Construction of Diverse Dihydrodibenzofuranones by Migration/ Intramolecular Arylation of Iodonium Ylides

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A novel and facile methodology for synthesizing diverse dihydrodibenzofuranones from easily accessible cyclic iodonium ylides is achieved. This protocol proceeds through the aryl migration of iodonium ylide followed by Pd-catalyzed intramolecular arylation.

Keywords: Palladium, Cyclization, Iodonium ylide, Benzofuran, C—H activation

Introduction

Benzofurans are privileged heterocyclic frameworks found in many naturally occurring and biologically active compounds.[1] They have shown various biological activities such as antitumor, antimalarial, antifungal, antiarrhythmic, and antibacterial properties.[2] They also display pharmacological properties such as selective inhibitors of the butyrylcholinesterase enzyme (BChE) for Alzheimer's disease,[3] stimulation of neurite outgrowth of NGF-mediated PC12-cells,[4] streptococcus mutans sortase A,[5] and monoamine oxidase (MAO).[6] They are also used as building blocks for the synthesis of biologically active natural products and functional materials.[7] Among these, dihydrodibenzofuranone scaffolds were also isolated in nature (Figure 1) and they exhibited broad biological activities.[8]

Owing to their usefulness and significance, a number of synthetic approaches to benzofurans have been reported.[9] Among these, several methods for the construction of 3,4-dihydrodibenzofuranones have also been demonstrated, which include copper-catalyzed reaction of 1,3-hexanediones with dihalobenzenes (Scheme 1(a)),[10] gold(III)-catalyzed reaction of 1,3-cyclohexanediones with *o*-arylhydroxylamines (Scheme 1(b)).[11] The other typical methods are also reported, which could be accessed by copper/gold-catalyzed tandem Ullmann-Goldberg cross-coupling/cyclopalladation-reductive elimination of cyclohexenones with *O*-iodophenol (Scheme 1(c))[12] and transition-metal-free oxidative ring expansion of the cyclobutyl moieties (Scheme 1(d)).[13] Although several synthetic methodologies for 3,4-dihydrodibenzofuranones have been demonstrated, more general and efficient synthetic protocols are still highly needed.

Due to the broad reactivity, easy accessibility, and less toxicity as compared to diazo compounds, iodonium ylides have taken the spotlight as an alternative safer and efficient carbene precursors.[14] They are utilized as substrates or intermediates for versatile transformations via cyclopropanation,

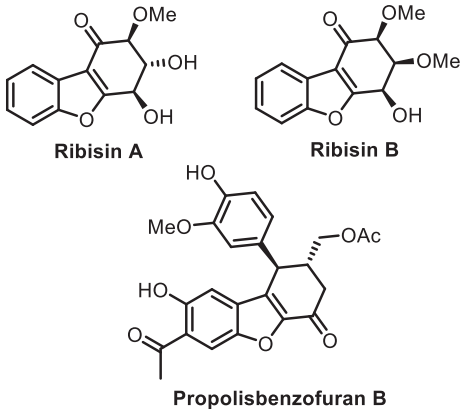
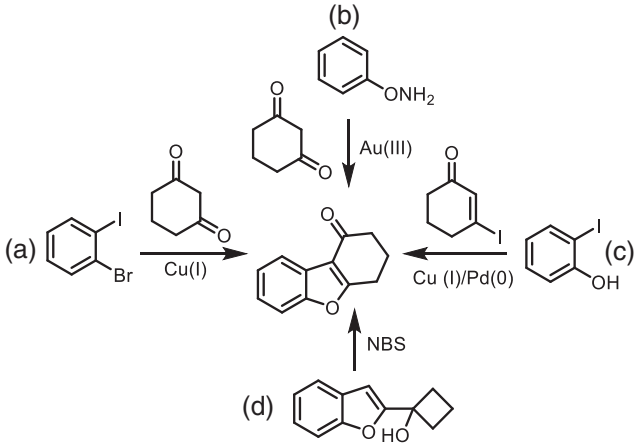


Figure 1. Selected bioactive natural products bearing dihydrodibenzofuranone skeletons.



Scheme 1. Reported general methodologies for the construction of dihydrodibenzofuranones.

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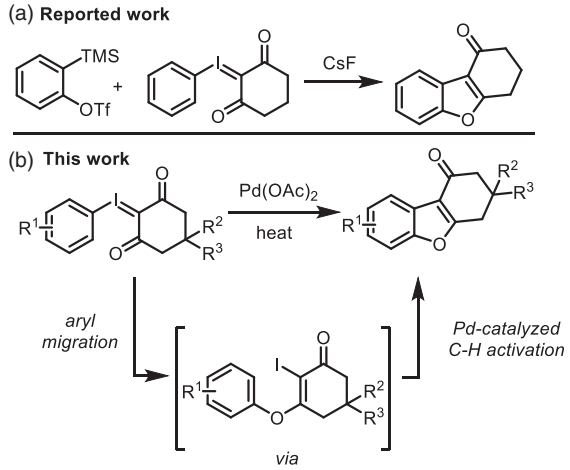
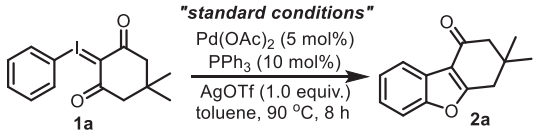


Scheme 2. Synthetic strategies for dihydrodibenzofuranones using iodonium ylides.

Table 1. Optimization of cyclic iodonium ylide **1a** for the formation **2a**.



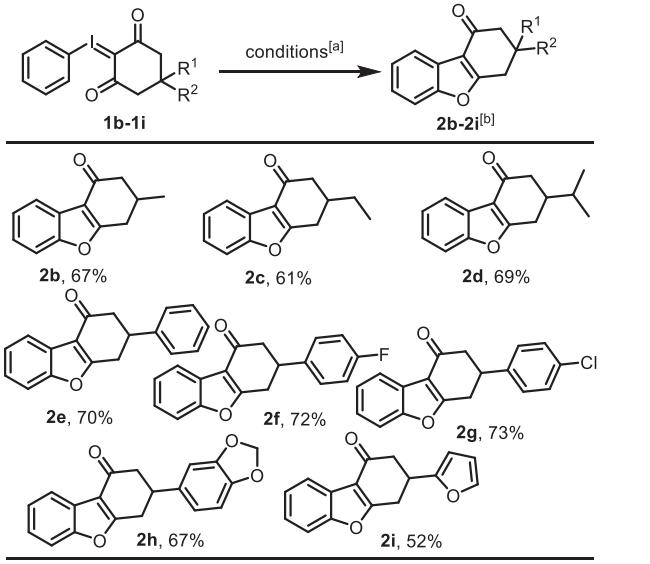
entry	modifications from standard conditions	yield (%)
1	***standard conditions***	***70***
2	$PdCl_2$ instead of $Pd(OAc)_2$	53
3	$Pd(TFA)_2$ instead of $Pd(OAc)_2$	62
4	THF instead of toluene	0
5	DMF instead of toluene	0
6	Ag_2O instead of AgOTf	0
7	$K_2S_2O_8$ instead of AgOTf	0

cycloaddition, and rearrangement reactions.[15] Inspired by the protocols that utilize iodonium ylides, we were interested in the use of iodonium ylides as the starting materials for organic transformations.[16] In 2008, Li group developed CsF promoted cycloaddition of iodonium ylides with arynes generated from *o*-silyl aryltriflates to afford dihydrodibenzofuranone in only 25% yield (Scheme 2(a)).[17] However, there is no report on direct conversion to dihydrodibenzofuranones starting from iodonium ylides. We were interested in the possibility of making dihydrodibenzofuranones directly from iodonium ylides. Herein, we describe an *in situ* synthesis of functionalized dihydrodibenzofuranones from iodonium ylides via thermal aryl migration of iodonium ylides followed by palladium-catalyzed intramolecular arylation (Scheme 2(b)).

Results and Discussion

As a model study, reaction of iodonium ylide **1a** as a starting material was first investigated under palladium

Table 2. Formation of diverse dihydrodibenzofuranones **2b–2i** by the reaction of various cyclic iodonium ylides **1b–1i**.



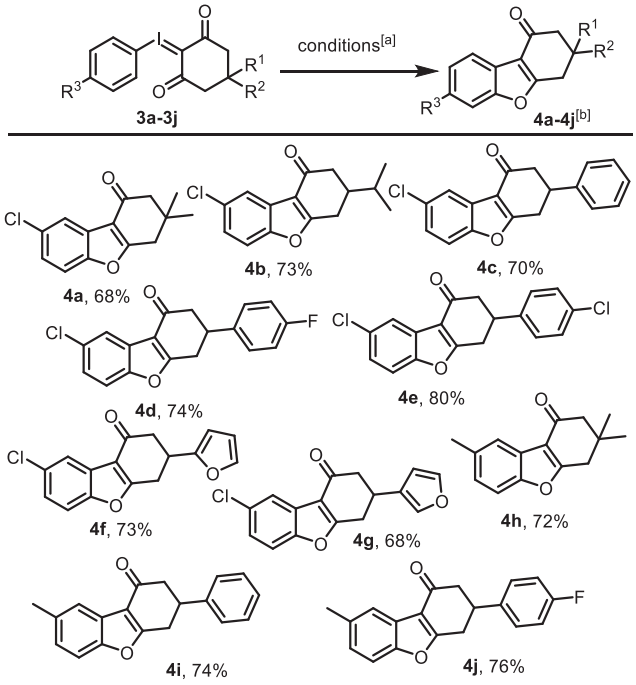
[a]Reaction conditions: **1b-1i** (1.0 mmol), $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), and AgOTf (1.0 equiv.) in toluene (5.0 mL) at 90 °C for 8 h.
[b]Isolated yield after column chromatography.

catalysts and oxidants (Table 1). Reaction of **1a** in the presence of $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), and AgOTf (100 mol %) in toluene (5 mL) at 90 °C for 8 h provided the product **2a** in 70% yield (entry 1). When $PdCl_2$ (5 mol %) or $Pd(TFA)_2$ was used as catalyst, **2a** was isolated in 53% and 62% yields, respectively (entries 2 and 3). On the other hand, **2a** was not formed at all when THF or DMF was used as a solvent (entries 4 and 5). In addition, a change in oxidant from AgOTf to Ag_2O or $K_2S_2O_8$ did not provide the product **2a** (entries 6 and 7).

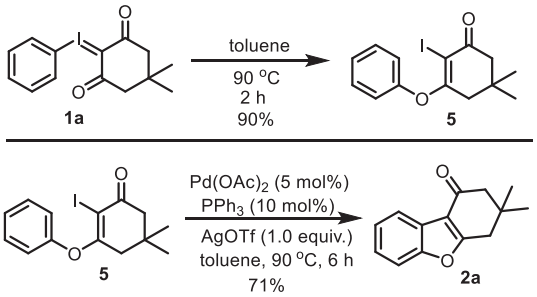
For the scope and generality of this protocol, additional *in situ* reactions of various cyclic iodonium ylides **1b–1i** were attempted (Table 2). Treatment of **1b–1e** bearing electron-donating methyl, ethyl, isopropyl, and phenyl groups on the 5-position of the 1,3-cyclohexanedione ring afforded the desired products **2b–2e** in 61–70% yield. Further reactions of **1f–1h** bearing electron-withdrawing and donating groups on the aromatic ring of cyclohexane moieties successfully provided **2f–2h** in 67–73% yield. In addition, iodonium ylide **1i** bearing 2-furanyl moiety on the cyclohexanedione ring led to the desired product **2i** in 52% yield.

The scope of this methodology was further assessed by examining the possibility of using different cyclic iodonium ylides **3a–3j** bearing substituents such as Cl and Me groups on iodobenzene moieties (Table 3). Iodonium ylides **3a–3g** with a Cl group on the iodobenzene moiety and dimethyl, *i*-propyl, phenyl, aryl, and furanyl substituents on the 1,3-cyclohexanedione ring delivered the products **4a–4g** in

Table 3. Formation of dihydrodibenzofuranones **4a**–**4j** bearing substituents on the benzofurans moieties by the reaction of various cyclic iodonium ylides **3a**–**3j**.



[a]Reaction conditions: **3a**–**3j** (1.0 mmol), $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), and AgOTf (1.0 equiv.) in toluene (5.0 mL) at 90 °C for 8 h.
[b]Isolated yields.

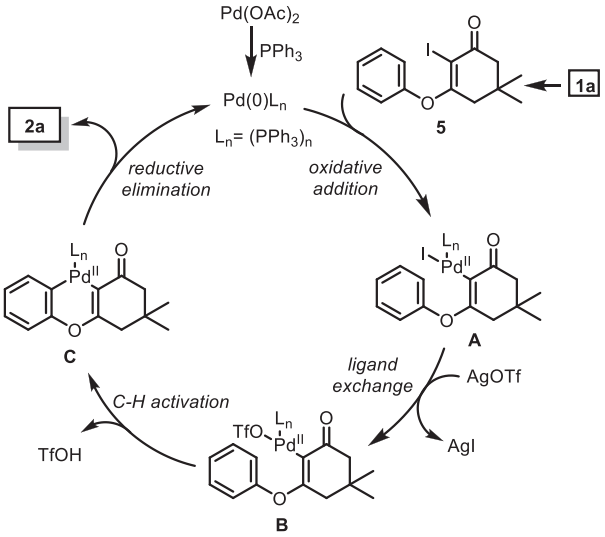


Scheme 3. Control experiments.

68–80% yield. Similarly, iodonium ylides **3h**–**3j** with a methyl group on the iodobenzene moiety and dimethyl, phenyl, and aryl groups on the 1,3-cyclohexaneones afforded the desired products **4h**–**4j** in 72–76% yield (see Supporting Information).

To elucidate the reaction mechanism, some control experiments were performed (Scheme 3). When **1a** was heated in toluene at 90 °C for 2 h, product **5** was isolated in 90% yield.[16a] Further reaction of **5** under standard reaction condition led to the product **2a** in 71% yield.

On the basis of the control experiments and previous literature,[18] a putative mechanism for the formation of **2a** is



Scheme 4. Proposed reaction mechanism for the formation of **2a**.

proposed in Scheme 4. Intermediate **5** generated from **1a** could be converted to palladium complex **A** in the presence of $Pd(OAc)_2$ and PPh_3. In the presence of AgOTf, intermediate **A** gives intermediate **B** via ligand exchange, which undergoes the C—H activation to give palladated intermediate **C**. Reductive elimination of intermediate **C** proceeds to give final product **2a** and regenerates $Pd(0)L_n$ to complete the catalytic cycle.

Conclusion

In summary, we have developed an efficient and powerful tool for the construction of dihydrodibenzofuranones via *in situ* thermal aryl rearrangement of iodonium ylides and Pd-catalyzed arylation. With its atom economic feature, this protocol provides diverse and functionalized dihydrodibenzofuranones in good yields.

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Supporting Information. Additional supporting information is available in the online version of this article.

Conflict of interest. The authors declare no conflict of interest.

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