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Synthesis of Isoquinoline-1,3(2H,4H)-dione Derivatives via Cascade Reactions of *N*-Alkyl-*N*-methacryloyl Benzamide with Aryl Aldehydes

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A cascade reaction between *N*-alkyl-*N*-methacryloylbenzamide and aryl aldehydes was developed to generate isoquinoline-1,3(2H,4H)-dione derivatives. The reaction involves oxidative cross coupling of the activated alkene from the *N*-alkyl-*N*-methacryloylbenzamide with the aldehyde functional group (-CHO), followed by radical addition to aromatic ring to afford isoquinoline-1,3(2H,4H)-dione derivatives in good yields under mild reaction conditions without either metal catalyst or organic solvents involved.

There is a growing demand for complex functionalized molecules for high-throughput screening (HTS) in order to find valuable biological probes and lead molecules for drug discovery.[1] Isoquinoline-1,3(2H,4H)-dione derivatives are complex functionalized molecules, which have attracted considerable synthetic interest due to different biological activities.[2] In figure 1, four representative bioactive isoquinoline-1,3(2H,4H)-dione derivatives are shown.[3] These bioactivities include aldose reductase (ALR2) inhibitors;[3a] antitumor activity against human pancreatic carcinoma cell line;[3b] potent and selective inhibitors of cyclin-depedent kinase 4;[3c] inhibitors of Lck kinase.[3d] So there is a strong need to develop quick and efficient synthetic methods to access a large variety of complex functionalized molecules. A cascade reaction which can produce them in a one pot process under environmentally friendly condition would be especially valuable.

Traditional methods to synthesize isoquinoline-1,3(2H,4H)-dione derivatives have been reported.[4] Recently, a few efficient synthetic methods of producing these derivatives have been developed, including direct intramolecular carbotrifluoromethylation, aryltrifluoromethylation and arylphosphonylation of activated

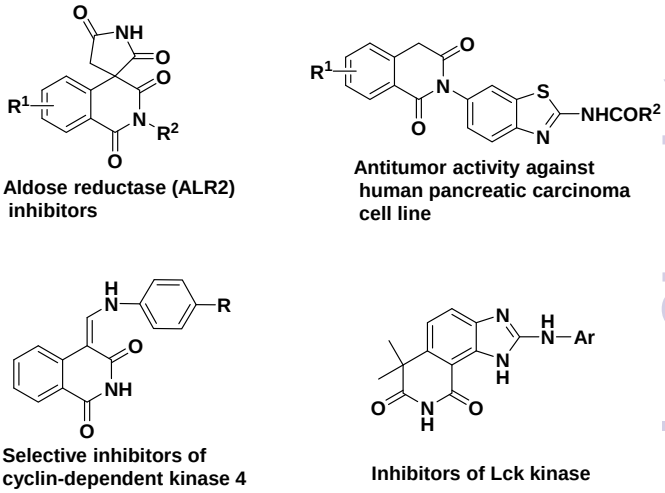


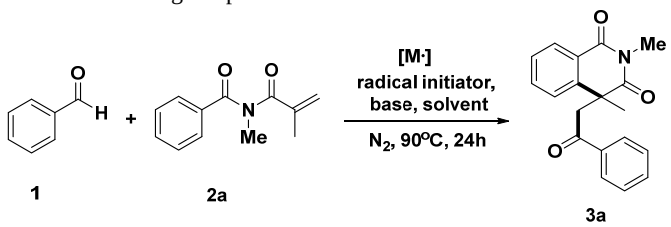
Figure 1 Biologically active isoquinoline-1,3(2H,4H)-dione derivatives

alkenes.[5] In these multistep reactions, *N*-alkyl-*N*-methacryloylbenzamide was used as a core reaction substrate. By careful design and reactant selecting, several isoquinoline-1,3(2H,4H)-dione-containing structures were obtained in one pot with good yields.

There is still a need for evaluating different structures of complex functionalized isoquinoline-1,3(2H,4H)-dione derivatives. To further develop this chemistry, we focused on using different aromatic aldehydes as reagents to react with *N*-alkyl-*N*-methacryloyl-benzamides to obtain isoquinoline-1,3(2H,4H)-dione derivatives via a one pot reaction cascade to obtain other valuable keto-type derivatives.

To find suitable reaction conditions for this cascade, different metal catalysts and radical initiators were screened (Table 1) based on our previous research results.[6] In entry 1, $CuCl_2$ (10% mol) was used as a catalyst in the presence of TBHP (*tert*-butyl hydroperoxide, 70% in water, 3.0 equiv) and $NaHCO_3$. Excess benzaldehyde (5 equiv) was used to promote the reaction, giving **3a** in a yield of 48%. Using a combination of $FeCl_3$, TBHP and $NaHCO_3$ gave about 20% of **3a**. Using $CuBr_2$ and CuI as catalysts afforded none or only traces of **3a** (entries 3, 4). In entry 5, H_2O_2 was used as an initiator instead of TBHP, but no **3a** was obtained. When TBHP was replaced by DTBP (*tert*-butyl peroxide) in the presence of $NaHCO_3$, **3a** was produced in 58% yield. Using solvents DCE, toluene (entries 7, 8) afforded none or only traces of **3a**, while CH_3CN and EtOAc (entry 9, 10) afforded 24% and 38% of expected product **3a**, respectively. Using TBHP itself in the presence of $NaHCO_3$ gave **3a** in good yield of 80%. Based on these screening results, the optimized conditions for this reaction were: aldehyde (5 equiv), TBHP (3 equiv), 90°C, $NaHCO_3$ (1 equiv), 24h.

Table 1 Screening to optimize reaction conditions[a]

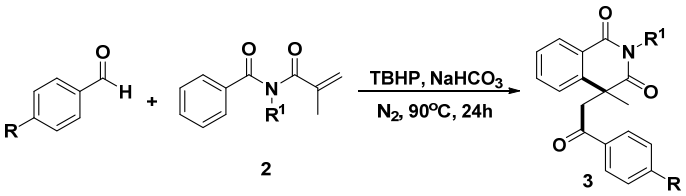


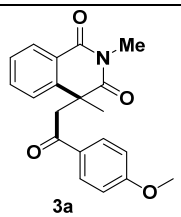
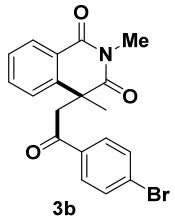
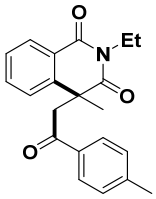
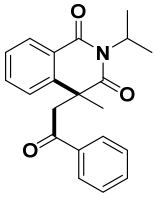
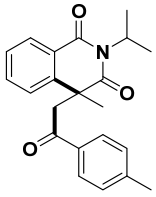
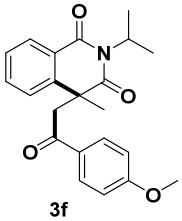
Entry	Cat. (mol%)	Reagent	Solvent	Yield[b] (%)
1	$CuCl_2$ (10)	TBHP, $NaHCO_3$	---	48
2	$FeCl_3$ (10)	TBHP, $NaHCO_3$	---	20
3	$CuBr_2$ (10)	TBHP, $NaHCO_3$	---	trace
4	CuI (10)	TBHP, $NaHCO_3$	---	trace
5	---	H_2O_2, $NaHCO_3$	---	---
6	---	DTBP, $NaHCO_3$	---	58
7	---	TBHP, $NaHCO_3$	DCE	trace
8	---	TBHP, $NaHCO_3$	Toluene	trace
9	---	TBHP, $NaHCO_3$	CH_3CN	24
10	---	TBHP, $NaHCO_3$	EtOAc	38
11	---	TBHP, $NaHCO_3$	---	80

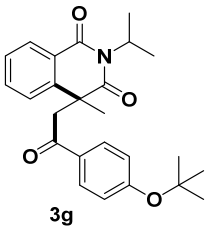
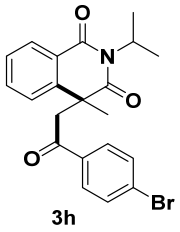
[a] Reaction conditions: benzaldehyde (5 equiv), *N*-methyl-*N*-phenylmethacrylamide (1 equiv), TBHP (70 wt % in water, 3 equiv), H_2O_2 (30 wt % in water, 3equiv) and DTBP (3 equiv); yield is based on reactant **2a**. [b] Yield of isolated **3a**. [c] The reaction was run for 24 h.

Under these conditions, eight reactions with different substituents were investigated (Table 2) at the optimized conditions. These cascade reactions all gave 3-methyl-3-aroyloxindole derivatives **3a-h** in good yields in one pot.

Table 2 Oxidative cascade coupling reaction[a]

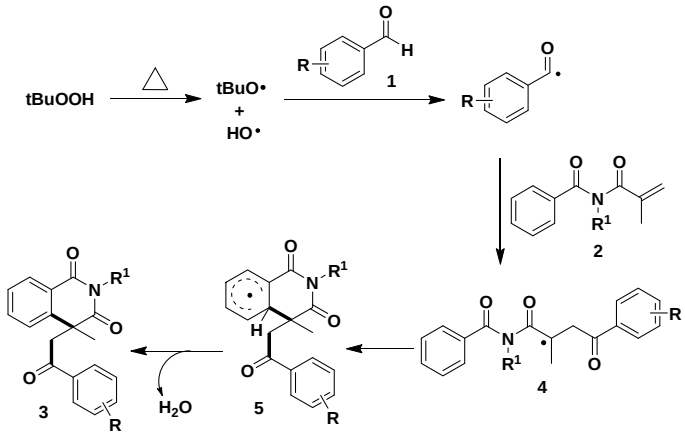


Entry	R	R^1	Product **3**	Yield[b] (%)
1	MeO	Me	 **3a**	72
2	Br	Me	 **3b**	66
3	Me	Et	 **3c**	75
4	H	*i*-Pr	 **3d**	80
5	Me	*i*-Pr	 **3e**	84
6	MeO	*i*-Pr	 **3f**	82

7	*t*-Bu	*i*-Pr	 3g	88
8	Br	*i*-Pr	 3h	78

[a] Reaction conditions: aldehyde (5 equiv), *N*-alkyl-*N*-phenylacrylamide (1 equiv), aqueous TBHP (70 wt % in water, 3 equiv), yield calculation is based on reactant **2**. [b] Yield of isolated **3a-h.**

Based on previous reports and these new results,[7] a reaction mechanism is proposed in Scheme 1. First TBHP splits to give tBuO• and •OH radicals when heated. These radicals abstract a hydrogen atom from the aryl aldehyde **1** to generate the acyl radical. This radical adds to the double bond of *N*-alkyl-*N*-methacryloylbenzamide to give radical **4**. Radical **4** attacks the aromatic ring to generate radical **5**. Radical **5** then looses a hydrogen atom to •OH radical to afford product **3**.



Scheme 1 Proposed cascade coupling reaction mechanism.

In summary, we have developed a novel metal-free cascade reaction between *N*-alkyl-*N*-methacryloylbenzamides and aryl aldehydes to generate isoquinoline-1,3(2H,4H)-dione derivatives. The reaction involves oxidative cross coupling of the activated alkene in the *N*-alkyl-*N*-methacryloylbenzamides with the aldehyde functional group (-CHO), followed by intramolecular radical addition to the aromatic ring to afford isoquinoline-1,3(2H,4H)-dione derivatives in good yields under mild reaction conditions without any toxic catalysts or organic solvents involved. This cascade reaction is quite suitable for compound library production of keto-type isoquinoline-1,3(2H,4H)-dione derivatives for the purpose of biological activity screening. This route also enriches the current C(sp2)-H functionalization chemistry.

Acknowledgments

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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/c000000x/

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Graphic abstract