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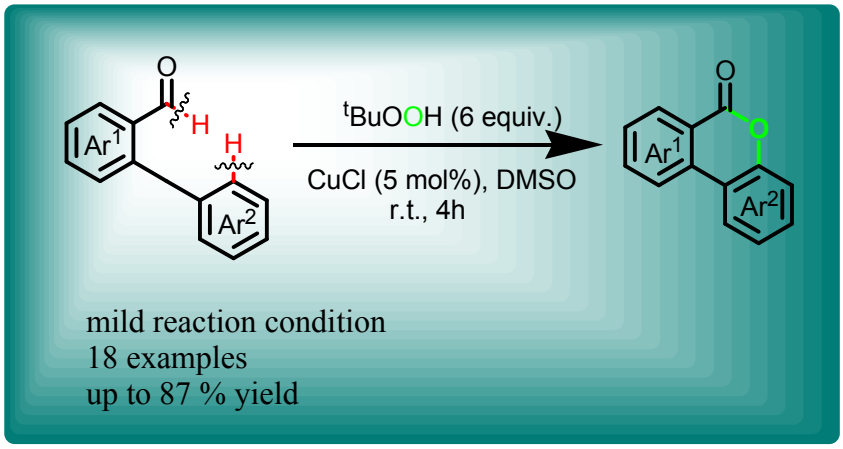

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ARTICLE TYPE

Copper catalyzed room temperature lactonization of aromatic C-H bond: A novel and efficient approach for the synthesis of dibenzopyranones

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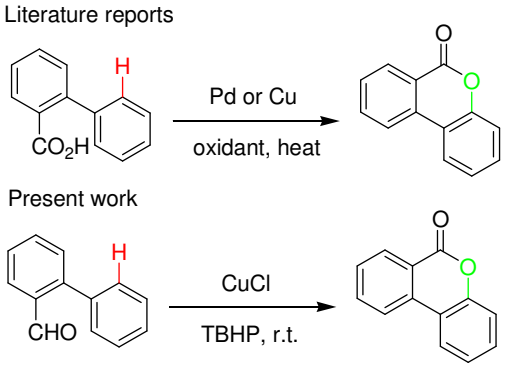
We have developed a novel and efficient methodology for the intramolecular aryl C-H oxidative lactonization of 2-arylbenzaldehyde using the cheap CuCl catalyst and TBHP as the oxidant at room temperature. We have applied the methodology for the synthesis of a series of dibenzopyranones.

Transition metal catalyzed un-activated aromatic C-H bond functionalization is a very powerful synthetic strategy for the synthesis of complex molecules from simple precursors.[1] Of these reactions, the oxidative lactonization of aromatic C-H bond gives an access for the synthesis of important lactone containing molecules. Very recently a number of methods have been reported in literature for the sp^2C-H lactonization with carboxylic acid group in presence of expensive transition metal catalysts along with various oxidants and additives at elevated temperature.[2] Thus, the development of a newer methodology for the oxidative C-H bond lactonization using a cheaper catalyst and under mild reaction conditions especially at room temperature is highly desirable.

Herein, we are reporting a methodology for the synthesis of dibenzopyranones through copper catalyzed intra-molecular aryl C-H oxidative lactonization of 2-arylbenzaldehydes at room temperature (Scheme 1).



Scheme 1: Literature reports and present work

Dibenzopyranone is an interesting class of lactones found as the core structure of many natural products such as autumnariol (Fig.1, **1**), alternariol, altenuisol, autumnariniol, and graphislactones (Fig. 1, **2**) and bioactive compounds.[3] Dibenzopyranone scaffolds have been used as intermediates in the synthesis of many pharmaceutically interesting compounds such as progesterone,[4] androgen receptor ligands,[5] glucocorticoids[6] and endothelial cell proliferation inhibitors.[7] Dibenzopyranones are also found in various naturally occurring food sources such as citrus fruits, herbs and vegetables.[8] Furthermore such lactones are also present in human metabolites such as urolithins . Urolithins A-C (Fig. 1, **3a-c**) are produced by in vitro fermentation of punicalagins.[9]

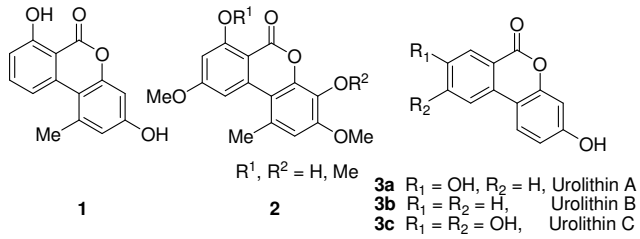
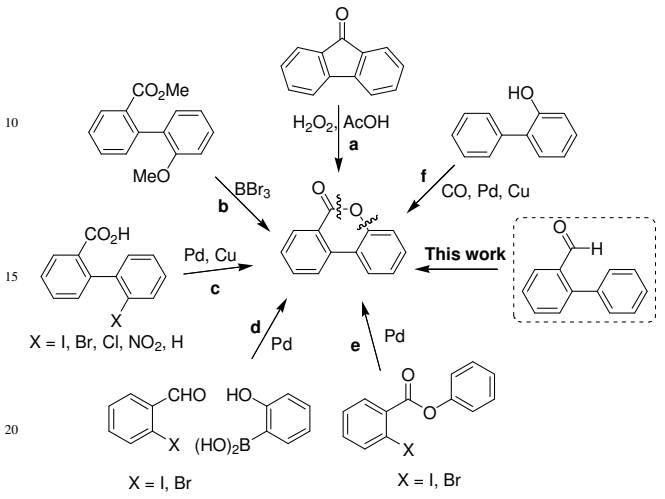


Figure 1 Structure of some natural products and bioactive compounds

In literature, several methods are available for the synthesis of dibenzopyranones. Most of the popular methods involve: 1) Baeyer-Villiger oxidation of fluorenone (Scheme 2, path a);[10] 2) Lewis acid or metal mediated lactonization of ester and methoxy groups (path b);[11] 3) lactonization of 2-halobiarylcarboxylic acid derivative (Scheme 2, path c);[12] 4) cross coupling of 2-halobenzaldehyde and *o*-hydroxyarylboronic acid and followed by lactonization (path d);[13] 5) cross coupling of aryl *o*-halobenzoate (path e);[14] and 6) C-H activation/carbonylation of 2-arylphenol (path f).[15] All the present methods in spite of their individual advantages suffers from some drawbacks such as, (a) multistep procedures, (b) extremely low (-78 °C) or high temperature reaction conditions, (c) use of readily unavailable starting materials, (d) requirement of pre-functionalization of the

starting materials, and (e) the use of poisonous CO gas. To overcome all of the above drawbacks a mild, efficient and room temperature reaction procedure starting from readily synthesizable starting materials is highly desirable. Herein we are reporting a CuCl catalyzed reaction for the synthesis of dibenzopyranones at room temperature.



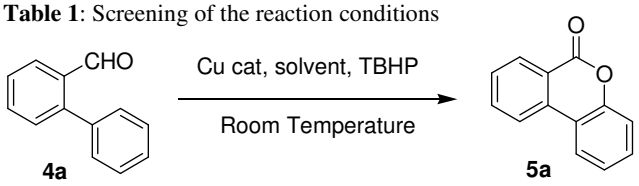
Scheme 2: Literature reports and present work

Our investigation was started by the reaction 2-phenylbenzaldehyde in presence of CuBr catalyst and TBHP (2 equiv.) as oxidant in acetonitrile solvent at room temperature and it gave the desired product dibenzopyranone in 33% yield along with the unconsumed substrate. Then we varied the amount of TBHP, catalyst and solvent to get the optimized reaction condition and the results are shown in Table 1.

At first, we had increased the amount of oxidant TBHP to 4 equivalents and the yield was increased to 54% along with the unconsumed substrate. The yield was improved to 68% on further increasing the amount of TBHP to 6 equivalents and the substrate also vanished within 8h. Then we had varied the nature of solvent (Table 1, entries 3-8) and the DMSO was come out as the best solvent. Then we had used different copper catalysts and we found that CuCl catalyst gave the highest yield of 78 % (Table 1, entry 10). The Cu(II)acetate also promoted the reaction but gave the lower yield. The reaction did not occurred in absence of either the catalyst or TBHP (entries 13 and 14).

Thus the optimized reaction conditions are the substrate (0.25 mmol), CuCl catalyst (5 mol %), DMSO solvent (2 mL), TBHP (6 equiv.) stirred at room temperature for 4h. After getting the optimized reaction conditions we applied it on different substrates to examine the scope of this methodology and the results are summarized in Table 2. The substrate 2-arylbenzaldehydes (**4**) were synthesized by the Suzuki-Miyaura cross coupling of 2-bromobenzaldehydes and arylboronic acid derivatives. We applied the optimized reaction condition on the substrates (**4**) bearing a range of electron withdrawing and donating group on both of the aryl rings and we got the corresponding dibenzopyranones in good to excellent yields (Table 2, entries 5a-5p). In presence of the electron withdrawing group on either of the aryl rings, biaryl substrates gave lower yield (Table 2, entries 5c, 5i-k) while the electron donating groups on aryl rings gave higher yield (Table 2, entries 5d-e, 5l, 5p-r). The yield was lower for the entries 5f and 5g due to the presence of steric repulsion between methoxy group and peri hydrogen of the adjacent phenyl ring. The substrate 2-(*m*-tolyl)benzaldehyde gave two possible pyranone derivatives in 3:2 ratio (entry 2n). The substituents at *ortho*-position of Ar_2 ring were unfavourable for the product formation (entry 5m, 5o). Finally the methyl ethers of natural product Urolithins A-C were obtained from the corresponding suitably substituted starting materials in excellent yields due to the presence of electron donating methoxy group (Table 2, entries 5p-r).

Table 1: Screening of the reaction conditions

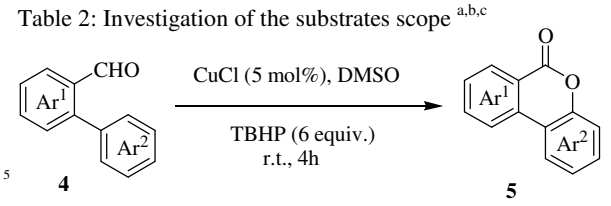


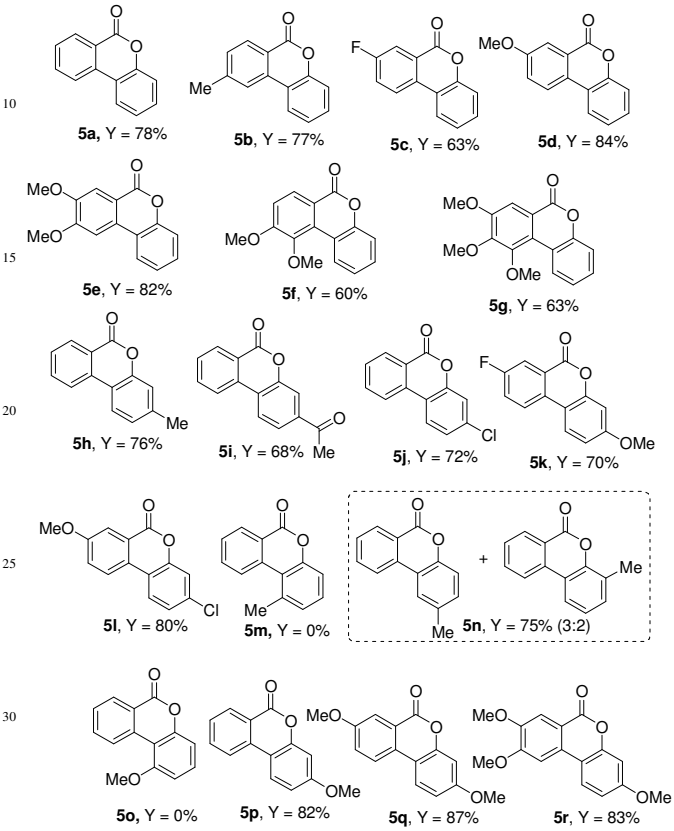
Entry	solvent	catalyst	TBHP (equiv.)	time (h)	yield[a]
1	CH_3CN	CuBr	2	24	33
2	CH_3CN	CuBr	4	24	54
3	CH_3CN	CuBr	6	8	68
4	DMF	CuBr	6	24	0
5	DMA	CuBr	6	24	trace
6	DMSO	CuBr	6	4	74[b]
7	DCM	CuBr	6	4	66
8	H_2O	CuBr	6	24	19[c]
9	DMSO	CuI	6	24	trace
10	DMSO	CuCl	6	4	78[d]
11	DMSO	CuCl	6	24	70[e]
12	DMSO	$Cu(OAc)_2$,2 H_2O	6	24	38
13	DMSO	CuCl	0	24	0
14	DMSO	------	6	24	trace

[a]Isolated yield. [b]About 6 % of fluorenone was formed along with the normal product. [c] About 27% of 2-phenylbenzoic acid was isolated. [d]Optimized reaction condition: the substrate 4a (0.25 mmol), CuCl (5 mol%), DMSO (2 mL), TBHP (6 equiv.) stirred at room temperature for 4h. [e]The catalyst 2 mol% of CuCl was used.

After getting success in the synthesis of a series of dibenzopyranones, the methodology was applied on fused *o*-phenylnaphthaldehydes and the results are given in Table 3. Under the optimized reaction condition, the substrate *o*-phenylnaphthaldehydes took longer reaction time for completion of the reaction and the product naphthochromens were formed along with a significant amount of fluorenone derivatives. Finally, the yield of the reaction was lower in comparison to the benzochromen systems.

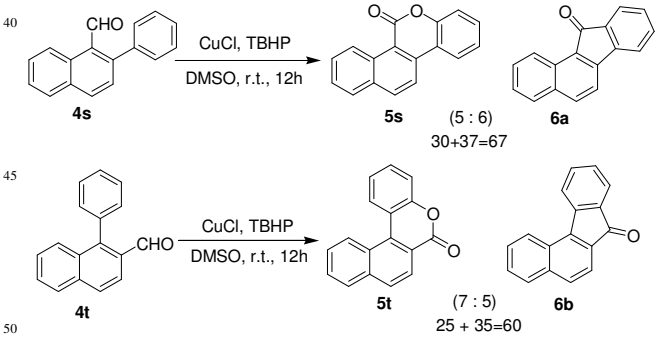
Table 2: Investigation of the substrates scope [a,b,c]





[a]Reaction conditions: 2-arylbenzaldehyde (0.25 mmol), CuCl (5 mol%), DMSO (2 mL), TBHP (6 equiv.) stirred at room temperature for 4h.[b]Isolated yield.[c]5n isomers as an NMR ratio.

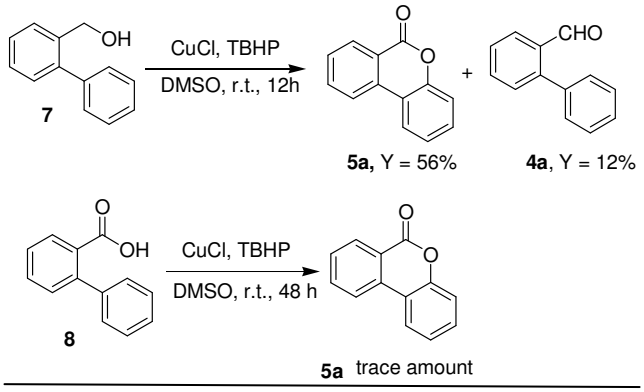
Table 3: Extension of the reaction scope for the synthesis of naphthochromens[a,b]



[a]Reaction conditions: 2-arylbenzaldehyde (0.25 mmol), CuCl (5 mol%), DMSO (2 mL), TBHP (6 equiv.) stirred at room temperature for 12 h.[b]Isolated yield.

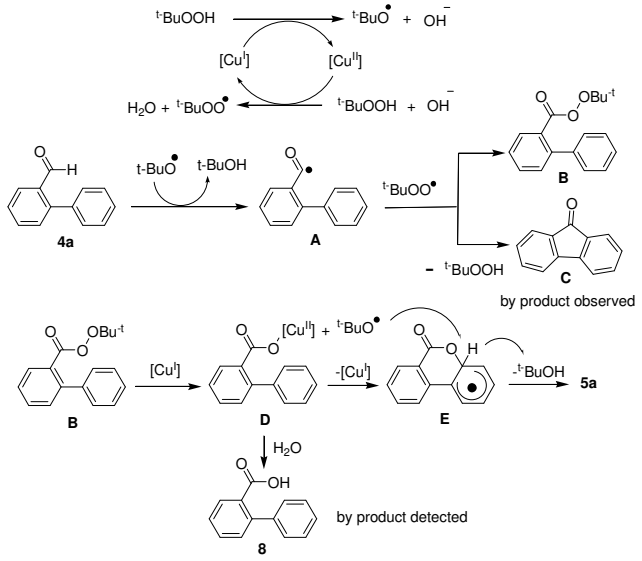
After the successful application of this methodology on different *o*-arylbenzaldehyde derivatives, we thought that the methodology could also be applicable on 2-arylbenzylalcohol or benzoic acid derivatives and for that we had applied the methodology on 2-phenylbenzylalcohol and 2-phenylbenzoic acid. The substrate 2-phenylbenzylalcohol promoted the reaction successfully and gave the product dibenzopyranone along with the unreacted intermediate 2-phenylbenzaldehyde under the optimized reaction condition (Table 4). However, the 2-phenylbenzoic acid gave the product dibenzopyranone in trace amount even after 48 h.

Table 4: Investigation on the scope of the reaction[a]



[a]Reaction conditions: 2-arylbenzaldehyde (0.25 mmol), CuCl (5 mol%), DMSO (2 mL), TBHP (6 equiv.) stirred at room temperature for the required time.

Scheme 3: Plausible reaction mechanism



We observed that the substrate 4a under the optimized reaction conditions gave the product 5a in 22% yield only in presence of radical scavenger TEMPO (2.0 equiv.).

On the basis of our experimental results and literature reports,[16] the tentative mechanism of the reaction is described in Scheme 3. At first, in the presence of CuCl catalyst the TBHP decomposes

to generate *tert*-butoxyl and *tert*-butylperoxy radicals. Then the *tert*-butoxyl radical abstracts the aldehyde proton from **4a** and gives the radical intermediate **A**. Then the intermediate **A** either combines with *tert*-butylperoxy radical to give the perester intermediate **B** or combines with the adjacent phenyl ring to form the fluorenone (C) which was isolated as the by product in trace amount. In presence of Cu(I) catalyst the intermediate **B** decomposes to form the intermediate **D** and *tert*-butoxyl radical. Then the intermediate **D** combines with adjacent phenyl ring to give the radical intermediate **E** which forms the product **5a** after abstraction of a proton by *tert*-butoxyl radical. The intermediate **D** gave 2-phenylbenzoic acid when the reaction was performed in water (Table 1, entry 8).

In conclusion, we have developed a novel and efficient methodology for the synthesis of dibenzopyranones involving the CuCl catalyzed intramolecular oxidative lactonization of aromatic C-H bond with aldehyde group in 2-arylbenzaldehyde derivatives. We have successfully applied our methodology for the synthesis of methyl ether of natural product Urolithins A-C. Finally we believe that the methodology will be widely exploited by synthetic organic chemists because of low cost CuCl catalyst, ambient reaction temperature, easily synthesizable starting materials, scalable[17] and finally the good to excellent yields of the reaction. The mechanistic details and the application of this methodology for the synthesis other benzochromen containing natural products are under progress in our laboratory.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

‡ Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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17. A 10 mmol biphenyl-2-carbadehyde under the optimized reaction conditions afforded 71% yield.