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Iron-catalyzed oxidative dehydrogenative coupling of ethers with aryl tetrazoles

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ABSTRACT

An iron-catalyzed oxidative dehydrogenative coupling of ethers with aryl tetrazoles has been developed. A wide variety of tetrazoles and ethers survived the reaction conditions to deliver the corresponding hemiaminal derivatives in moderate to good yields.

Tetrazoles as well as their derivatives are very important *N*-containing heterocycles that showed wide applications in organic chemistry,[1] medicinal chemistry,[2] and material science.[3] They were also employed as directing groups in C–H activation reactions.[4] Thus, development of efficient methods for functionalization of tetrazoles is of great importance.

The N-alkylation and arylation of tetrazoles are the most straightforward methods for the synthesis of tetrazole derivatives. In recent years, transition-metal-catalyzed N-arylation of tetrazoles has been well-established.[5] The N-alkylation of tetrazoles, however, has a limited scope. Generally, they were prepared via nucleophilic substitution reaction between a tetrazole and an alkyl halide.[6] The major drawbacks associated with this procedure were the utilization of alkyl halides, extra bases, and the formation of isomeric dialkylated mixtures. Just recently, our group reported a metal-free alkylation of aryl tetrazoles with benzylic C–H substrates using *n*-Bu_4NI as catalyst and *t*-BuOOH as oxidant.[7] Later, we reported a direct amination of ethers with aryl tetrazoles and triazoles under the same reaction conditions.[8] However, high catalyst loading and a large excess of alkyl ethers were used, and moderate yields were obtained in most cases. We hypothesized that the low solubility of tetrazoles in alkyl ethers contributed to the low conversion. Therefore, an efficient method for this reaction is still highly desirable.

As a cheap, readily available, and nontoxic metal, iron catalysts have received wide attention in organic synthesis.[9] Particularly, iron-catalyzed cross-dehydrogenative coupling (CDC) reactions are highly attractive from both environmental and economic points of view;[10] which provides a facile approach to construct various *N*-containing heterocycles. In conjunction with our current interest in the functionalization of tetrazoles,[4c,7,8] we herein report an iron-catalyzed oxidative dehydrogenative coupling of ethers with aryl tetrazoles (Scheme 1).

Initially, reaction of 5-phenyl-2*H*-tetrazole **1a** and tetrahydrofuran (THF) **2a** was investigated to optimize the reaction conditions (Table 1). Interestingly, the desired product **3a** was obtained in 17% yield in the presence of 5 equiv of *tert*-butyl hydroperoxide (TBHP) using THF as solvent (Table 1, entry 1). Addition of $FeCl_3{\cdot}6H_2O$ (5 mol %) greatly promoted the reaction, providing **3a** in 66% yield (Table 1, entry 2). The reaction did not occur in the absence of TBHP, indicating that both iron catalyst and TBHP were essential for this transformation. Considering the low solubilities of tetrazoles in other alkyl ethers, various solvents were examined (Table 1, entries 4–8). Ethyl acetate and 1,2-dichloroethane turned out to be the best solvents, giving the desired product **3a** in 85% and 83% yield, respectively. Moderate yields were obtained using dichloromethane or acetonitrile as a solvent. Reaction in *N*,*N*-dimethylformamide, however, afforded trace amounts of **3a**. Other iron catalysts were also tested and relatively lower yields were obtained (Table 1, entries 9–13). Further studies showed that reducing the amount of $FeCl_3{\cdot}6H_2O$, TBHP as well as THF led to lower yield (48%, 65%, and 67% yields, respectively). Oxidants were also crucial for this reaction, and other

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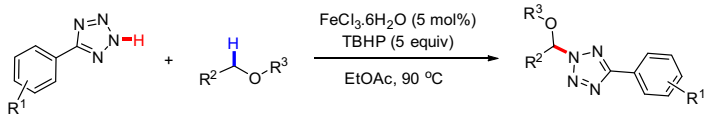
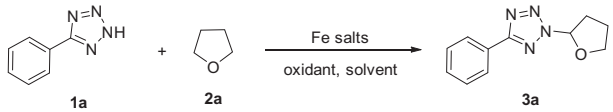


Scheme 1. Iron-catalyzed amination of alkyl ethers with aryl tetrazoles.

Table 1
Optimized the reaction conditions[a]



1a 2a 3a

Entry	Catalyst (mol %)	**2a** (equiv)	Oxidant (equiv)	Solvent	Yield[b] (%)
1	—	—	TBHP (5)	THF	17[c]
2	$FeCl_3·6H_2O$ (5)	—	TBHP (5)	THF	66[c]
3	$FeCl_3·6H_2O$ (5)	—	—	THF	NR[c,d]
4	$FeCl_3·6H_2O$ (5)	10	TBHP (5)	EtOAc	85
5	$FeCl_3·6H_2O$ (5)	10	TBHP (5)	DCM	70
6	$FeCl_3·6H_2O$ (5)	10	TBHP (5)	DCE	83
7	$FeCl_3·6H_2O$ (5)	10	TBHP (5)	CH_3CN	63
8	$FeCl_3·6H_2O$ (5)	10	TBHP (5)	DMF	Trace
9	$FeCl_3$ (5)	10	TBHP (5)	EtOAc	71
10	$FeBr_3$ (5)	10	TBHP (5)	EtOAc	72
11	$Fe(acac)_3$ (5)	10	TBHP (5)	EtOAc	52
12	$FeCl_2$ (5)	10	TBHP (5)	EtOAc	28
13	$Fe(OAc)_2$ (5)	10	TBHP (5)	EtOAc	21
14	$FeCl_3·6H_2O$ (2.5)	10	TBHP (5)	EtOAc	48
15	$FeCl_3·6H_2O$ (10)	10	TBHP (5)	EtOAc	74
16	$FeCl_3·6H_2O$ (5)	10	TBHP (3)	EtOAc	65
17	$FeCl_3·6H_2O$ (5)	5	TBHP (5)	EtOAc	67
18	$FeCl_3·6H_2O$ (5)	10	H_2O_2 (5)	EtOAc	NR[d]
19	$FeCl_3·6H_2O$ (5)	10	DTBP (5)	EtOAc	23
20	$FeCl_3·6H_2O$ (5)	10	TBHP (5)	EtOAc	75[e], 82[f]

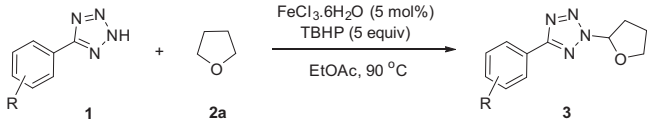
[a] Reaction conditions: **1a** (0.3 mmol), **2a**, catalyst, oxidant, and solvent (1 mL) were heated at 90 °C under nitrogen for 12 h.
[b] Isolated yields.
[c] THF as substrate and solvent.
[d] No reaction.
[e] Reaction at 80 °C.
[f] Reaction at 100 °C.

oxidants including H_2O_2 and di-*tert*-butyl peroxide (DTBP) resulted in poor yields (Table 1, entries 18 and 19). Reaction temperature was finally evaluated. The results clearly showed that 90 °C was the optimum.

With the optimized yields in hand, a series of substituted tetrazoles were employed to explore the generality of this protocol using THF **2a** as standard substrate (Table 2).[11] The results are summarized in Table 2. As shown from the table, most of aryl tetrazoles reacted with THF to give the desired products **3** in moderate to good yields (45–85%). Functional groups such as methyl, methoxyl, chloro, fluoro, and trifluoromethyl survived the reaction conditions. When 5-(3-nitrophenyl)-2*H*-tetrazole was applied under the standard conditions, trace amounts of product was detected. *para*-Hydroxyl substituted tetrazole, however, did not survive. Moreover, alkyl tetrazole such as 5-benzyl-2*H*-tetrazole was also checked (although it is not shown in Table 2); however, rather poor yield was obtained. It was also worth noting that coupling site took place mainly at the N2-position, with only trace amounts of N1-alkylated isomers.[6]

Various alkyl ethers were then evaluated and the results are summarized in Table 3. Tetrahydropyran also gave the desired product **3k** in 59% yield. For substrate 1,4-dioxane and 1,3-dioxolane, different results were obtained. The former reaction gave product

Table 2
Reaction scope for aryl tetrazoles[a]



1 2a 3

Entry	R	Product	Yield[b] (%)
1	H	**3a**	85
2	*o*-CH_3	**3b**	71
3	*m*-CH_3	**3c**	57
4	*p*-CH_3	**3d**	53
5	*p*-OCH_3	**3e**	61
6	*p*-Cl	**3f**	68
7	*p*-F	**3g**	46
8	*p*-CF_3	**3h**	45
9	*m*-NO_2	**3i**	Trace
10	*p*-OH	**3j**	NR[c]

[a] Reaction conditions: **1** (0.3 mmol), **2a** (3 mmol), $FeCl_3·6H_2O$ (0.015 mmol, 5 mol %), TBHP (1.5 mmol, 5 equiv), and EtOAc (1 mL), 90 °C, N_2, 12 h.
[b] Isolated yields.
[c] No reaction.

3l in 64% yield using DCE as solvent; however, no amination product **3m** was detected (**3m** was obtained as the product in TBAI/TBHP system[8]). Instead, this reaction provided two other compounds **3n** and **3o**.[12] Similarly, only compound **3n** (43%) was detected when diethyl ether was used as the substrate. Other straight chain ethers also showed good compatibilities and provided the corresponding products **3q** and **3r** in 51% and 80% yields, respectively. In addition, unsaturated alkyl ethers such as 3,4-dihydro-2*H*-pyran was employed to check the regioselectivity. Interestingly, neither allylated tetrazole nor hemiaminal **3s** was obtained. Instead, a double bond addition reaction occurred between tetrazole and 3,4-dihydro-2*H*-pyran, giving product **3k** in 82% yield.

Control experiments were performed to gain insights into the mechanism (Scheme 2). Initially, when 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO) was added, the reaction was completely suppressed. Meanwhile, the TEMPO-adduct **4** was obtained (Eq. 1). This result indicated that a radical pathway may be involved in this reaction. Moreover, kinetic isotopic effect (KIE) experiment was carried out under the standard reaction conditions (Eq. 2). The result shows a significant isotopic effect (k_H/k_D = 2.7), indicating that the C–H bond cleavage is the rate-determining step of this transformation.

Based on the above results and the similar study that previously reported,[10h,13,14] a possible mechanism was proposed (Scheme 3). Barton and co-workers confirmed that Fe(III) salt reacted with TBHP to generate *tert*-butylperoxy radical and Fe(II) in their study (step a).[12] TBHP can decompose into *tert*-butoxyl radical and hydroxyl anion in the presence of the ferrous catalyst (step b).[10h] Thus, we believe that one hydrogen atom of ether is abstracted by either *tert*-butylperoxy radical or *tert*-butoxyl radical to form radical **A**, followed by oxidation by Fe^{3+} to generate oxonium ion **B** (step c). Meanwhile, deprotonation of tetrazole gives **C** (step d). Finally, nucleophilic addition of **C** to **B** provides the desired product (step e).