One-pot Synthesis of Dibenzofurans *via* S_NAr and Subsequent Ligand-free Palladium-catalyzed Intramolecular Aryl-aryl Cross-coupling Reactions under Microwave Irradiation

Zhiping Che and Hui Xu

Laboratory of Pharmaceutical Design & Synthesis, College of Science, Northwest A&F University, Yangling 712100, Shaanxi Province, China

Reprint requests to Prof. Dr. Hui Xu. Fax: +86(0)29/87091952. E-mail: orgxuhui@nwsuaf.edu.cn

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An efficient one-pot synthesis of dibenzofurans, *via* S_NAr reaction of aryl halides and *ortho*-bromophenols in the presence of anhydrous K_2CO_3 and subsequent ligand-free palladium-catalyzed intramolecular aryl-aryl cross-coupling cyclization under microwave irradiation, is described.

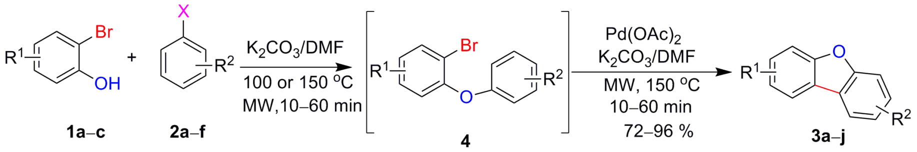
Key words: Dibenzofurans, Ligand-free, Microwave, S_NAr Reaction, Cross-coupling

Introduction

Dibenzofuran derivatives, besides their uses for molecular recognition [1 – 3], catalytic reactions [4, 5] and metal-binding sites [6], also display interesting biological activities, such as against the human immunodeficiency virus (HIV)-1 [7] and for protein tyrosine phosphatase 1B (PTP1B) inhibition [8]. Therefore, much attention has been paid to the construction of dibenzofurans. Ames *et al.* reported the synthesis of dibenzofurans, but step-wise procedures were needed there, and the yields were usually low [9]. Although dibenzofurans could also be prepared by the reaction of *ortho*-iodophenols with silylaryl triflates in the presence of CsF and palladium, expensive excess base and other not easily available starting materials were needed [10]. Another innovative route for the synthesis of substituted dibenzofurans has been described by Goel *et al.*, however, special starting materials must be used for this tedious procedure [11]. In our previous work, we have reported a one-pot synthesis of dibenzofurans directly from 2-bromophenols with aryl halides *via* an S_NAr reaction and subsequent palladium-catalyzed intramolecular aryl-aryl coupling under conventional heating, but triphenylphosphane was involved as a ligand, and especially for some aryl halides, such as 4-fluorobenzonitrile and 2-fluorobenzonitrile, the results were often not satisfactory even if the reaction time was prolonged [12]. In the meantime, due to the efficiency of microwave flash-heating, microwave-assisted organic synthesis (MAOS) has been growing in different fields of organic and medicinal chemistry [13 – 16]. Based on the above-mentioned reports, and in continuation of our program aimed at the development of new methods for the construction of heterocycles, consequently, in the work presented in this paper we wanted to investigate the synthesis of dibenzofurans from 2-bromophenols with aryl halides *via* an S_NAr reaction and subsequent ligand-free palladium-catalyzed intramolecular aryl-aryl coupling cyclization under microwave irradiation.

Results and Discussion

As outlined in Scheme 1, firstly, 2-bromophenols **1a – c** were reacted with aryl halides **2a – f** for 10 – 60 min in the presence of anhydrous K_2CO_3



Scheme 1. The synthetic route to dibenzofuran derivatives **3a – j**.

Table 1. One-pot synthesis of dibenzofurans **3a – j** from 2-bromophenols and aryl halides under microwave irradiation.

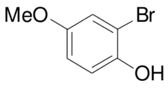
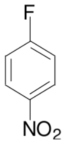
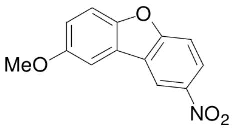
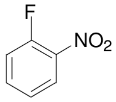
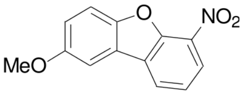
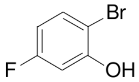
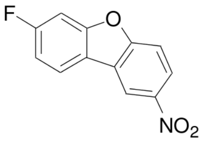
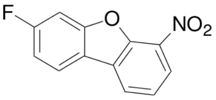
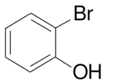
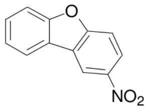
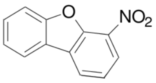
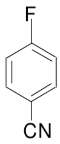
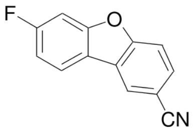
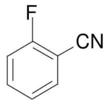
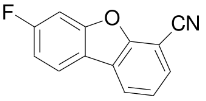
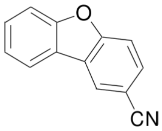
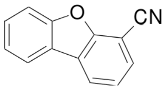
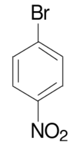
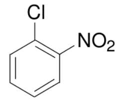
Entry	2-Bromophenols (**1**)		Aryl halides (**2**)		Dibenzofurans (**3**)		Time (min)[a]	Yield (%)[b]
1		**1a**		**2a**		**3a**	10 (100 °C) + 20 × 6 (100 °C)	93
2		**1a**		**2a**		**3a**	10 (100 °C) + 10 (150 °C)	96
3		**1a**		**2b**		**3b**	10 (100 °C) + 30 (150 °C)	88
4		**1b**		**2a**		**3c**	10 (100 °C) + 10 (150 °C)	82
5		**1b**		**2b**		**3d**	10 (100 °C) + 30 (150 °C)	89
6		**1c**		**2a**		**3e**	10 (100 °C) + 10 (150 °C)	95
7		**1c**		**2b**		**3f**	10 (100 °C) + 30 (150 °C)	89
8		**1b**		**2c**		**3g**	30 × 2 (150 °C) + 30 (150 °C)	72
9		**1b**		**2d**		**3h**	30 × 2 (150 °C) + 30 (150 °C)	75
10		**1c**		**2c**		**3i**	30 × 2 (150 °C) + 30 × 2 (150 °C)	88
11		**1c**		**2d**		**3j**	30 × 2 (150 °C) + 30 (150 °C)	86
12		**1a**		**2e**		**3a**	30 (150 °C) + 10 (150 °C)	72

Table 1 (continued).

Entry	2-Bromophenols (**1**)	Aryl halides (**2**)	Dibenzofurans (**3**)	Time (min)[a]	Yield (%)[b]
13	**1a**	 **2f**	**3b**	30 (150 °C) + 30 (150 °C)	81
14	**1b**	**2e**	**3c**	30 (150 °C) + 10 (150 °C)	75
15	**1b**	**2f**	**3d**	30 (150 °C) + 30 (150 °C)	78
16	**1c**	**2e**	**3e**	30 (150 °C) + 10 (150 °C)	77
17	**1c**	**2f**	**3f**	30 (150 °C) + 30 (150 °C)	85
18[c]	**1c**	**2c**	**3i**	370 (150 °C) + 30 (150 °C)	75

[a] “10 (100 °C) + 20 × 6 (10 °C)” means 10 min at 100 °C for the S_NAr reaction of compounds **1** and **2** in the presence of K_2CO_3, and 20 × 6 min at 10 °C for the subsequent ligand-free palladium-catalyzed intramolecular arylaryl coupling reaction, reaction temperature is given in parentheses; [b] isolated yields; [c] under conventional heating.

(1.0 mmol) under microwave irradiation to afford the intermediates **4** *via* an S_NAr reaction, which were then used directly for the subsequent ligand-free palladium-catalyzed intramolecular aryl-aryl coupling cyclization. With microwave irradiation for 10 – 60 min, dibenzofurans **3a** – **j** were smoothly obtained in 72 – 96 % yields.

As shown in Table 1, the reaction temperature for the subsequent ligand-free palladium-catalyzed intramolecular aryl-aryl coupling cyclization was important. For example, 4-methoxy-2-bromophenol (**1a**) completely reacted with 4-fluoronitrobenzene (**2a**) under microwave irradiation for 10 min at 100 °C to give the intermediate **4a**, which was further catalyzed by Pd(OAc)$_2$ at 100 °C for 20 × 6 min to produce 8-methoxy-2-nitrodibenzofuran (**3a**) in 93 % yield; however, when **4a** was exposed to Pd(OAc)$_2$ at 150 °C only for 10 min, **3a** was obtained in 96 % yield (entry 1 *vs.* entry 2). A steric effect was also observed in the palladium-catalyzed intramolecular cyclization of 4-fluoronitrobenzene (**2a**) and 2-fluoronitrobenzene (**2b**). For the **2a** series, it only took 10 min at 150 °C to finish the subsequent cyclization, while on the contrary, it usually took 30 min for the **2b** series at the same reaction temperature to transform the intermediates into the final products (entry 1 *vs.* entry 3; entry 4 *vs.* entry 5; entry 6 *vs.* entry 7). Based on the results of our previous research that the S_NAr reaction of 5-fluoro-2-bromophenol (**1b**) or 2-bromophenol (**1c**) with 4-fluorobenzonitrile (**2c**) or 2-fluorobenzonitrile (**2d**) is more difficult as compared with **2a** and **2b** [12], the corresponding reaction temperature was then directly raised to 150 °C for the first-step S_NAr reaction. As expected, even at 150 °C the reaction time needs also to be prolonged to 1 h to improve the yields of the S_NAr reaction. The results of **1c** reacting with **2c** under microwave irradiation were compared with those under conventional heating (entry 10 *vs.* entry 18), and it was obvious that under microwave irradiation the reaction time could be sharply reduced from 670 min to 120 min.

Finally, **1a**, **1b** or **1c** reacted with 4-bromonitrobenzene (**2e**) or 2-chloronitrobenzene (**2f**), respectively (entries 12 – 17). As described in Table 1, due to the nature of the leaving ability of the halogens of the aryl halides, the main difference in this tandem reaction between 4-fluoronitrobenzene or 2-fluoronitrobenzene and 4-bromonitrobenzene or 2-chloronitrobenzene lies in the S_NAr reaction. Compared with the fluoro derivatives, although the S_NAr reaction took a relatively long time at a higher reaction temperature for **2e** or **2f**, these results have demonstrated that the fluoro derivatives might be replaced by the corresponding bromo or chloro compounds without causing a significant decrease in the yields (entry 1 *vs.* entry 12; entry 3 *vs.* entry 13; entry 4 *vs.* entry 14; entry 5 *vs.* entry 15; entry 6 *vs.* entry 16; entry 7 *vs.* entry 17).

Conclusion

We have reported an efficient one-pot synthesis of dibenzofuran derivatives in 72 – 96 % yields in short reaction times *via* the S_NAr reaction of aryl halides and 2-bromophenols in the presence of anhydrous K_2CO_3 and subsequent ligand-free palladium-catalyzed intramolecular aryl-aryl cross-coupling cyclization under microwave irradiation.

Experimental Section

All reagents and solvents were of reagent grade. Analytical thin-layer chromatography (TLC) was performed with silica gel plates using silica gel 60 GF_{254} (Qingdao Haiyang Chemical Co., Ltd.). Melting points were determined on a digital melting point apparatus and are uncorrected. Proton nuclear magnetic resonance spectra (^1H NMR) were recorded on a Bruker Avance DMX 400 MHz instrument, using TMS as the internal standard and $CDCl_3$ as the solvent. Electron ionization mass spectrometry (EI-MS) was carried out with a Thermo DSQ GC/MS instrument. High-resolution mass spectra (HR-MS) were carried out with an APEX II Bruker 4.7T AS instrument. Microwave irradiation was performed in a CEM Discover Synthesis Unit (CEM Corp., Matthews, NC, made in USA).

*General procedure for the synthesis of dibenzofuran derivatives **3a**–**j***

A mixture of **1a**–**c** (0.5 mmol), **2a**–**f** (0.5 mmol), anhydrous K_2CO_3 (1.0 mmol), and DMF (2 mL) was placed in a 10-mL glass tube, which was sealed with a septum and placed into the microwave cavity. Microwave irradiation of 50 W for 100 °C and 100 W for 150 °C was used, the temperature being raised from r. t. to 100 or 150 °C. Once the given temperature was reached, the reaction mixture was held at this temperature for 10 – 30 min. The reaction progress was checked by TLC at the end of each irradiation period. When the starting materials were nearly consumed, $Pd(OAc)_2$ (0.025 mmol) was added to the mixture, the reaction being continued under microwave irradiation for 10 – 60 min. When the reaction was completed according to TLC analysis, the vessel was allowed to cool to r. t., and the mixture was poured into ice water (20 mL) and extracted with EtOAc (3×40 mL). Then the organic phases were combined and dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by silica gel column chromatography to give the pure dibenzofurans **3a** – **j** in 72 – 96 % yields. Compounds **3a** – **j** were all known compounds and identified by comparison of the data as described in our previous paper [12].

Acknowledgement

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