toluene | 150    | 61        |
| 6     | 3            | ¹BuOK (1.5)| Dioxane | 150    | 31        |
| 7     | 3            | ¹BuOK (1.5)| Xylene | 150    | 85        |
| 8     | 3            | ¹BuOK (1.5)| Xylene | 150    | 53        |
| 9     | 3            | ¹BuOK (1.5)| Xylene | 150    | –         |
| 10    | 3            | ¹BuOK (1.5)| Xylene | 150    | 81        |
| 11    | 2.5          | ¹BuOK (1.5)| Xylene | 150    | 80        |
| 12²   | 1            | ¹BuOK (1.5)| Xylene | 150    | 17        |

²Reaction conditions: 1a (0.5 mmol), 2a (0.5–1.5 mmol), base (0.6–0.75 mmol), cat. I (0.02 mmol), TMAO (0.04 mmol), and solvent (2 ml) in a Schlenk flask under N₂, 24 h.
³Isolated yield.
⁴No catalyst loading.
⁵2-Mono-substituted benzimidazole product was obtained with 3a in 6% yield.

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**Table 2** | Catalyst screening.

| Entry | Alcohol (eq) | base (eq) | Solvent | T (°C) | Yield (%) |
|-------|--------------|-----------|---------|--------|-----------|
| 1     | 3            | –         | Toluene | 130    | –         |
| 2     | 3            | K₂CO₃ (1.5)| Toluene | 130    | Trace     |
| 3     | 3            | KOH (1.5) | Toluene | 130    | 21        |
| 4     | 3            | ¹BuOK (1.5)| Toluene | 130    | 42        |
| 5     | 3            | ¹BuOK (1.5)| Toluene | 150    | 61        |
| 6     | 3            | ¹BuOK (1.5)| Dioxane | 150    | 31        |
| 7     | 3            | ¹BuOK (1.5)| Xylene | 150    | 85        |
| 8     | 3            | ¹BuOK (1.5)| Xylene | 150    | 53        |
| 9     | 3            | ¹BuOK (1.5)| Xylene | 150    | –         |
| 10    | 3            | ¹BuOK (1.5)| Xylene | 150    | 81        |
| 11    | 2.5          | ¹BuOK (1.5)| Xylene | 150    | 80        |
| 12²   | 1            | ¹BuOK (1.5)| Xylene | 150    | 17        |

²Reaction conditions: 1a (0.5 mmol), 2a (1.5 mmol), BuOK (0.75 mmol), cat. I (0.02 mmol), TMAO (0.04 mmol), and xylene (2 ml) in Schlenk flasks under N₂, 24 h, 150°C.
³Isolated yield in parentheses.
⁴Cat. I (0.015 mmol) and TMAO (0.03 mmol).
⁵Cat. I (0.025 mmol) and TMAO (0.05 mmol).
⁶Cat. I (0.025 mmol) and TMAO (0.05 mmol).
TABLE 3 | Scope of alcohols⁴,⁵.

| Reaction conditions: 1a (0.5 mmol), 2 (1.5 mmol), tBuOK (0.75 mmol), cat. I (0.02 mmol), TMAO (0.04 mmol), and xylene (2 ml) in a Schlenk flask under N₂, 24 h, 150 °C. |
|---|
| Isolated yield in parentheses. |
| R = aryl, heteroaryl, alkyl |
| 3a (85%) |
| 3b (82%) |
| 3c (78%) |
| 3d (83%) |
| 3e (75%) |
| 3f (81%) |

TABLE 4 | Scope of diamines⁴,⁵.

| Reaction conditions: 1 (0.5 mmol), 2a (1.5 mmol), tBuOK (0.75 mmol), cat. I (0.02 mmol), TMAO (0.04 mmol), and xylene (2 ml) in a Schlenk flask under N₂, 24 h, 150 °C. |
|---|
| Isolated yield in parentheses. |
| Mixture could not be isolated. |
| 5a (81%) |
| 5b (81%) |
| 5c (26%+56%) |
| 5d (20%) |

TABLE 5 | Synthesis of 1,2-disubstituted benzimidazoles from 6⁴,⁵.

| Reaction conditions: 6 (0.25 mmol), 2 (0.325 mmol), tBuOK (0.25 mmol), cat. I (0.005 mmol), TMAO (0.01 mmol), and xylene (2 ml) in a Schlenk flask under N₂, 24 h, 150 °C. |
|---|
| Isolated yield in parentheses. |
| 7a (80%) |
| 7b (70%) |
| 7c (81%) |

also investigated (Table 4). Under the same conditions, the reaction of 4,5-dimethyl-1,2-diaminobenzene with 2a proceeded smoothly and afforded the product in was also investigated good yield (5a, 81%). On the other hand, 3,4-diaminotoluene and 4-chloro-1,2-diaminobenzene gave a mixture of 1-benzyl-2-phenyl-benzimidazole products (5b and 5c). To explore the possibility of imidazole formation, we employed 1,2-diphenyl-1,2-ethylenediamine as a substrate. Unfortunately, the corresponding imidazole product was obtained in very low yield (5d, 20%).
The above successful results led us to further investigate the reaction generality. *N*-Benzy1-1,2-diaminobenzene 6 was designed for the selective introduction of a substituent on the *N*-1 or *C*-2 position of benzimidazole. As shown in Table 5, benzylic alcohol 2 usually participates in the annihilation process and is located on *C*-2 and its substituents on the benzimidazole product (7a–e). In contrast, five-membered heteroaromatic methyl alcohols gave *N*-1-heteroarylmethyl-*C*-2-phenyl-benzimidazole products (7f and 7g). This opposite selectivity is expected to depend on the electron density of the aromatic group. Furthermore, we applied the iron complex to achieve the direct *N*-alkylation of benzimidazole 8 with 2a (Scheme 3). Unfortunately, no desired product was observed; however, this result suggests that the reaction mechanism did not proceed through benzimidazole as an intermediate. Besides benzimidazole, 2-phenyl benzothiazole 10 was also successfully synthesized in high yield (87%) using 2-aminobenzenethiol 9 under optimized reaction conditions (Scheme 4).

Based on the above observations and previous reports (Xu et al., 2017, 2018; Das et al., 2018), we proposed a plausible mechanism as shown in Scheme 5. Initially, aldehyde A was generated from alcohol via iron-catalyzed dehydrogenation. Then, the formation of bisimine intermediate B took place through the condensation of diamine 1 with aldehyde 1. Bisimine B underwent intramolecular cyclization, followed by rearrangement to give 1,2-disubstituted benzimidazole 3 (Path a) (Chebolu et al., 2012). As mentioned in Table 2, we also identified diamine 4 as a side product, which might be generated from bisimine B through Fe-H₂-mediated hydrogenation. On the other hand, *N*-benzy1-1,2-diaminobenzene 6 also reacted with the aldehyde A and generated imine intermediate D.
CONCLUSION

In conclusion, we have reported the first iron-catalyzed synthesis of 1,2-disubstituted benzimidazoles using alcohol oxidation-level substrates via the ADC strategy. The Knölker-type catalysts, tricarbonyl (η⁵-cyclopentadienone) iron complexes, were successfully employed in the dehydrogenative coupling of alcohol with 1,2-diaminobenzene, followed by annulation to give the 1,2-disubstituted benzimidazole products in good yields. Under the developed conditions, the reaction of N-benzyl-1,2-diaminobenzene with alcohols also provided 1,2-disubstituted benzimidazoles, and the regioselectivity of the substituents depends on the electron density of the alcohol substrate. In addition to benzimidazole, benzothiazole was also synthesized well using the developed method. Iron is an earth-abundant and low-toxicity metal, and water and hydrogen gas are liberated as by-products in the reaction. Therefore, this methodology provides an eco-friendly alternative for the selective synthesis of 1,2-disubstituted benzimidazoles.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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