Organic LETTERS

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Substrate Directed C−H Activation for the Synthesis of Benzo[*c*]cinnolines through a Sequential C−C and C−N Bond Formation

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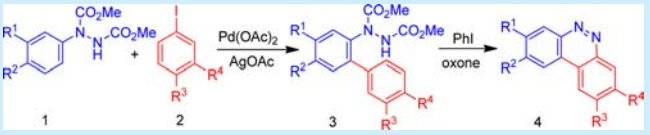
Supporting Information

ABSTRACT: A wide range of benzo[*c*]cinnolines are prepared through a sequential C−C and C−N bond formation by means of an oxidative C−H functionalization. The reaction proceeds via the *C*-arylation of 1-arylhydrazine-1,2-dicarboxylate with aryl iodide using $Pd(OAc)_2$/AgOAc followed by an oxidative *N*-arylation in the presence of PhI/oxone in trifluoroacetic acid. It is entirely a new strategy to generate the benzo[*c*]cinnoline libraries with a diverse substitution pattern.



Cinnolines are important structural motifs that are often found in various biologically active molecules. They are known to display interesting pharmacological properties such as antibacterial, anticancer, antimicrobial, anti-inflammatory, antifungal, antihypertensive, and antiulcer activities.[1] In particular, benzo[*c*]cinnolines are considered privileged scaffolds in medicinal chemistry due to their promising anticancer properties.[2] Subsequently, various cinnoline derivatives such as dibenzo[*c*,*h*]cinnoline, 11*H*-isoquino[4,3-*c*]cinnolin-12-ones, and indolo[3,2-*c*]cinnolines have been identified as potent anticancer agents (Figure 1).[3]

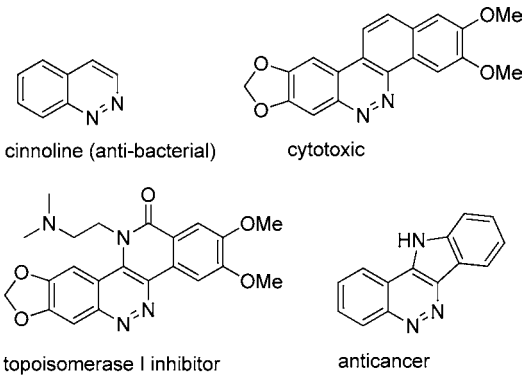


Figure 1. Biologically active cinnoline derivatives.

Consequently, there have been some reports on the synthesis of cinnoline derivatives.[4,5] Recently, Willis et al. reported a two-step reaction for the synthesis of cinnolines through annulation of 2-(2-bromoalkenyl)aryl bromide with diethyl-1,2-hydrazinedicarboxylate.[6] Simultaneously, Ge et al. reported an intramolecular dehydrogenative cyclization of *N*-methyl-*N*-phenylhydrazones for the production of cinnolines.[7] However, many of these methods involve a multistep reaction sequence and require prefunctionalization of the substrate. Therefore, the development of a simple and efficient method to construct the cinnoline core with a diverse substitution pattern is well appreciated. Recently, there are some reports on sequential C−C and C−N bond formations to construct the fused heterocycles.[8]

Following our interest in C−H functionalization,[9] we herein report a novel strategy for the synthesis of benzo[*c*]cinnoline derivatives through a sequential C−C and C−N bond formation. As the outset, we attempted the *ortho*-arylation of dimethyl 1-(3,4-dimethylphenyl)hydrazine-1,2-dicarboxylate with 1-chloro-4-iodobenzene in the presence of $Pd(OAc)_2$ (10 mol %) and AgOAc (1.5 equiv) in acetic acid at 100 °C (Table 1, entry a). However, the desired product **3a** was obtained only in 30% yield after 6 h. To improve the yield, the reaction was further performed under different reaction conditions (Table 1). To our delight, **3a** was isolated in 85% yield, when the reaction was conducted at 135 °C (Table 1, entry c). $Pd(OAc)_2$ was found to be superior than $PdCl_2$ and $Pd(OOCCF_3)_2$ (Table 1, entries j and k). No product formation was observed when $Cu(OAc)_2$ or $PhI(OAc)_2$ was used as a co-oxidant (Table 1, entries e−f). Low yields were obtained when the reaction was performed either in dioxane or in DCE (Table 1, entries h and i). Furthermore, TFA was found to be less effective than acetic acid (Table 1, entry d). The use of 10 mol % of $Pd(OAc)_2$ and 1.5 equiv AgOAc in AcOH at 135 °C is crucial to achieve high conversions. After having optimized conditions in hand, further reactions were carried out under the above conditions.

The scope of this strategy is exemplified by a diverse range of substrates (Figure 2). Interestingly, several aryl iodides such as 4-iodo-1,2-dimethylbenzene, 1-ethyl-4-iodobenzene, 4-iodotoluene, 4-iodoacetophenone, 1-iodo-4-(phenoxymethyl)-

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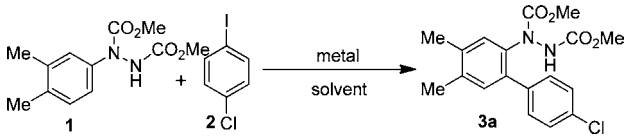
Table 1. Study of Catalysts in the Formation of 3a



entry	catalyst (10 mol %)	oxidant (1.5 equiv)	solvent	time (h)	temp (°C)	yield (%)[a]
a	$Pd(OAc)_2$	AgOAc	–	6	100	30
b	$Pd(OAc)_2$	AgOAc	AcOH	8	120	65
c	$Pd(OAc)_2$	**AgOAc**	**AcOH**	**8**	**135**	**85**
d	$Pd(OAc)_2$	AgOAc	TFA	8	135	75
e	$Pd(OAc)_2$	$Cu(OAc)_2$	AcOH	10	135	0
f	$Pd(OAc)_2$	$PhI(OAc)_2$	AcOH	8	135	0
g	$Pd(OAc)_2$	$PhI(OAc)_2$	TFA	10	135	0
h	$Pd(OAc)_2$	AgOAc	dioxane	12	135	10
i	$Pd(OAc)_2$	AgOAc	DCE	12	120	15
j	$PdCl_2$	AgOAc	AcOH	15	135	60
k	$Pd(OOCCF_3)_2$	AgOAc	AcOH	10	135	75

[a]Yield refers to pure products after column chromatography.

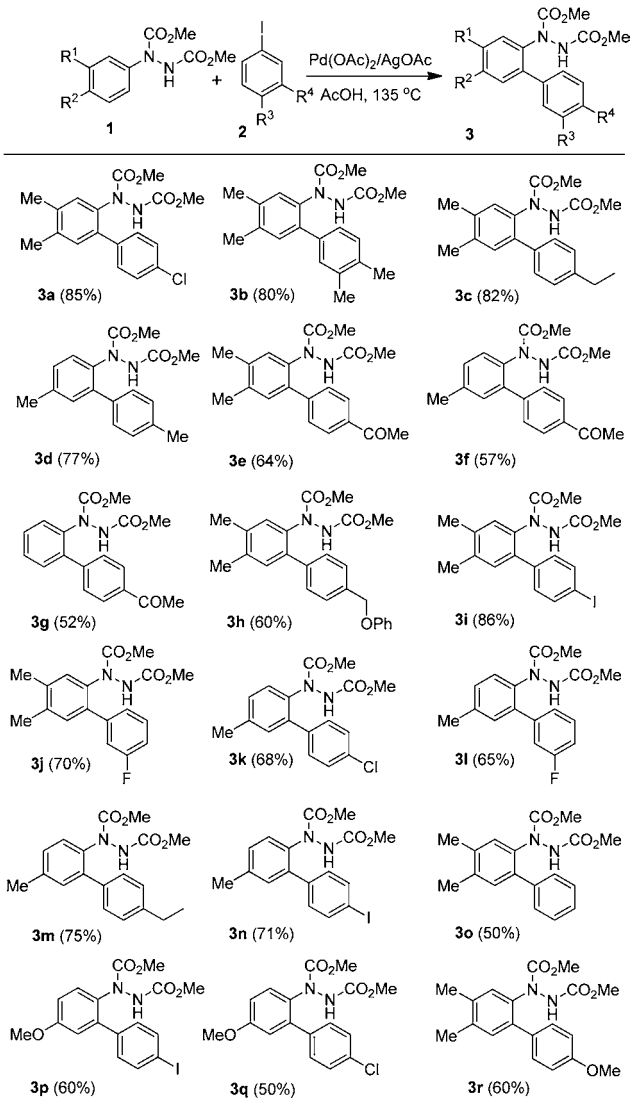


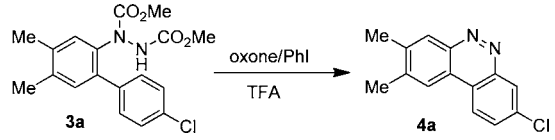
Figure 2. *ortho*-Arylation of arylhydrazine dicarboxylates. Yield refers to pure products after column chromatography.

benzene, 1,4-diiodobenzene, 1-chloro-4-iodobenzene, 1-fluoro-3-iodobenzene, and 1-iodo-4-methoxybenzene participated effectively in the C–C bond formation. In the case of 1-chloro-4-iodobenzene and 1-fluoro-3-iodobenzene, the substitution occurs exclusively at the iodo functionality as iodo is more labile than the chloro or fluoro substituent. In the case of 1,4-diiodobenzene, the monoarylated product was obtained as a major component along with a trace amount of bis-arylated product. The substituent present on the aromatic ring had shown some effect on the conversion. Alkyl substituted aryl iodides such as methyl and ethyl (Figure 2, entries b,c,d) are more effective than methoxy- or acetyl- or benzyloxy-containing aryl iodides (Figure 2, entries r,e,f,g,h). Furthermore, electron-deficient aryl iodides such as nitro- and cyano-derivatives failed to participate in the reaction. Similarly, methyl substituted aryl hydrazides are more effective than unsubstituted or methoxy-containing substrates (Figure 2).

The structure of products was established by NMR and HRMS analysis. Further the structure of **3c** was confirmed by a single crystal X-ray diffraction (Supporting Information).[10]

In order to show the application of biphenyl hydrazines, we attempted the oxidative cyclization of dimethyl 1-([1,1′-biphenyl]-2-yl)hydrazine-1,2-dicarboxylates (**3**) to generate the benzo[*c*]cinnoline derivatives (**4**) (Table 2). Accordingly,

Table 2. Study of Oxidants in the Formation of 4a



entry	oxidant	additive	solvent	temp (°C)	yield[a] (%)
a	oxone (1.5 equiv)	PhI	TFA	0	65
b	oxone (1.5 equiv)	PhI	TFA	25	65
c	**oxone (2.0 equiv)**	**PhI**	**TFA**	**0**	**80**
d	oxone (2.0 equiv)	PhI	TFA	25	80
e	oxone (2.0 equiv)	–	TFA	25	0
f	$PhI(OAc)_2$ (1.8 equiv)	–	TFA	0	70
g	$PhI(OAc)_2$ (1.8 equiv)	–	TFA	25	75
h	$PhI(OAc)_2$ (2.3 equiv)	–	TFA	25	80
i	$PhI(OAc)_2$ (2.3 equiv)	–	TFA	0	75
J	*m*-CPBA (2.5 equiv)	PhI	AcOH	25	0
k	*m*-CPBA (2.5 equiv)	PhI	TFA	25	65
l	$PhI(OOCCF_3)_2$ (1.8 equiv)	–	TFA	25	79

[a]Yield refers to pure products after column chromatography.

treatment of **3a** with $PhI(OOCCF_3)_2$ generated in situ from PhI and oxone in TFA gave the desired benzo[*c*]cinnoline **4a** in 80% yield (Table 2, entry c). The reaction proceeds in three steps, but in one pot through a sequential amination, ester hydrolysis, and decarboxylation. To optimize the conditions, we screened various oxidants such as oxone, $PhI(OAc)_2$, and *m*-CPBA at different temperatures in the conversion of **3a** into **4a**. Among them, the combination of PhI (30 mol %) and oxone (2.0 equiv) in trifluoroacetic acid was found to be superior either at 0 °C or at 25 °C. Alternately, 2.3 equiv of $PhI(OAc)_2$ in TFA were also equally effective for this conversion. In the absence of PhI, no C–N bond formation was observed when the reaction was performed using oxone in TFA (Table 2, entry e). This result obviously indicates the formation of $PhI(OOCCF_3)_2$ from PhI, oxone, and TFA. This was further

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confirmed by performing the reaction directly using PhI-$(OOCCF_3)_2$. To our surprise, no cyclization was observed using PhI, *m*-CPBA in AcOH (Table 2, entry j).

We further extended this method for different substrates, and the results are presented in Figure 3. A large number of

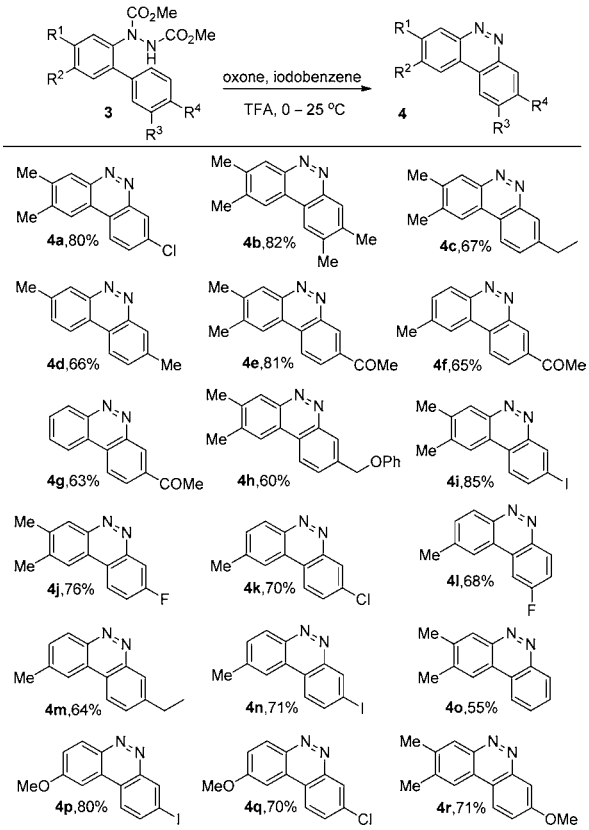


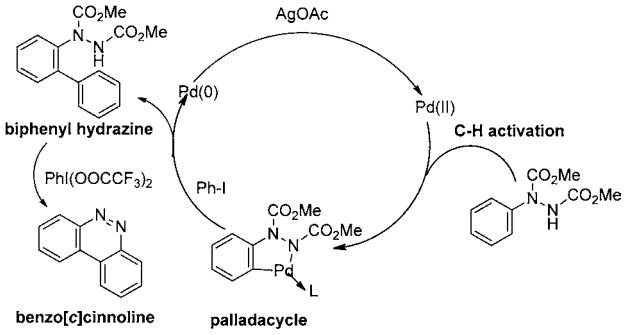
Figure 3. Synthesis of benzo[*c*]cinnoline derivatives. All products were characterized by NMR and HRMS analysis.

biologically relevant benzo[*c*]cinnoline scaffolds were prepared using this procedure. This method is compatible with various functional groups such as halide, acetyl, methoxy, and phenoxy that are present on the aromatic ring (Figure 3). It is noteworthy to mention that the iodo group is unaffected under the reaction conditions (Figure 3, **4i**, **4n**, **4p**).

Based on our previous observations,[9] we proposed a plausible reaction mechanism. The reaction likely proceeds through the formation of a five-membered transition state by the oxidative insertion of Pd(II) into an aromatic C−H bond.[8f] Thus, the formed palladacyle reacts with aryl iodide to facilitate the *ortho*-arylation. In this process, Pd(0) reoxidizes to Pd(II) by AgOAc to complete the catalytic cycle. A subsequent oxidative *N*-arylation of biphenyl hydrazine dicarboxylate in the presence of PhI/oxone in trifluoroacetic acid results in the formation of benzo[*c*]cinnoline (Scheme 1).[8a]

In summary, we have developed a novel strategy for the synthesis of benzo[*c*]cinnoline derivatives through a sequential C−C and C−N bond formation by means of C−H activation. This method provides a direct access to biologically relevant benzo[*c*]cinnoline scaffolds from aryl hydrazine dicarboxylates via the substrate-directed oxidative functionalization. However, this method fails to generate biaryls with electron-deficient nitro- and cyano-substituted aryl iodides.

Scheme 1. A Plausible Reaction Pathway



■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra of products, ortep diagram, and cif files for product **3c**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01717.

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Notes

The authors declare no competing financial interest.

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(10) CCDC 1061397 contains supplementary crystallographic data for **3c**. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html.

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