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Direct C2-Alkylation of Azoles with Alcohols and Ethers through Dehydrogenative Cross-Coupling under Metal-Free Conditions

Tao He,[†] Lin Yu,[†] Lei Zhang,[†] Lei Wang,*[,†,‡] and Min Wang*[,†]

Department of Chemistry, Huaibei Normal University, Huaibei, Anhui 235000, P.R. China, and State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Shanghai 200032, P.R. China

leiwang@chnu.edu.cn; wangmin204@chnu.edu.cn

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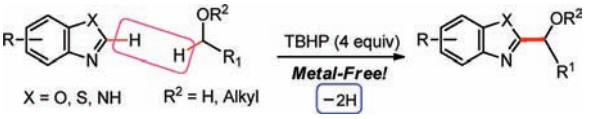
ABSTRACT



A metal-free novel, simple, and highly efficient method for the direct C2-alkylation of azoles with alcohols and ethers has been developed on the basis of an oxidative C−H activation process. The dehydrogenative C−C cross-coupling reactions of α-position sp^3 C−H in alcohols and ethers with the 2-position sp^2 C−H in azoles proceeded smoothly in the presence of *tert*-butyl hydroperoxide (TBHP) under neat reaction conditions, which generated the corresponding products in good yields.

Heterocyclic compounds are widely distributed, such as in biological systems, pharmaceuticals, materials, agriculture, and photography, and are essential to life.[1] The heterocyclic compounds, especially those containing azole skeletons, are very important units in biologically active natural products and unnatural pharmaceuticals and organic functional materials.[2] Recently, the direct functionalization of C−H bonds in azoles has received significant attention in organic synthesis because of their potential possibility for diverse transformation into a variety of useful derivitatives.[3] Transition-metal-catalyzed bond formation reactions through the direct C−H functionalization of heterocyclic compounds have received much attention in recent years.

[†] Huaibei Normal University.
[‡] Shanghai Institute of Organic Chemistry.

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In particular, great progress has been achieved for the C−N and C−C bond formations of azoles with various reagents. The following direct cross-coupling reactions have been reported: arylation of azoles with aryl halides, mesylates, triflates, and organosilicon reagents;[4] alkylation of azoles with alkyl halides;[5] benzylation and allylation of azoles with *N*-tosylhydrazones, benzyl carbonates, and benzyl chlorides;[6] alkynylation of azoles with alkynyl bromides, terminal alkynes, and 1,1-dibromo-1-alkenes;[7] amination or amidation of azoles with formamides, chloroamines, amines, and hydroxylamines;[8] arylation of azoles with arylboronic acids;[9] carboxylation of azoles with carbon dioxide;[10] cyanation of azoles with NaCN;[11] and dehydrogenative cross-couplings azoles with arenes and azoles.[12] However, the above methodologies for the funtionalization of azoles require a transition-metal catalyst, such as Pd, Cu, Co, Fe, or Ni, and a strong base, such as *t*-BuOLi, *t*-BuOK, or CsOH in most cases.[3−12] Thus, the development of a simple, mild, economic, and environmentally friendly method for the synthesis of azoles derivatives through the direct C−H functionalization is highly desirable. On the other hand, transition-metal salts, such as Fe, Co, and Cu salts, could be used as the active catalysts in the activation and/or functionalization of the sp^3 C−H bond in the presence of a radical initiator, such as *tert*-butyl hydroperoxide and di-*tert*-butyl peroxide.[13] To the best of our knowledge, the direct C2-alkylation of azoles with alcohols and ethers has not been studied. Herein, we report a novel and simple method for the direct C2-alkylation of azoles with alcohols and ethers through dehydrogenative C−C cross-coupling of the α-position sp^3 C−H in alcohols and ethers with 2-position sp^2 C−H bond in azoles in the presence of TBHP under metal-,[14] base-free, and neat reaction conditions, which generated the corresponding products in good yields.

The initial investigation was focused on the optimization of reaction conditions. A direct alkylation of benzothiazole (**1a**) with ethanol (**2b**) was chosen as model reaction. For screening of effect of metal salt on the model reaction, the direct alkylation of **1a** with **2b** could be performed in the presence of the combination of a transition-metal salt (10 mol %), such as $FeCl_3$, $FeCl_2$, $Pd(OAc)_2$, $Mn(OAc)_3$, $Zn(OAc)_2$, $CoCl_2$, $CuCl_2$, or CuI, with *tert*-butyl hydroperoxide (TBHP, 4 equiv) in a sealed tube at 120 °C for 6 h. The product **3b** was isolated in 15−61% yields (Table 1, entries 1−8). To our delight, an 89% yield of **3b** was obtained, representing one of the best results, when 4 equiv of TBHP was used without metal salt (Table 1, entry 9). It is obvious that the transition metal could not assist the model reaction and, conversely, restrained the reaction. A variety of other oxidants besides TBHP were examined for their effect on the model reaction, and the results are also summaried in Table 1. It was found that organic peroxides, such as *tert*-butyl perbenzoate (TBPB), cumene hydroperoxide (CHP), CH_3CO_3H, dicumyl peroxide (DCP), $(C_6H_5COO)_2$, $(t\text{-}C_4H_9O)_2$, and cyclohexanone peroxide, were subsequently inferior and generated **3b** in 13−63% yields, respectively (Table 1, entries 10−16). A moderate yield of **3b** was obtained when 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) was used as oxidant (Table 1, entry 17). However, only a trace amount of **3b** was detected when $C_6H_5I(OAc)_2$ was used instead of TBHP. Unfortunately, inorganic oxidants, such as $K_2S_2O_8$, $(NH_4)_2S_2O_8$, Ag_2O, CuO, $KBrO_3$, and I_2, were no longer the effective oxidants in the reaction, and no desired **3b** was isolated. With respect to the amount of oxidant used in the reaction, 4 equiv of TBHP was found to be optimal. The model reaction was not completed with less than 4 equiv of TBHP. However, no significant increased yield of **3b** was observed with more than 4 equiv of TBHP (Table 1, entries 18 and 19). However, TBHP (aq) used in the reaction gave an inferior product yield compared to that of TBHP (anhydrous, 5.0−6.0 M in decane, Table 1, entry 20). It should be noted that a trace amount of **3b** was detected when the reaction temperature was below 80 °C, even prolonging the reaction time.

The effect of solvent on the model reaction was also examined. Among the solvents tested, ethanol, as well as one of the substrates, was the most suitable reaction media for the model reaction. Ethyl acetate, benzene, chlorobenzene, dimethyl sulfoxide, toluene, 1,2-dichloroethane, acetonitrile, *N*-methyl-2-pyrrolidone, 1,2-dibromoethane, and nitromethane were subsequently inferior (see the Supporting Information). The corresponding alcohol or ether,

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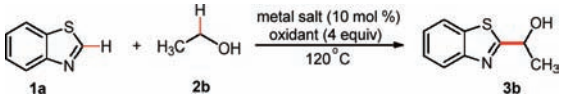
Table 1. Screening of Metal Salt and Oxidant for the Reaction[a]



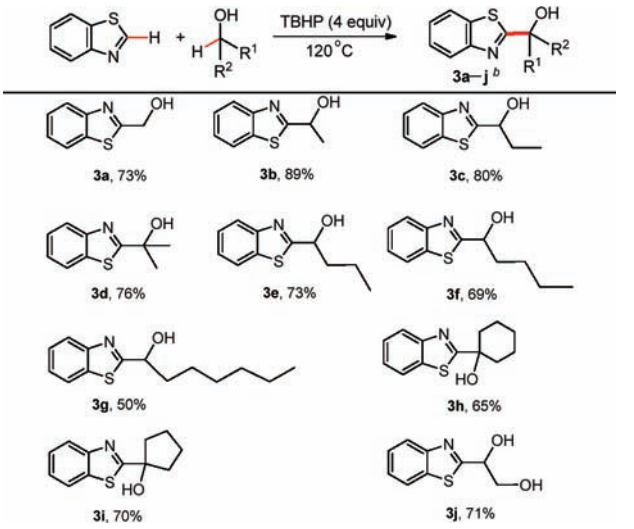
entry	metal salt (mol %)	oxidant (equiv)	**3b** [%][b]
1	$FeCl_3$ (10)	TBHP (4)	21
2	$FeCl_2$ (10)	TBHP (4)	18
3	$Pd(OAc)_2$ (10)	TBHP (4)	41
4	$Mn(OAc)_3$ (10)	TBHP (4)	49
5	$Zn(OAc)_2$ (10)	TBHP (4)	61
6	$CoCl_2$ (10)	TBHP (4)	15
7	$CuCl_2$ (10)	TBHP (4)	23
8	CuI (10)	TBHP (4)	58
9		TBHP (4)	89
10		*tert*-butyl perbenzoate (4)	63
11		cumene hydroperoxide (4)	62
12		CH_3CO_3H (4)	54
13		dicumyl peroxide (4)	34
14		$(C_6H_5COO)_2$ (4)	18
15		$(t\text{-}C_4H_9O)_2$ (4)	15
16		cyclohexanone peroxide (4)	13
17		DDQ (4)	51
18		TBHP (3)	70
19		TBHP (5)	89
20		TBHP (aq, 4)	69
21		TBHP (4)	47[c]

[a] Reaction conditions: benzothiazole (0.5 mmol), ethanol (2.0 mL), oxidant (2.0−5.0 equiv), transition-metal salt (0.05 mmol) if necessary, sealed tube, 120 °C, air, 6 h. [b] Isolated yields . [c] At 100 °C for 24 h.

acting as both one of the reactant and solvent, was chosen in the following reaction considering its high efficiency, environmental friendliness, and low cost.

Under the optimized reaction conditions, the scope of the alcohol in the direct alkylation of benzothiazole (**1a**) with a variety of alcohols was investigated. The results are shown in Scheme 1. As can be seen from Scheme 1, the reactions of benzothiazole with aliphatic alcohols, such as methanol, ethanol, *n*-propanol, 2-propanol, *n*-butanol, *n*-pentanol, *n*-heptanol, cyclopentanol, and cyclohexanol, produced the corresponding dehydrogenative cross-coupling products **3a**−**i** in moderate to good yields. It is obvious that the isolated yield of the corresponding product was decreased along with the increase of chain length in the aliphatic normal primary alcohols (**3b**, **3c**, and **3e**−**g**). It is caused probably by the molar ratio of **2**:**1a** decreased with longer chain length of **2** (**2b**, **2c**, and **2e**−**g**) under neat conditions (2.0 mL of **2**). Furthermore, the lowest yield **3g** probably also arises from the intramolecular hydrogen atom abstraction of the initially formed radical, which further led to other byproducts. It should be noted that the reaction of methanol with benzothiazole gave the corresponding product **3a** in 73% yield, lower than that of **3b** and **3c**, due to its relatively lower reactivity and boiling point.

Scheme 1. Scope of Alcohol in the Reaction[a]



[a] Reaction conditions: benzothiazole (0.5 mmol), TBHP (5.0−6.0 M in decane, 0.4 mL, 2.0−2.4 mmol), alcohol (2.0 mL), sealed tube, 120 °C, under air, 6 h. [b] Isolated yields.

The cross-coupling reaction of *n*-propanol with benzothiazole gave the corresponding alcohol **3c** in good yield, while 2-propanol generated the relatively lower yield of **3d**. The direct alkylation of benzothiazole with cyclic secondary alcohols, such as cyclopentanol and cyclohexanol, also provided the corresponding products **3i** and **3h** in 70% and 65% yields, respectivity. Fortunately, the reaction of benzothiazole with ethylene glycol also proceeded smoothly to generate the anticipated product **3j** in 71% yield. However, when benzyl alcohol, allyl alcohol, or propargyl alcohol was used as alcohol substrate, no desired cross-coupling product was observed, and benzothiazole **1a** was recovered in over 85% yield along with the dimer of **1a** around 7% yields.

Because of the similar structure of the α-position sp^3 C−H in ether with alcohol, we next tried the direct alkylation of azoles with ethers under the optimization reaction conditions. In order to expand the scope of azoles, a number of azoles were surveyed through dehydrogenative cross-coupling reactions of azoles with tetrahydrofuran in the presence of TBHP. As can be seen from Scheme 2, the reactions of tetrahydrofuran and 1,4-dioxane with fused azoles, such as benzothiazole, benzoxazole, 5-methylbenzoxazole, and benzimidazole, proceeded smoothly to generate the corresponding cross-coupling products **4a**−**d**, **4f**, and **4g** in moderate to good yields, and no *N*-alkyl product was observed during the formation of **4g**.[15] On the other hand, benzothiazole reacted with chain ethers, such as di-*n*-butyl ether, to generate the corresponding product **4e** in 80% yield. Meanwhile, when diethyl ether reacted with benzothiazole or benzoxazole under the recommended

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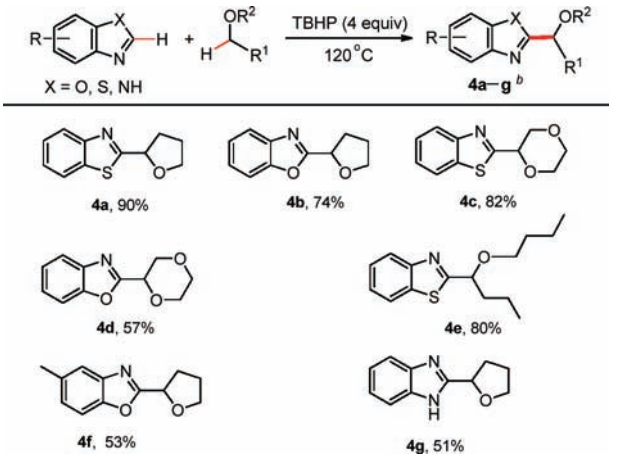
Scheme 2. Scope of Ether and Azole in the Reaction[a]



[a] Reaction conditions: azole (0.5 mmol), TBHP (5.0–6.0 M in decane, 0.4 mL, 2.0–2.4 mmol), ether (2.0 mL), sealed tube, 120 °C, under air, 6 h. [b] Isolated yields.

reaction conditions, no desired product was isolated owing to its relatively low boiling point.

A plausible mechanism for this reaction is proposed in Scheme 3. It may involve a free-radical process.[16] Initiatelly, a hydroxyl radical and an alkoxyl radical were generated from a homolytic cleavage of *tert*-butyl hydroperoxide. The obtained free radicals subsequently underwent hydrogen atom abstraction from the 2-position sp^2 C–H of benzothiazole and the α-position sp^3 C–H of ethanol, forming the corresponding free radicals. Finally, carbon–carbon bond formation via termination of two radicals afforded the desired cross-coupling product (major), along with homocoupling products (minor). It should be noted that the reaction was suppressed by a radical scavenger, such as TEMPO and ascorbic acid.[17]

We also investigated the regioselectivity of the direct alkylation of benzothiazole with ethylene glycol dimethyl ether under the present reaction conditions. The results indicated that an 86% total yield of **5a** and **5a′** was isolated in a ratio of 4:5 (Scheme 4). It accounts for the combination of the stability of the free radical intermediate and the steric hindrance of the α-position sp^3 C–H in ethylene glycol dimethyl ether.

In conclusion, a novel, simple, and highly efficient method for the direct C2-alkylation of azoles with alcohols

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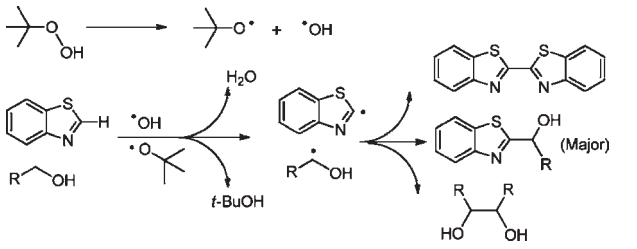
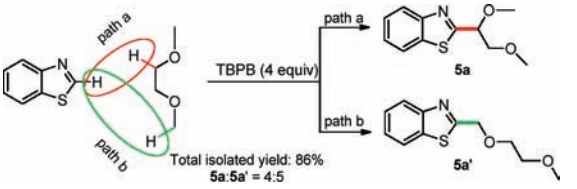
Scheme 3. Proposed Reaction Mechanism



Scheme 4. Regioselectivity of the Reaction



and ethers has been developed under metal- and base-free reaction conditions. The dehydrogenative cross-coupling reactions of the α-position sp^3 C–H bonds in alcohols and ethers with the 2-position sp^2 C–H bonds in azoles proceeded smoothly in the presence of *tert*-butyl hydroperoxide (TBHP) under neat reaction conditions, which generated the corresponding products in good yields. The findings offer a new, simple, and mild method for the synthesis of useful azoles derivatives. A detailed mechanistic study and further investigation on the application of this kind of oxidant under metal- and base-free are currently underway in our laboratory.

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Supporting Information Available. Analytical data and spectra (^1H and ^{13}C NMR) for all products; typical procedure. This material is available free of charge via the Internet at http://pubs.acs.org.

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