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Direct amidation of azoles with formamides *via* metal-free C–H activation in the presence of *tert*-butyl perbenzoate†

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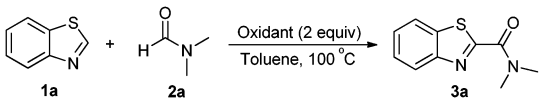
A novel and simple method for the direct amidation of azoles with formamides has been developed. The reaction could occur smoothly in the presence of *tert*-butyl perbenzoate (TBPB) as an oxidant under metal- and base-free conditions. Direct dehydrogenative cross-coupling of formamides and azoles generated the corresponding products in good yields.

Azoles and their derivatives play an important role in agriculture, pharmaceuticals and material sciences.[1] Recently, studies on the direct functionalization of C–H bonds in azoles have received significant attention in organic synthesis owing to their potential possibility for diverse transformation into useful molecules.[2] Up to now, great progress has been achieved for the direct C–N and C–C bond formations of azoles with various electrophiles through the direct cross-coupling reactions.[3] For example, a variety of functional groups, such as alkyl,[4] alkenyl,[5] alkynyl,[6] aryl,[7] amino,[8] cyano,[9] carbonyl[10] and ester groups,[11] could be directly anchored onto the C2 position of azoles in the presence of transition-metal catalysts. However, the above developed methodologies for the functionalization of azoles require a catalytic amount of transition-metal catalyst, such as Pd, Cu, Co, Rh and Ni, and a strong base, such as *t*-BuOLi, in most cases.[3–11] In 1995, Anderson *et al.* have described a C2 acylation of azoles in which stoichiometric cuprous iodide was used.[10a] Most recently, Yu *et al.* developed an iron-catalyzed direct amination of azoles by using formamides.[12] To the best of our knowledge, the direct C2 *amidation* of azoles has not been studied. Thus, the development of a simple and economic method for the synthesis of azoles derivatives has aroused great interest. Herein, we wish to report a novel and simple method for the direct C2 *amidation* of azoles with formamides under metal- and base-free reaction conditions.

As summarized in Table 1, the initial study was conducted by examining the suitable oxidant including organic and inorganic ones in the model reaction of benzothiazole (**1a**) with *N*,*N*-dimethylformamide (**2a**). Firstly, we found that the model reaction could proceed in the presence of dicumyl peroxide (DCP) and generated the desired product **3a** in 23% yield (entry 1). Further, we found that other organic peroxides, such as $(t\text{-}C_4H_9O)_2$, $(C_6H_5COO)_2$ and *tert*-butyl hydroperoxide (TBHP), showed lower reactivity than that of *tert*-butyl perbenzoate (TBPB), which gave the highest yield of **3a** of up to 75% yield (entries 2–5).† Under the same reaction conditions, 35% and 59% yields of **3a** were obtained when the inorganic oxidants $K_2S_2O_8$ and $(NH_4)_2S_2O_8$ were used as oxidants respectively (entries 6 and 7). Unfortunately, cyclohexanone peroxide, I_2, $C_6H_5I(OAc)_2$, Ag_2O and Ag_2CO_3 did not work in the model reaction and no desired product was isolated (entries 8–12). With respect to the amount of **2a** in the reaction, it was found that 4.0 equiv. of **2a** was optimal. When less than 4.0 equiv. of **2a** was used, the reaction could not completely finish (entry 13). However, the yield of **3a** was not improved with 5.0 equiv. of **2a** used in the reaction (entry 14).

It was reported that 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 sp3 C–H bond through a radical initiator, such as TBHP and $(t\text{-}C_4H_9O)_2$.[13]

Table 1 Screening of oxidant in the direct amidation of benzothiazole (**1a**) with formamide (**2a**)[a]



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

Entry	Oxidant	Yield[b] (%)
1	Dicumyl peroxide (DCP)	23
2	$(t\text{-}C_4H_9O)_2$	51
3	$(C_6H_5COO)_2$	31
4	*tert*-Butyl hydroperoxide (TBHP)	45
5	*tert*-Butyl perbenzoate (TBPB)	75
6	$K_2S_2O_8$	35
7	$(NH_4)_2S_2O_8$	59
8	Cyclohexanone peroxide	N.R.
9	I_2	N.R.
10	$C_6H_5I(OAc)_2$	N.R.
11	Ag_2O	N.R.
12	Ag_2CO_3	N.R.
13[c]	TBPB	62
14[d]	TBPB	75

[a] Reaction conditions: benzothiazole (**1a**, 0.5 mmol), *N*,*N*-dimethylformamide (**2a**, 2.0 mmol), toluene (3.0 mL), 100 °C for 12 h. [b] Isolated yield. [c] **2a** (3.0 equiv.) was used. [d] **2a** (5.0 equiv.) was used.

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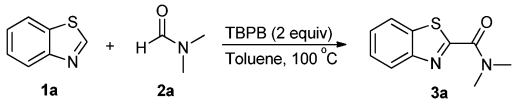
Table 2 Screening of transition metal catalyst in the direct amidation of **1a** with **2a**[a]



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

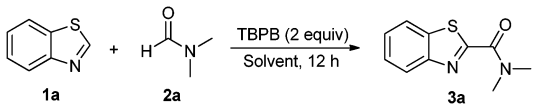
Entry	Transition metal catalyst/mol%	Yield[b] (%)
1	$FeCl_3$ (10)	57
2	$FeCl_2$ (10)	26
3	$Fe(OAc)_2$ (10)	65
4	$Cu(OAc)_2$ (10)	23
5	$CuBr_2$ (10)	14
6	$CoCl_2$ (10)	32
7	$Pd(OAc)_2$ (10)	N.R.

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (2.0 mmol), TBPB (1.0 mmol), toluene (3.0 mL), 100 °C for 12 h. [b] Isolated yield.

Subsequently, several transition-metal salts were investigated to examine their effect on the direct amidation of **1a** with **2a** (Table 2). When Fe^{II} or Fe^{III} salt, such as $FeCl_2$, $FeCl_3$, or $Fe(OAc)_2$ (10 mol%), was used as catalyst and TBPB as oxidant, 20–65% yields of **3a** were isolated (entries 1–3). In similar reaction conditions, $Cu(OAc)_2$, $CuBr_2$ and $CoCl_2$ also showed less reactivity and only 14–32% yields of **3a** were obtained (entries 4–6). It is evident that the Fe, Cu or Co salt could not accelerate the reaction, but restrained the reaction to a certain extent. Unfortunately, the direct amidation reactions were completely shut off in the presence of 10 mol% of $Pd(OAc)_2$ as catalyst (entry 7). Obviously, these results let us suspect that the transition metal might not participate in the coupling reaction. Fortunately, 75% yield of **3a** was obtained when the model reaction was carried out in the presence of TBPB under metal- and base-free reaction conditions. With further investigation, it was found that the yields of **3a** were not improved after changing the added amount of TBPB up to 2 equiv. (see ESI† for details).

The effect of solvent on the reaction was also examined. Interestingly, the reaction showed strong dependence on the solvent (Table 3). We found that no desired product **3a** was obtained when CH_3CN, THF, dioxane, or DMSO was used as solvent for the model reaction (entries 1–4). Toluene, a solvent having low polarity and good solubility, was found to be the best among the solvents tested (entry 5). *p*-Xylene, chlorobenzene and benzene were inferior and generated **3a** in 67, 60 and 55% yields respectively (entries 6–8). When the model reaction was carried out at 80 °C and 120 °C for 12 h, **3a** was obtained in 52 and 34% yields, respectively, indicating the decomposition of TBPB at high temperature (entries 9 and 10). Hence, the optimal reaction conditions were involved in formamide (4.0 equiv.), benzothiazole (1.0 equiv.), TBPB (2.0 equiv.) in toluene at 100 °C for 12 h without metal and base.

Table 3 Screening of solvent in the direct amidation of **1a** with **2a**[a]



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

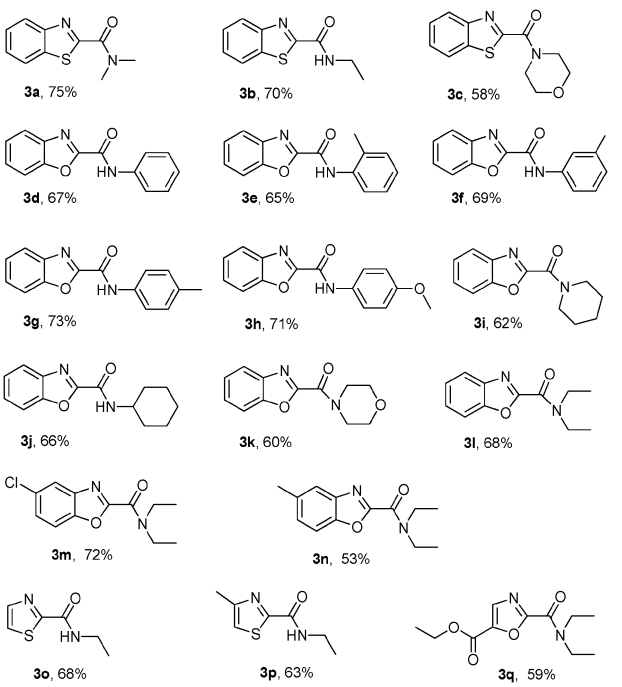
Entry	Solvent/temp. (°C)	Yield[b] (%)
1	CH_3CN/80	N.R.
2	THF/70	N.R.
3	Dioxane/100	N.R.
4	Dimethyl sulfoxide (DMSO)/100	N.R.
5	Toluene/100	75
6	*p*-Xylene/100	67
7	Chlorobenzene/100	60
8	Benzene/80	55
9	Toluene/80	52
10	Toluene/120	34

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (2.0 mmol), TBPB (1.0 mmol), solvent (3.0 mL), 12 h. [b] Isolated yield.

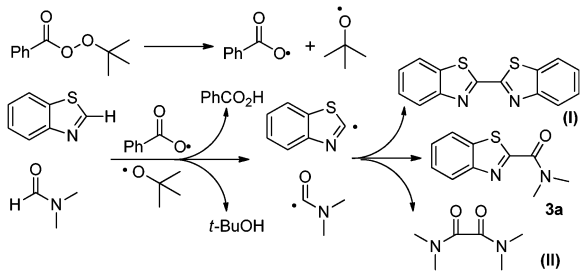
After establishing the optimized reaction conditions for the direct dehydrogenative cross-coupling reaction of benzothiazole with formamide, several substituted thiazole and oxazoles were synthesized according to the literature[12] and then applied to explore the scope of amidation under the present reaction conditions. As can be seen from Table 4, the reactions of benzothiazole (**1a**) with formamides bore with different substituted groups gave good yields of the products. For the substituted formamides, the cyclic aliphatic amino moiety resulted in the lower yields of the products than that of formamides derived from linear aliphatic amines (**3c** *vs.* **3a** and **3b**). It was showed that larger bulky groups on nitrogen atoms lead to poor yields. On the other hand, benzoxazole (**1b**), 5-chlorobenzooxazole (**1c**) and 5-methylbenzoxazole (**1d**)

Table 4 Screening of substrate scopes in the direct amidation of azoles with formamides[a]

1a-g **2a-j** **3a-q**[b]



[a] Conditions: **1** (0.5 mmol), **2** (2.0 mmol), TBPB (1.0 mmol), toluene (3.0 mL), 100 °C for 12 h. [b] Isolated yields.



Scheme 1 Proposed reaction mechanism.

also reacted with formamides, which derived from aromatic and aliphatic amines in good yields under the recommended reaction conditions (**3d–n**). A similar phenomenon was also observed in the reaction of benzoxazoles with formamides (**3l** and **3m** *vs.* **3j** and **3k**). The *N*-phenyl formamides derived from aromatic amines reacted with benzoxazole (**1b**) smoothly to generate the direct dehydrogenative cross-coupling products (**3d–h**) in good yields under present reaction conditions. When the *para*-positions of the phenyl rings in *N*-(substituted phenyl)formamides were occupied by a methyl or a methoxy group, the product yields were superior to that of *N*-phenyl formamide (**3g** and **3h** *vs.* **3d**). Meanwhile, when the *ortho*- or *meta*-positions of the phenyl rings in *N*-(substituted phenyl)-formamides were attached with a methyl group, the product yields were comparable to that of *N*-phenyl formamide (**3d** *vs.* **3e** and **3f**). It is obvious that *ortho*-position effect was not observed in the reaction of *N*-(2-methylphenyl)formamide as one of the substrates (**3e**). More simple oxazole and thiazole derivatives also reacted with formamides to afford the corresponding products in good yields (**3o–q**).

A plausible mechanism for this reaction was proposed in Scheme 1. It may involve a free radical process. Firstly, radical initiator TBPB underwent a homolytic cleavage to generate a carboxyl radical and an alkoxyl radical. Subsequently, they abstract hydrogens from benzothiazole and DMF, forming the corresponding free radicals, which react with each other to generate the corresponding cross-coupling product through termination of two radicals. The homo-coupling product (**I**) was also obtained in 10% yield, and no (**II**) was observed in the reaction. It should be noted that the reaction was suppressed by a radical scavenger, such as TEMPO in a dose-dependent manner.[14]

In summary, we have developed a metal- and base-free approach toward the direct C2 amidation of azoles with formamides *via* C–H activation. Benzothiazole, thiazoles, as well as benzoxazoles and oxazole reacted with diverse formamides smoothly in the presence of commercially available TBPB at 100 °C in toluene to generate the direct dehydrogenative cross-coupling products in good yields. The findings offer a new, simple and mild method for the synthesis of useful azoles derivatives[15] and the detailed mechanistic study is currently underway.

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