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Graphical Abstract

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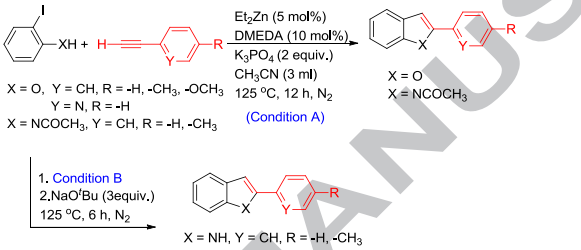

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ABSTRACT

Transition metal catalyzed cross-coupling reactions are one of the predominant strategies for the construction of heterocyclic structures which possess wide applications in the synthesis of natural products, pharmaceuticals, polymers etc. Due to the vast importance of substituted benzofurans and indoles, numerous synthetic methodologies have been introduced for their synthesis. Among these methods, transition metal catalyzed cyclization reactions possess a unique position. In this manuscript, we disclose the first and efficient zinc-catalyzed protocol for the cyclization reactions of alkynes with 2-iodophenol and 2-iodoaniline leading to benzofurans and indoles respectively via a tandem Sonogashira coupling-cyclization process. Among the different metal catalysts, zinc has enormous potential due to its great availability, non-toxicity, eco-friendly and inexpensive nature.

Zn(II) with N,N'-dimethylethylenediamine represents a suitable and efficient catalytic system for the desired tandem C-C coupling-cyclization reactions, and a broad spectrum of functional groups are tolerated during the catalysis. A variety of substituted benzofurans and indoles have been successfully prepared in moderate to good yields under this new protocol.

Introduction

The substituted benzofurans and indoles represent a privileged structural framework in a number of natural products as well as biologically, physiologically and pharmaceutically active molecules.[1] Notable amongst different benzofuran derivatives are compounds: vibsanol **I**, [2] known as an inhibitor for lipid peroxidation; and the machicendiol **II**, [3] used in the treatment of asthma, ulcers and rheumatism. Some potent indole derivatives are etodolac **III**, [4] a clinically effective entity applicable in the treatment of rheumatoid arthritis and inflammatory diseases; and sumatriptan **IV**, [5] used for the treatment of migraine (Figure 1). Moreover, there exist a large number of important and potent benzofuran and indole moieties in nature.[6] Due to the obvious interest in this class of compounds, various conventional methods have been developed over the years for elaborating the benzofurans and indole skeletons.[7] Among the different methods, the most popular and extensively studied reaction is the transition metal-based Sonogashira cross-coupling followed by 5-*endo*-*dig* cyclization of *o*-iodo phenols or *o*-iodo anilines with terminal alkynes.[8] Most of these reports involve the use of palladium,[9] copper,[10] gold[11] and rhodium-based[12] catalytic systems.

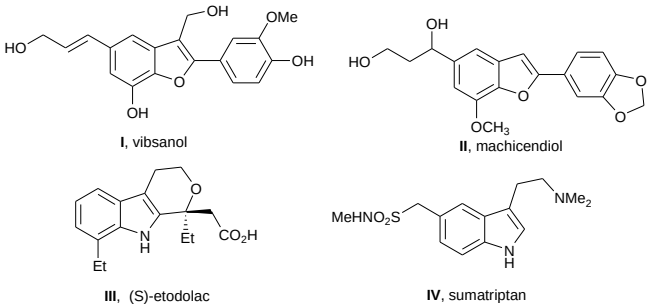


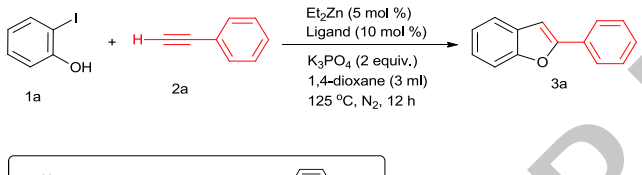
Figure1. Biologically relevant benzofuran and indole moieties

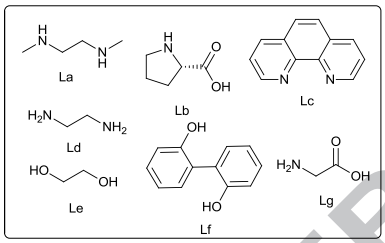
To the best of our knowledge, no Zn-catalyzed similar cyclization reaction of *o*-iodo phenols or *o*-iodo aniline with terminal alkynes has been reported so far. There are a few reports on zinc-mediated cyclization of *o*-alkynyl arylaniline, [13] but no previous reports exist for Zn-catalyzed synthesis of 2-substituted benzofurans and indoles directly *via* Sonogashira-type cyclization of *o*-iodo phenols or *o*-iodo aniline with terminal alkynes.

Results and Discussion

In continuation of our efforts[14] to develop novel synthetic strategies, we have recently reported an efficient protocol for the zinc-catalyzed Sonogashira type cross-coupling reaction.[15] On exploring the substrate scope of the above mentioned reaction, we observed that the reaction between 2-iodo aniline and phenylacetylene gave the expected *ortho*-substituted product along with a small amount of 2-phenyl substituted indole. Similarly on performing the reaction with 2-iodo phenol and phenylacetylene, only the 2-phenyl substituted benzofuran was obtained instead of the expected *ortho*-substituted 2-phenylethynylphenol. The analysis of the structure (NMR and HRMS) of the above obtained products strongly confirms the formation of cyclized product and these results prompted us to develop a new zinc-catalyzed methodology for the tandem Sonogashira type C-C coupling followed by cyclization leading to heterocycles from *o*-iodo phenols and *o*-iodo aniline with terminal alkynes. In our pursuit of the development of zinc-catalyzed benzofuran derivatives, we initiated our studies using 2-iodo phenol and phenylacetylene as model substrates under various catalytic conditions. The reactions were carried out in a previously dried sealed tube in the presence of K_3PO_4 in 1,4-dioxane at 125 ^oC under nitrogen atmosphere (Table 1).

Table 1: Ligand screening studies for the synthesis of 2-phenylbenzofuran [a]





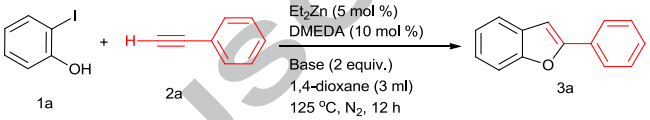
Entry	Ligand	Yield (%)[b]
1	**La**	80
2	**Lb**	79
3	**Lc**	traces
4	**Ld**	28
5	**Le**	nd[c]
6	**Lf**	nd
7	**Lg**	traces

a: Reaction conditions: phenylacetylene (1 mmol), 2-iodo phenol (1.1 mmol), K_3PO_4 (2 equiv.), Et_2Zn (5 mol %), DMEDA (10 mol %), 1,4-dioxane (3 ml), 125 ^oC, under N_2, b: Isolated yield, c: Not detected.

We carried out the screening of reactions with the commonly available ligands **La-Lg**. When the reaction of **1a** and **2a** was conducted in the presence of ligands N,N'-dimethylethylenediamine (**DMEDA, La**) or L-proline (**Lb**) resulted the product **3a** in promising yield of 80 and 79 % respectively (Table 1, Entries 1 and 2**)**. The greater reactivity of these secondary amines may presumably be due to the formation of more reactive catalytic complex and is also attributable to the more basicity of secondary amines compared to primary and tertiary amines in this case. In the presence of the simplest ligand ethylenediamine (**Ld**), very small amount of the product was observed (Table 1, Entry 4**)**. But with C_2-bridged O,O-ligands **Le** and **Lf** no product was obtained (Table 1, Entries 5 and 6**)**. Traces of the product were obtained with 1,10-phenanthroline (**Lc**) and glycine (**Lg**) (Table 1, Entries 3 and 7**)**.

We decided to use **La** as the optimum ligand over L-proline (**Lb**) since the former is simple and achiral. After confirming the structure of the product **3a** by NMR and mass spectrometric analyses, we decided to conduct base, solvent and temperature optimization studies in detail (Table 2).

Table 2: Screening of bases for the synthesis of 2-phenylbenzofuran[a]

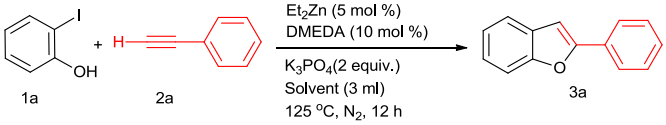


Entry	Base (2 equiv.)	Yield[b] (%)
1	K_3PO_4	80
2	K_2CO_3	28
3	Cs_2CO_3	40
4	NaO^tBu	nd[c]
5	KO^tBu	nd
6	KOH	nd
7	NaOH	nd
8	Et_3N	nd

a: Reaction conditions: phenylacetylene (1 mmol), 2-iodo phenol (1.1 mmol), Base (2 equiv.), Et_2Zn (5 mol %), DMEDA (10 mol %), 1,4-dioxane (3 ml), 125 ^oC, under N_2, b: Isolated yield, c: Not detected.

Screening of bases such as K_3PO_4, K_2CO_3, Cs_2CO_3, NaO^tBu, KO^tBu, KOH, NaOH and Et_3N revealed that $K_3PO_4$is the best base since it gave the maximum yield of 80% under the previously optimized conditions (Table 2, Entry 1**)**. A logical explanation for the superior nature of K_3PO_4 in comparison to other bases is difficult. However, we believe that K_3PO_4 favours the removal of the acetylene hydrogen and subsequent oxidative addition with the catalyst under the reaction conditions.

Table 3: Analysis of solvent effect in the synthesis of 2-phenylbenzofuran[a]



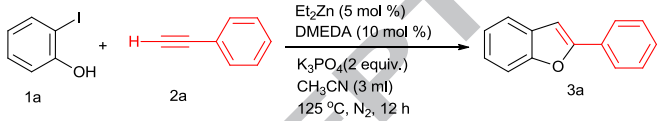
Entry	Solvent (3 ml)	Yield[b] (%)
1	1,4-dioxane	80

2	THF	48
3	DME	20
4	CH_3CN	93
5	toluene	27
6	DMF	nd[c]
7	isoamylalcohol	33
8	^tBuOH	21
9	DMSO	nd
10	NMP	nd

a: Reaction conditions: phenylacetylene (1 mmol), 2-iodophenol (1.1 mmol), K_3PO_4 (2 equiv.), Et_2Zn (5 mol %), DMEDA (10 mol %), solvent (3 ml), 125 ^oC, under N_2, b: Isolated yield, c: Not detected.

Different solvents were then tested to find the best solvent. Among these CH_3CN served as the best, in which the desired product **3a** was obtained in excellent yield (Table 3, Entry 4**)**. 1,4-Dioxane also gave good yield but the yield was less in comparison to CH_3CN (Table 3, Entry 1). Lower yields were observed when THF, DME and toluene were used as solvents (Table 3, Entries 2, 3 and 5**)**. Alcoholic solvents such as isoamyl alcohol and ^tBuOH also afforded less amount of the required product **3a** (Table 3, Entries 7 and 8). Solvents such as DMF, DMSO, and NMP were found to be ineffective for this zinc-catalyzed transformation (Table 3, Entries 6, 9 and 10).

Table 4: Control experiments for the synthesis of 2-phenylbenzofuran [a]

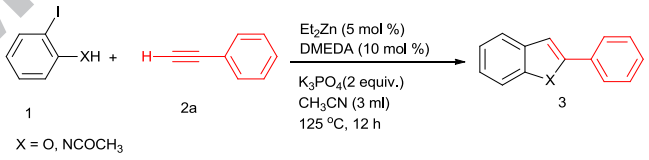


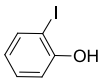
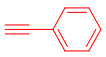
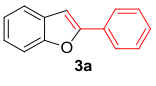
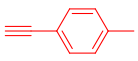
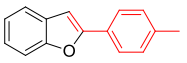
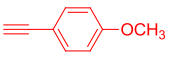
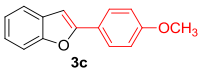
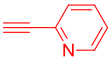
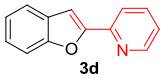
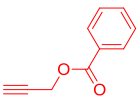
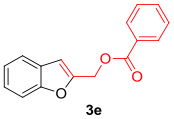
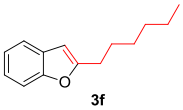
Entry	Temperature (^oC)	Base (2 equiv.)	Yield[b] (%)
1	125	K_3PO_4	93
2	80	K_3PO_4	30
3[c]	125	K_3PO_4	20
4[d]	125	K_3PO_4	nd[e]
5[f]	125	K_3PO_4	nd
6[g]	125	K_3PO_4	52
7[h]	125	K_3PO_4	59
8	125	-	nd
9[i]	125	K_3PO_4	19
10[j]	125	K_3PO_4	60

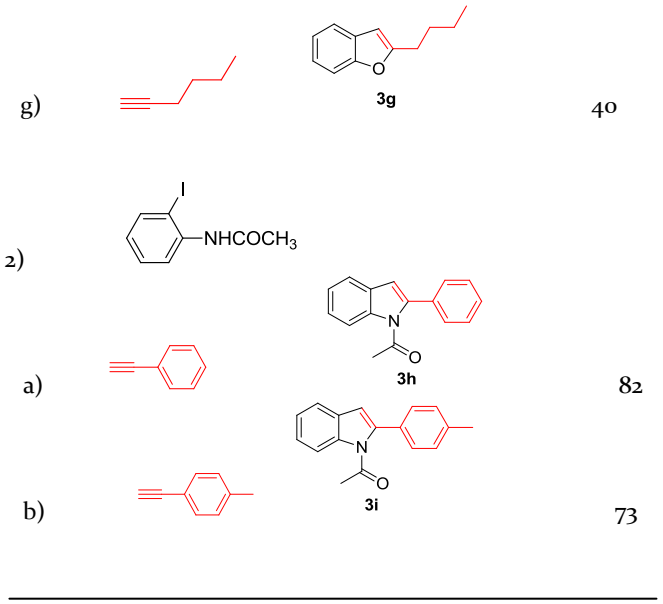
a: Reaction conditions: phenylacetylene (1 mmol), 2-iodophenol (1.1 mmol), K_3PO_4 (2 equiv.), Et_2Zn (5 mol %), DMEDA (10 mol %), CH_3CN (3 ml), 125 ^oC, under N_2, b: Isolated yield, c: Absence of DMEDA, d: Absence of Et_2Zn, e: Not detected, f: Absence of both DMEDA & Et_2Zn, g: 1:1 ratio of DMEDA & Et_2Zn, h: 1 Equivalent of K_3PO_4, i: Absence of N_2 atmosphere, j: 2 mol % of Et_2Zn.

Finally the influence of temperature in the reaction was studied and the results showed that only 30 % of the coupled product was obtained along with the phenylacetylene homocoupled product. (Table 4, Entry 2). A series of control experiments were performed in the absence of base, ligand and catalytic system. No product was obtained in the absence of base, catalytic system or Et_2Zn (Table 4, Entries 4, 5 and 8). The yield of the product got decreased in the absence of DMEDA (Table 4, Entry 3). Lower catalytic activity was experienced with 1:1 combination of Et_2Zn and DMEDA (Table 4, Entry 6). Reduction in the amount of product **3a** was observed on carrying out the reaction with 1 equivalent of K_3PO_4 (Table 4, Entry 7). Running the reaction in air gave only a trace amount of the desired cyclized product along with the homo coupled product of phenylacetylene (Table 4, Entry 9). Carrying out the reaction with lower catalyst loading also decreased the yield of the required product **3a** (Table 4, Entry 10). In order to make sure that the reaction was carried out by Zn and not by any other metal present as impurity, we conducted ICP-mass spectrometry which showed the presence of only Zn. Other metal impurities including palladium and copper were found below the detection levels.

Table 5: Synthesis of 2-substituted benzofurans and 1,2-disubstituted indoles *via* zinc-catalyzed cross-coupling/cyclization reaction[a]

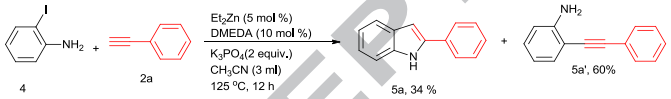


Entry	Aryl halides-Alkynes	Product	Yield[b] %
1			
a)		 3a	93
b)		 3b	78
c)		 3c	94
d)		 3d	69
e)		 3e	72
f)		 3f	45



a: Reaction conditions: phenylacetylene (1 mmol), 2-iodophenol (1.1 mmol), K_3PO_4 (2 equiv.), Et_2Zn (5 mol %), DMEDA (10 mol %), CH_3CN (3 ml), 125 ^oC, under N_2, b: Isolated yield.

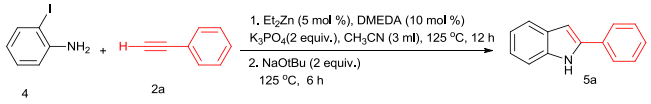
We then applied the optimized reaction protocol to other substrates in order to study the scope of the reaction. The phenylacetylene derivatives bearing $–CH_3$ and $–OCH_3$ substituents provide the products in good yields (Table 5, Entries 1b, 1c). Apart from substituted phenylacetylenes the present zinc-catalyzed tandem Sonogashira-type coupling-cyclization reaction proceeds well in the case of heterocyclic alkynes also (Table 5, Entry 1d).It is noteworthy that the developed protocol also works well in the case of terminal aliphatic alkynes and resulted the respective cyclized product in appreciable yield (Table 5, Entry 5).

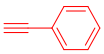
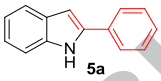
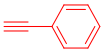
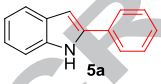
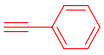
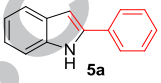
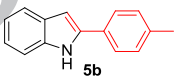


Scheme 1. Zinc-catalyzed cross-coupling of 2-iodo aniline with phenylacetylene

But the optimum reaction condition for the synthesis of 2-phenylbenzofuran and 2-iodoacetanilde were found not suitable for the synthesis of 2-phenylindole. The reaction between 2-iodo aniline and phenylacetylene under the above mentioned reaction conditions gave the *ortho*-substituted Sonogashira product as the major product along with a small amount of the expected 2-phenyl substituted indole (Scheme1). The difference in reactivity of 2-iodoaniline and 2-iodoacetanilde is attributable to the lesser basicity of acetanilide substituent compared to the simple amine group. In this context, we had to add an excess of a suitable base for further conversion of the uncyclized 2-phenylethynylaniline into 2-phenylindole. Screening of bases revealed that the suitable base for the second step of the reaction was NaO^tBu (Table 6, Entry 3). The bases such as K_3PO_4 and Cs_2CO_3 also worked but the yields were low (Table 6, Entry 1, 2). Next we explored the generality and functional group compatibility of this transformation under the optimized reaction conditions. It is noteworthy that the present zinc-catalyzed Sonogashira type coupling-cyclization reaction proceeds well in the case of substituted phenylacetylene also (Table 6, Entry 4).

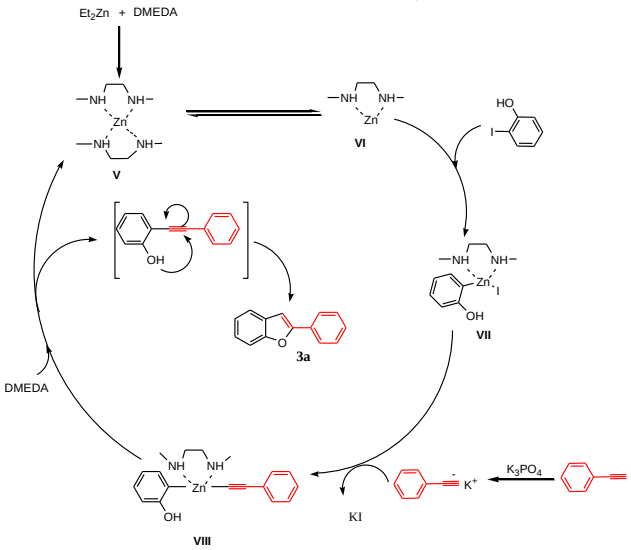
Table 6: Synthesis of 2-substituted indoles via zinc-catalyzed reaction between 2-iodoaniline and terminal alkynes[a]



Entry	Alkynes	Product	Yield (%)[b]
1[c]			53
2[d]			54
3			89
4			74

a: Reaction conditions:1. phenylacetylene (1.1 mmol), 4-iodoaniline (1 mmol), K_3PO_4 (2 equiv.), Et_2Zn (5 mol %), DMEDA (10 mol %), CH_3CN (3 ml), 125 ^oC, 12h, 2. NaO^tBu (2 equiv.), 6 h, b: Isolated yield, c:K_3PO_4 (2 equiv.) was used for the second step, 6 h, d: Cs_2CO_3 (2 equiv.), was used for the second step, 6 h.

Since extensive mechanistic studies are required to ascertain the mechanistic details of the process and very little is known about the mechanism of Zn-catalyzed coupling reactions, we propose a tentative mechanistic pathway for the novel tandem coupling-cyclization protocol by taking into account the requirement of 1:2 ratio of Zn:DMEDA catalyst, limited oxidation states of Zn and the theoretical calculations carried out for Zn-catalyzed Sonogashira type coupling (Scheme 2).[14b]



Scheme 2. A plausible mechanism for the tandem Sonogashira coupling-cyclization

Conclusions

In conclusion, we have developed the first and expedient zinc-catalyzed methodology for the tandem Sonogashira-type coupling-cyclization reactions. It is presumed that the reaction proceeds first through a Sonogashira cross-coupling reaction by an *in situ* generated Zn–DMEDA complex followed by base promoted cyclization. Our protocol tolerates a broad range of functional groups and can be used for the synthesis of varieties of both substituted benzofurans and indoles. The present method is efficient in terms of yield, catalyst loading, reaction conditions and catalyst toxicity. The simplicity of this reaction protocol makes it a feasible alternative to the commonly employed routes in heterocycle synthesis. To the best of our knowledge, the present report is the first example of a practical use of Et_2Zn in the synthesis of substituted benzofurans and indoles from the respective *o*-iodo phenol and *o*-iodo aniline.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at

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Highlights

- ✓ The first Zn-catalyzed tandem Sonogashira cross-coupling-cyclization disclosed
- ✓ Zn-catalyzed one pot synthesis of benzofurans and indoles in excellent yields
- ✓ Heterocycles achieved with Et_2Zn and N,N'-dimethylethylenediamine
- ✓ A broad spectrum of functional groups tolerated in the catalysis.