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ARTICLE TYPE

Iodine(III)-Mediated Construction of Dibenzoxazepinone Skeleton from 2-(Aryloxy)benzamides through Oxidative C-N Formation

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Dibenzoxazepinone compounds were conveniently synthesized from 2-(aryloxy)benzamides through hypervalent iodine(III)-mediated oxidative cyclization under mild reaction conditions. Differing from the existing strategies, this metal-free approach features an oxidative C-N bond-forming process for the construction of the skeleton in the final step.

The dibenzoxazepinone skeleton is an important heterocyclic motif which have been found to show many biological activities, such as antidepressant,[1] antitumor,[2] and anti-HIV[3] activities. Besides, they also show pharmacological and neurochemical activities and can be used as potential central nervous system agents[4] and potential atypical antipsychotics.[5] For examples, both dibenzoxazepinone (**A**),[3] a potent non-nucleoside HIV-1 reverse transcriptase inhibitor and histone deacetylase (HDAC) inhibitor (**B**)[2] possess the dibenzoxazepinone skeleton in their chemical structures. Furthermore, the dibenzoxazepinone compounds could also be used as the building blocks for the synthesis of other pharmaceutical agents with various biological activities. For instances, Sintamil **I** (**C**) was reported to be used as an antidepressant agent.[1] Amoxapine (**D**),[5] a derived skeleton of dibenzoxazepinone, was a marketed antidepressant drug. Loxapine (**E**), bearing a dibenzoxazepinone skeleton and a methylpiperazine system,[6] is a drug used in the treatment of schizophrenia.

Owning to its wide occurrence in biological compounds, many synthetic efforts have been devoted to the construction of this privileged skeleton. In 1982, Nagai reported an intermolecular acylation of 1-iso-cyanato-2-phenoxybenzens, affording dibenzoxazepinone in good yield[7] (Figure 2, path a). In 2006, Bunce and Schammerhorn realized the synthesis of dibenzoxazepinone through a reduction-lactamization reaction under dissolving metal conditions using iron and acetic acid[8] (Figure 2, path b). In 2011, Ma reported an effective regioselective synthesis of fused oxazepinone skeleton via Smiles rearrangement reaction using commercially available *N*-substituted salicylamides and 1,2-difluorobenzenes[9] (Figure 2, path c). An intramolecular carbonylation reaction has also been applied by Lu and Alper, using 2-iodophenol and substituted 1-fluoro-2-nitrobenzene as starting materials[10] (Figure 2, path d). Besides, Klunder reported a method involving the condensation of 2-aminophenols with 2-chloro-5-nitrobenzoyl chloride using THF as solvent[3] (Figure 2, path e). An alternative approach

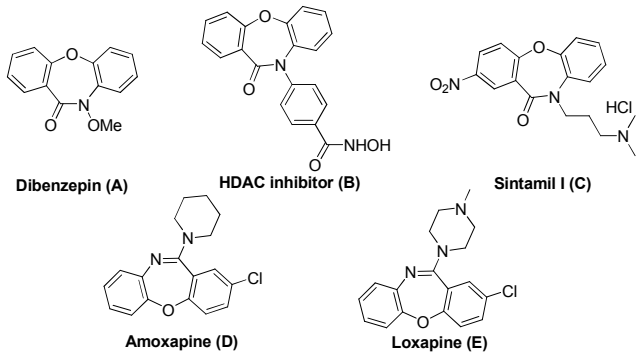


Figure 1 Representative active biologically dibenzoxazepinones and their derivatives.

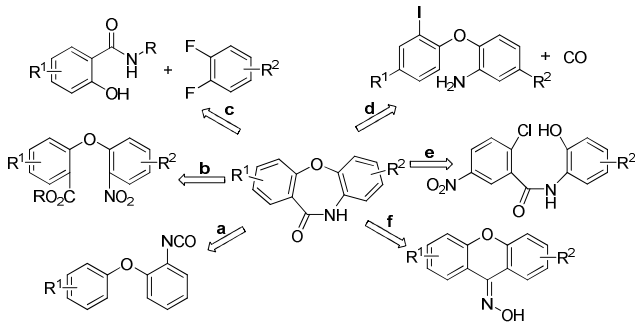


Figure 2 The existing strategies for the construction of dibenzoxazepinone skeleton.

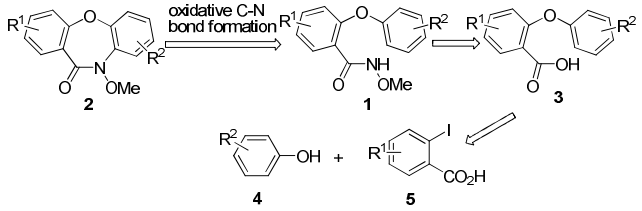
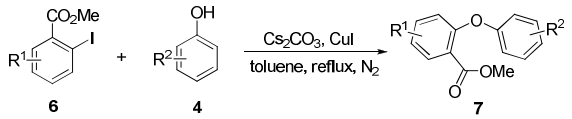


Figure 3 A general retrosynthetic analysis for the construction of dibenzoxazepinone skeleton.

involves the heating of xanthen-9-one oximes with phosphorus pentachloride, providing the dibenzoxazepine system via Beckmann rearrangement[11] (Figure 2, path f).

Although existing methods have their own advantages in the preparation of the corresponding dibenzoxazepine compounds,

Table 1 CuI-mediated coupling reaction of methyl 2-phenoxybenzoate[a]



6 4 7

Entry	R^1	R^2	Product **7**	Yield[b](%) of **7**
1	H	H	**7a**	64
2	*m*-Me	H	**7b**	52
3	*m*-Br	H	**7c**	61
4	*m*-F	H	**7d**	53
5	*m*-Cl	H	**7e**	58
6	*m*-F	*p*-Br	**7f**	57
7	H	*p*-Br	**7g**	58
8	H	*p*-Cl	**7h**	56
9	*m*-Br	*p*-Br	**7i**	46
10	*p*-Cl	*p*-Br	**7j**	47
11	*m*-Me	*p*-Br	**7k**	60
12	*p*-Cl	*p*-Cl	**7l**	51
13	*m*-Me	*p*-Cl	**7m**	59
14	*m*-OMe	H	**7n**	63
15	H	*p*-Me	**7o**	45
16	H	2,3-dimethyl	**7p**	49

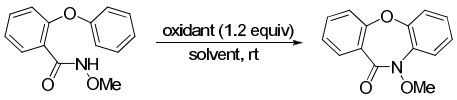
[a]General conditions: **6** (1.0 equiv), **4** (1.2 equiv) in toluene (0.5 M), then added Cs_2CO_3 (1.5 equiv) and CuI (1.0 equiv), stirred at reflux for 10 h.

some of them require the use of transition metals or harsh conditions. In this paper, we report an alternative construction of the dibenzoxazepinone skeleton from the readily available substituted 2-(aryloxy)benzamides through an intramolecular cyclization involving a direct oxidative C−N bond formation in the final step.

Hypervalent iodine reagent have been widely used as a non-metallic oxidant for the construction of C-N bonds,[12] especially the intramolecular cyclization of *N*-methoxyamide derivatives through a nitrenium ion intermediates. For example, our group has reported the assemblage of the 1,4-benzodiazepine framework from the readily available substituted *N*-methoxy-2-(methylphenylamino)benzamide through an intramolecular oxidative C−N bond formation.[12j] Inspired by this work, we envisaged that dibenzoxazepinone, an analog of 1,4-benzodiazepine by changing the N moiety with an O atom, may also be accessed by using the same strategy.

Figure 3 describes the retrosynthesis for the construction of the desired dibenzoxazepinone **2**. We envisaged that tricycle **2** could be formed through the intramolecular oxidative C−N bond formation of **1**, and substrate **1** could be accessible by the amidation of carboxylic acid **3**.[13] Through the known ross-coupling reaction, we anticipated that acid **3** could be prepared from the substituted phenol **4** and 2-iodobenzoic acid **5**.[14] However, although we found that when *o*-iodobenzoic acid **5** bearing electron-withdrawing group could be converted to the desired coupled **3** in acceptable yields, the method was not applicable to the substrates bearing electron-donating groups since the yield of the desired product to be trace. After many trials we finally found that methyl *o*-iodobenzoate, upon treatment with cuprous iodide and cesium carbonate, provided the cross-coupled product in moderated to good yield (see Table 1). Under the optimal conditions, a variety of the cross-coupled products were prepared in moderate to good yields. Through

Table 2 Conditions optimization of the cyclization reaction[a]



1a 2a

Entry	Oxidant	Solvent	Conc. (M)	Yield[b](%) of **2a**
1	PIFA	DCE	0.05	37
2	PIDA	DCE	0.05	46
3	PIDA	DMF	0.05	66
4	PIDA	THF	0.05	70
5	PIDA	toluene	0.05	43
6	PIDA	TFA	0.05	32
7	PIDA	HFIP	0.05	84
8	PIDA	TFE	0.05	89
9	PIDA	TFE	0.1	83
10	PIDA	TFE	0.2	80
11	PhIO	DCE	0.05	trace
12	DMP	DCE	0.05	ND
13	IBX	DCE	0.05	ND

[a]Reaction conditions: **1a** (1.0 mmol) and oxidant (1.2 mmol), in solvent (20 mL), 40 min, rt. [b]Isolated yield.

hydrolysis[15] and the subsequent *N*-methoxyamidation,[13] cross-coupled esters were converted to amides **1** for cyclization purpose (see Supporting Information for details).

N-Methoxy-2-phenoxybenzamide **1a** was chosen as the model substrate to probe the feasibility of the proposed cyclization reaction. At first, phenyliodine bis(trifluoroacetate) (PIFA) was used as oxidant and DCE as solvent, and the reaction at room temperature for 40 minutes revealed that the product was exactly the target compound, with the yield of 37% (Table 2, entry 1). Replacing phenyliodine bis(trifluoroacetate) (PIFA) with the less potent phenyliodine diacetate (PIDA) could increase the yield to 46% (Table 2, entry 2). Other hypervalent iodine oxidants such as Iodosobenzene (PhIO), Dess-Martin periodinane (DMP) and *o*-iodoxybenzoic acid (IBX) were also tested, but none of them was effective for the reaction (Table 2, entries 11-13). Further solvent screening studies showed that the reaction in THF afforded **2a** in a moderate yield of 70% (Table 2, entry 4). Further optimization study found that using TFE as solvent, and adjusting the substrate concentration to 0.05 M, the yield of the desired product **2a** could be enhanced to 89% (Table 2, entry 8).

With the optimal conditions in hand, we next explored other 2-(aryloxy)benzamides to examine the scope and limitation of the method. As results in Table 3 indicated, the method was found to tolerate a range of different substituents on the phenyl ring in the substrates. When the phenyl ring B bears no substituents, the corresponding substrates were converted into the dibenzoxazepinone products in excellent yields (Table 3, entries 1−5), respectively. The substrates with halogen substituted on phenyl ring B also proceed successfully to afford the desired products in moderate to good yields (Table 3, entries 6−13). Unfortunately, when the substrates bearing electron-donating group on ring B (Table 3, entries 14−15) were applied, the reaction was found to give a complex mixture. Reducing the temperature or the concentration of reaction did not lead a better result. Finally, when treated these electron-rich substrates with iodosobenzene (PhIO) in TFE and reflux temperature, the desired

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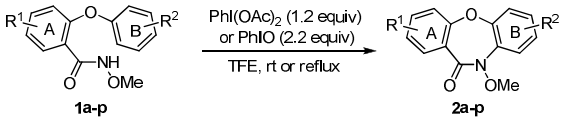
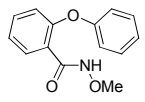
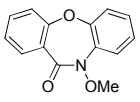
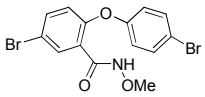
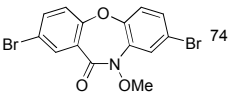
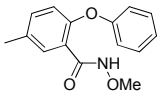
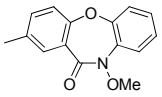
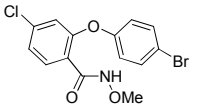
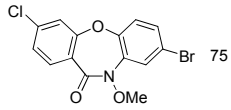
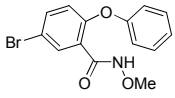
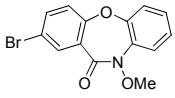
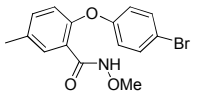
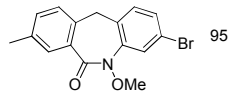
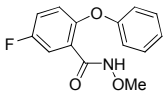
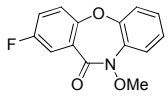
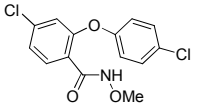
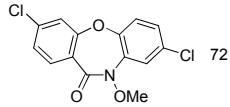
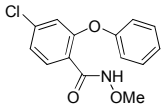
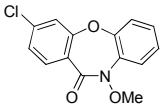
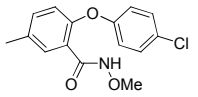
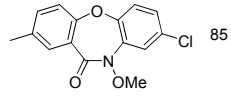
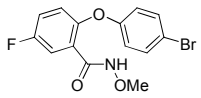
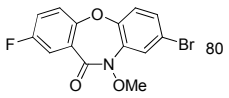
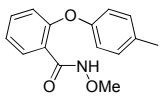
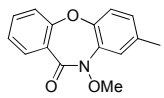
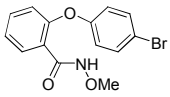
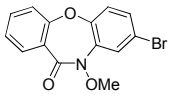
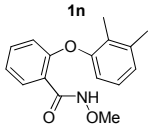
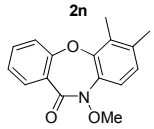
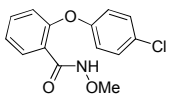
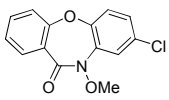
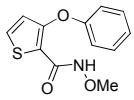
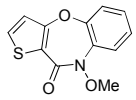
Table 3 Iodine(III)-mediated synthesis of dibenzoxazepinone derivatives[a]

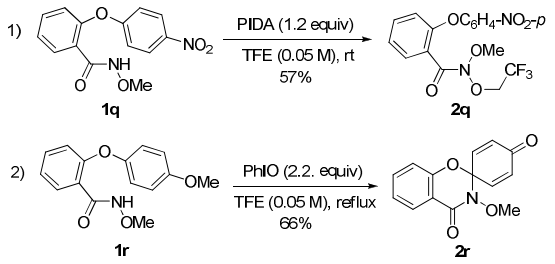


Entry	Substrate 1	Product 2	Yield(%)[b]	Entry	Substrate 1	Product 2	Yield(%)[b]
1	 1a	 2a	89	9	 1i	 2i	74
2	 1b	 2b	93	10	 1j	 2j	75
3	 1c	 2c	95	11	 1k	 2k	95
4	 1d	 2d	89	12	 1l	 2l	72
5	 1e	 2e	96	13	 1m	 2m	85
6	 1f	 2f	80	14	 1n	 2n	59
7	 1g	 2g	91	15	 1o	 2o	43
8	 1h	 2h	91	16	 1p	 2p	33

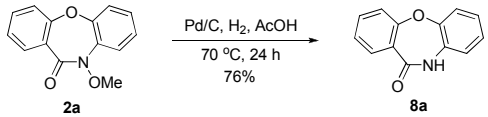
[a]General conditions for **1a-m**: **1** (1.0 equiv), PIDA (1.2 equiv) in TFE (0.05 M), rt, 40 min; General conditions for **1n-p**: **1** (1.0 equiv), PhIO (2.2 equiv) in TFE (0.05 M), stirred at reflux for 15 h. [b]Isolated yields.

cyclized products could be achieved in acceptable yields. It is worthy to note that when the ring A was a thienyl ring, the desired cyclized product could also be obtained in an acceptable 33% yield (Table 3, entry 16). Exceptionally, when the substrate bears a strong electron-withdrawing NO_2 group at the para position in ring B, the cyclization did not occur and the reaction afforded product **2q**, not the desired cyclized product (Scheme 1, eq 1). This result indicates that the presence of a strong electron-withdrawing group in the phenyl ring B prevents the cyclization which allows the generated nitrenium ion intermediate to be

captured by a nucleophilic trifluoethanol. It is worthy to note that, when the para position of ring B was a methoxy group, substrate **1r** was converted to the spiro **2r** in 62% yield under standard conditions (Scheme 1, eq 2). It is evident that the presence of the methoxy group facilities the ipso attack of the



Scheme 1 Other models that failed to afford dibenzoxazepinone



Scheme 2 The removal of methoxy group in **2a**

nitrenium ion onto the ring B. The *N*-unsubstitued products are also potential building block for the synthesis of important pharmaceutical agents with biological activities.[1-6] As illustrated in Scheme 2, the *N*-methoxy dibenzoxazepinone could be readily converted to *N*-unsubstitued dibenzoxazepinone, through palladium catalyzed hydrogenation reaction,[16] which allows for the further derivatization of the free NH moiety for synthesizing antidepressant dibenzoxazepinone and HDAC inhibitor **B**[2].

Conclusions

In summary, we have developed a novel method for the construction of the biologically interesting 2-(aryloxy)benzamides through an iodine(III)-mediated intermolecular C-N bond formation. Advantages of the method include the readily availability of the starting materials, the mild reaction conditions, and the transition- metal-free feature. Moreover, the transformation tolerates a wide range of functional groups, and the *N*-methoxy group in the final products can be readily removed and allows for further derivatization.

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Notes and references

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