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Iron-catalyzed [3 + 2]-cycloaddition of *in situ* generated *N*-ylides with alkynes or olefins: access to multi-substituted/polycyclic pyrrole derivatives†

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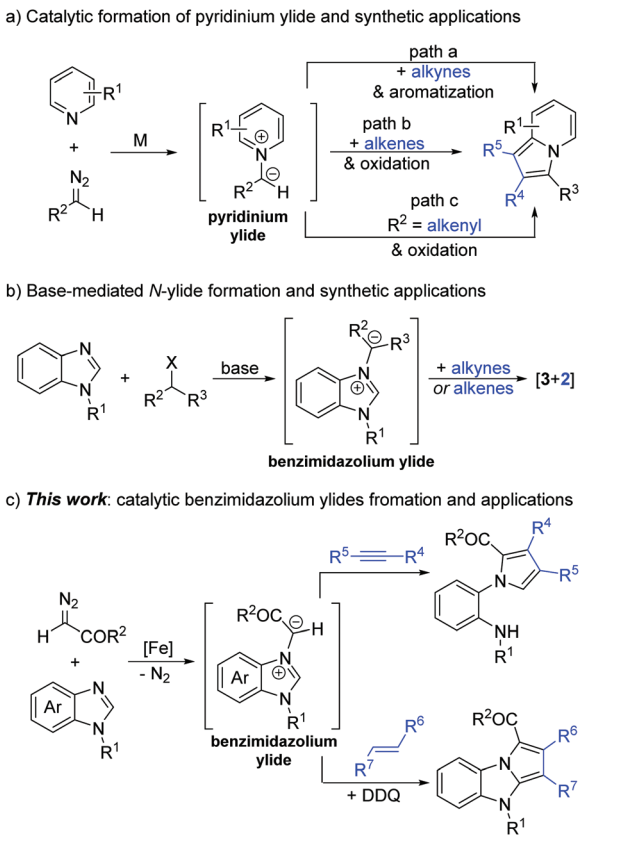
An iron-catalyzed one-pot three-component reaction of 1-substituted benzimidazoles with diazoacetates and electron-deficient alkynes or alkenes has been reported. Mechanistically, the reaction goes through a 1,3-dipolar cycloaddition of catalytically generated benzimidazolium *N*-ylides with various activated alkynes or alkenes, leading to multi-substituted and polycyclic fused pyrrole derivatives, respectively.

The pyrrole derivatives are ubiquitous structural units in aromatic heterocycles, which are present in a variety of advanced materials,[1] natural products,[2] and pharmaceutical compounds.[3] In particular, polycyclic pyrrole frameworks are of particular interest because of their unique structural architectures that have been found in many biologically active molecules exhibiting a variety of activities, including anticancer,[4] antimalarial,[5] anti-inflammatory,[6] antiviral,[7] and antinociceptive[8] activities. Thus, the development of efficient and practical synthetic methods towards this library of compounds with structural diversity has attracted great attention in recent decades and continues to be an appealing and active research area.[9–11] Generally, the 1,3-dipolar cycloaddition reactions of pyridinium ylides,[12] which are catalytically generated from pyridines and diazo compounds, with activated alkynes (Scheme 1a, path a) or alkenes (Scheme 1a, path b) provide a straightforward way of generating a large number of condensed indolizine derivatives.[13] The analogous [3 + 2]-cycloaddition of pyridines with vinyl diazoacetates also forms indolizine derivatives (Scheme 1a, path c).[14] Among these published procedures, the substrate scope was seriously limited to a very narrow range of aromatic heterocycles, such as pyridine, quinoline, and isoquinoline derivatives. Thus, the development of effective catalytic approaches for the practical synthesis of pyrrole derivatives with structural diversity, especially for the polycyclic frameworks, from readily available and stable materials with non-noble metal catalysts is highly desirable.



Scheme 1 Formation of *N*-ylides and their synthetic applications.

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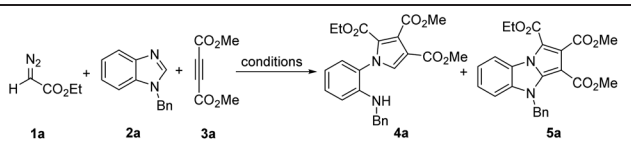
On the other hand, the deprotonation of benzimidazolium salts, which are generated from benzimidazoles and their corresponding haloalkanes, is an alternative approach for the generation of benzimidazolium *N*-ylides (Scheme 1b).[15,16] Inspired by these advances, and as a continuation of our interest in catalytic carbene transformations,[17,18] we are intrigued by the possibility of using the catalytically generated benzimidazolium *N*-ylide species for the [3 + 2]-cycloaddition with activated alkynes or alkenes. Thus, it could enable synthetically appealing access to polycyclic pyrrole derivatives in terms of step- and atom-economy. Herein, we report an iron-catalyzed one-pot three-component of 1-substituted benzimidazoles with diazoacetates and electron-deficient alkynes or alkenes, which provides general access to multi-substituted pyrroles and pyrrolo[1,2-*a*]benzimidazole derivatives through the 1,3-dipolar cycloaddition of catalytically generated benzimidazolium *N*-ylides with activated alkynes or alkenes, respectively (Scheme 1c). Notably, this is a rare example of using catalytically generated benzimidazolium *N*-ylides for the [3 + 2]-cycloaddition.[16f] In addition, these polycyclic pyrrole frameworks, including pyrrolo[1,2-*a*]quinoxalinone derivatives that are easily accessible from these generated substituted pyrroles under thermal conditions, are present in many biologically and pharmaceutically active compounds.[4–8]

To conduct the optimization of the designed reaction, ethyl diazoacetate **1a**, *N*-benzyl benzimidazole **2a**, and dimethyl succinate **3a** were chosen as model substrates (Table 1). The initial exploration of a variety of commercially available metal catalysts in dichloromethane (DCM) at room temperature showed that both [Fe(TPP)Cl] (TPP = tetraphenylporphyrin) and $[(MeCN)_4Cu]PF_6$ could yield tetrasubstituted pyrrole **4a** as the major product instead of the fused product **5a** in 82% and 63% yields, respectively (entries 3 and 4).[19] In the cases with $Rh_2(OAc)_4$ or CuBr as the catalysts, no desired adduct with **3a** was observed, although the decomposition of **1a** occurred under these conditions (entries 1 and 2). Notably, when the reaction was conducted under an open air atmosphere, **5a** was obtained in 56% yield combined with **4a** in 28% yield (entry 5), which implied that the oxygen in air prompted the oxidative aromatization process after the cycloaddition step, instead of ring-opening aromatization to form **4a**. Next, a thorough screening of the solvents in the presence of [Fe(TPP)Cl] at room temperature showed the superiority of 1,4-dioxane over all the other tested solvents in terms of yield and selectivity (entries 6–10), and the corresponding reaction produced **4a** in 90% yield (entry 7). It is noteworthy that in these iron-catalyzed reactions, 4 Å molecular sieves were added to ensure the high catalytic efficiency of this catalyst in different solvents, and the reaction was totally shut down in the absence of 4 Å molecular sieves in 1,4-dioxane (entry 11), whilst comparable reactivity was observed in DCM with or without the 4 Å molecular sieves. Furthermore, 86% isolated yields were obtained when the reaction was conducted on a 0.2 mmol scale in 1,4-dioxane catalyzed by [Fe(TPP)Cl] (entry 12).

Table 1 Condition optimization for the synthesis of multi-substituted pyrroles[a]

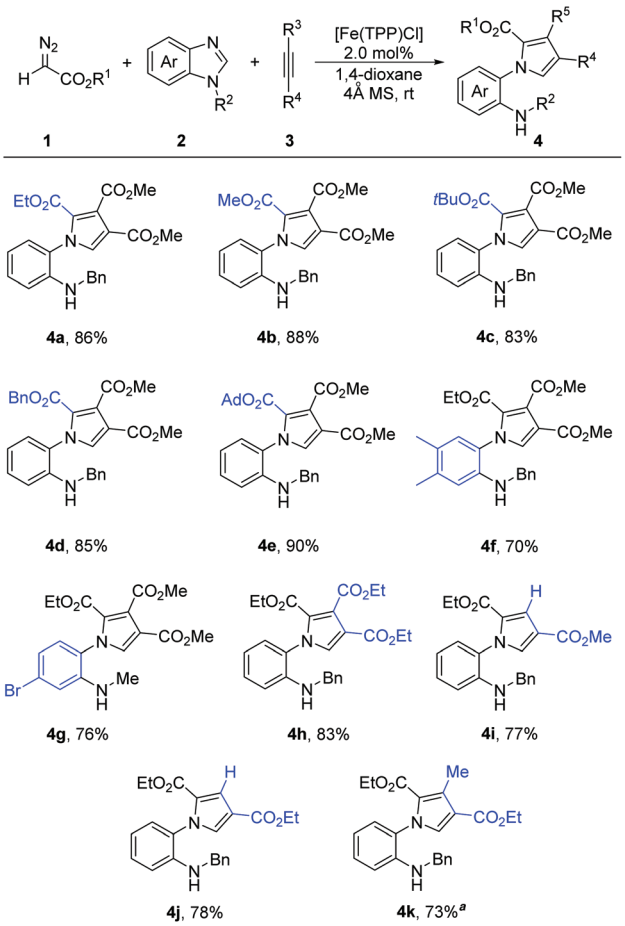


Entry	Cat (x mol%)	Solvent	Yields **4a**/**5a**[b] (%)
1[c]	$Rh_2(OAc)_4$ (2.0)	DCM	ND/ND
2[c]	CuBr (20)	DCM	ND/ND
3	$[(MeCN)_4Cu]PF_6$ (5.0)	DCM	63/9
4	[Fe(TPP)Cl] (2.0)	DCM	82/18
5[d]	[Fe(TPP)Cl] (2.0)	DCM	28/56
6[e]	[Fe(TPP)Cl] (2.0)	THF	50/23
7[e]	[Fe(TPP)Cl] (2.0)	1,4-Dioxane	90/<10
8[e]	[Fe(TPP)Cl] (2.0)	DCE	61/33
9[e]	[Fe(TPP)Cl] (2.0)	MeCN	29/43
10[e]	[Fe(TPP)Cl] (2.0)	Toluene	81/19
11	[Fe(TPP)Cl] (2.0)	1,4-Dioxane	NR
12[e]	[Fe(TPP)Cl] (2.0)	1,4-Dioxane	86[f]/<10

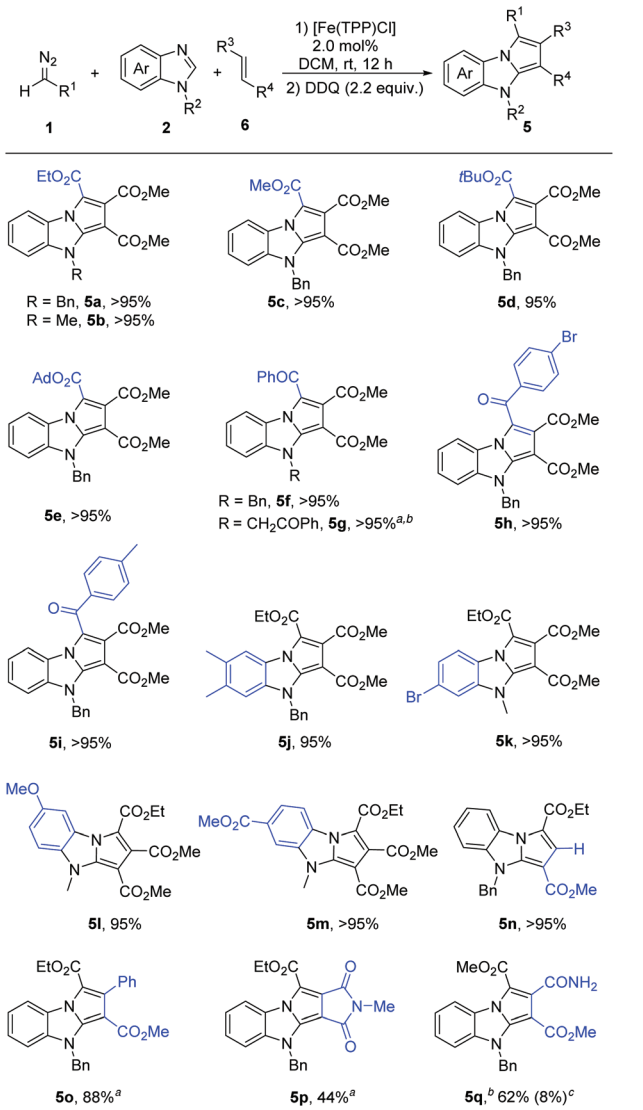
[a] Unless otherwise noted, all reactions were carried out on a 0.1 mmol scale (**1a** : **2a** : **3a** = 1.5 : 1.2 : 1) under an argon atmosphere at room temperature. [b] The yields were determined by proton NMR of the crude reaction mixture with *p*-nitrobenzaldehyde as an internal standard. [c] Only decomposition of **1a** was observed, and most of the **2a** was recovered. [d] Under an open air atmosphere. [e] The reaction was carried out in the presence of 100 mg 4 Å MS (50 mg). [f] The reaction was conducted on a 0.2 mmol scale and the yield given is the isolated yield. ND = not detected. NR = no reaction.

With the optimal reaction conditions being established, we set out to explore the substrate generality of this cycloaddition reaction (Scheme 2). This iron-catalyzed cycloaddition proved to be a general method for the facile construction of multi-substituted pyrroles. Diazo compounds **1** with a variety of ester groups afforded the corresponding products in >83% yields (**4a–4e**), although the α-alkyl or α-aryl substituted diazoacetates gave a complex mixture. Substituted *N*-benzyl benzimidazoles worked well under current conditions, leading to products **4f** and **4g** in 70% and 76% yields, respectively. Then, different propiolate derivatives were investigated, including diethyl but-2-ynedioate, ethyl propiolate, methyl propiolate, and ethyl but-2-ynoate, and all of them underwent the desired transformation to give the cycloaddition products in 73%–83% yields (**4h–4k**).

Encouraged by the above results, we further investigated the reaction for the synthesis of pyrrolo[1,2-*a*]benzimidazoles **5**. Due to the favourable ring-opening aromatization process after the cycloaddition of *in situ* generated benzimidazolium *N*-ylides with alkynes, the multi-substituted pyrroles **4** were formed as the major products in this case. We envisioned that by using alkenes as the dipolarophiles, instead of alkynes, the formed corresponding [3 + 2]-cycloaddition adduct **7** would not automatically lead to the analogous ring-opening aromatization process, thus the oxidative aromatization pathway could be selectively enabled in the presence of an appropriate oxidant to form the fused polycyclic pyrrole derivatives **5**. With this conception in mind, we conducted the condition optimization for this transformation (see Table S1 in the ESI†),

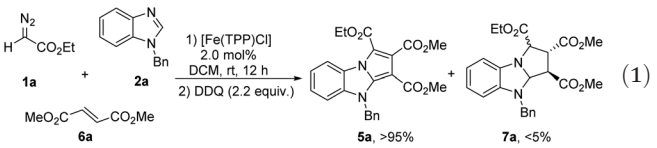


Scheme 2 Substrate scope for the synthesis of multi-substituted pyrroles. Reaction conditions: **1** (0.3 mmol), **2** (0.24 mmol), **3** (0.2 mmol), 4 Å MS (100 mg), and [Fe(TPP)Cl] (2.0 mmol%) in 1,4-dioxane (4.0 mL) for 12 h under an argon atmosphere at room temperature. The yields given are the isolated yields. [a] 3.0 equiv. of the diazo compound **1a** were used instead of 1.5 equiv. Ad = adamantyl.



Scheme 3 Substrate scope for the synthesis of polycyclic pyrroles. Reaction conditions: **1** (0.3 mmol), **2** (0.24 mmol), **6** (0.2 mmol), and [Fe(TPP)Cl] (2.0 mol%) in DCM (4.0 mL) for 12 h, then DDQ (0.44 mmol) was added and stirred for 1 h. The yields given are the isolated yields. [a] 3.0 equiv. of the diazo compound **1a** were used instead of 1.5 equiv. [b] THF was used as the solvent instead of DCM due to the low solubility of the materials (**2g** and **6q**). [c] The result in the parenthesis is the yield for the other regioisomer.

and above 95% isolated yield was obtained when the reaction was conducted on a 0.2 mmol scale in DCM catalyzed by [Fe(TPP)Cl] in the presence of 2.2 equiv. of DDQ (eqn (1)).[16]

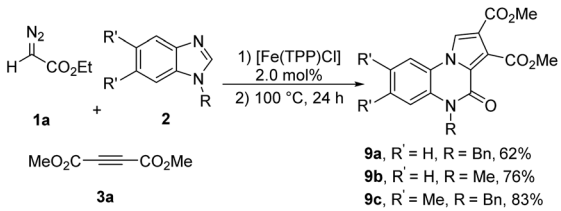


(1)

Subsequently, the substrate generality of this catalytic and oxidative [3 + 2] cycloaddition was evaluated under the above optimized conditions (Scheme 3). In all these tested substrates, including a variety of diazoacetates (**5a–5e**)[16g] or diazoketones (**5f–5i**), substituted *N*-benzyl benzimidazoles (**5j–5m**), and different types of alkenes (**5n**[20]–**5q**), smoothly afforded the corresponding polycyclic products in good to excellent yields, and with most of them in nearly quantitative yields (**5a–5o**). The lower yield of **5q** may be due to the potential side reaction; however, no identifiable by-product has been isolated.[21] In the case of non-protected benzimidazole, 3.0 equiv. of diazoketone were used, which not only contributed to the formation of *N*-ylide with benzimidazole, but also reacted with free N–H species to give the corresponding insertion product (**5g**, >95% yield). *N*-Methylmaleimide also tolerated under current conditions, delivering the tetracyclic product **5p** in 44% yield. Notably, the non-symmetric alkene, methyl (*E*)-4-amino-4-oxobut-2-enoate, selectively produced the corresponding adduct **5q** in 62% yield combined with the minor regioisomer in 8% yield (Scheme 3, noted).

To understand the mechanism of the reaction, some control experiments were carried out. In the absence of an oxidant, the corresponding [3 + 2]-cycloaddition adduct **7a** was isolated in quantitative yields (see the ESI† for details).[20] This adduct could be quantitatively converted to pyrrolo[1,2-*a*]benzimidazole **5a** in >95% isolated yields in the presence of an oxidant. Moreover, no reaction occurs between benzimidazole **2a** and the electrophilic alkyne **3a** or alkene **6a** in the absence of the diazo compound under the current conditions (see Fig. S1 and S2 in the ESI† for details). The diazo-cycloadducts, which are generated from **1a** and **3a** in the presence of iron-catalyst, could not yield the pyrrole product **4a** by adding **2a** to the above crude reaction mixture (see Fig. S3 in the ESI† for details). Based on these observations and related literature reports,[13–16] a possible mechanistic pathway is proposed (Scheme 4). Initially, benzimidazolium *N*-ylide **I** was catalytically generated as the key intermediate in the presence of iron catalyst from **1** and **2**.[13,14] In the subsequent cycloaddition with alkynes, tricyclic 2,5-dihydropyrrole **II** was generated followed by a fast isomerization, which is a thermodynamically favourable ring-opening aromatization process, giving the multi-substituted pyrroles **4**. Although competitive oxidative aromatization might occur, it would lead only to the corresponding polycyclic fused pyrrole derivatives **5** in minor or trace amounts due to the slow reaction rate. During cycloaddition with alkenes that follows the rule of *syn*-addition,[20] pyrrolidine species **III** was formed, which is relatively stable in comparison with **II**, and the ring-opening aromatization process could not take place for this intermediate, thus, oxidative aromatization of this intermediate in the presence of DDQ smoothly led to the polycyclic fused pyrroles **5** in quantitative yields in most cases.

To demonstrate the synthetic utility of the current method, further transformations with this product were conducted. The intramolecular ester to amide interconversion occurred smoothly under thermal conditions, delivering the tricyclic pyrrolo[1,2-*a*]quinoxalinone products **9** in good to high yields (eqn (2)).[16*h*] The reduction product and hydrolysis product were generated from the tricyclic pyrrolo[1,2-*a*]benzimidazole **5f** under mild conditions in 77% and 63% yields, respectively (see the ESI† for details).



(2)

In conclusion, we have disclosed an iron-catalyzed one-pot three-component reaction of 1-substituted benzimidazoles with diazoacetates and electron-deficient alkynes or alkenes. A broad range of important multi-substituted pyrroles, pyrrolo[1,2-*a*]benzimidazole and pyrrolo[1,2-*a*]quinoxalinone derivatives were selectively generated in good to excellent yields under mild conditions. This method features an inexpensive iron catalyst, readily available starting materials, mild reaction conditions and operational simplicity. Mechanistically, the reaction goes through a 1,3-dipolar cycloaddition of catalytically generated benzimidazolium *N*-ylides with activated alkynes or alkenes. Potential applications using this strategy for the construction of structural appealing molecules are under exploration in the laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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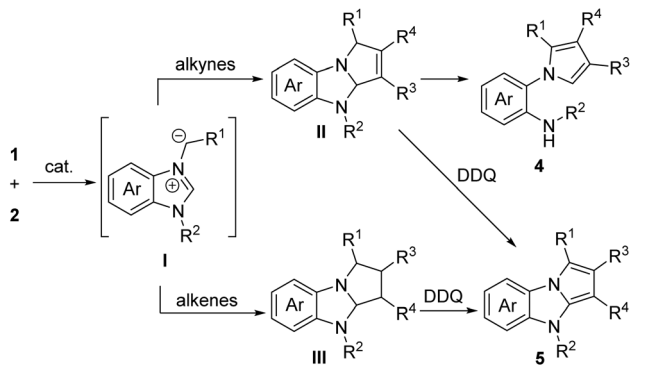

Scheme 4 Proposed reaction sequence.

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