Synthesis of elaborate benzofuran-2-carboxamide derivatives through a combination of 8-aminoquinoline directed C–H arylations and transamidations

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Abstract

Benzofurans are everywhere in nature and they have been extensively studied by medicinal chemists over the years because of their chemotherapeutic and physiological properties. Herein, we describe a strategy that can be used to access elaborate benzo-2-carboxamide derivatives, which involves a synthetic sequence of 8-aminoquinoline directed C–H arylations followed by transamidations. For the directed C–H arylations, Pd catalysis was used to install a wide range of aryl and heteroaryl substituents at the C3 position of the benzofuran scaffold in high efficiency. Directing group cleavage and further diversification of the C3-arylated benzofuran products were then achieved in a single synthetic operation through the utilization of a two-step transamidation protocol. By bocylating the 8-aminoquinoline amide moiety of these products, it proved possible to activate them towards aminolysis with different amine nucleophiles. Interestingly, this aminolysis reaction was found to proceed efficiently without the need of any additional catalyst or additive. Given the high efficiency and modularity of this synthetic strategy, it constitute a very attractive approach for generating structurally-diverse collections of benzofuran derivatives for small molecule screening.

Introduction

The benzofuran core is present in many biologically active natural products, and as a result it has become a popular scaffold to explore when designing drugs.[1] Today, a great number of benzofuran-based drugs are available on the market, which include examples such as Methoxsalen that is used against psoriasis and eczema, the antiarrhythmic medications Amiodarone and Dronedarone, as well as the antidepressant Vilazodone (Figure 1).[1] Furthermore, many benzofuran derivatives have shown to display antimicrobial and anticancer properties, which have made them useful against a variety of indications.[1,2] Because of the vast applications of benzofuran-based drugs in today's medicine, there exists a considerable interest from the medicinal chemistry community for novel synthetic methodologies that can provide expedient access to new kinds of benzofuran derivatives.

The benzofuran scaffold is a heterocyclic motif that is composed of a fused benzene and furan ring, and different synthetic strategies can be used to introduce substituents on these two parts (Scheme 1a,b).[3] Substituents at the benzene part often originate from the synthetic precursor from which the benzofuran scaffold was built. Synthetic methods that are commonly used for assembling the benzofuran scaffold typically involve acid-catalyzed cyclizations,[4] carbonylative cyclizations *via* Sonogashira reactions,[5] Heck-type cyclizations,[6] photocyclizations,[7] radical

cyclizations[8] and other types of transition-metal catalyzed processes.[9] To functionalize the furan part, a considerable number of methods are available that allow for direct C2 and C3 functionalizations.[10] Of these, the functionalization of the C2 position is generally easier to achieve selectively as this is significantly more reactive than the C3 position.[11]

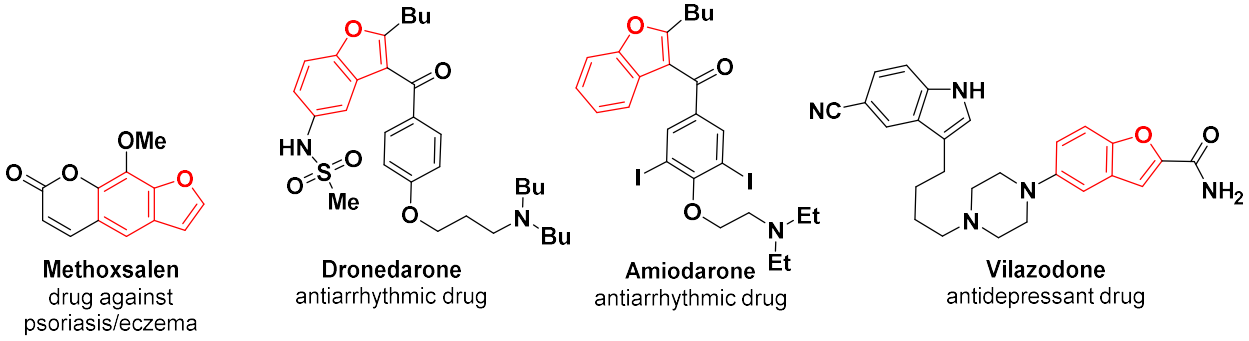
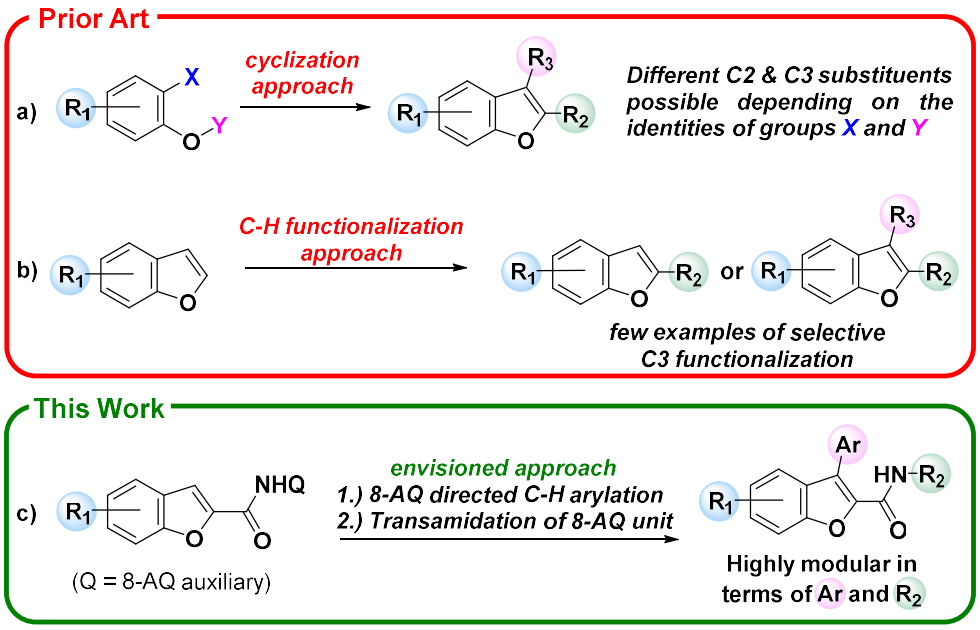


Figure 1. Examples of drugs containing the benzofuran scaffold.

In our group, we saw an interesting opportunity to access a diverse set of structurally elaborate benzofuran-2-carboxamide derivatives that carries different substituents in the C3 position through a strategic use of 8-aminoquinoline (8-AQ) directed C–H functionalization chemistry followed by a two-step transamidation method of 8-AQ amides developed within our group (Scheme 1c).[12] 8-AQ directed C–H functionalizations have is the recent decade become very popular within the fields of drug discovery[13] and natural product synthesis,[14] since they often enable for rapid assembly of molecular complexity.



Scheme 1. Different synthetic strategies towards highly functionalized benzofurans. a-b) General representations of prior cyclization- and C–H functionalization-based approaches. c) The herein reported approach towards elaborate benzofuran-2-carboxamide derivatives enabled by a combination of 8-AQ directed C–H arylations and transamidations.

In our envisioned synthetic approach, it was planned to start from the simple and commercially available building block, benzofuran-2-carboxylic acid, into which the 8-AQ auxiliary would be installed. The 8-AQ amide **1a** was anticipated to be a suitable substrate for Pd-catalyzed C–H functionalization chemistry, which can for example be used to install different aryl and heteroaryl substituents into the adjacent C3 position. Then, by drawing advantage of our previously developed transamidation protocol designed specifically for 8-AQ amides,[12] it would be possible to replace the 8-AQ auxiliary with different amine groups in a straight-forward fashion. Here, the transamidation is achieved effectively over two steps, where the 8-AQ amide is first treated with Boc_2O and DMAP to form the corresponding *N*-acyl-Boc-carbamate intermediate, which is then reacted with an amine to produce the desired product amine. Interestingly, the latter aminolysis step generally proceeds efficiently at mild temperatures without the need of any catalyst or additive.

Results & Discussion

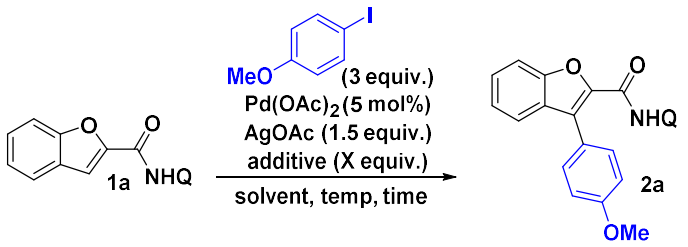
For installing the 8-AQ auxiliary into benzofuran-2-carboxylic acid, we used a coupling procedure involving HATU/DIPEA in DCM, which gave the desired 8-AQ amide substrate **1a** in 73% yield after 5 h (for further details, see Supporting Information, SI).[15] With 8-AQ amide **1a** in hand, we next turned our attention to the C–H arylation reaction, and here our initial efforts were focused on identifying conditions under which this transformation could proceed efficiently. In this optimization study, the effects of several reaction parameters on the arylation of **1a** with 4-iodoanisole were investigated. The reaction conditions for our first trial reaction were selected based on a previous C–H functionalization protocol for furans that had been reported by Padmavathi *et al.*[16] By performing the arylation of 8-AQ amide **1a** with 4-iodoanisole, using $Pd(OAc)_2$ (5 mol%) and AgOAc (1.5 equiv.) in toluene (0.5 M) at 110°C for 7 h, a promising first yield of 46% of product **2a** could be obtained (Entry 1). Allowing this reaction to stir for a longer time (16 h) was found to result in a higher yield of product **2a** (65% yield, Entry 2). However, increasing the temperature of the reaction to 120°C led to a reduced yield of product **2a** over 7 h (30%, Entry 3). The choice of additive, on the other hand, was found to have a more pronounced positive impact on model C–H arylation reaction. For example, using 0.2 equiv. of PivOH as an additive allowed the yield of product **2a** to be improved to 61% after 7 h (Entry 4). Unfortunately, the use of increased amounts of PivOH (0.5 equiv. and 1.0 equiv.) did not offer any further improvements in terms of the yield of product **2a** (Entries 5 and 6). The addition of NaOAc was also found to be beneficial for the C–H arylation reaction (Entries 8–10), and here 1 equiv. appeared to be the optimal amount, which furnished product **2a** in 78% yield after 7 h. The reaction with both 0.25 equiv. PivOH and 1.0 equiv. NaOAc was unfortunately found to perform worse than the one with only 1.0 equiv. of NaOAc as the additive (56% vs 78%, Entries 11 and 9).

Also, no further improvements of the model C–H arylation reaction were observed upon variation of the Pd source (see SI, Table S1). Furthermore, Ag_2CO_3 proved to be an inferior silver source compared to AgOAc, allowing product **2a** to only be obtained in 49% yield after 7 h (See SI, Table S1). However, we were delighted to see that the model C–H arylation reaction could be further improved through change of solvent (Entries 12–16). The green solvents *tert*-amyl-OH, methyl-THF and CPME all showed to be better alternatives than toluene for this transformation (Entries 12–14 vs Entry 9). Of these, CPME allowed for the highest yield of product **2a** after 7 h

(93%, Entry 14). Lower yields of product **2a** were however observed in DCE and MeCN (Entries 15 and 16).

We also tested if it was possible to use a smaller excess of 4-iodoanisole (2 equiv.) and compensate this with either a longer reaction time or higher reaction concentration (Entries 17 and 18). Unfortunately, these alterations of the reaction conditions led to markedly lower yields of **2a** (80% and 73% yield, respectively, after 15 h). Therefore, it was decided to perform all further C–H arylation reactions with 3 equiv. of the aryl iodide and using $Pd(OAc)_2$ (5 mol%), AgOAc (1.5 equiv.) and NaOAc (1 equiv.) in CPME (0.5 M) at 110°C.

Table 1. Optimization of the Pd-catalyzed C–H arylation of substrate **1** with 4-iodoanisole.[a]



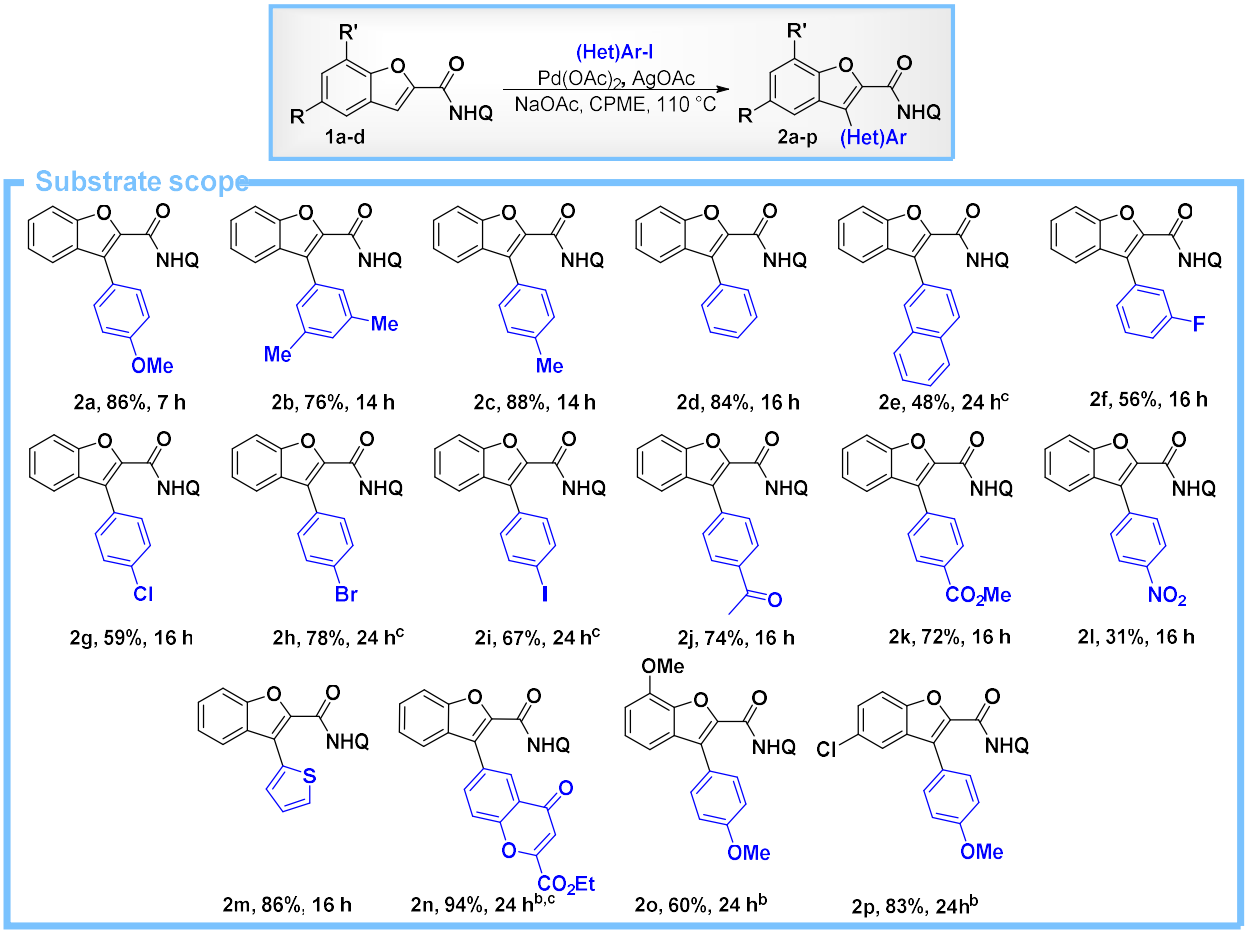
Entry	Additive (equiv.)	Solvent (M)	T (°C)	Time (h)	Yield (%)
1	none	Toluene	110	7	46
2	none	Toluene	110	16	65
3	none	Toluene	120	7	30
4	$(BnO)_2PO_2H$ (0.2)	Toluene	110	7	28
5	PivOH (0.2)	Toluene	110	7	61
6	PivOH (0.5)	Toluene	110	7	48
7	PivOH (1.0)	Toluene	110	7	17
8	NaOAc (0.5)	Toluene	110	7	62
9	NaOAc (1.0)	Toluene	110	7	78
10	NaOAc (2.0)	Toluene	110	7	70
11	PivOH+NaOAc (0.2+1.0)	Toluene	110	7	56
12	NaOAc (1.0)	t-amyl OH	110	7	91
13	NaOAc (1.0)	MeTHF	110	7	81
14	NaOAc (1.0)	CPME	110	7	93
15	NaOAc (1.0)	DCE	110	7	69
16	NaOAc (1.0)	MeCN	110	7	18
17[b]	NaOAc (1.0)	CPME	110	15	80
18[b,c]	NaOAc (1.0)	CPME	110	15	73

[a] Reagents and conditions: Substrate **1** (0.1 mmol), 4-iodoanisole (3 equiv.), $Pd(OAc)_2$ (5 mol%), AgOAc (1.5 equiv.), and the additive(s) were dissolved in solvent (0.5 M) and heated at the given temperature under inert atmosphere. [b] 2 equiv. of 4-iodoanisole were used. [c] concentration = 1 M.

As a part of the substrate scope study, the catalytic protocol was evaluated for different aryl iodides and benzofuran substrates (Figure 2). Here, some of the formed C–H arylation products were found to display limited solubility in a number of common organic solvents (**2e**, **2h**, **2i**, and **2n**), which prevented purification by column chromatography.[17] For these compounds, an alternate purification procedure was developed in which the crude reaction mixtures were first loaded onto a silica pad and where the remaining starting material and excess aryl iodide were then

eluted with a EtOAc wash. To recover the C–H arylation products from the silica pad, it was transferred to a Soxhlet apparatus and extracted overnight with refluxing CH_2Cl_2. With this alternative purification protocol, we could obtain these more problematic C–H arylation products in high yields and excellent purity.

Figure 2. Scope of the C–H arylation protocol in terms of different (hetero)aryl iodides and benzofuran substrates.[a]



[a] Reagents and conditions: Benzofuran substrate (0.15 mmol), (hetero)aryl iodide (3.0 equiv.), $Pd(OAc)_2$ (5 mol%), AgOAc (1.5 equiv.), and NaOAc (1 equiv.) were all dissolved in CPME (0.5 M) and heated at 110 °C under inert atmosphere for the times given above. All reported yields refer to isolated yield (see SI for further details). [b] 10 mol% $Pd(OAc)_2$ was used. [c] Soxhlet extraction with CH_2Cl_2 was used in the purification procedure.

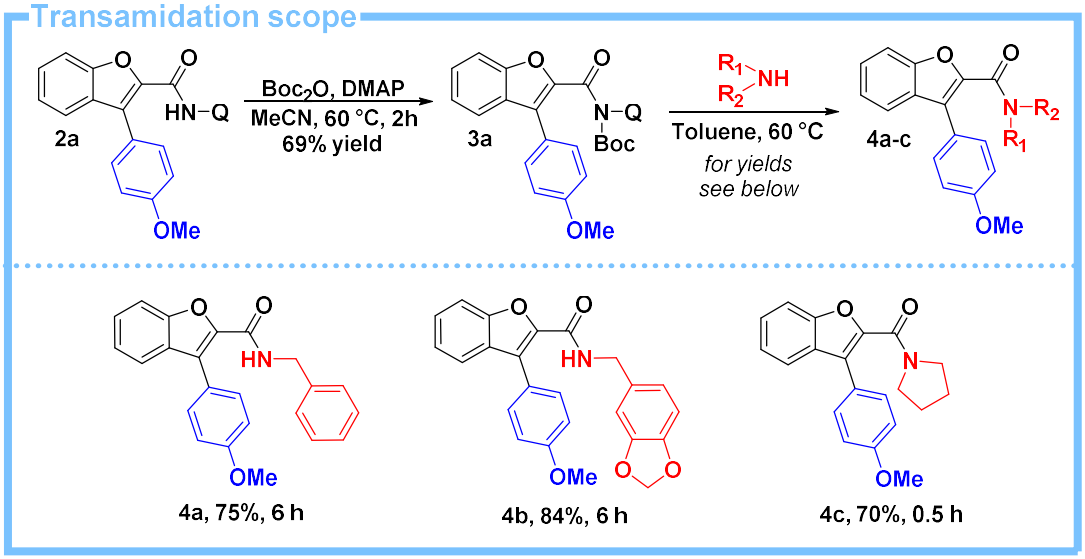
In terms of aryl iodides, the C–H arylation protocol was found to benefit from those carrying electron-donating substituents. This trend was best exemplified by the reaction to form product **2a**, which could be isolated in 86% yield after 7 h. Good results were also obtained when using 5-iodo-*meta*-xylene and 4-iodotoluene, and from these reactions products **2b** and **2c** could be isolated in 76% and 88% yield, respectively, after 14 h. A slightly longer reaction time (16 h) was required for the arylation with iodobenzene, but also here a high yield of 84% of product **2d** was obtained. However, in the cases of the reactions with 2-iodonaphtalene and aryl iodides carrying additional halogen substituents, lower yields of the desired C–H arylation products **2e–i** were typically observed (48-78% yield after 16-24 h). On the other hand, the reactions involving aryl iodides with

a keto or ester group proceeded well, and here products **2j** and **2k** were acquired in 74% and 72% yield, respectively, after 16 h. Unfortunately, the reaction using 1-iodo-4-nitrobenzene as the arylating agent gave a complicated mixture of products from which only limited amounts of the desired product **2l** could be isolated (31% yield). To our delight, it also proved possible to install different heteroaromatic moieties into the benzofuran scaffolds using our catalytic protocol, as demonstrated by the C–H arylations to form the thiophene- and chromone-based products **2m** and **2n** in 86% and 85% yield, respectively. However, for the latter reaction it proved necessary to use 10 mol% $Pd(OAc)_2$ and a reaction time of 24 h in order to ensure a high yield of product **2n**.

Higher catalyst loadings and longer reactions times were also required when conducting the C–H arylation on different substituted benzofuran substrates. However, by using these more forcing conditions we were able to show that this catalytic protocol can be used to prepare the 7-OMe- and 5-Cl-substituted products **2o** and **2p** in respectable yields (60% and X%, respectively).

Having surveyed the scope of the C–H arylation reaction, we next turned our attention to the removal of the 8-AQ auxiliary. Here, we were interested in evaluating our previously reported transamidation protocol,[12] since it would enable direct and convenient access to elaborate benzofuran-2-carboxamide derivatives without the need of proceeding *via* the intermediate carboxylic acids. As a proof of concept, we demonstrated this two-step transamidation for the C–H arylation product **2a** with three different amines (Figure 3). Conversion of product **2a** into the corresponding *N*-acyl-Boc-carbamate **3a** could be done in 69% yield using Boc_2O and DMAP in MeCN over 2 h at 60 °C.[18] The aminolysis of carbamate **3a** with benzyl amine gave the amide product **4a** in a good yield of 75% after 6 h. Efficient aminolysis of **4a** was also observed with piperonylamine within 6 h, and from this reaction it was possible to isolate amide **4b** in 84% yield. Interestingly, the aminolysis of **4a** with pyrrolidine was found to be significantly faster, and here 70% yield of the amide product **4c** could be obtained after 30 min.

Figure 3. Two-step transamidation of **2a** with three different amines.[a]



[a] Reagents and conditions: Boc activation: Product **2a** (1.0 equiv), $(Boc)_2O$ (2.0 equiv), DMAP (0.1 equiv) in MeCN (0.1 M), 60 °C, 2 h. Transamidation: Carbamate **3a** (1.0 equiv) and amine (1.5 equiv) in toluene (0.5 M), 60 °C for the times given above.

Conclusions

In summary, we have described a short and modular synthetic strategy that can be used to access elaborate benzofuran-2-carboxamide derivatives with a diverse set of substitution patterns. This is accomplished by a sequence consisting of a 8-AQ directed C–H arylation followed by a two-step transamidation. To our delight, the developed C–H arylation method was found to work well for a wide range of aryl iodides and benzofuran substrates, which allowed for the preparation of a variety of C3-arylated benzofuran products. Moreover, we could as a proof-of-concept demonstrate the efficient transamidation of a C–H arylation product with three different amines. On-going efforts in our laboratory are focused on further improving and expanding the scope of this transamidation protocol, and we hope to be able to present more examples of elaborate amide products once this work is communicated to a journal.

Acknowledgment

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Conflict of Interest

The authors have no conflict of interest to declare.

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[18] Purification of **3a** involved passing the worked up reaction mixture through a pad of silica. The carbamate **3a** was found to decompose slightly upon contact with silica, and thus on-going work is focused on finding alternative purification methods that can allow for a higher isolated yield of **3a**.