ORGANIC LETTERS

2012
Vol. 14, No. 11
2722–2725

Iron-Catalyzed 2-Arylbenzoxazole Formation from *o*-Nitrophenols and Benzylic Alcohols

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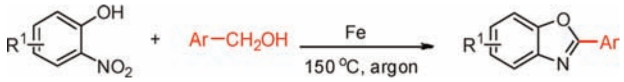
Received April 11, 2012

ABSTRACT



The iron-catalyzed 2-arylbenzoxazole formation from *o*-nitrophenols and benzylic alcohols using hydrogen transfer is described. Various 2-arylbenzoxazoles were selectively obtained in good to excellent yields. The reaction tolerated a wide range of functionalities. The alcohol oxidation, nitro reduction, condensation, and dehydrogenation were realized in a cascade without external reducing reagent and oxidant.

Aryl-substituted benzoxazoles are common building blocks for the synthesis of pharmaceuticals, natural products, functional materials, and agrochemical compounds. These compounds have been extensively studied for their biological and therapeutic activities.[1] Consequently, development of efficient methods for rapid construction of aryl-substituted benzoxazoles has stimulated considerable interest. Recently, the activation of C−H bonds has received much attention for the straightforward construction of C−C and C−hetero bonds.[2] Various aryl-substituted benzoxazoles have been successfully synthesized by direct C−H activation and subsequent C−C bond formation with aryl halides,[3] arylsilanes,[4] aromatic carboxylic acids,[5] aryl boronic acids,[6] sodium sulfinates and aryl triflates,[7] and even arene C−H bonds via double C−H activations.[8]

The conventional methods for the synthesis of these important compounds typically involve two approaches. One is the metal-catalyzed intramolecular cyclization of *o*-haloanilides or their analogues (Scheme 1, a).[9] The second approach mainly involves the condensation of 2-aminophenol with either a carboxylic acid derivative under strong acid/high temperature conditions or an aromatic

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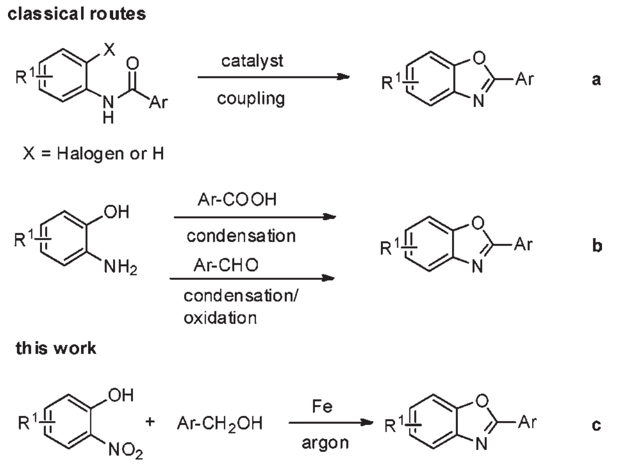
Scheme 1. Different Pathways for the 2-Arylbenzoxazole Formation



aldehyde under strong oxidative conditions (Scheme 1, b).[10] Recently, catalytic oxidative reactions using oxygen as the terminal oxidant have received much attention. However, these reactions require the use of large amounts of the catalyst or excess base.[11] To overcome these limitations, Han et al. developed an aerobic oxidative synthesis of 2-substituted benzoazoles catalyzed by 4-methoxy-TEMPO using oxygen as the oxidant.[12] Williams et al. developed an iridium-catalyzed 2-arylbenzoxazole formation from aldehydes and *o*-aminophenols even in the absence of oxidant.[13] Kobayashi et al. disclosed a supported Pt-catalyzed aerobic oxidation of phenolic imines under very mild conditions.[14] In most cases, 2-aminophenols are used as the starting materials for the preparation of 2-arylbenzoxazoles. There are few examples for 2-arylbenzoxazole formation from 2-nitrophenols and aldehydes (or trimethyl orthobenzoate) using large amount of metals as nitro group reductants.[15] 2-Nitrophenols was also successfully coupled with benzylic amines to give 2-arylbenzoxazoles under high reaction temperatures (> 200 °C).[16]

Very recently, we and others developed various catalytic systems for direct C—N bond formation from nitroarenes and alcohols[17] or cyclohexanones[18] using the borrowing hydrogen methodology (or hydrogen transfer).[19] In this process, nitroarenes were reduced in situ using the borrowed hydrogen generated from the alcohol or cyclohexanone oxidation step. This method afforded a shortcut for C—N bond formation using stable starting materials without any external reducing reagent and oxidant. However, noble catalysts such as ruthenium, palladium, or iridium were used in most cases. The use of cheap and nontoxic iron catalyst for C—N bond formation would be highly desirable.[20] Herein, we report an iron-catalyzed 2-arylbenzoxazole formation from *o*-nitrophenols and benzylic alcohols, affording the aryl-substituted benzoxazoles in high yields (Scheme 1, c).

We began our study by examining the reaction of 2-nitrophenol (**1a**) and benzyl alcohol (**2a**) in toluene at 150 °C. When 2-nitrophenol reacted with 2.5 equiv of benzyl alcohol in the absence of any catalyst, no desired product **3a** was obtained as determined by GC and ^{1}H NMR methods (Table 1, entry 1). Then various iron salts were investigated for this reaction under similar reaction conditions. $FeSO_4$, $Fe(NO_3)_3$, Fe_2O_3, and $Fe_2(SO_4)_3$ were proved to be ineffective catalysts for this kind of transformation (entries 2—5). The desired product was obtained in 18% and 31% yields when ferrocene and $Fe(acac)_3$ were used (entries 6 and 7). The reaction yields could be further improved to 79% and 81% when 5 mol % of $FeCl_3$ and $FeCl_2$ were employed (entries 8 and 9). Among the various iron salts examined, dppf [1,1′-bis(diphenylphosphino)-ferrocene] was the most effective, and its use resulted in the formation of **3a** in 82% yield (entry 10). The choice of solvents was crucial for this reaction. The use of NMP,

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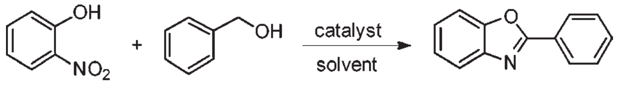
diglyme and DMF all resulted much lower yields (entries 11–13). Other solvents such as *p*-xylene, anisole, and chlorobenzene were proven to be also good solvents for this reaction (entries 15–17). Interestingly, slightly higher yields were obtained when the catalyst loading was decreased to 3 or even 2 mol % (entries 18 and 19). The reaction temperature is another important factor for the yield of the product. The reaction yield decreased to 67% when the temperature was decreased to 130 °C (entry 20). Good yield still could be achieved when the reaction was carried out under an atmosphere of air (entry 21).

Table 1. Optimization of the Reaction Conditions[a]



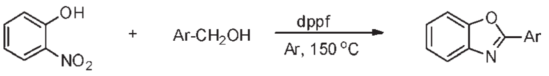
1a **2a** **3a**

entry	catalyst (mol %)	solvent	yield[b] (%)
1		toluene	0
2	$FeSO_4$ (5)	toluene	trace
3	Fe_2O_3 (5)	toluene	trace
4	$Fe(NO_3)_3$ (5)	toluene	trace
5	$Fe_2(SO_4)_3$ (5)	toluene	trace
6	ferrocene (5)	toluene	18
7	$Fe(acac)_3$ (5)	toluene	31
8	$FeCl_3$ (5)	toluene	79
9	$FeCl_2$ (5)	toluene	81
10	dppf (5)	toluene	82
11	dppf (5)	NMP	41
12	dppf (5)	diglyme	32
13	dppf (5)	DMF	33
14	dppf (5)	1,4-dioxane	62
15	dppf (5)	*p*-xylene	76
16	dppf (5)	anisole	76
17	dppf (5)	PhCl	77
18	dppf (3)	toluene	89
19	dppf (2)	toluene	89
20[c]	dppf (2)	toluene	67
21[d]	dppf (2)	toluene	75

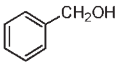
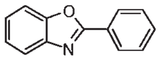
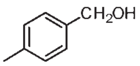
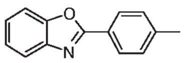
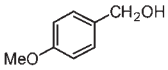
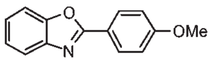
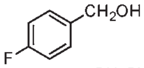
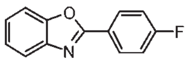
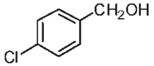
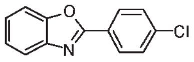
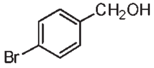
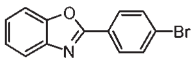
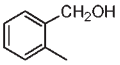
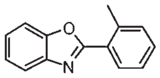
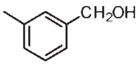
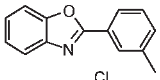
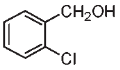
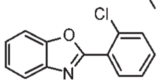
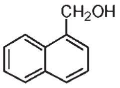
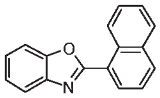
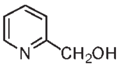
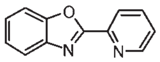
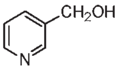
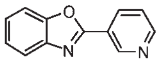
[a] Conditions: **1a** (0.2 mmol), **2a** (0.5 mmol), solvent (0.5 mL), 24 h, 150 °C under argon. [b] GC yield. [c] At 130 °C. [d] Under air.

With the optimized reaction conditions established, the scope of the reaction with respect to 2-nitrophenol (**1a**) and various benzylic alcohols (**2**) was investigated (Table 2). The reactions with benzylic alcohols bearing electron-donating groups (entries 2 and 3) and electron-withdrawing substituents at the aromatic ring (entries 4 and 5) proceeded smoothly to give the desired products in good yields. Good yield was obtained when 4-bromobenzyl alcohol (**2f**) was used, and the desired product was achieved in 84% yield (entry 6). The position of the substituents on the phenyl ring of benzyl alcohols affected the reaction yield slightly. Good yields were obtained when 2-methylbenzyl alcohol (**2g**), 3-methylbenzyl alcohol (**2h**), 2-chlorobenzyl alcohol (**2i**), and 1-naphthalenemethanol (**2j**) were used as starting materials (entries 7–10). Notably, the coupling of hetero benzylic alcohols such as 2-pyridinemethanol (**2k**) and 3-pyridinemethanol (**2l**) with **1a** afforded **3k** and **3l** in 82 and 78% yields, respectively (entries 11 and 12). Unfortunately, aliphatic alcohols are not suitable substrates for this kind of transformation under the optimal conditions.

Table 2. Reactions of **1a** with Various Benzylic Alcohols[a]



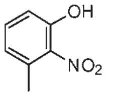
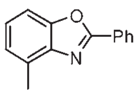
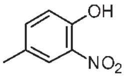
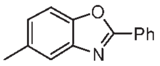
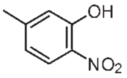
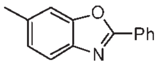
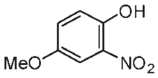
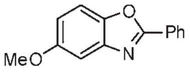
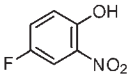
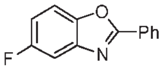
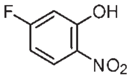
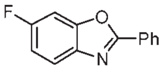
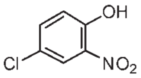
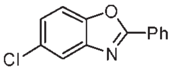
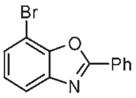
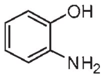
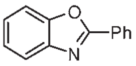
1a **2** **3**

entry	alcohol		product		yield (%)[b]
1		**2a**		**3a**	85
2		**2b**		**3b**	88
3		**2c**		**3c**	84
4		**2d**		**3d**	78
5		**2e**		**3e**	84
6		**2f**		**3f**	84
7		**2g**		**3g**	79
8		**2h**		**3h**	75
9		**2i**		**3i**	75
10		**2j**		**3j**	85
11		**2k**		**3k**	82
12		**2l**		**3l**	78

[a] Conditions: **1a** (0.2 mmol), **2** (0.5 mmol), dppf (2 mol %), 150 °C, 24 h under argon. [b] Isolated yields based on **1a**.

To further explore the scope of the reaction, various 2-nitrophenols were employed to react with **2a** under the optimized conditions (Table 3). A series of functional groups including methyl, methoxy, chloro, bromo, and fluoro were well tolerated under the optimal reaction conditions, and the desired products were obtained in moderate to good yields (Table 3, entries 1–8). The position of the substituents on the phenyl ring of 2-nitrophenol slightly affected the reaction yield (entries 1–3). Interestingly, the reaction of 2-aminophenol with benzyl alcohol under optimized conditions resulted much lower yield (entry 9).

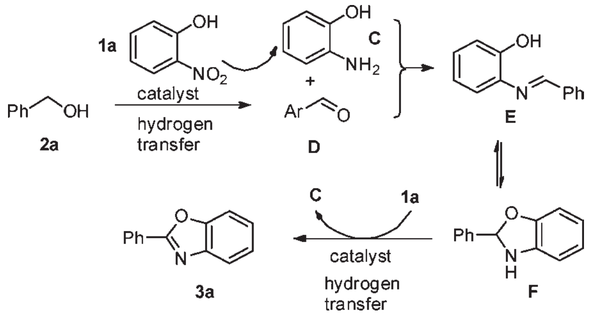
Table 3. Reactions of **2a** with Various Nitrophenols[a]

entry	nitrophenol		product		yield (%)[b]
1		**1b**		**3m**	82
2		**1c**		**3n**	79
3		**1d**		**3o**	81
4		**1e**		**3p**	83
5		**1f**		**3q**	55
6		**1g**		**3r**	76
7		**1h**		**3s**	80
8		**1i**		**3t**	82
9		**1j**		**3a**	23

[a] Conditions: **1** (0.2 mmol), **2a** (0.5 mmol), dppf (2 mol %), 150 °C, 24 h under argon. [b] Isolated yields based on **1**.

A plausible mechanism to rationalize this transformation is illustrated in Scheme 2. Oxidation of **2a** generates the corresponding aldehyde **D** and reduces **1a** to **C**. Condensation of **D** with **C** generates an intermediate imine **E**, which can be in equilibrium with dihydrobenzazole **F**. A second hydrogen-transfer process from **F** to **1a** provides the desired product **3a**. In the whole process, nitro group acts as hydrogen acceptor (oxidant) two times.

Scheme 2. Proposed Mechanism



In summary, we have developed an iron-catalyzed 2-arylbenzoxazole formation from *o*-nitrophenols and benzylic alcohols using a hydrogen-transfer strategy. The alcohol acted both as coupling reagent and reductant. Functional groups such as methyl, methoxy, fluoro, chloro, and bromo were all well tolerated under the optimized reaction conditions. The alcohol oxidation, nitro reduction, heterocycle formation, and heterocycle oxidation were realized in a cascade. The scope, mechanism, and synthetic applications of this reaction are under investigation.

Acknowledgment. This work was supported by the National Natural Science Foundation of China (20902076, 21172185), the Hunan Provincial Natural Science Foundation of China (11JJ1003), the New Century Excellent Talents in University from Ministry of Education of China (NCET-11-0974), and the Scientific Research Foundation for Returned Scholars, Ministry of Education of China (2011-1568).

Supporting Information Available. General experimental procedure and characterization data of the products. This material is available free of charge via the Internet at http://pubs.acs.org.
