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Iron-Catalyzed One-Pot 2,3-Diarylquinazolinone Formation from 2-Nitrobenzamides and Alcohols

Huamin Wang,[†] Xiangxiang Cao,[†] Fuhong Xiao,[†] Saiwen Liu,[†] and Guo-Jun Deng*[,†,‡]

Key Laboratory of Environmentally Friendly Chemistry and Application of Ministry of Education, College of Chemistry, Xiangtan University, Xiangtan 411105, China, and Key Laboratory of Molecular Recognition and Function, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100080, China

gjdeng@xtu.edu.cn

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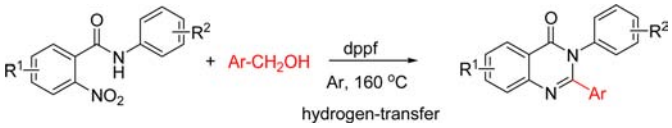
ABSTRACT



A novel approach for the synthesis of 2,3-diarylquinazolinones using iron as catalyst is described. Various 2-nitro-*N*-arylbenzamides reacted with benzylic alcohols to selectively give the corresponding products in the absence of external oxidant or reductant.

Quinazolinone occurs widely in natural products such as rutaecarpine from a Chinese herbal drug and luotonin A from a Chinese plant (*Peganum nigellastrum*) (Figure 1).[1] Substituted quinazolinones are assigned as privileged structures in drug discovery. They play important roles as key building blocks in the synthesis of a variety of drugs such as anticonvulsant, antibacterial, anti-inflammatory, and anticancer agents.[2] As a result, there are numerous efforts aimed at developing efficient and mild approaches for the synthesis of substituted quinazolinones.[3] Conventional routes to substituted quinazolinones mainly rely on coupling *o*-aminobenzamides with aldehyde,[4] alcohol,[5] as well as other coupling reagents.[6] 2-Aminobenzoic acid and its derivatives[7] and 2-halogen-substiuted anilines[8] are also often used as starting materials for the preparation of substituted quinazolinones. However, the presence of an amino group sometimes resultes in product instability or preparation difficulties. In recent years, replacing *ortho*-functionalized anilines with other functionalized compounds has attracted considerable interest. Among them, *o*-bromobenzoic acid derivatives were the most used

[†] Xiangtan University.
[‡] Chinese Academy of Sciences.

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starting materials for substituted quinazolinone preparation with amides, amines, or amidines as the coupling partners.[9] Dehydrogenation[10] and replacement[11] of heterocycles also provided alternative routes to substituted quinazolinones.

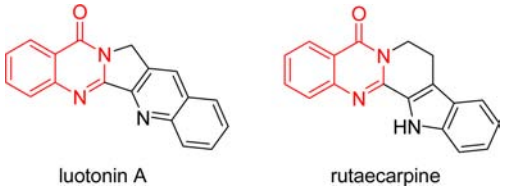
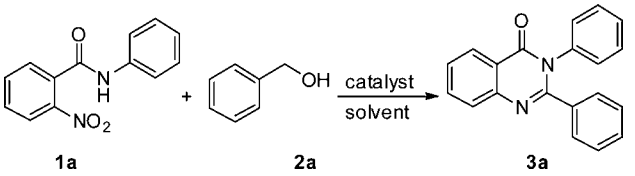


Figure 1. Structures of rutaecarpine and luotonin.

Usually, the amino group is prepared from the corresponding nitro group via a reduction process using a stoichiometric amount of metal/acid or hydrogen.[12] To discover a shortcut for the construction of new carbon–nitrogen bonds, we and other groups recently developed several approaches for direct amination reactions from nitroarenes using hydrogen transfer strategy.[13] In this process, hydrogen generated from an alcohol[14] or cyclohexanone[15] via dehydrogenation acted as an internal reducing reagent. Various transition metals were successfully used as catalysts for direct amination of nitroarenes. This method afforded a novel amination reaction approach using readily available and stable starting materials. Although there are numerous methodologies for substituted quinazolinone preparation, facile methods for 2,3-diarylquinazolinones in one pot are still rare.[16] Based on our previous research, we envisaged that it might be possible to prepare 2,3-diarylquinazolinones directly from nitroarenes using hydrogen transfer strategy.[17] *Herein, we report a new approach to 2,3-diarylquinazolinones from 2-nitrobenzamides and benzylic alcohols using cheap and nontoxic iron as the catalyst.*

Table 1. Investigation of Optimized Reaction Conditions[a]



1a 2a 3a

entry	catalyst (mol %)	solvent	yield[b] (%)
1	$RuCl_3$(5)	toluene	30
2	$FeCl_3 \cdot 6H_2O$ (5)	toluene	31
3	Fe_2O_3 (5)	toluene	0
4	$Fe(NO_3)_3$(5)	toluene	17
5	$Fe_2(SO_4)_3$ (5)	toluene	21
6	ferrocene (5)	toluene	18
7	$FeCl_2$ (5)	toluene	26
8	$Fe(acac)_3$ (5)	toluene	34
9	dppf (5)	toluene	73
10	dppf (3)	toluene	74
11	dppf (3)	NMP	22
12	dppf (3)	diglyme	46
13	dppf (3)	DMF	30
14	dppf (3)	1,4-dioxane	23
15	**dppf (3)**	**PhCl**	**88**
16	dppf (3)	*p*-xylene	40
17	dppf (3)	anisole	60
18[c]	dppf (3)	PhCl	trace
19[d]	dppf (3)	PhCl	74

[a] Conditions: **1a** (0.2 mmol), **2a** (0.5 mmol), solvent (0.5 mL), 24 h, 160 °C under argon. [b] GC yield. [c] At 140 °C. [d] Under air.

Initial experiments were carried out using 2-nitro-*N*-phenylbenzamide (**1a**) and benzyl alcohol (**2a**) as starting materials. In our previous research, ruthenium and iron both proved to be effective for coupling nitroarenes with alcohols via hydrogen-transfer methodology. Hence, $RuCl_3$ and iron catalysts were screened for this kind of transformation. The corresponding 2,3-diphenylquinazolin-4(3*H*)-one (**3a**) product was obtained in 30% yield using toluene as solvent under an argon atmosphere when $RuCl_3$ was used as catalyst (Table 1, entry 1). Inspired by this discovery, various iron salts were then investigated (entries 2–9). The use of 5 mol % of Fe_2O_3 as catalyst completely inhibited the reaction (entry 3). Other iron salts were more effective for this kind of transformation. Among the various iron catalysts investigated, dppf [1,1′-bis(diphenylphosphino)ferrocene] showed the best efficiency and **3a** was obtained in 73% yield (entry 9). Interestingly, **3a** still could be obtained in 74% yield when we

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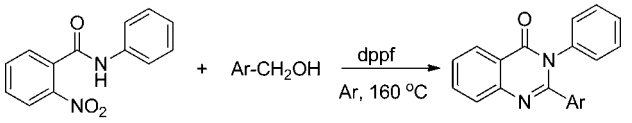
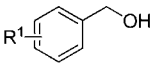
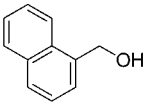
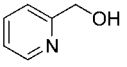
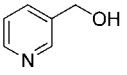
Table 2. Reaction of **1a** with Substituted Benzylic Alcohols[a]

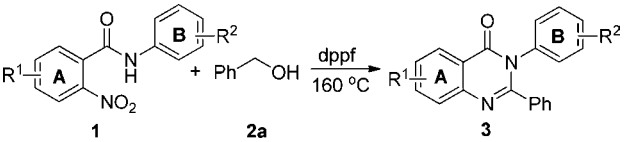


1a **2** **3**

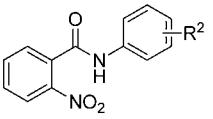
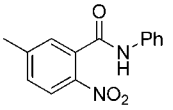
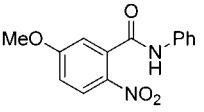
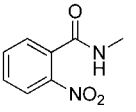
entry	substrate		product	yield (%)[b]
				
1	R^1 = H	**2a**	**3a**	85
2	R^1 = 4-Me	**2b**	**3b**	70
3	R^1 = 4-OMe	**2c**	**3c**	70
4	R^1 = 4-F	**2d**	**3d**	72
5	R^1 = 4-Cl	**2e**	**3e**	78
6	R^1 = 4-Br	**2f**	**3f**	86
7	R^1 = 2-Cl	**2g**	**3g**	40
8	R^1 = 2-Me	**2h**	**3h**	58
9	R^1 = 3-Me	**2i**	**3i**	67
10		**2j**	**3j**	68
11		**2k**	**3k**	80
12		**2l**	**3l**	30

[a] Conditions: **1a** (0.2 mmol), **2** (0.5 mmol), dppf (3 mol %), 160 °C, 24 h under argon. [b] Isolated yields based on **1a**.

Table 3. Reactions of **2a** with Substituted Amides[a]



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

entry	amide		product	yield (%)[b]
				
1	R^2 = 4-Me	**1b**	**3m**	50
2	R^2 = 4-OMe	**1c**	**3n**	66
3	R^2 = 4-F	**1d**	**3o**	73
4	R^2 = 4-Cl	**1e**	**3p**	72
5	R^2 = 4-Br	**1f**	**3q**	53
6	R^2 = 4-CF_3	**1g**	**3r**	70
7	R^2 = 4-OCF_3	**1h**	**3s**	82
8	R^2 = 2-Me	**1i**	**3t**	42
9	R^2 = 3-Me	**1j**	**3u**	48
10		**1k**	**3v**	84
11		**1l**	**3w**	89
12		**1m**	**3x**	64

[a] Conditions: **1** (0.2 mmol), **2a** (0.5 mmol), dppf (3 mol %), 160 °C, 24 h under argon. [b] Isolated yields based on **1**.

decreased the catalyst loading to 3 mol % (entry 10). With the best catalyst in hand, we then investigated the impact of solvents on reaction yield (entries 11−17). The reaction yield decreased significantly when NMP, diglyme, DMF and 1,4-dioxane were used as reaction media. Chlorobenzene proved to be a good solvent for this kind of reaction, and its use could remarkably improve the reaction yield to 88% (entry 15). High reaction temperature is necessary to get satisfactory yield. Most of **1a** could be recovered when the reaction temperature was decreased to 140 °C (entry 18). The reaction is less efficient in air, and slightly lower yield was observed (entry 19).[18]

With the optimal reaction conditions in hand (dppf, chlorobenzene, 160 °C, 24 h, argon), the reaction scope was investigated first focusing on the influence of various benzylic alcohols on the reaction. Reaction of **1a** and **2a** afforded **3a** in 85% isolated yield under the given reaction conditions (Table 2, entry 1). Benzlic alcohols with electron-donating substituents at the contraposition (**2b** and **2c**) both smoothly reacted with **1a** to give the desired products in 70% yield (entries 2 and 3). Halogen substituents on benzylic alcohols were well tolerated during the hydrogen transfer process (entries 4−6). When (4-bromophenyl)methanol (**2f**) was employed for the transformation, the desired product 2-(4-bromophenyl)-3-phenylquinazolin-4(*3H*)-one (**3f**) was obtained in 86% yield (entry 6). Substituent position on benzyl alcohols showed a dramatic influence on the reaction yield. Only 40% yield was obtained when (2-chlorophenyl)methanol (**2g**) was used (entry 7). Similarly, lower yields were observed using *o*-tolylmethanol (**2h**) and *m*-tolylmethanol (**2i**) as coupling partners (entries 8 and 9). Notably, 2-pyridinemethanol (**2k**) also smoothly coupled with **1a** and afforded **3k** in 80% yield (entry 11). However, the use of 3-pyridinemethanol (**2l**) dramatically decreased the reaction yield to 30% (entry 12). Besides benzylic alcohols, simple aliphatic alcohols such as cyclohexanol and 1-butanol were also investigated and neither was active for this kind of transformation.

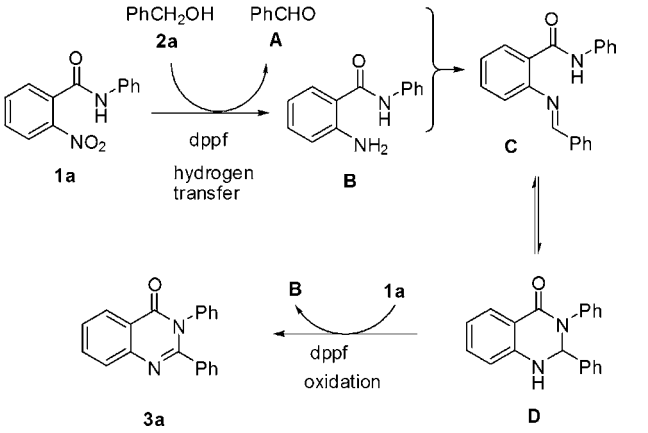
(18) According to ref 14e, three equiv of alcohols are necessary. However, in our case, 2.5 equiv of alcohol is enough since dehydrogenation of the dihydroquinazoline intermediate (**D**) also can provide hydrogen reductant.

Substituent effects on the aromatic rings **A** and **B** of the amide were also examined. Substrates bearing electron-donating substituents on aromatic ring **B** could be successfully coupled with benzyl alcohol and afforded the products in moderate yields (Table 3, entries 1 and 2). Much higher yields were obtained when the same substituents were presented on aromatic ring **A** (entries 10 and 11). Again, active halogen substituents such as fluoro and chloro survive the optimized coupling conditions (entries 3 and 4). However, a bromo substituent on ring **B** was less stable, and its use resulted in much lower yield (entry 5). Electron-withdrawing functional groups, such as 4-CF_3 (**1g**) and 4-OCF_3 (**1h**), on aromatic ring **B** are well tolerated, giving products in good yields (entries 6 and 7). The position of a methyl substituent on aromatic ring **B** slightly affected the reaction yield, and lower yields were obtained when the methyl group was located at the *ortho* or *meta* site (entries 8 and 9). Methyl substituted substrate (**1m**) also could be used for this kind of reaction although the efficiency was slightly lower (entry 12).

On the basis of these preliminary results and our previous works, a catalytic cycle for this transformation is proposed as shown in Scheme 1. Nitroarene **1a** is reduced to **B** by the hydrogen generated during the alcohol oxidation step via a hydrogen-transfer process in the presence of iron catalyst, and **2a** is oxidized into the corresponding aldehyde **A**. Subsequent condensation of **A** with **B** affords an imine intermediate **C**. Cyclization reaction of the amide NH with the imine generates intermediate **D**. This intermediate can be converted into the corresponding product **3a** via a hydrogen-transfer process.

In conclusion, we have developed a simple and efficient iron-catalyzed method for the synthesis of 2,3-diarylquinazolinones via a hydrogen-transfer strategy from nitrobenzamides and alcohols. The nitro group is reduced in situ by hydrogen generated from an alcohol oxidation process, and no external reducing reagent is required. Halogens as well as other active groups were well tolerated under the given reaction conditions. This reaction provides a complementary method for constructing medicinally important 2,3-diarylquinazolinones from stable nitrobenzamides and alcohols. Further studies on the reaction scope and the mechanism are under investigation in our laboratory.

Scheme 1. Proposed Reaction Mechanism



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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.

The authors declare no competing financial interest.