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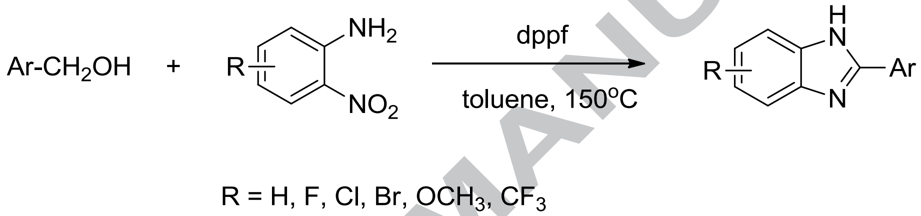

We herein report a new efficient method for the synthesis of benzimidazoles with hydrogen transfer procedure. This method involves alcohol oxidation, nitro reduction, condensation and dehydrogenation in a cascade.

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[*] Corresponding author. Tel.: +86 10 63165244; fax: +86 10 63165244; e-mail: joyce@imm.ac.cn

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Abstract: The iron-catalyzed heterocyclizations from 2-nitroanilines and benzylic alcohols to form benzimidazoles using hydrogen transfer reaction were investigated in this study. In the presence of dppf in toluene at 150°C, various benzimidazoles were obtained in moderate to good yields within 24 h. The reaction was proposed to proceed via a cascade of alcohol oxidation, nitro reduction, condensation and dehydrogenation.

Key words: benzimidazole, hydrogen transfer, dppf, one-pot synthesis.

Benzimidazoles are present as useful building blocks for the development of molecules that are important in medicinal chemistry. This moiety is frequently used as an important pharmacophore in drug discovery. Substituted benzimidazoles have been extensively studied for their antiviral, antifungal, antiulcer, antihypertensive, antihistaminic and anticancer activities.[1] Thus, various synthetic methods have been developed to construct substituted benzimidazoles, with the most common method being the heterocyclization of *o*-diaminoarenes with carboxylic acids or their derivatives under acidic conditions and several other conditions.[2]

Recently the benzimidazole formation from *o*-diaminobenzene and benzylic alcohol under oxidative conditions, using hydrogen transfer reaction has been developed.[3] Inspired by this highly atom economic method, we pay more attention to the application and mechanism of hydrogen transfer reaction. Hydrogen transfer reaction was widely used for the oxidation of a range of organic substrates. In particular, the oxidation of alcohols to carbonyl compounds by hydrogen transfer to a suitable acceptor represents a useful alternative to other oxidation reactions.[4] More recently, using hydrogen transfer reaction, a simple and efficient iron-catalyzed one-pot synthesis of benzoxazole has been reported.[5] We believe that the same concept can be applied to the synthesis of benzimidazoles as the reaction mechanism may be similar to that of the benzoxazole formation reaction. Herein we report the development of one-pot synthesis of iron-catalyzed heterocyclization toward benzimidazoles starting from 2-nitroanilines and benzylic alcohols.

First we screened various iron salts, temperature and solvent that might promote the heterocyclization (**Table 1**).The results indicated that dppf [1,1’-bis(diphenylphosphino)-ferrocene] was the most effective, and its use resulted in the formation of **3a** in 74% yield (**entry 4**).[6] The choice of solvents was also crucial for the reaction. The use of xylene resulted much lower yield and PEG400 gave no reaction. Toluene and benzylic alcohol were proved to be good solvents for this reaction(**entry 4, 6**). Benzylic alcohol was not easy to remove so we chose toluene as the reaction solvent. The reaction temperature plays a key role in this reaction. The reaction yield decreased to 30% when the temperature was decreased from 150^{o}C to 130^{o}C. The reaction could also be carried out at normal atmospheric pressure under argon with moderate yield (**entry 7**).

Encouraged by this promising result, the scope of the method for benzimidazole synthesis was then investigated. To our delight, the substituted benzylic alcohol substrates **1a-m** smoothly underwent heterocyclization to afford benzimidazoles **3a-m** in good yields. However, when allyl alcohol **1n** and ethanol **1o** were used as substrates to react with 2-nitroaniline **2a** under the optimized conditions respectively, the reactions did not occur (**Table 2**). It was noticed that the benzylic alcohol substrates with electron-donating groups and halogen substituents, such as **1b, 1c, 1d, 1f, 1k, 1l** and **1m** gave higher yields, while substrates bearing electron-withdrawing groups such as **1i** and **1j** gave lower yields. Moreover, the coupling of hetero benzylic alcohols such as **1g, 1h** and **1i** with **2a** afforded **3g, 3h** and **3i**, respectively, in moderate yields. In addition, phenylallylic alcohol **1e** reacted with **2a** to smoothly afford **3e** in 71% yield.

To further explore the scope of the reaction, various 2-nitroanilines with electron-donating and electron-withdrawing substituent were employed to react with **1a** under the optimized conditions (**Table 3**). The desired products were obtained in moderate to good yields and a series of functional groups including fluoro, chloro, bromo, trifluoromethyl and methoxy were well tolerated under the optimal reaction conditions (**entries 1-7**). It was noticed that the 2-nitroanilines with single halogen substituent, such as **2a, 2b** and **2c** gave higher yields, while 2-nitroanilines with multiple halogen substituents, such as **2d** and **2e** gave moderate yields. Compounds with electron-donating group (**2g**) and strong electron-withdrawing group (**2f**) gave lower yields under optimized conditions.

In order to clarify the proposed reaction mechanism, three reactions in **Scheme 1** were run and it was found that the reaction hardly occurred before the first hydrogen transfer reaction of **1a** to **A** and **2a** to **B**. So the first hydrogen transfer reaction was the rate-determining step of this transformation. After the important step, the reaction smoothly proceeded to the desired product **3a**. We also monitored the reaction at 2h, 6h, 12h and 24h. We can only observe the desired product **3a** and starting materials at these time points, without **C** and **D** in **Scheme 1**. The result told us that when intermediate **A** and **B** were generated, the following condensation and dehydrogenation were very fast.

A plausible mechanism based on our experiments and previous articles is proposed in **Scheme 2**.[3,5,7] Firstly, the benzylic alcohol **1a** is oxidized to the corresponding aldehyde **A** and in the meantime **2a** is reduced to **B** by hydrogen transfer. Then aldehyde **A** is then condensed with **B** to form **C**. Intramolecular cyclization of **C** generates dihydrobenzimidazole **D**. At last, dehydrogenation of **D** affords the desired product **3a** by a second hydrogen-transfer process. The nitro group acts as a hydrogen acceptor twice in the whole process. Oxidation of **1a** where aromatization could act as a driving force for loss of hydrogen is crucial for this reaction. Most of the benzylic alcohol substrates with electron-donating groups are easier to be oxidized and this could be the possible reason why benzylic alcohol substrates with electron-donating groups gave higher yields.

In conclusion, we have described a simple and efficient method for an iron-catalyzed reaction to prepare benzimidazoles from 2-nitroanilines and benzylic alcohols by hydrogen transfer reaction. This method involves alcohol oxidation, nitro reduction, condensation and dehydrogenation in a cascade. This useful method could potentially be complementary to the existing methods for the synthesis of benzimidazoles.

Acknowledgements

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References and notes

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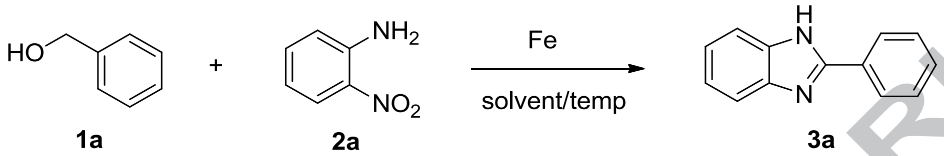
5. Wu, M.; Hu, X.; Liu, J.; Liao, Y.; Deng, G. J. *Org. Lett.* **2012,** *14*, 2722.
6. **General procedure:** the preparation of 2-phenyl-1*H*-benzoimidazole (**3a**): A 15 mL capped tube was charged with 2-nitroaniline (0.36 mmol), benzyl alcohol (0.094 mL, 0.90 mmol) and dppf (0.018 mmol). The tube was flushed with argon for 10 min. Then the degassed toluene (3 mL) was added. The tube was flushed with argon, capped, and heated at 150^{o}C for 24 h. After cooling to room temperature, the reaction mixture was then concentrated in vacuo, and the residue was purified by column chromatography (silica gel, petroleum ether/ ethyl acetate=4:1) to afford the pure **3a** as a white solid. The product was identified by NMR and MS and the data are identical to the reported values.
7. Kim, J.; Kim, J.; Lee, H.; Lee, B. M.; Kim, B. H. *Tetrahedron* **2011,** *67*, 8027.

Table 1

Iron-catalyzed heterocyclization of 2-nitroaniline (1 equiv) with benzylic alcohol (2.5 equiv) under different reaction conditions



Entry	Catalyst[c]	Temperature(℃)	Solvent	Yield[d](%)
1[a]	dppf	90	toluene	trace
2[a]	dppf	110	toluene	trace
3[a]	dppf	130	toluene	30
4[a]	dppf	150	toluene	74
5[a]	dppf	150	xylene	36
6[a]	dppf	150	benzyl alcohol	78
7[b]	dppf	150	benzyl alcohol	50
8[a]	dppf	150	PEG400	NR[e]
9[a]	$FeSO_4$	150	toluene	trace
10[a]	$Fe(NO_3)_3$	150	toluene	trace
11[a]	$FeCl_2$	150	toluene	trace
12[a]	$FeCl_3$	150	toluene	trace
13[a]	ferrocene	150	toluene	NR
14[a]	-	150	toluene	NR

[a] Reaction was run in a sealed tube under argon, 24h.

[b] Reaction was run at normal atmospheric pressure under argon, 24h.

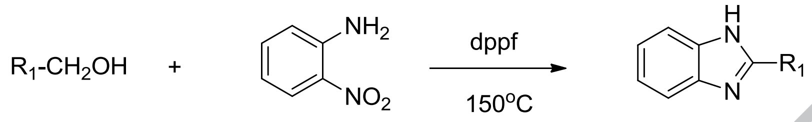
[c] Using 5% of the catalyst.

[d] Isolated yields.

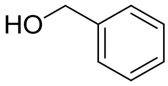
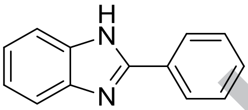
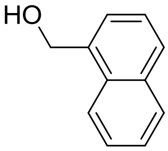
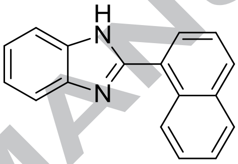
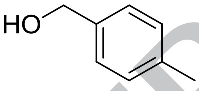
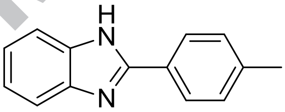
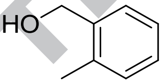
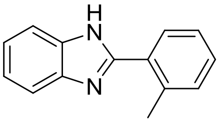
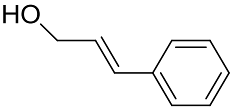
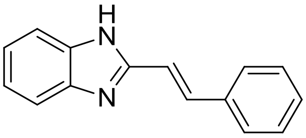
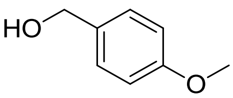
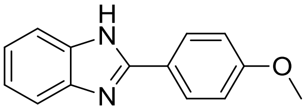
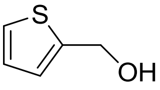
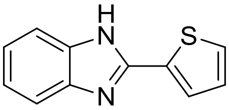
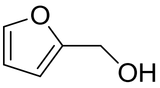
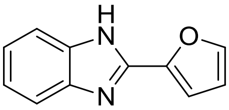
[e] No reaction.

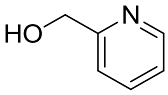
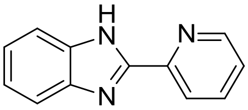
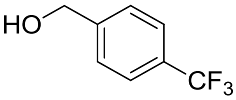
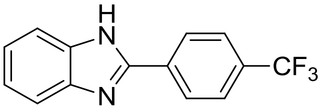
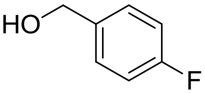
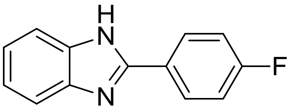
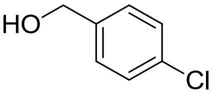
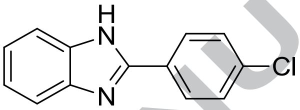
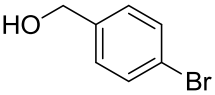
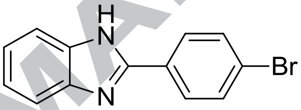
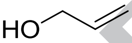
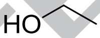
Table 2

Iron-catalyzed heterocyclization of 2-nitroaniline (1 equiv) with substituted benzylic alcohol substrates (2.5 equiv) in the presence of dppf (0.05 equiv) in toluene at 150°C



1 **2a** **3**

Entry	Alcohol	Product	Yield[a](%)
1	 **1a**	 **3a**	74
2	 **1b**	 **3b**	81
3	 **1c**	 **3c**	70
4	 **1d**	 **3d**	78
5	 **1e**	 **3e**	71
6	 **1f**	 **3f**	66
7	 **1g**	 **3g**	63
8			55

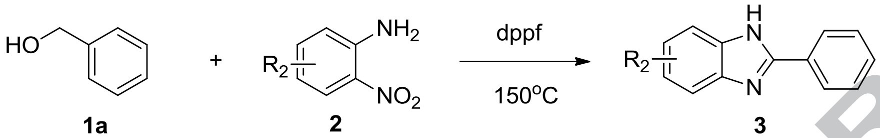
	1h	**3h**	
9	 **1i**	 **3i**	45
10	 **1j**	 **3j**	46
11	 **1k**	 **3k**	88
12	 **1l**	 **3l**	75
13	 **1m**	 **3m**	68
14	 **1n**	-	NR[b]
15	 **1o**	-	NR

[a] Reaction was run in a sealed tube under argon for 24 h, isolated yields.

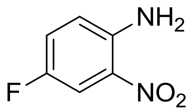
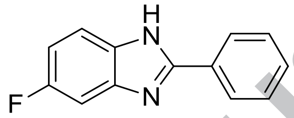
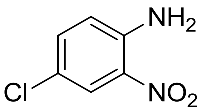
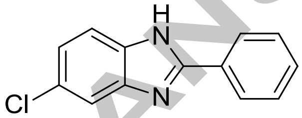
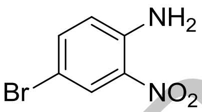
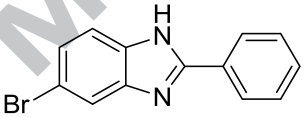
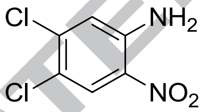
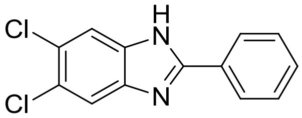
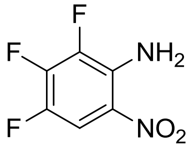
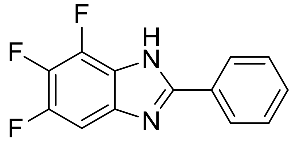
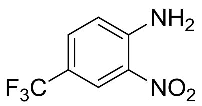
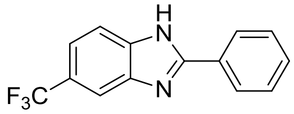
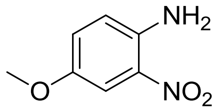
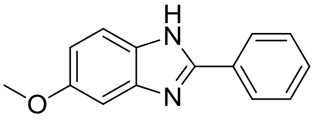
[b] No reaction.

Table 3

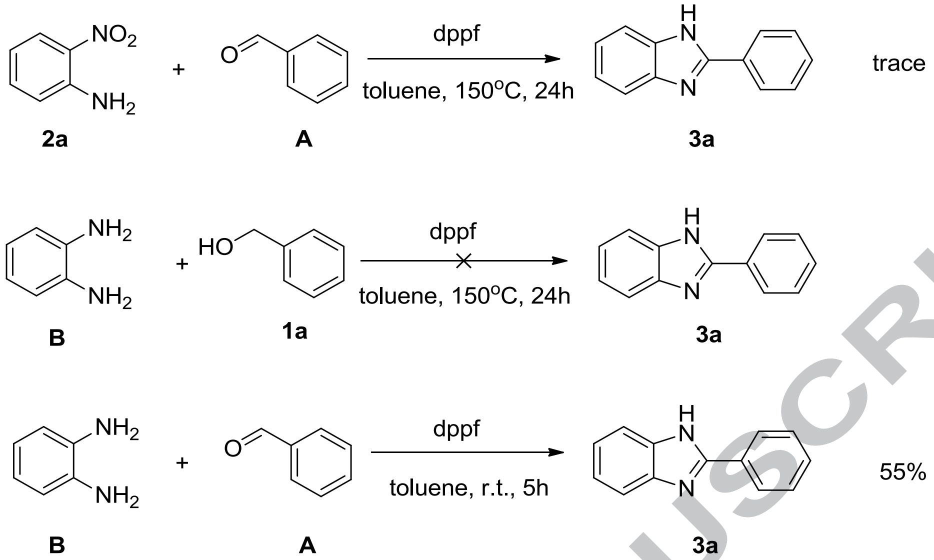
Iron-catalyzed heterocyclization of 2-nitroanilines (1 equiv) with benzylic alcohol (2.5 equiv) in the presence of dppf (0.05 equiv) in toluene at 150°C



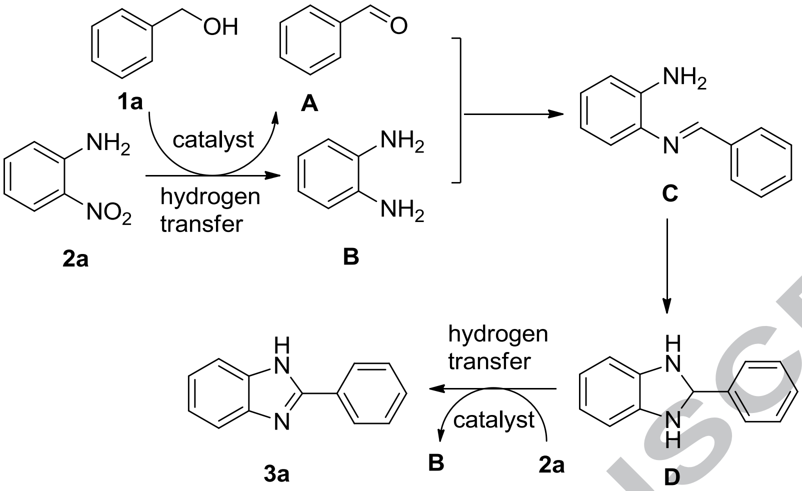
1a **2** **3**

Entry	Nitroaniline	Product	Yield[a](%)
1	 **2a**	 **3n**	73
2	 **2b**	 **3o**	70
3	 **2c**	 **3p**	73
4	 **2d**	 **3q**	62
5	 **2e**	 **3r**	56
6	 **2f**	 **3s**	53
7	 **2g**	 **3t**	40

[a] Reaction was run in a sealed tube under argon for 24 h, isolated yields.



Scheme 1. Exploration of the mechanism

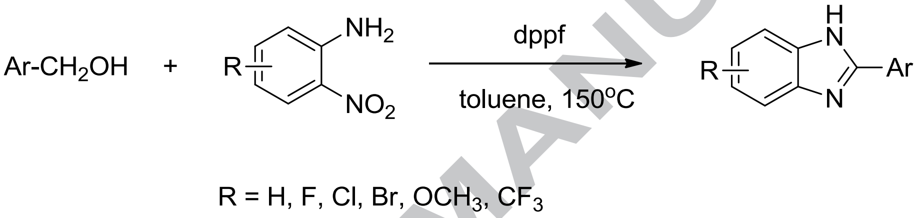


Scheme 2. Proposed mechanism for benzimidazole synthesis

Iron-catalyzed one-pot synthesis of benzimidazoles from 2-nitroanilines and benzylic alcohols

*Gang Li, Jin Wang, Baokun Yuan, Dongfeng Zhang, Ziyun Lin, Peng Li, Haihong Huang**

State Key Laboratory of Bioactive Substances and Function of Natural Medicine & Beijing Key Laboratory of Active Substance Discovery and Druggability Evaluation, Institute of Materia Medica, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing 100050, P. R. China



We herein report a new efficient method for the synthesis of benzimidazoles with hydrogen transfer procedure. This method involves alcohol oxidation, nitro reduction, condensation and dehydrogenation in a cascade.

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*Corresponding author. Tel.: +86 10 63165244; fax: +86 10 63165244; e-mail: joyce@imm.ac.cn