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Synthetic Methods

Metal-Free One-Pot Synthesis of Benzofurans

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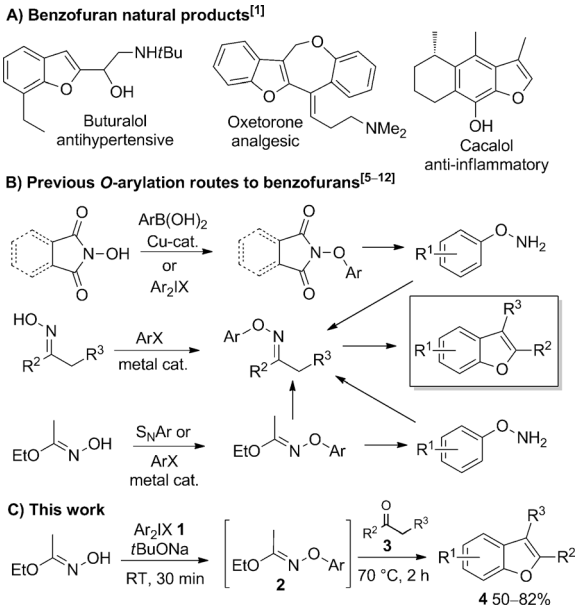
Abstract: Ethyl acetohydroxamate was efficiently arylated with diaryliodonium salts at room temperature under transition-metal-free conditions. The obtained *O*-arylated products were reacted in situ with ketones under acidic conditions to yield substituted benzo[*b*]furans through oxime formation, [3,3]-rearrangement, and cyclization in a fast and operationally simple one-pot fashion without using excess reagents. Alternatively, the *O*-arylated products could be isolated or transformed in situ to aryloxyamines or *O*-arylaldoximes. The methodology was applied to the synthesis of Stemofuran A and the formal syntheses of Coumestan, Eupomatenoid 6, and (+)-machaeriol B.

The benzo[*b*]furan backbone is found in a variety of natural products and pharmaceuticals, and the array of reported biological activities includes anti-inflammatory, analgesic, and antifungal activities (Scheme 1 A).[1] Furthermore, benzofurans have recently been exploited in materials chemistry.[2]

The major interest in benzofuran applications has resulted in the development of a wide range of synthetic methods towards this target. Benzofurans are commonly synthesized by transition-metal-catalyzed cross-coupling reactions of 2-halophenols and alkynes, followed by cyclization.[3] Other metal-catalyzed cross-coupling strategies have been reported as well,[4] but despite the efficiency of metal-catalyzed reactions, drawbacks remain that include high temperatures, prolonged reaction times, the need for complex ligands, the use of excess reagents, and trace-metal impurities remaining in the products.

Aryloxyamines are important precursors of *O*-aryloximes and benzofurans.[5] They can be synthesized by the Cu-catalyzed arylation of *N*-hydroxyphthalimide with arylboronic acids, followed by cleavage with hydrazine (Scheme 1 B).[6] Ketoximes with α-hydrogen atoms can be arylated under metal-catalyzed conditions to give *O*-arylketoximes,[7] which can undergo an acid-promoted [3,3]-rearrangement/cyclization sequence, closely resembling the Fischer indole synthesis.[8] This strategy has been employed in the synthesis of several biologically active benzofurans.[9]



Scheme 1. Benzofuran structures and synthesis.

Finally, ethyl acetohydroxamate can be converted to aryloxyamines by S_NAr arylation with electron-deficient aryl fluorides, followed by acid-promoted hydrolysis.[10] Buchwald and coworkers recently reported a more general palladium-catalyzed arylation of ethyl acetohydroxamate with aryl halides in the presence of air-sensitive alkyl-arylphosphine ligands.[11] The products were subsequently transformed into benzofurans in one pot through *O*-arylketoximes and a [3,3]-rearrangement/cyclization sequence.

We have recently described the metal-free arylation of *N*-hydroxyimides with diaryliodonium salts under novel hydrolytic conditions to yield aryloxyamines (Scheme 1 B).[12] To obtain benzofurans without having to isolate the aryloxyamines, we took inspiration from Buchwald's two-step route and set out to develop a metal-free one-pot arylation of ethyl acetohydroxamate with diaryliodonium salts **1** and subsequent reaction of intermediates **2** with ketones **3** to form benzofurans **4** (Scheme 1 C).

Herein, we present our preliminary results on the first one-pot arylation, hydrolysis, oxime formation, [3,3]-rearrangement, and cyclization sequence to yield benzofurans in good yields and short reaction times.

The arylation of ethyl acetohydroxamate with diphenyliodonium triflate (**1 a**) to yield *O*-phenylated product **2 a** was optimized at ambient temperature (Table 1). A solvent screening with potassium *tert*-butoxide as base revealed that acetonitrile

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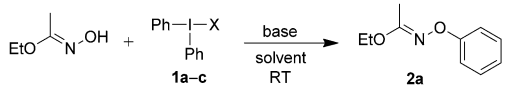
Table 1. Optimization of the arylation.[a]



Entry	1 ([equiv])	X	Base ([equiv])	Solvent	Time [h]	Yield [%][b]
1	**1a** (1.2)	OTf	*t*BuOK (1.2)	THF	15	50
2	**1a** (1.2)	OTf	*t*BuOK (1.2)	toluene	15	42
3	**1a** (1.2)	OTf	*t*BuOK (1.2)	DMF	15	73
4	**1a** (1.2)	OTf	*t*BuOK (1.2)	dioxane	15	68
5	**1a** (1.2)	OTf	*t*BuOK (1.2)	CH_2Cl_2	15	78
6	**1a** (1.2)	OTf	*t*BuOK (1.2)	CH_3CN	15	91
7	**1a** (1.2)	OTf	*t*BuONa (1.2)	CH_3CN	15	93
8	**1a** (1.2)	OTf	K_2CO_3 (1.2)	CH_3CN	15	82
9	**1a** (1.2)	OTf	KOH (1.2)	CH_3CN	15	80
10	**1a** (1.3)	OTf	*t*BuONa (1.3)	CH_3CN	15	90
11	**1a** (1.1)	OTf	*t*BuONa (1.1)	CH_3CN	15	91
12	**1a** (1.1)	OTf	*t*BuONa (1.1)	CH_3CN	0.5	93
13[c]	**1a** (1.1)	OTf	*t*BuONa (1.1)	CH_3CN	0.5	92
14[c]	**1b** (1.1)	BF_4	*t*BuONa (1.1)	CH_3CN	0.5	88
15[c]	**1c** (1.1)	OTs	*t*BuONa (1.1)	CH_3CN	0.5	87

[a] Ethyl acetohydroxamate (0.25 mmol) and base were stirred in anhydrous solvent (1.5 mL) for 15 min at RT before addition of **1**. [b] ^{1}H NMR yield with 1,3,5-trimethoxybenzene as internal standard. [c] 1 mL of solvent was used.

was the best solvent (entries 1–6). Sodium *tert*-butoxide was equally efficient as potassium *tert*-butoxide, whereas other bases gave a slightly lower yield of **2a** (entries 7–9). The reaction proved as efficient with only 1.1 equivalents of salt **1a** and sodium *tert*-butoxide as base (entries 10 and 11), and a reaction time of 30 min was sufficient to obtain **2a** in excellent yield (entries 12 and 13).

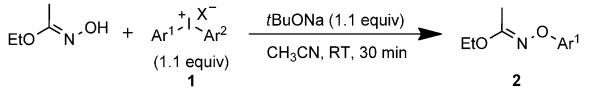
Finally, iodonium tetrafluoroborate **1b** and tosylate **1c** were employed to examine the anion tolerance of the reaction. Fortunately, salts with these anions also provided **2a** in high yield, which is important because a wide anion tolerance simplifies the synthesis of substituted diaryliodonium salts.

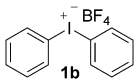
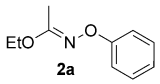
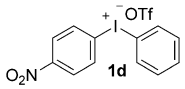
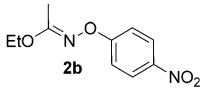
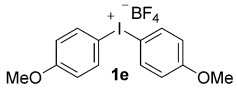
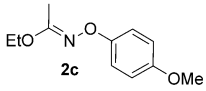
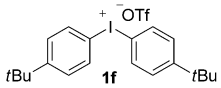
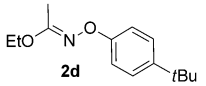
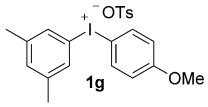
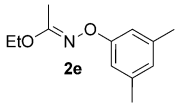
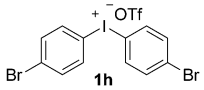
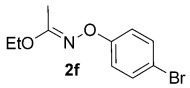
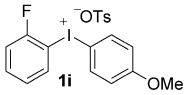
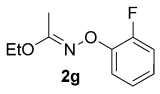
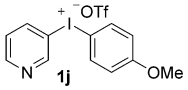
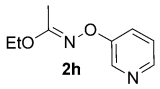
The generality of this arylation was subsequently investigated by employing differently substituted iodonium salts **1**,[13] and high isolated yields were obtained with a variety of salts despite the volatility of the corresponding products **2** (Table 2).[11] Unsymmetric salts were used when this facilitated the synthesis of the salt, and complete chemoselectivity was obtained in all cases.[14]

The electron-deficient 4-nitrophenyl group was chemoselectively transferred from unsymmetric salt **1d** to give **2b** in 89% yield (entry 2). Importantly, also the novel 4-methoxy product **2c** could be obtained in good yield by slightly increasing the amount of the reagents (entry 3), which is in contrast to our previous arylation of N–O substrates to give *N*-aryloxyimides.[12] Electron-rich products are difficult to obtain by S_NAr reactions with hydroxylamine equivalents, and metal-catalyzed arylations of this substrate class failed or are low-yielding.[6,11]

As expected, alkyl substituents were well tolerated (**2d** and **2e**), and the bromo-substituted product **2f** was formed in good yield (entries 4–6). Bromide substituents are difficult to

Table 2. Arylation scope of ethyl acetohydroxamate.



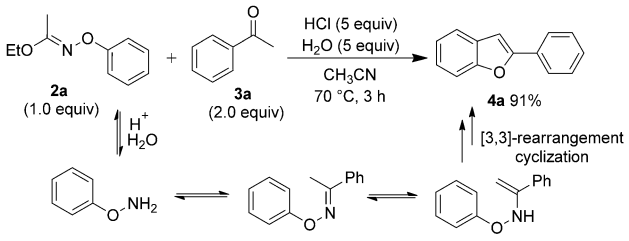
Entry	Salt **1**	Product **2**	Yield [%][a]
1			87
2			89
3[b]			74
4			77
5			64
6			78
7			51
8			81

[a] Isolated yields. [b] 1.3 equiv of salt and base, 1 h reaction time.

transfer in metal-catalyzed arylations and can serve as useful handles for further synthetic manipulations (see below). *Ortho*-substituted aryl groups could be transferred in moderate yields, as exemplified by the incorporation of the 2-fluorophenyl group in **2g** (entry 7). Furthermore, heteroaryl salts could be employed, and a pyridyl group was chemoselectively transferred from unsymmetric salt **1j** to give compound **2h** in 81% yield (entry 8).

With the optimized arylation conditions at hand, we envisioned a sequential one-pot arylation and oxime ether formation/rearrangement to form benzofurans **4** without the isolation of the volatile compounds **2**. Buchwald and coworkers have reported the reaction of **2** with ketones in the presence of HCl and water in refluxing dioxane to yield benzofurans.[11]

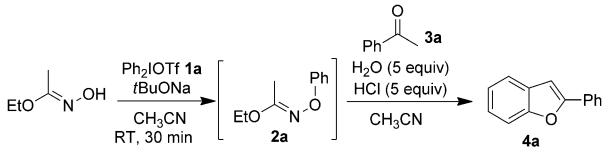
The feasibility of our one-pot strategy was first investigated by treating **2a** with acetophenone (**3a**) under modified Buchwald conditions by using acetonitrile instead of dioxane (Scheme 2). This gratifyingly delivered benzofuran **4a** in 91% yield through hydrolysis, *O*-aryloxime formation, [3,3]-rearrangement, and cyclization.[8]



Scheme 2. Benzofuran synthesis under modified Buchwald conditions.

Having demonstrated the solvent compatibility between the arylation and the benzofuran formation, an optimization of the second step in the envisioned one-pot reaction was performed (Table 3). To our delight, benzofuran **4a** was formed in an impressive yield of 82% when the two steps were combined (entry 1). The reaction time was screened and 2 h proved sufficient (entries 2 and 3). The atom efficiency was improved by reducing the amount of **3a** to 1.2 equivalents (entry 4), while lowering the temperature to 50 °C had a negative impact on the yield (entry 5).

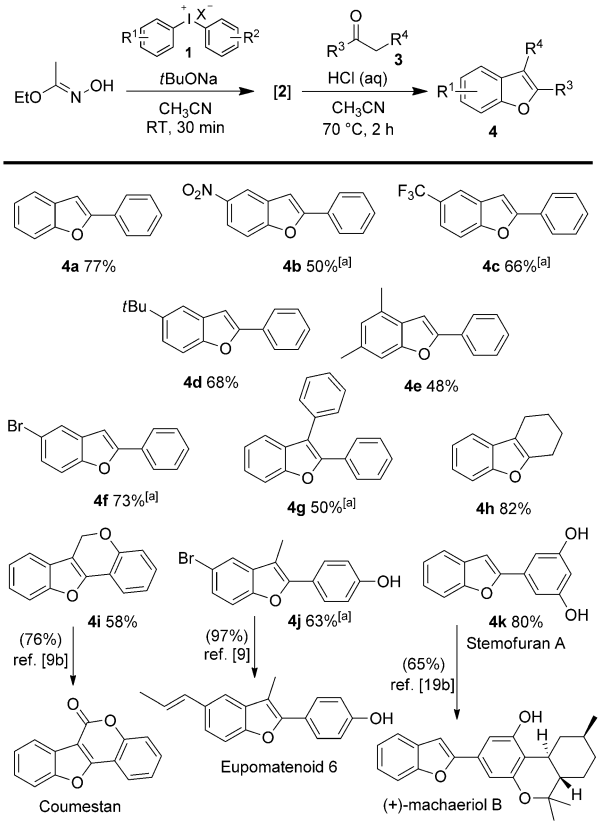
Table 3. Optimization of the one-pot synthesis of benzofurans.[a]



Entry	**3a** [equiv]	HCl source	Temp. [°C]	Time [h]	Yield [%][b]
1	2.0	4 M in dioxane	70	3	82
2	2.0	4 M in dioxane	70	2	84
3	2.0	4 M in dioxane	70	1	75
4	1.2	4 M in dioxane	70	2	82
5	1.2	4 M in dioxane	50	2	50
6[c]	1.2	37% (aq)	70	2	82

[a] Step 1: ethyl acetohydroxamate (0.25 mmol), base (1.1 equiv) and **1a** (1.1 equiv), see Table 1, entry 13. Step 2: **3a**, H_2O, and HCl were added at RT and the vial was purged with argon. [b] ^{1}H NMR yield with 1,3,5-trimethoxybenzene as internal standard. [c] No H_2O was added.

With these efficient, fast, and practical reaction conditions at hand, the one-pot synthesis of benzofurans was applied to a range of diaryliodonium salts **1** and ketones **3** (Scheme 3). By variation of iodonium salts **1**, important functional groups such as nitro, trifluoromethyl, alkyl, and bromide were introduced to yield products **4a**–**f**. In agreement with previous reports, benzofuran formation from the oxime ether intermediate was slow with electron-withdrawing substituents;[8d] hence, products **4b** and **4c** required a longer reaction time to reach useful conversions.[15]



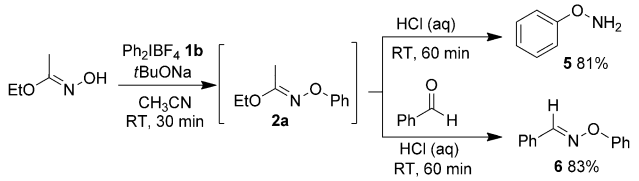
Scheme 3. Scope of the one-pot synthesis of benzofurans. [a] Longer reaction time in step 2, see the Supporting Information.

Next, variation of the ketone structure was explored, and 2,3-diphenylbenzofuran **4g** was successfully obtained. Cyclohexanone was an excellent substrate, delivering tricyclic product **4h** in 82% yield. Considering that the overall transformation consists of five steps (arylation, hydrolysis, oxime ether formation, rearrangement, and cyclization), yields in this range correspond to an average reaction efficiency of >95% per step.

The one-pot reaction was subsequently utilized in the synthesis of several biologically active benzofurans, without the use of protective groups. Tetracyclic benzofuran **4i** can be oxidized in one step to Coumestan, which is the central core in the Coumestans, some of which show estrogenic activity.[9b,16] Ketones with unprotected hydroxyl groups were employed to give phenolic compounds **4j** and **4k**. Benzofuran **4j** can be converted to Eupomatenoid 6, having antifungal, insecticidal, and antioxidant activity, in one step.[9,17]

Stemofurans are a subgroup of 2-arylbenzofurans with hydroxyl substituents, which show antifungal activity, and are used in the treatment of respiratory disorders in traditional medicine.[18] Stemofuran A (**4k**) was obtained in 80% yield, which also constitutes a metal-free formal synthesis of (+)-machaeriol B, an antimicrobial and antimalarial agent.[19]

Finally, the arylation was combined with an acidic hydrolysis at room temperature to provide aryloxyamine **5** in 81% yield



Scheme 4. One-pot synthesis of aryloxyamine **5** and aryloxime **6**.

(Scheme 4). The one-pot reaction could also be extended to the synthesis of *O*-arylaldoxime **6** by the addition of benzaldehyde under otherwise identical conditions. These reactions further illustrate the simplicity of the described protocol, which is performed under milder reaction conditions and with a shorter reaction time than previous methodologies towards **5** and **6**.[5a,6,10–12]

In all cases, the arylations with unsymmetric iodonium salts **1** were completely chemoselective. As previously reported, the iodoarenes formed in the reactions with salts **1** can be recovered in excellent yields and used for the synthesis of **1**, thereby further improving the atom efficiency of these arylations.

To summarize, the first one-pot synthesis of benzo[*b*]furans from hydroxylamine equivalents is described. The reaction is metal-free, fast, and avoids excess reagents. Furthermore, the isolation of *O*-aryl ethyl acetohydroxamates **2** is described with both electron-deficient and electron-rich diaryliodonium salts, and a fast one-pot arylation and hydrolysis gave aryloxyamine **5** at room temperature.

The efficiency of the protocol is demonstrated by the synthesis of Stemofuran A, and the formal syntheses of Coumestan, Eupomatenoid 6, and (+)-machaeriol B. The methodology should find vast application in the synthesis of biologically interesting benzofurans.

Experimental Section

One-pot synthesis of benzofurans 4

Ethyl acetohydroxamate (0.5 mmol) was added to an oven-dried re-sealable cap vial, dissolved in anhydrous CH_3CN (2.0 mL) and the vial was capped with a rubber septum. *t*BuONa (0.55 mmol) was added in one portion at 0 °C and the mixture was stirred vigorously at RT for 15 min. The reaction vial was then submerged into a water bath at ambient temperature and salt **1** (0.55 mmol) was added in one portion (**note**: slightly exothermic reaction). The reaction mixture was stirred vigorously at RT for 30 min. Ketone **3** (0.6 mmol) was then added and the vial was purged with argon and submerged into a water bath at ambient temperature. HCl (37% (aq), 2.5 mmol) was added dropwise through a volumetric pipette. The vial was purged with argon, sealed, and stirred at RT for 15 min and then stirred at 70 °C for 2 h. The reaction mixture was diluted with diethyl ether (4 mL), quenched with NaOH (1 M, 3 mL), extracted with diethyl ether, washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography using pentane and Et_2O, EtOAc, or CH_2Cl_2 as eluents to give benzofuran **4**.

Acknowledgements

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Keywords: arylation · aryloxyamines · cyclization · diaryliodonium salts · *O*-aryloximes · sigmatropic rearrangement

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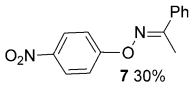
[15] Formation of the oxime ether was facile, and 30% of product **7** was isolated despite a prolonged reaction time.



7 30%

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Synthetic Methods

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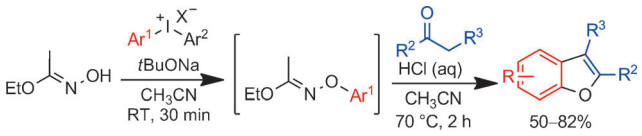
Metal-Free One-Pot Synthesis of Benzofurans



Just add salt! A metal-free, room temperature arylation of ethyl acetohydroxamate, followed by an in situ reaction with ketones under acidic conditions yielded substituted benzo[*b*]furans in a fast and operationally simple one-pot fashion without using excess reagents (see scheme). Alternatively, the *O*-arylated products could be isolated, hydrolyzed in situ to aryloxyamines, or transformed to *O*-arylaldoximes. The efficiency of the methodology was demonstrated by the formal synthesis of several biologically active benzofurans.