DOI: 10.1002/cjoc. 201200690

Iron(III)-Catalyzed Direct *N*-Alkylation of Azoles via Oxidative Transformation of sp^3 C—H Bonds under Solvent-Free Conditions

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A new approach to synthesize *N*-alkylation of azoles by iron(III)-catalyst under solvent-free conditions was developed. The method is broad in scope and highly efficient.

Keywords azoles, *N*-alkylation, solvent-free, iron catalyst, C—H activation

Introduction

Azoles[1] and their derivatives[2] are important heterocycles in natural products and commercial drugs (like the antiviral, anticonvulsant, antiulcer, anti-inflammatory). They have also been frequently used as backbones in dyes[3] and high-temperature polymers.[4] Developing efficient methods for the preparation of functional azoles has caused a lot of attention.[5] The most common route is a nucleophilic substitution reaction with an electrophile (RX, X=halide, OTs, OTf, *etc*.), and a following deprotonation step. Although they are efficient methods for azoles, most of them make use of strong bases, generating stoichiometric amount of wasteful organic salts and low secondary/tertiary amine product selectivity. It is another way to synthesize azoles through the functionalization of C—H/N—H directly, and the direct method provides a possible transformation from azoles into a variety of useful derivatives.[6] The direct way processed well these years. Hamze, Alami and co-workers[7] realized the synthesis of azoles from *N*-tosylhydrazones in the presence of Cs_2CO_3. This system showed a wide application potential and high efficiency under mild conditions. However, it must prepare substrates in advance, and solvents were required in the reaction. Very recently, Schnürch and coworks[8] described the synthesis of diarylmethylamine by C—H arylation, this proves the utility of such compounds. In recent years, iron is a particularly attractive catalyst in many reactions because of its sustainability, easy availability, low price, and environmentally friendly characteristics.[9] There is also a report that Chen and his co-workers[10] make C—N coupling of imidazoles and benzylic compounds via iron-catalyzed oxidative activation of C—H bonds with a high efficiency. This efficient method also required some complex condition like organic solvent, high temperature, long reaction time, and a nitrogen atmosphere.

In summary, there are many approaches to synthesize the *N*-alkylation azoles, but most of them required high temperature, prolonged reaction time, toxic oxidants, solvents, and functionalized substrates. In recent years, solvent-free reactions[11] and organic aqueous phase reactions[12] have been regarded as a promising alternative to replace reactions in various solvents. Here we found a simple and efficient way to make *N*-alkylation of azoles in the solvent free system. This solvent free reaction worked well in the air catalyzed by $FeCl_3$, and it proceeded in a good yield at relatively lower temperature within a short time.

Experimental

Typical procedure for the preparation of 1-benzhydryl-1*H*-benzo[*d*]imidaole 3aa

Benzimidazole **1a** (58 mg, 0.50 mmol), $FeCl_3$ (20 mmol%), *tert*-butyl hydroperoxide (171 μL, 2.5 equiv.) and diphenylmethane **2a** (2.0 mmol) were added to a flask with a magnetic stirring bar. The resulting mixture was stirred for 10 h at 100 ℃. After cooling to room temperature, the mixture was diluted with ethyl acetate and filtered. The filtrate was removed under reduced pressure to get the crude product, which was further purified by silica gel chromatography (petroleum/ethyl

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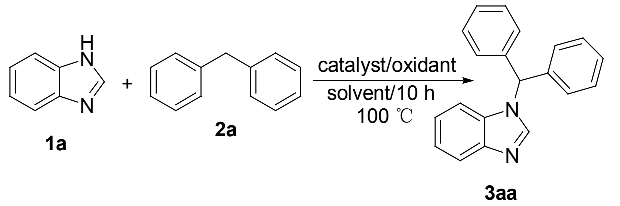
Received July 8, 2012; accepted July 30, 2012.
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/cjoc.201200690 or from the author.

acetate = 1/1 as eluent) to give product **3aa** as a white solid. The identity and purity of the products were confirmed by ^{1}H and ^{13}C NMR spectroscopic analysis. ^{1}H NMR (300 MHz, $\mathrm{CDCl_3}$) δ: 7.845—7.818 (d, 1H), 7.610 (s, 1H), 7.368—7.267 (m, 6H), 7.245—7.124 (m, 7H), 6.745 (s, 1H); ^{13}C NMR (75 MHz, $\mathrm{CDCl_3}$) δ: 144.052, 142.533 138.050, 134.051, 128.976, 128.477, 128.171, 122.925, 122.364, 120.372, 110.719, 63.

Results and Discussion

In our initial study, we investigated the reaction of benzimidazole (**1a**) with diphenylmethane (**2a**) in the presence of $\mathrm{FeCl_3}$ (10 mmol%) to optimize the reaction conditions (Table 1). In this preliminary experiment, the *N*-alkylation reaction was carried out with different oxidants. 2,3-Dichloro-5,6-dicyanobenzoquinone (DDQ), $\mathrm{Ag_2CO_3}$, $\mathrm{O_2}$, benzoyl peroxide (BPO) and *t*-BuOOBu-*t* showed little effectiveness on promoting the reaction; using aqueous *tert*-butyl hydroperoxide (TBHP) as the oxidant afforded *N*-alkylation product **3aa** in 30% yield (Table 1, Entries 1—6). Then, solvent was conducted. Among the solvents, DMSO, PhCl, and $\mathrm{CH_3CN}$ were harmful to the transformation (Table 1, Entries 7, 8, 9), but solvent-free and $\mathrm{PhNO_2}$ showed good performance (Table 1, Entries 10, 11). Obviously, choosing solvent free system is more favorable to develop an economical and environmentally friendly reaction. Moreover, the yield of the desired product **3aa** could be improved by increasing the amount of $\mathrm{FeCl_3}$ gradually. It is noteworthy that the yield of **3aa** was enhanced to 90% when the amount of $\mathrm{FeCl_3}$ was 20 mmol%, and the high loading (>20 mmol%) resulted in the decrease of the yield (Table 1, Entriy 14). However, TBHP (5.0—6.0 mol/L in decane) used in the reaction gave an inferior product yield compared with that of aqueous TBHP (Table 1, Entry 13). It should be noted that this reaction did not work in the absence of $\mathrm{FeCl_3}$ or TBHP. Morever, a trace amount of **3aa** was detected when the reaction temperature was below 80 ℃.

Table 1 Optimization of the reaction condition[a]



Entry	Oxidant	Catalyst/mmol%	Solvent	Yeild[b]/%
1	DDQ	$\mathrm{FeCl_3}$ (10)	DCE	0
2	$\mathrm{Ag_2CO_3}$	$\mathrm{FeCl_3}$ (10)	DCE	trace
3	TBHP	$\mathrm{FeCl_3}$ (10)	DCE	30
4	$\mathrm{O_2}$	$\mathrm{FeCl_3}$ (10)	DCE	0
5	*t*-BuOOBu-*t*	$\mathrm{FeCl_3}$ (10)	DCE	0
6	BPO	$\mathrm{FeCl_3}$ (10)	DCE	15
7	TBHP	$\mathrm{FeCl_3}$ (10)	DMSO	0
8	TBHP	$\mathrm{FeCl_3}$ (10)	PhCl	20
9	TBHP	$\mathrm{FeCl_3}$ (10)	$\mathrm{CH_3CN}$	trace
10	TBHP	$\mathrm{FeCl_3}$ (10)	$\mathrm{PhNO_2}$	38
11	TBHP	$\mathrm{FeCl_3}$ (10)	Neat	50
12	TBHP	$\mathrm{FeCl_3}$ (15)	Neat	64
13	**TBHP**	**$\mathrm{FeCl_3}$ (20)**	**Neat**	**90** (50[c])
14	TBHP	$\mathrm{FeCl_3}$ (25)	Neat	70

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (2.0 mmol), catalyst (20 mmol%), oxidant (2.5 equiv.), solvent (1 mL), 100 ℃, 10 h. [b] Isolated yields. [c] TBHP (5.0—6.0 mol/L in decane).

The scope of the reaction was investigated under the optimized reaction conditions described above. The results were shown in Table 2. The 5-substituted azoles **1** containing electron-withdrawing groups showed slightly higher yields than electron-donating ones (Table 2, Entries 7—12). That steric hindrance at the 2-position of benzimidazoles had only a slight impact on the yields. However, **3ba**, **3ca**, **3ea** and **3fa** were obtained in moderate yields unless using more TBHP, prolonging the reaction times or at higher temperature (Table 2, Entries 1—6). Benzitriazole also gave higher yield but they do not have the same level of selectivity. It is caused probably by strong steric effect. Substrates substituted by $\mathrm{CH_3}$, Cl, or $\mathrm{NO_2}$ groups gave a mixture of regioisomers. The combined yields ranged from 71% to 99%, and the ratio of isomers varied from 1 : 1.1 to 1 : 1.22, confirmed by ^{1}H NMR and ^{13}C NMR except benzimidazole and benzitriazole substrates with methyl group on the phenyl ring, which yielded single regioisomers. In addition, new product **3ma** in 99% yield was observed when 3,5-dimethyl-1*H*-pyrazole reacted with diphenylmethane.

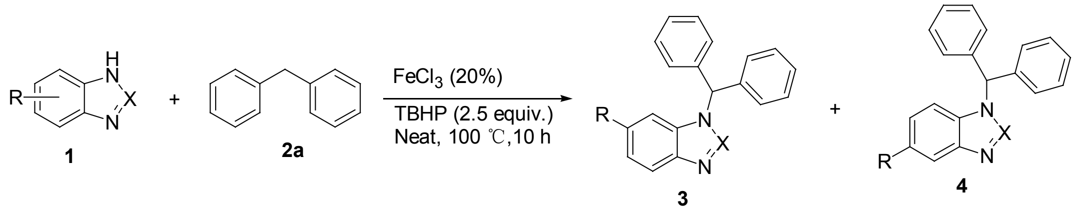
The reaction scope was also investigated relating to other coupling partners (Table 3). As you can see in Table 3, the reactions of azoles with benzylic compounds produced the corresponding cross-coupling products (Table 3, Entries 1—5) in moderate to good yields. The reaction was also applicable to ethers, such as 1,4-dioxane and tetra-hydrofuran (Table 3, Entries 6—10).

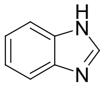
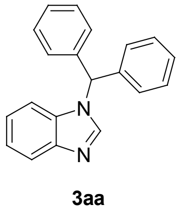
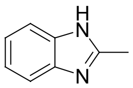
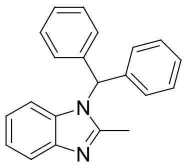
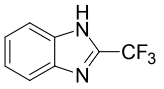
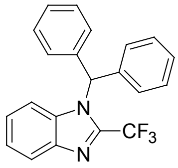
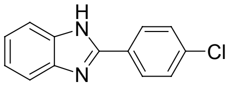
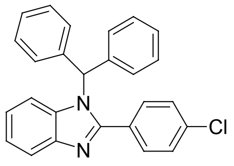
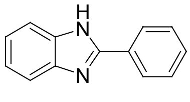
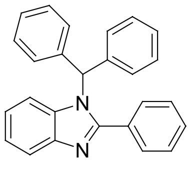
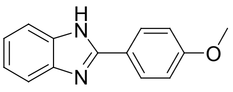
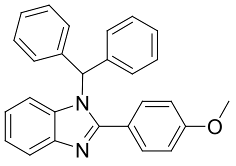
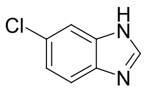
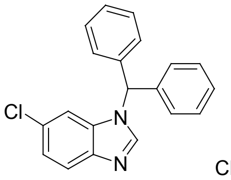
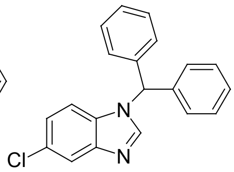
A plausible mechanism for this reaction was proposed in Scheme 1. It may involve a free-radical process. The reaction started with abstraction of H from **2** by *t*-BuOOH, giving R^{1}CHR^2 radical (**A**). Subsequently, $\mathrm{FeCl_3}$ oxidized **A** to **B**. $\mathrm{FeCl_2}$, produced during transformation of **A** to **B**, reacted with HCl under oxidization of TBHP condition giving $\mathrm{FeCl_3}$ and *t*-BuOH or $\mathrm{H_2O}$ to complete iron-catalyst cycle. Finally, nucleophilic reaction of **1** with **B** produced the target product **3**. We will focus on the systematic investigation in future studies.

Conclusions

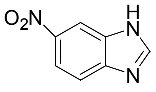
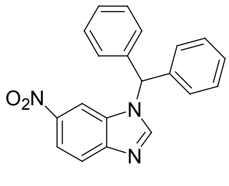
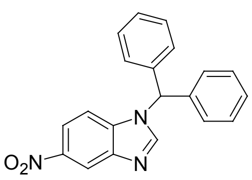
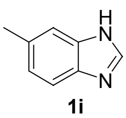
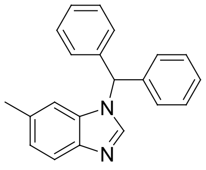
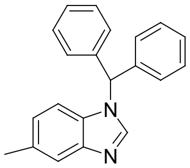
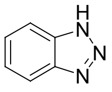
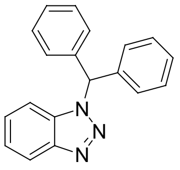
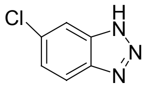
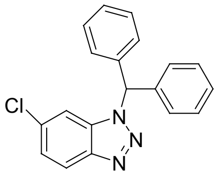
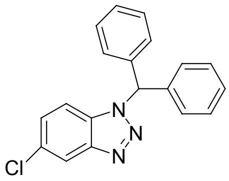
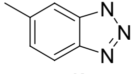
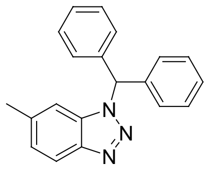
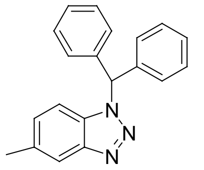
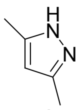
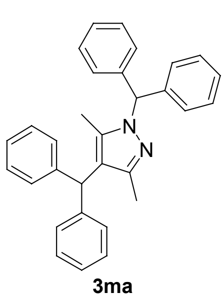
In conclusion, we developed an iron-catalyzed, environmentally friendly, economical and efficient method

Table 2 Reactions of diphenylmethane **2a** with various azoles



Entry	**1**		Product		Yeild[b]/%
1		**1a**		**3aa**	90
2		**1b**		**3ba**	49[c]
3		**1c**		**3ca**	73[c]
4		**1d**		**3da**	81
5		**1e**		**3ea**	47[d]
6		**1f**		**3fa**	53[e]
7		**1g**	 **3ga**  **4ga**		99 (**3ga** : **4ga**=1 : 1.1)

Continued

Entry	**1**	Product	Yeild[b]/%
8	 **1h**	 **3ha**  **4ha**	99 (**3ha** ∶ **4ha**＝1 ∶ 1.2)
9	 **1i**	 **3ia**  **4ia**	65
10	 **1j**	 **3ja**	72
11	 **1k**	 **3ka**  **4ka**	78 (**3ka** ∶ **4ka**＝1 ∶ 1.2)
12	 **1l**	 **3la**  **4la**	71
13	 **1m**	 **3ma**	99

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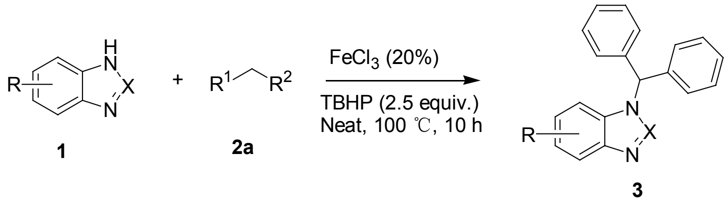
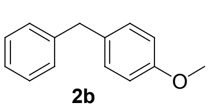
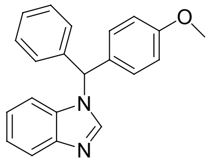
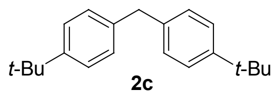
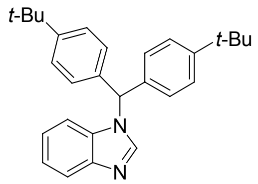
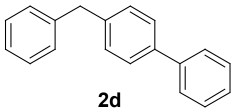
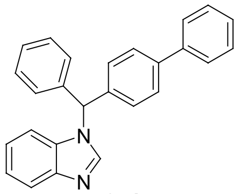
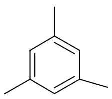
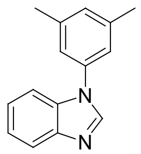
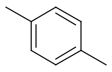
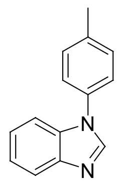
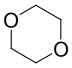
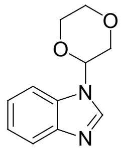
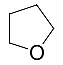
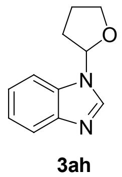
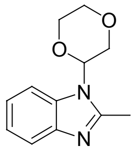
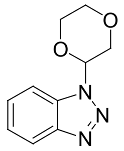
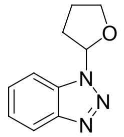
[a] Reaction conditions: **1** (0.5 mmol), **2** (3.0 mmol), catalyst (20 mmol%), oxidant (171 μL, 2.5 equiv.), 100 ℃, 10 h. [b] Isolated yields. [c] TBHP (5.0 equiv.). [d] At 120 ℃. [e] 24 h.

Table 3 Reactions of azoles with various active C—H bond



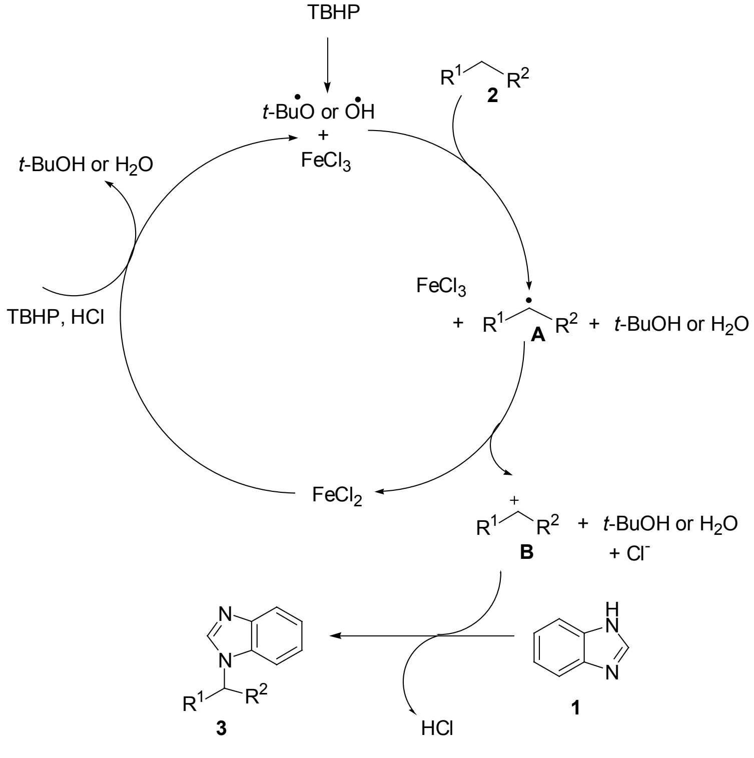
Entry	**1**	**2**	Product	Yield[b]/%
1	**1a**	 **2b**	 **3ab**	83
2	**1a**	 **2c**	 **3ac**	60
3	**1a**	 **2d**	 **3ad**	75
4	**1a**	 **2e**	 **3ae**	50
5	**1a**	 **2f**	 **3af**	61[c]
6	**1a**	 **2g**	 **3ag**	77[d]
7	**1a**	 **2h**	 **3ah**	78

Continued

Entry	**1**	**2**	Product	Yield[b]/%
8	**1b**	**2g**	 **3bg**	76[d]
9	**1j**	**2g**	 **3jg**	55[d]
10	**1j**	**2h**	 **3jh**	74

[a] Reaction conditions: **1** (0.5 mmol), **2** (2.0 mmol), catalyst (20 mmol%), oxidant (171 μL, 2.5 equiv.), 100 ℃, 10 h. [b] Isolated yields. [c] At 120 ℃. [d] TBHP (5 equiv.).

Scheme 1 A plausible reaction mechanism



for *N*-alkylation of azoles via iron-catalyst and oxidative transformation of sp^3 C—H bonds under solvent-free conditions. The most attractive feature of this noval method is simple. It is just an easy one step reaction with available substrates. Furthermore, the reaction conditions were relatively mild.

Acknowledgement

We are grateful for the support of this project from the Scientific Research Foundation of the State Education Ministry (No. 107108) and the National Natural Science Foundation of China (No. J0730425).

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