



Synthesis of bis-benzoquinoline derivatives catalyzed by iodine via ring-opening of furan



Dong-Sheng Chen, Yu-Ling Li, Yun Liu, Xiang-Shan Wang*

School of Chemistry and Chemical Engineering, Jiangsu Key Laboratory of Green Synthetic Chemistry for Functional Materials, Jiangsu Normal University, Xuzhou Jiangsu 221116, PR China

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ABSTRACT

A three-component reaction of aromatic aldehyde, naphthalene-2-amine, and tetrahydro-2,5-dimethoxyfuran in methanol catalyzed by iodine, is described in this paper. With the ring-opening of furan, a series of 3-aryl-2-(3-arylbenzo[*f*]quinolin-2-yl)benzo[*f*]quinoline derivatives were obtained in moderate yields.

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1. Introduction

Multicomponent reactions (MCRs), combining three or more reactants to a one-pot procedure to generate a complex organic molecule, have become increasingly popular during the last decade.¹ They are considered as a new type of green chemistry in economical reaction steps, because the ordinary multi-step syntheses produce considerable amounts of waste in the process of separation and purification for each step. Therefore, MCRs provide a powerful tool toward the one-pot synthesis of diverse and complex compounds as well as small and drug-like heterocycles.

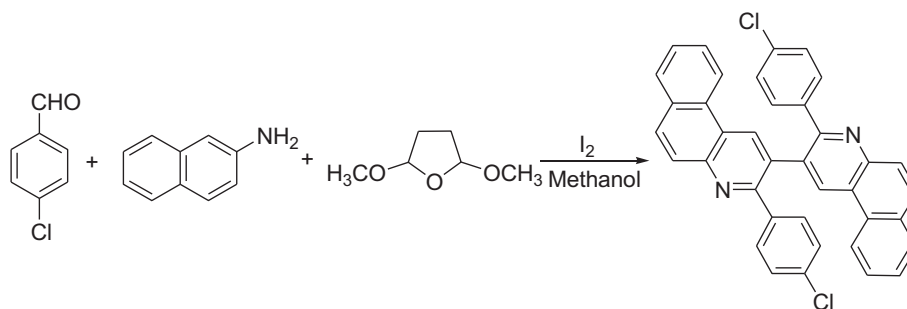
It is reported that quinoline and its derivatives are very useful compounds in the fields of biological and pharmacological chemistry. Some of them were used as DNA methylation modulators for the treatment of cancer and hematological disorders,² and as antimalarial agents in the treatment of malarial infections.³ In addition, they also exhibited the good antimicrobial,⁴ antiproliferative,⁵ and antituberculosis activities.⁶ Accordingly, novel strategies for the synthesis of quinolines continued to receive considerable attention in the field of synthetic organic chemistry⁷ besides the classical synthetic methods, for example, the Skraup, Doebner–Von Miller, Conrad-Limbach, Combes, and Pfitzinger quinoline syntheses.⁸

In recent years, it is well known that imino-Diels–Alder reaction, also named Povarov reaction, provides an easy access to the preparation of quinoline skeleton. The imines derived from aromatic amines act as the heterodienes, while the dienophiles are various kinds of electron-rich double bonds. Generally, they are 2,3-dihydrofuran, 3,4-dihydro-2*H*-pyran, vinyl ether, enol induced from aldehyde or ketone, and indiole.^{9–14}

Previously, we have reported an unusual THF-involved reaction of benzaldehyde, naphthalene-2-amine catalyzed by iodine.¹⁵ The ring-opening of THF was found to produce 2-(3-arylbenzo[*f*]quinolin-2-yl)ethanol derivatives unexpectedly. As part of a continuing effort in our laboratory toward this novel ring-opening reaction, tetrahydro-2,5-dimethoxyfuran was chosen to react with 4-chlorobenzaldehyde and naphthalene-2-amine with 1:1:1 molar ratio (Scheme 1). To our delight, the designed reaction proceeded smoothly in methanol catalyzed by iodine, and afforded bis-benzo[*f*]quinoline derivatives unexpectedly in 42% yield.

Subsequently, we repeated this novel reaction using 4-chlorobenzaldehyde, naphthalene-2-amine and tetrahydro-2,5-dimethoxyfuran as model substrates with 2:2:1 molar ratio to optimize reaction conditions. Several parameters were explored as shown in Table 1. No desired product was obtained when the reaction was carried out in the absence of iodine (Table 1, entry 1), and much greater in the presence of various quantities of the iodine, a maximum of 76% yield was obtained with 5 mol % iodine (Table 1, entries 2–4). Other metal Lewis acids, such as CuI, AlCl₃, ZnCl₂, AgOTf, Cu(OTf)₂, Yb(OTf)₃ were also tested in this reaction

* Corresponding author. E-mail address: xswang1974@yahoo.com (X.-S. Wang).



Scheme 1. The model reaction.

Table 1
Synthesis of **4a** under different reaction conditions^a

Entry	Cat.	Amount/mol %	Solvent	Yields ^b /%
1	—	0	Methanol	0
2	I ₂	1	Methanol	62
3	I ₂	5	Methanol	76
4	I ₂	10	Methanol	75
5	CuI	5	Methanol	0
6	AlCl ₃	5	Methanol	Trace
7	ZnCl ₂	5	Methanol	Trace
8	AgOTf	5	Methanol	42
9	Cu(OTf) ₂	5	Methanol	15
10	Yb(OTf) ₃	5	Methanol	53
11	I ₂	5	Toluene ^c	58
12	I ₂	5	CH ₃ CN ^d	62
13	I ₂	5	EtOH ^d	51
14	I ₂	5	DMF ^c	53

^a Reagents and conditions: **1** (280 mg, 2.0 mmol), **2** (286 mg, 2.0 mmol), **3** (132 mg, 1.0 mmol), solvent (10 mL).

^b Isolated yields.

^c 80 °C.

^d Reflux.

(Table 1, entries 5–10), and iodine was found to be the best choice (Table 1, entry 3). Different solvents, such as toluene, CH₃CN, DMF, and EtOH were also tested, and methanol appeared to be the best medium for this transformation (entry 3 vs 11–14).

Similarly, various kinds of aromatic aldehydes were selected to react with naphthalen-2-amine and tetrahydro-2,5-dimethoxyfuran, and it was found they all gave 3-aryl-2-(3-arylbenzo[*f*]quinolin-2-yl)benzo[*f*]quinoline derivatives expectedly. The results are summarized in Table 2. It is observed that the process can tolerate both electron-donating and electron-withdrawing substituents in the

Table 2
Synthetic results of **4** catalyzed by iodine^a

Entry	Ar	Products	Time/h	Yields ^b /%
1	4-ClC ₆ H ₄	4a	11	76
2	4-FC ₆ H ₄	4b	15	82
3	4-BrC ₆ H ₄	4c	12	68
4	4-CH ₃ C ₆ H ₄	4d	18	65
5	4-CH ₃ OC ₆ H ₄	4e	11	75
6	4-NO ₂ C ₆ H ₄	4f	12	78
7	3-BrC ₆ H ₄	4g	10	69
8	3-FC ₆ H ₄	4h	15	80
9	3,4-Cl ₂ C ₆ H ₃	4i	12	82
10	2-FC ₆ H ₄	4j	17	64
11	C ₆ H ₅	4k	15	69
12	3-CH ₃ C ₆ H ₄	4l	15	75
13	2-Thienyl	4m	12	65
14	3-NO ₂ C ₆ H ₄	4n	12	71
15	3-CH ₃ OC ₆ H ₄	4o	15	76
16	3-ClC ₆ H ₄	4p	12	72

^a Reagents and conditions: **1** (2.0 mmol), **2** (286 mg, 2.0 mmol), **3** (132 mg, 1 mmol), I₂ (13 mg), methanol (10.0 mL).

^b Isolated yields.

benzaldehydes. In all cases, the reactions proceeded efficiently at reflux under mild conditions to afford the corresponding products in moderate yields (Scheme 2).

However, we failed to get the desired products when aliphatic aldehydes were used as the reactants, because the aliphatic aldehydes, such as propyl aldehyde and butyl aldehyde, not only could react with aniline to produce Schiff base as a diene, but also act as a dienophile induced by iodine.¹⁶ In order to expand the application of amines, anilines, such as piperonylamine and 3,4-dimethoxyaniline were also tested in our lab, however, the reactions generated a very complicated system. Subsequent purification by column chromatography only gave the poor yields (Scheme 3). All the products were characterized by ¹H NMR, ¹³C NMR, IR, and HRMS, and the data were in good agreement with the preconceived structures.

According to the structure of the product and literature,¹⁵ we think twice Povarov reactions and aromatizations, ring-opening of furan may take place to give the final product **4**. The best reason to explain the poor yields for anilines is that the activity of naphthalen-2-amine is higher than those of anilines. In the intermediate III, the position 1 is not only the α -cite of amino group, but also is the α -cite of another benzene. The possible reaction mechanism was outlined in Scheme 4 as follows.

In order to get more insight into the reaction mechanism, tetrahydro-2,5-dimethoxyfuran was dissolved in CDCl₃, and the ¹H NMR was determined for control-experiment. Subsequently, a little amount of iodine was added to the above solution for 30 min, the second ¹H NMR was carried out, and new peaks were found at 5.96 and 6.26 ppm, which were identified as the hydrogen atoms of double bonds in hydrofuran. This result indicated that the double bond may form from tetrahydro-2,5-dimethoxyfuran. According to the result, furan and 2-methylfuran were selected to this reaction, however, they did not involve in the designed reaction. Perhaps, the aromaticity for furan prevented the further continuation of Povarov reaction.

In conclusion, we found a novel and efficient method for the synthesis of 3-aryl-2-(3-arylbenzo[*f*]quinolin-2-yl)benzo[*f*]quinoline derivatives using 5 mol % iodine as catalyst. The three-component reaction includes the interesting ring-opening of tetrahydro-2,5-dimethoxyfuran to construct bis-benzoquinolines in mild reaction conditions, good yields and operational simplicity.

2. Experimental section

2.1. General procedure for the syntheses of bis-benzoquinoline **4** and bis-quinoline derivatives **5**

Aromatic aldehyde (2.0 mmol), amine (2.0 mmol), tetrahydro-2,5-dimethoxyfuran (132 mg, 1.0 mmol), I₂ (13 mg), and methanol

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