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Iron-Catalyzed *N*-Alkylation of Azoles via Oxidation of C−H Bond Adjacent to an Oxygen Atom

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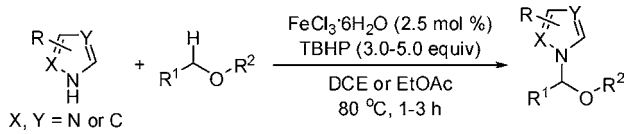
ABSTRACT



Azole derivatives were synthesized by iron-catalyzed oxidative reactions of azoles and ethers in good to excellent yields. A wide variety of azoles and ethers were selectively transformed into the corresponding oxidative coupling products under neutral reaction conditions.

Azoles, specifically imidazoles and triazoles, are widely used as fungicides in agriculture and antifungal agents in pharmaceuticals.[1] Azole derivatives have also been broadly used as the precursors of *N*-heterocyclic carbenes (NHC)[2] and ionic liquids.[3] Consequently, the development of highly efficient methods for the synthesis of functional azoles is of great interest. The *N*-alkylation and *N*-arylation of azoles present the most straightforward method for the synthesis of azole derivatives with the consideration of a large number of readily available N−H heterocycles. In recent years, transition-metal-catalyzed *N*-arylation of azoles has become a well-established technique for the synthesis of *N*-arylazoles.[4] Traditionally, the *N*-alkylation of azoles usually requires a deprotonation step followed by a nucleophilic substitution reaction with an electrophile (alkyl halide or tosylate).[5] Drawbacks of these reactions include the following: (1) strong base is commonly applied due to low acidity of the NH group; (2) alkyl or aryl halides are generally used; and (3) overalkylation of the product gives quaternary salts. Addition to the C=C bond and substitution with alcohols present alternative methods for the synthesis of azole derivatives in modern synthetic chemistry. However, these methodologies suffer from significant limitations. In the former case, the C=C bond is generally activated via conjugation with an electron-withdrawing group.[6] In the latter

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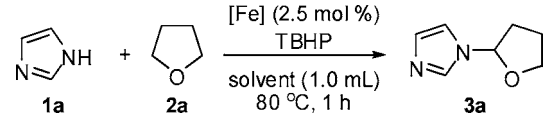
case, only methanol and phenyl methanol are effective partners.[7] Therefore, a selective and efficient method for *N*-alkylation of azoles is highly desirable.[8]

The readily available and nontoxic iron catalysts are highly attractive for chemical synthesis from environmental and economic points of view.[9] Therefore, the development of iron-catalyzed C−N cross-coupling methods is one of the valuable goals for the preparation of various nitrogen-containing compounds.[10] In conjunction with our recent results on oxidative functionalization of C−H bonds adjacent to heteroatoms,[11] we herein report a novel protocol of *N*-alkylation of azoles via iron-catalyzed oxidative C−N bond formation.

The reaction of imidazole **1a** and tetrahydrofuran (THF) **2a** was investigated to examine suitable reaction conditions (Table 1). Various iron salts were tested for the proposed reaction using 1,2-dichloroethane (DCE) as a solvent and *tert*-butyl hydroperoxide (TBHP) as an oxidant (entries 1−7). $FeCl_3$•$6H_2O$, which is relatively inexpensive and easy to handle, showed relative higher catalytic efficiency compared with other iron salts and thus was chosen as the catalyst for further optimization. The yields of **3a** were further improved when the amount of **2a** and TBHP was increased (entries 8−10). It should be noted that an excess amount of THF **2a** used as a solvent instead of DCE led to almost quantitative conversion of **1a** with 100% selectivity (entry 11). Moderate yields of the desired oxidative product **3a** were obtained using ethyl acetate or acetonitrile as a solvent (entries 12 and 13). Other solvents resulted in lower yields of **3a**, for example, nitromethane (37%), toluene (48%), and *tert*-butyl methyl ether (34%) (entries 14−16). The formation of **3a** was not observed in the absence of a catalyst or an oxidant (entries 17 and 18). Therefore, both iron catalyst and peroxide are crucial for this transformation.

Subsequently, the scope of azoles was examined for the present transformation using THF **2a** as a standard substrate (Table 2). Imidazole **1a** and benzimidazole **1b** led to the corresponding products **3a** and **3b** with good to excellent yields under various conditions (entries 1−5). Although the

Table 1. Optimization of the Reaction Conditions[a]



entry	[Fe]	**2a** (equiv)	solvent	TBHP (equiv)	yield[b] (%)
1	$FeCl_2$	4	DCE	1	31
2	$FeBr_2$	4	DCE	1	20
3	$FeCl_3$	4	DCE	1	38
4	$Fe(OAc)_2$	4	DCE	1	20
5	$Fe_2(CO)_9$	4	DCE	1	17
6	$Fe(acac)_3$	4	DCE	1	28
7	$FeCl_3$•$6H_2O$	4	DCE	1	42
8	$FeCl_3$•$6H_2O$	8	DCE	1	64
9	$FeCl_3$•$6H_2O$	8	DCE	3	88
10	$FeCl_3$•$6H_2O$	10	DCE	3	92
11	$FeCl_3$•$6H_2O$		THF	3	96[c]
12	$FeCl_3$•$6H_2O$	8	EtOAc	3	70
13	$FeCl_3$•$6H_2O$	8	MeCN	3	73
14	$FeCl_3$•$6H_2O$	8	$MeNO_2$	3	37
15	$FeCl_3$•$6H_2O$	8	PhMe	3	48
16	$FeCl_3$•$6H_2O$	8	*t*-BuOMe	3	34
17		4	DCE	1	N.D.[d]
18	$FeCl_3$•$6H_2O$	4	DCE		N.D.

[a] Conditions: **1a** (0.5 mmol) and TBHP (5−6 M in decane) under nitrogen, unless otherwise noted. [b] Detected by ^{1}H NMR using CH_2Br_2 as an internal standard. [c] THF and **2a** (1.0 mL) were used; 3 h. [d] Not detected by TLC.

reactions of 4-phenyl-1*H*-imidazole **1c** with THF **2a** gave moderate yields of **3c** when 10 equiv of **2a** was applied (entries 6 and 7), a 96% yield of **3c** was obtained when **2a** was used as a solvent (entry 8). The regioselectivity of **3c** was confirmed by NOE anaylsis. 4,5-Diphenyl-1*H*-imidazole **1d** reacted with **2a** to afford the corresponding product **3d** with moderate to excellent yields (entries 9−11). 2-Substituted imidazoles **1e** and **1f** gave moderate yields of the desired oxidative coupling products **3e** and **3f** due to the steric effect (entries 12−15). Moderate yields of azole derivatives were obtained when 3,5-dimethyl-1*H*-pyrazole **1g** and 1*H*-1,2,4-triazole **1h** were applied (entries 16−19). Although only **3h** was isolated from the reaction mixture, a trace amount of its regioisomer was observed from crude NMR analysis (entry 19). When 4-nitro-1*H*-imidazole was applied under various reaction conditions, a substantial low conversion (<8%) of it was observed. We hypothesized that the low solubility and nucleophilic ability of 4-nitro-1*H*-imidazole contributed to the low conversion in this case.

Furthermore, the scope of ether derivatives were also investigated using benzimidazole **1b** as the nucleophile (Table 3). Benzyl C−H bonds showed high reactivity using ethyl acetate as a solvent, and the corresponding products **3i**−**k** were obtained in excellent yields (entries 1−3). When 2-methyltetrahydrofuran was used, the C−N bond was formed at the less substituted carbon in a regiospecific fashion with a 1:1 ratio of two diastereomers (entry 4). The reactivity and the regioselectivity of this reaction indicated

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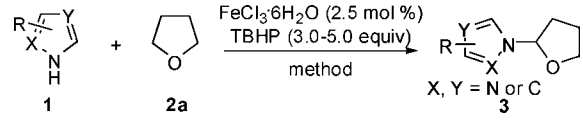
Table 2. Reactions of Azoles with THF **2a**[a]

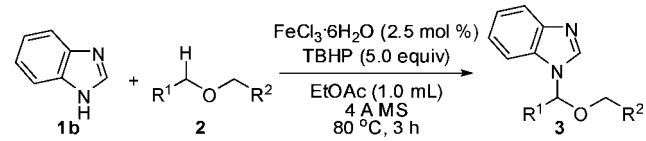


1 **2a** **3**

entry	azole **1**	product **3**	method[b]	yield(%)[c]
1	**1a**	**3a**	A	92(88)
2			C	96(90)
3	**1b**	**3b**	A	92(89)
4			B	89
5			C	93(86)
6	**1c**	**3c**	A	72
7			B	75
8			D	96(91)
9	**1d**	**3d**	A	70
10			B	69
11			D	94(90)
12	**1e**	**3e**	A	72
13			D	86(82)
14	**1f**	**3f**	A	62
15			D	90(83)
16	**1g**	**3g**	A	71
17			C	84(78)
18	**1h**	**3h**	A	73
19			C	79(72)

[a] Conditions: **1** (0.5 mmol); 80 °C. [b] Method A: **2a** (5.0 mmol), TBHP (1.5 mmol), and DCE (1.0 mL) for 1 h. Method B: **2a** (5.0 mmol), TBHP (2.5 mmol), 4 Å MS (200 mg), and EtOAc (1.0 mL) for 1 h. Method C: **2a** (1.0 mL), and TBHP (1.5 mmol) for 3 h. Method D: **2a** (1.0 mL), TBHP (2.5 mmol), and 4 Å MS (200 mg) for 3 h. [c] NMR yield; the isolated yield was given in the parentheses.

Table 3. Reactions of Ethers with Benzimidaole **1b**[a]



1b **2** **3**

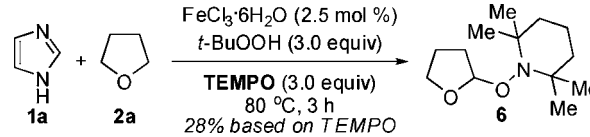
entry	product **3**	yield(%)[b]	entry	product **3**	yield(%)[b]
1	**3i**	95(90)	6	**3n**	85(80)
2	**3j**	93(90)	7	**3o** (1:1)	88(85)
3	**3k**	96(82)	8	**3p**	51(46)
4	**3l**	69(65)[c]		**3p′**	45(40)
5	**3m**	97(93)	9	**3q**	78(73)

[a] Conditions: **1b** (0.5 mmol), **2** (5.0 mmol), TBHP (2.5 mmol), and 4 Å MS (200 mg). [b] NMR yield; the isolated yield was given in the parentheses. [c] 2-Methyl-THF (1.0 mL) was used without EtOAc.

that the steric effect of ethers plays an important role in the reactions. Linear dialkyl ethers could also be applied for the present transformation (entries 5−9). A 97% yield of **3m** was obtained when diethyl ether was used (entry 5). Dibutyl ether afforded the corresponding product **3n** in a slight lower yield (entry 6). Butyl ethyl ether led to two regioisomers **3o** with a 1:1 ratio (entry 7). Two regioisomers, **3p** and **3p′**, were obtained with an excellent combined yield when 1,2-diethoxyethane was used (entry 8). Importantly, 2-ethoxyethyl acetate gave only one regioisomer product **3q** (entry 9). These results indicated that the electronic effect of the ethers also influences the regioselectivity of ethers.

Imidazole salts continue to attract much attention due to their widespread applications as precursors to *N*-heterocyclic carbenes employed as ligands in metal-catalyzed reactions. With the easy and efficient synthetic method for the ethereal azole derivatives in hands, we are interested in their potential applications as a class of C−O donor ligand.[12] Therefore, we investigated the *N*-alkylation of **3a** leading to the formation of the corresponding imidazole salts **5** (Table 4). The desired salts **5** were obtained in near-quantitative yields via the reactions of imidazole **3a** with various alkylating agents.[13]

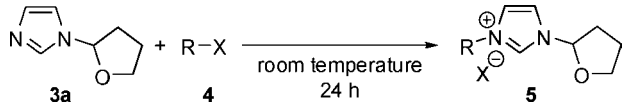
In order to explore the possible mechanism of the present transformation, TEMPO, a radical-trapping reagent, was added into the reaction (eq 1). The formation of the desired product **3a** was completely suppressed, and the TEMPO-adduct product **6** was formed as a major product. This result suggested that a radical process was involved in the initial steps of the transformation. It should be noted that neither **3a** nor **6** was observed in the absence of TBHP.



1a **2a** **6** (1)

Moreover, a competition experiment was investigated to address the influences of the electronic properties of azoles

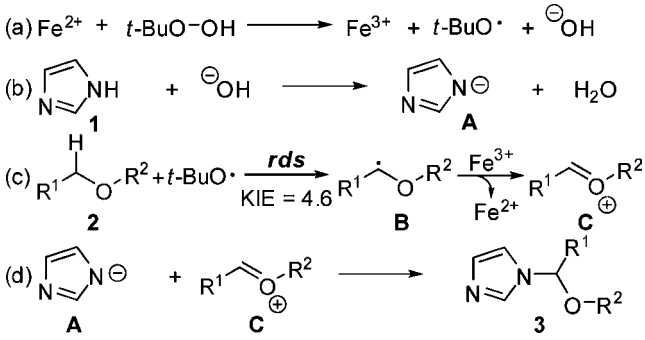
Table 4. Synthesis of Imidazolium Salts **5**[a]



entry	4	5	NMR yield (%)[b]
1	MeI **4a**	**5a**	98
2	Br **4b**	**5b**	96
3[c]	BnBr **4c**	**5c**	95

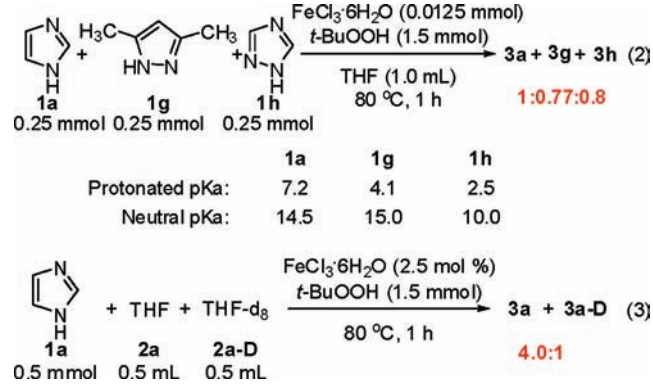
[a] Conditions: **3a** (0.25 mmol), **4** (1.0 mL), room temperature, and 24 h; unless otherwise noted. [b] Detected by ^{1}H HMR using CH_2Br_2 as an internal standard. [c] Ethyl acetate (1.0 mL) was added; 40 °C.

Scheme 1. Plausible Pathways for the Formation of **3**



in the present C−N bond formation (eq 2). The results indicated that the reactivity of azoles was related to the nucleophilicity of the conjugated bases of azoles rather than the acidity of azoles, which agrees with the regular nucleophilic reaction. Moreover, kinetic isotopic effect (KIE) experiments were carried out under the standard reaction conditions (eq 3). The reaction shows a $k_H/k_D = 4.0 \pm 0.1$.[14]

This significant isotopic effect indicates that the C−H bond cleavage is the rate-determinating step of this transformation.



On the basis of the above results, a plausible mechanism of the present oxidative C−N bond formation is illustrated in Scheme 1. TBHP decomposes into *tert*-butoxyl radical and hydroxyl anion in the presence of the ferrous catalyst (step a). Deprotonation of azole gives the anion species **A** (step b). On the other side, a hydrogen abstraction of C−H bond adjacent to an oxygen atom affords **B**, which could be trapped by TEMPO, and followed by ferric oxidation to generate oxonium ion **C** (step c). Finally, the nucleophilic addition of **A** to **C** provides the desired coupling product **3** (step d). Overall, the Fe^{2+}−Fe^{3+} redox processes[15] play key roles in the present C−N bond formation, which are the reductive heterolytic cleavage of O−O bond in the peroxide (step a) and the oxidation of the carbon radical to oxonium (step c).

In summary, we demonstrated a novel and efficient method of azole derivative synthesis via iron-catalyzed oxidation of ethers. The high efficiency of the present transformation and the wide variety of the functional azoles make the present methodology attractive for future applications.

Acknowledgment. We thank the NSFC (20832002) for financial support. H.L. thanks RUC (2009030026) for financial support. We also thank Prof. Zhenfeng Xi, Peking University, for helpful discussions.

Supporting Information Available: Representative experimental procedure, characterization of all new compounds, and ^{1}H NMR and ^{13}C NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

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