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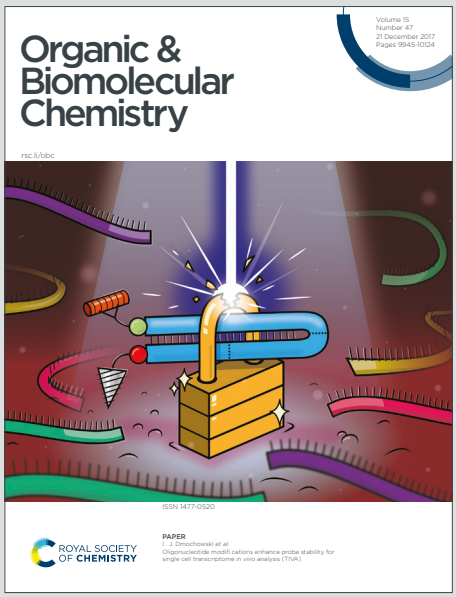

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ARTICLE

α-Angelica lactone catalyzed oxidation of benzylic sp³ C–H bonds of isochromans and phthalans

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A metal-free organocatalytic system has been developed for highly efficient benzylic C–H oxygenations of cyclic ethers using oxygen as an oxidant. This oxidation reaction utilizes α-angelica lactone as low cost/low molecular weight catalyst. The optimized reaction conditions allow the synthesis of valued isocoumarins and phthalides from readily available precursors in good yields. Mechanistic studies indicate that the reaction pathway likely involve a radical process via a peroxide intermediates.

Introduction

The isocoumarin and phthalide derived scaffolds are frequently encountered in many natural products and drug molecules that possess a broad range of biological activities (Figure 1).[1] Given the immense applications and significance of these compounds, a challenging study of interest is development of concise and efficient method to these oxygen-containing heterocyclic compounds. Direct oxidation of benzylic sp³ C–H bonds of isochromans and phthalansis one of the most effective means to enable expeditious synthesis due to the high step economy and synthetic efficiency. Traditionally, oxidation of benzylic sp³ C–H bonds is performed by using metal oxides of chromium.[2] Since chromium is toxic in nature, transition-metal catalysts using oxygen or peroxides as the oxidant were developed.The metal catalysts for oxidation of benzylic sp³ C–H bond include copper,[3] cobalt,[4] rhodium,[5] manganese[6] and iron.[7] Among them, iron catalyst containing a chiral pyridine bissulfonylimidazole ligand is mention worthy although it experiences low conversion.[7c] Use of photoredox methods[8] and strong base in the presence of oxygen are also known for benzylic oxidation which avoid metals.[9] Recently, application of TEMPO derived sulfonic salt catalyst and mineral acids for aerobic oxidation of benzylic sp³ C–H bonds of ethers and alkylarenes (Scheme 1a) has been reported.[10] DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) as catalyst in the presence of other co-catalytic system (50 mol% of *tert*-butyl nitrite) are also known in literature for such reactions (Scheme 1b).[11]

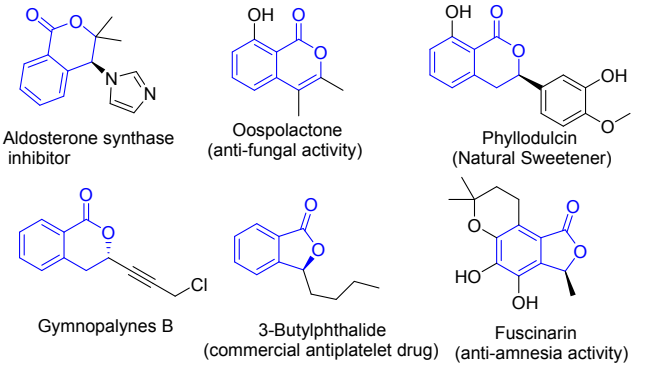
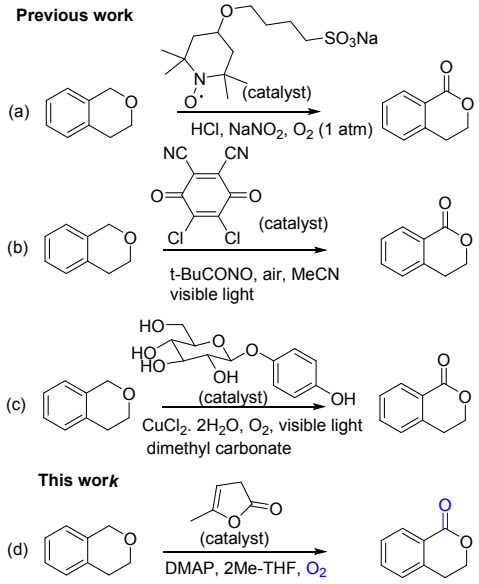


Fig. 1 Selected examples of natural products and drugs containing isocoumarin and phthalide core structure.



Scheme 1C–H Oxidation of Isochromans.

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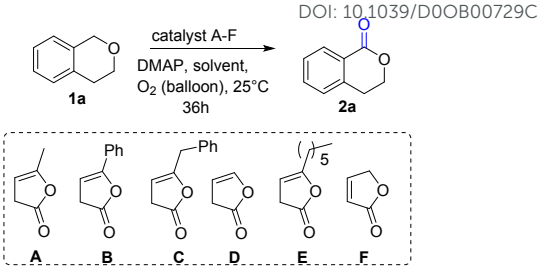
However, DDQ is toxic and liberates HCN upon contact with water. Therefore, a visible light mediated oxidation method using less toxic arbutin (source of 1,4-hydroquinone, BQH_2)as pre-oxidant in the presence of copper salt (electron transfer mediator) and oxygen gas has been developed (Scheme 1c).[12] Very recently, we reported α-angelica lactone as an organocatalyst for benzylic C–H oxidations of N-aryl tetrahydroisoquinolines and isoindolines in the presence of a base under oxygen atmosphere.[13] Herein, in continuation of our work on organocatalyzed oxidation with O_2 as a green oxidant, we describe a benzylic sp^3 C–H bond oxidation of isochromans and phthalans by using α-angelica lactone as an organocatalyst in the presence of a base for the synthesis of isocoumarin and phthalide derivatives (Scheme 1d). We have also found that the oxidation method is highly chemoselective in nature. α-Angelica lactone (a multicentered nucleophile) has been successfully employed as a nucleophile[14] but in the present case no oxidative cross-coupling product of cyclic benzylic ethers with α-angelica lactone is detected as reported earlier with aldehydes.[15] Recently, ACS Green Chemistry Institute® Pharmaceutical Roundtable (GCIPR) in its 10th anniversary report pointed that "*Aliphatic and aromatic C–H activation, using green oxidants and giving predictable site selectivities*" as one of the top 10 research areas[16] which compliments the elegance of our present research findings.

Results and discussion

As we realized the efficient catalytic activity of amines for the benzylic C-H oxidation in our previous research, we anticipated that the same might execute α-oxidation reaction of benzo-fused cyclic ethers. We selected isochroman**1a** as the model substrate for the desired transformation (Table 1). Most accessible oxygen gas is preferred as a source of oxidant which also enables high atom economy. We have carried out the oxidation reaction of isochroman**1a** in the presence oxygen gas, α-angelica lactone **A** (25 mol %) as an organocatalyst and 4-dimethylaminopyridine (DMAP, 3 equiv.) as a base were used in THF. The reaction proceeded at 25 °C to afford isocoumarin **2a** in 34% isolated yield in 36 h (entry 1). With the encouraging preliminary result, we first tried to figure out the role of different solvents in the reaction conditions. Acyclic ethers (diethyl ether and MTBE) were not found to be better than THF as they delivered low chemical yields (27 and 30% respectively, entries 2 and 3). Toluene and acetonitrile provided comparatively improved yields (41% and 47% respectively, entries 4 and 5). A significant improvement was observed when the reaction was performed at an elevated temperature (80 °C). The product was obtained in 68% isolated yield in acetonitrile (entry 6). A superior result was obtained when 2-methyltetrahydrofuran (2-Me THF) was employed at 80 °C (81% yield, entry 7). We have alsoscreened the catalyticefficacy of various lactones (**B-F**) and found them not so promising except lactone **E** which afforded the desired product in 71% yield (entries 8-12). Use of 25 mol% catalyst **A** was found to be optimum. A diminished yield was obtained when

Table 1. Optimization Studiesa



entry	catalyst	solvent	yield (%) [b]
1	**A**	THF	34
2	A	Et_2O	27
3	A	MTBE	30
4	A	toluene	41
5	A	CH_3CN	47
6[c]	A	CH_3CN	68
7[c]	A	2-Me THF	81
8[c]	B	2-Me THF	46
9[c]	C	2-Me THF	26
10[c]	D	2-Me THF	34
11[c]	E	2-Me THF	71
12[c]	F	2-Me THF	24
13[c,d]	A	2-Me THF	54
14[c,e]	A	2-Me THF	83

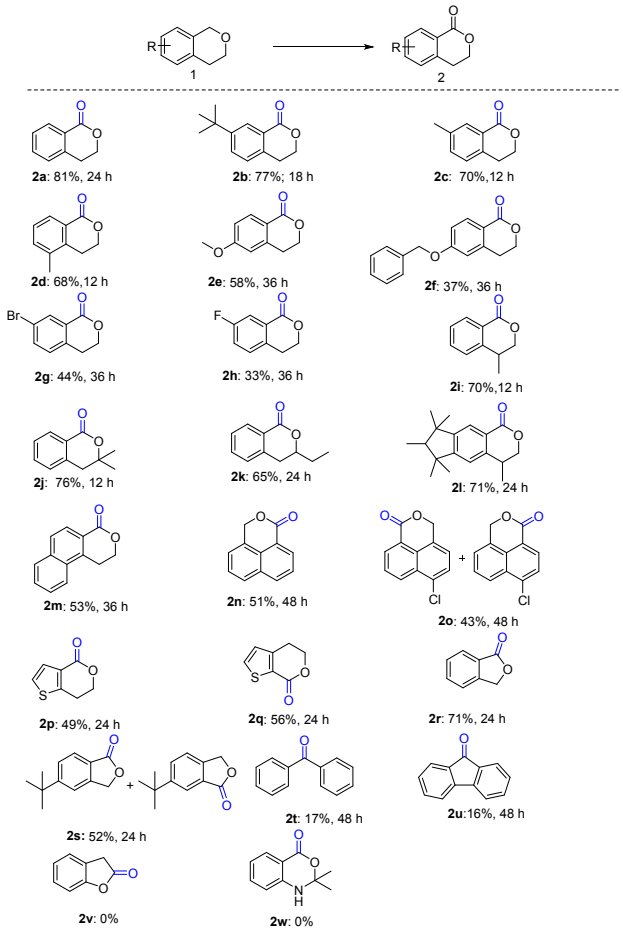
[a]Reaction condition: **1a** (0.1 mmol), DMAP (0.3 mmol), catalyst **A** (25 mol %), in solvent (0.5 mL) at rt for 36 h under O_2 (balloon) atmosphere. [b]Isolated yields. [c]at 80 °C for 24h. [d]With 10 mol% catalyst **A**. [e]With 30 mol% catalyst **A**.

catalyst loading was 10 mol% (54%, entry 13). And only marginal improvement in yield was noticed when 30 mol% catalyst was used (83%, entry 14). Further optimization, in terms of different bases and solvent concentrations were also performed and are detailed in the Supporting Information.

We have then explored the substrate scope of this angelica lactone (**A)** catalyzed oxidation reactions of different isochromans and pthalans and the results are summarized in Table 2. No over oxidation product was formed as confirmed by GC-MS and NMR studies. The reason could be instant deactivation of the ring by the inserted carbonyl group which prohibits further oxidation. Substituted isochromans **1a-1q** gave the corresponding oxidized products **2a-2q** in a moderate to excellent yields (33-81%). The optimized reaction condition successfully included substrates containing electron donating groups on aromatic ring of isochroman. The corresponding products **2b-2f** were obtained in 37-77% yields. Halogen substitutions (-Br, -F) on the phenyl ring of isochroman afforded the corresponding products **2g** and **2h** in 44 and 33% of yields. Isochromans with alkyl substitutions (methyl, dimethyl and ethyl groups) on the saturated ring were also well toleratedand the corresponding oxidized products (**2i**–**2k**) were obtained in 70%, 76% and 65% yields respectively. Musk chemical hexamethylisochromane **1l** (Galoxolide) was also found to be a suitable substrate. The corresponding product **2l** was obtained in 71% yield. Benzo-isochroman derivatives were responded well to our protocol and gave the corresponding lactones **2m-o** in 43-53% yields. Notably, in case of compound **2o**, which have two benzylic positions for oxidation,

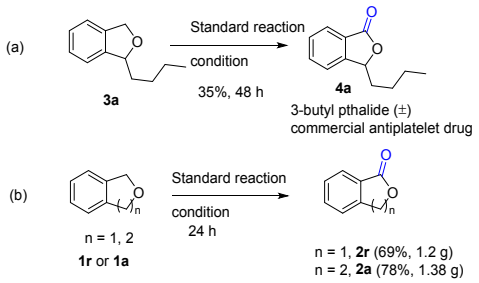
regioisomeric mixtures of isocoumarins were obtained in 60:40 ratios. We believe the less hindered product was obtained as the major isomer due to steric issues. Heteroaromatic isochromanes **1p-q** were also found to be suitable substrates and the corresponding products **2p-q** were obtained in 49 and 56% yields. The application of present catalytic system was also extended for the α-oxygenation of pthalans to the corresponding phthalides in good yields. Phthalide **2r** was obtained in 71% yield. Notably, in case of compound **2s**, regioisomeric mixtures of phthalides were obtained in 77:23 ratios in favor of *para* oxidation product possibly governed by electronic effect. Oxidation reaction of alkylarenes is of significant challenge.[9] We are delighted to include them in our catalytic system with slight modification of the reaction conditions (in toluene at 100 °C). Diphenylmethane and 9*H*-fluorene provided the corresponding ketones (**2t** and **2u**) in low isolated yields (17 and 16% respectively). However, 2,3-dihydrobenzofuran was not compatible with the present protocol and failed to afford the product **2v**.

Table 2 Substrate Scope: Isochromans[a,b]



[a] Reaction condition: 1a (0.1 mmol), DMAP (0.3 mmol), catalyst **A** (25 mol %), in 2-Me THF (0.5 mL) at 80 °C for indicated time under O_2 (balloon) atmosphere. [b] Isolated yields.

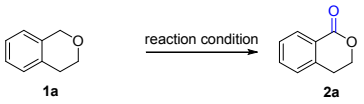
Benzoxazine derivative **1w** also remained irresponsive probably due to the presence of another heteroatom (N). The potential application of this benzylic oxidation was illustrated for the synthesis of racemic 3-butylphthalide (**4a**) using the standard reaction condition starting from 1-butyl phthalan**3a** in 35% yield (Scheme 2a). The reproducibility of the reaction was examined in gram-scale using optimized reaction conditions, the products **2r** (1.2 g, 69%) and **2a** (1.38 g, 78%) were isolated without any loss of chemical yield (Scheme 2b).



Scheme 2. Synthetic manipulation and gram-scale synthesis.

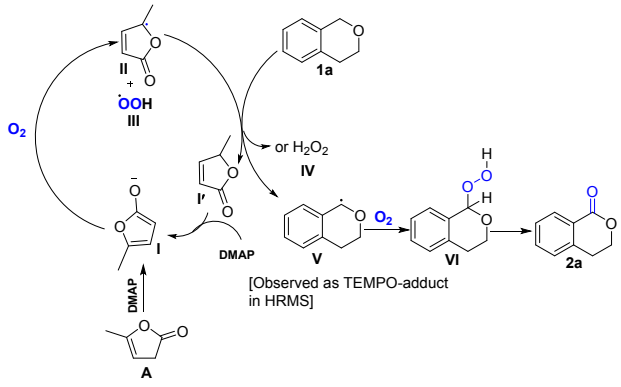
Control experiments were performed to understand the reaction mechanism (Table 3). We found that the reaction was not operational in absence of either base or catalyst **A** (with complete recovery of starting material **1a**, entries 1-2). Again no oxidation product was detected when the reaction was performed under inert (N_2 or argon) atmosphere which indicates that the source of oxygen atom in the lactone moiety is from air or moisture (entry 3). The reaction was also performed in the presence of H_2O^{18} in 2-Me-THF. However, no O-18 labelled product was detected in mass spectrum (entry 4). This observation indicates molecular O_2 as the source of lactone oxygen in the product. Again yield of product **2a** was dropped to <10% in the presence of stoichiometric amounts of radical scavenger like TEMPO or BHT which indicates that the reaction proceeds through radical intermediates (entry 5). Only trace amount of product was observed on addition of $CuCl_2$ in the reaction medium which indicates the operating single electron transfer during the course of the reaction (entry 6).[17]Additionally, only traces of **2a** were observed (13% yield) when the reaction was performed in the presence of catalase enzyme (H_2O_2 scavenger), which indicates presence of peroxide species (entry 7).[17, 18] Next, oxygen isotope labelling experiment was performed to ascertain the source of oxygen and to support the reaction mechanism.The GC-mass spectrum of the product **2a** (m/z = 148) was shifted two mass units higher to m/z = 150 (**2a'**) (82% ^{18}O labeled oxygen atom) when the reaction was carried out with $^{18}O_2$. This experiment clearly indicates that the incorporation of oxygen is from molecular oxygen (entry 8).

Table 3 Mechanistic Investigations



Entry	Condition	Result
1	No base	No reaction
2	No Cat. **A**	No reaction
3	N_2 or Argon atm.	No reaction
4	2Me-THF:H_2O^{18} (10 equiv.; 980µL:20µL)	>98% unlabeled, no ^{18}O
5	TEMPO or BHT (1 equiv.)	<10%
6	$CuCl_2$ ((1 equiv.)	No reaction
7	Catalase (70 mg)	13%
8	$^{18}O_2$ atm.	82% ^{18}O incorporation

On the basis of these experimental data and literature precedents[12,13,17] a plausible mechanism of this transformation is proposed (Scheme 3). Deprotonation of acidic proton of **A** by DMAP leads to a dienolate species **I** which captures triplet oxygen to form peroxide species[19] and then its homolytic cleavage leads to radical species **II** and **III**. Next, H-atom abstraction of **1a** by either the peroxy radical **III** or alkoxy radical **II** leads to radical species **V** [Formation of intermediate **V** was confirmed by the HRMS analysis, detection of **V**-TEMPO adduct] which reacts with oxygen to give hydroperoxide intermediate **VI** that can collapse to product **2a** by further H-removal by base. Alternatively, single electron transfer from the substrate **1a** may give a radical cation that can undergo H-atom transfer to give an oxocarbenium ion which on recombination with peroxy radical **III** provides intermediate **VI** (see SI).



Scheme 3 Plausible Mechanism.

Conclusions

In summary, we have developed an efficient and versatile synthetic strategy for direct oxidation of various isochromans and pthalans to corresponding lactones by employing inexpensive α-angelica lactone as catalyst. Moreover, this methodology utilizes oxygenas the green oxidant as well asoxygen atom source in lactones. The reaction conditions are compatible with a range of cyclic ethers. A reaction mechanism involving a radical pathway via a peroxide species as intermediates has been further supported by control experiments. This protocol is successfully applied for the direct synthesis of bioactive molecule 3-butylphthalide.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Table of contents entry

Oxidation of benzylic sp^3 C–H bonds of isochromans and phthalans to isocoumarins and phthalides has been achieved by employing α-angelica lactone as organocatalyst.