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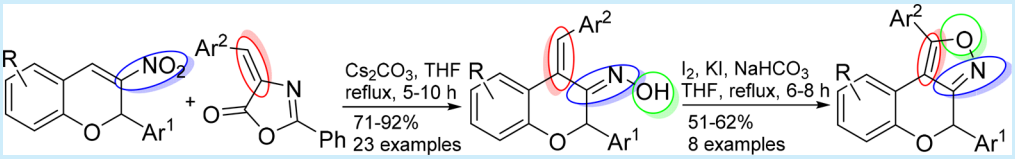
Cesium-Carbonate-Mediated Benzalation of Substituted 2-Aryl-3-nitro-2*H*-chromenes with Substituted 4-Benzylidene-2-phenyloxazol-5(4*H*)-ones

Chenlu Dai, Naili Luo, Shan Wang, and Cunde Wang*

School of Chemistry and Chemical Engineering, Yangzhou University, 180 Siwangting Street, Yangzhou 225002, P.R. China

Supporting Information



ABSTRACT: Cs_2CO_3-mediated domino benzalation reaction with a variety of 2-aryl-3-nitro-2*H*-chromenes and 4-benzylidene-2-phenyloxazol-5(4*H*)-ones has been realized. The reaction proceeds smoothly with a broad substrate scope, thus providing a variety of substituted (*Z*)-4-((*Z*)-benzylidene)chroman-3-one oximes in moderate to high yields, which were easily transformed into biologically important 4*H*-chromeno[3,4-*c*]isoxazoles.

Functionalized chromones are privileged scaffolds found in a wide variety of biologically active natural products and pharmaceuticals.[1−3] Among them, 2-aryl-3-nitro-2*H*-chromenes have shown a number of biological properties,[4] such as antiviral, antioxidant,[5] antitumor,[6] antimicrobial,[7] and antiproliferative[8] activities. They have also been recognized as important building blocks for the synthesis of natural products, pharmaceutical molecules, and functional materials.[3,4c] For the functionalized reactions of 2-aryl-3-nitro-2*H*-chromenes with a nitroolefin moiety, the nitro group of 3-nitro-2*H*-chromene derivatives can be transformed into various functional groups to produce new derivatives.[9] It is worth mentioning that Michael addition to the nitroolefin moiety employs the formation of C−C, C−N, C−O, or C−P bonds to synthesize chromene derivatives with important bioactivities.[10] Among these, direct alkylations of 3-nitro-2*H*-chromene are the most interesting and represent powerful tools for the introduction and construction of various carbocyclic and heterocyclic frameworks.[10d] Recently, great progress has been made in the C4-alkylations of 3-nitro-2*H*-chromene. Kodess et al. utilized the direct alkylation strategy for accessing chromanes containing the β-dicarbonyl fragment at position C4 by the nucleophilic addition of acetylacetone and ethyl acetoacetate at the double bond of 3-nitro-2*H*-chromenes.[11] Some similar strategies were disclosed to obtain functionalized Michael adducts using activated methylene such as malonates[12] and ketones.[13] In 2014, Woodward et al. demonstrated the tetrabutylammonium triphenyldifluorosilicate (TBAT)-mediated Michael addition of 3-nitro-2*H*-chromenes with trimethyl(trichloromethyl)silane ($TMSCCl_3$) to synthesis β-CCl_3-substituted 3-nitro-2*H*-chromenes.[14] Moreover, the use of a vinylogous Michael addition strategy that allows available α,α-dicyanoolefins to participate directly in Michael adduct formation appears to be rather efficient for the preparation of the functionalized polyheterocyclic benzopyran derivatives.[15] Subsequently, Hajra et al. reported a similar process through K_2CO_3-promoted Michael addition to 3-nitro-2*H*-chromenes from enols for the synthesis of functionalized furan-fused benzopyran derivatives.[16] Additionally, Michael addition to 3-nitro-2-phenyl-2*H*-chromene with 4-hydroxy coumarin as a classical enol substrate also was studied, following aerial oxidation to yield the coumarin−chromene hybrid compounds.[17] In 2012, Du et al. demonstrated the bis(thiazoline) Zn(II) complexes in combination with bis(oxazoline)-mediated Michael addition of 3-nitro-2-phenyl-2*H*-chromene with indoles to afford indolyl(nitro)chroman derivatives.[18] Recently, there has been a potential increase in Michael addition research of 3-nitro-2-phenyl-2*H*-chromene utilizing enamines as a nucleophilic reagent to access C4-substituted 2*H*-chromene derivatives.[19,20] These reported results indicated that 3-nitrochromenes are excellent building blocks for the preparation of various more complex heterocyclic compounds with important biological activity.[21]

Inspired by these results, in continuation of our interests in constructing polysubstituted fused coumarin derivatives,[22] we thus envisioned that 4-alkylene-3-nitrochromenes would readily take part in an intramolecular cyclization reaction or cycloaddition strategy for the synthesis of the polysubstituted fused coumarin derivatives. In the present work, based on the reported studies that show azlactones are one of the most versatile scaffolds in organic synthesis,[23] we have been seeking a direct approach toward functionalized 4-alkylene-3-nitrochromenes from 3-nitro-2*H*-chromenes with accessible azlactones. To the best of our knowledge, no benzalation of available 2-aryl-3-nitro-2*H*-chromenes with 4-benzylidene-2-phenyloxazol-5(4*H*)-ones has been realized to date. Herein, we disclose Cs_2CO_3-promoted

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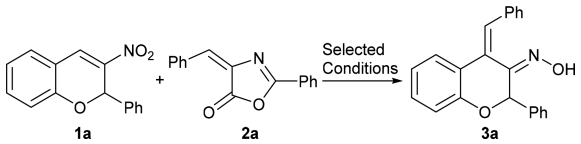
benzalation of 2-aryl-3-nitro-2*H*-chromene with 4-benzylidene-2-phenyloxazol-5(4*H*)-ones for the highly stereoselective synthesis of (*Z*)-4-((*Z*)-benzylidene)chroman-3-one oxime.

Initially, the reaction of **1a** with **2a** was conducted to screen the reaction conditions (see the Supporting Information for details). In the presence of 1.0 equiv of K_2CO_3 base, the reaction of **1a** with **2a** in a 1:1.2 molar ratio occurred in tetrahydrofuran at 60 °C, and after 12 h, although the starting materials completely disappeared, a messy mixture was obtained. Considering that azlactones opened the ring easily to afford the corresponding α-benzamidocinnamic acid in basic conditions, we thought the opening ring adduct should be a key intermediate for the following nucleophilic addition to 3-nitro-2-phenyl-2*H*-chromene.[24]

Thus, the mixture of **2a** with K_2CO_3 was stirred first at 60 °C for 3 h, and then to the resultant mixture was added **1a**, which was stirred sequentially for 12 h until full conversion of **1a** was achieved. We observed a benzalation reaction following the formation of oxime, thus rendering 25% yield of **3a** (Table 1, entry 1). When the base was changed to Cs_2CO_3, **3a** was obtained in 57% yield after 12 h (entry 2). However, when weak $NaHCO_3$ was used, **3a** was not observed, and a strong base such as NaOH gave a just slightly lower 37% yield (entry 4). Common organic bases were screened; surprisingly, the organic bases selected could not produce **3a** (Table 1, entries 5−7). Using 2.0 equiv of Cs_2CO_3 as base increased the yield to 87% for **3a** and needed a shorter reaction time (Table 1, entry 8), whereas a further increase in the amount of Cs_2CO_3 provided just slightly lower yield despite less reaction time (Table 1, entry 9). Subsequently, various temperatures and solvents were explored. When the temperature was decreased to 50 °C, the yield of **3a** was obviously reduced to 55% within 9 h (Table 1, entry 10). Increasing the temperature from 60 °C to reflux led to more efficient formation of **3a** in a shorter reaction time (Table 1, entry 11). Reaction of **1a** and **2a** in DMF or toluene solvent and in the presence of Cs_2CO_3 base at 65 °C also gave **3a** in lower yield (Table 1, entries 12 and 13). Ethanol as solvent failed to produce the desired product. Under the same reaction condition, acetonitrile solvent produced **3a** in just 5% yield because the partial hydrolysis of acetonitrile with water occurred to inhibit the title reaction. However, dried THF as solvent gave a slightly lower yield (Table 1, entry 16), and the dried THF together with 4 Å molecular sieves was used in the reaction to give **3a** in just 36% yield (Table 1, entry 17). The commercial THF contains a small amount of water help the reaction. Thus, THF solvent promoted the reaction most efficiently.

Table 1. Screening of Reaction Conditions for the Synthesis of 3a[a]



entry	base (equiv)	solvent	temp (°C)	time (h)	yield (%)[b]
1	K_2CO_3 (1.0)	THF	60	15	25
2	Cs_2CO_3 (1.0)	THF	60	12	57
3	$NaHCO_3$ (1.0)	THF	60	20	0
4	NaOH (1.0)	THF	60	15	37
5	DBU (1.0)	THF	60	20	0
6	DABCO (1.0)	THF	60	20	0
7	Et_3N (1.0)	THF	60	20	0
8	Cs_2CO_3 (2.0)	THF	60	6	87
9	Cs_2CO_3 (3.0)	THF	60	4	75
10	Cs_2CO_3 (2.0)	THF	50	9	55
11	Cs_2CO_3 (2.0)	THF	reflux	5	87
12	Cs_2CO_3 (2.0)	DMF	65	4	15
13	Cs_2CO_3 (2.0)	PhMe	65	20	36
14	Cs_2CO_3 (2.0)	C_2H_5OH	65	20	0
15	Cs_2CO_3 (2.0)	CH_3CN	65	15	5
16[c]	Cs_2CO_3 (2.0)	THF	60	6	81
17[d]	Cs_2CO_3 (2.0)	THF	60	6	36

[a]Reaction conditions: **1a** (1 mmol), **2a** (1.2 mmol), solvent (10 mL). [b]Isolated yield. [c]Dried THF. [d]Dried THF and 4 Å molecular sieves.

With the optimal reaction conditions identified, we explored the scope of this newly developed benzalation reaction in the presence of Cs_2CO_3 with a variety of 2-aryl-3-nitro-2*H*-chromenes and 4-benzylidene-2-phenyloxazol-5(4*H*)-ones. Our results on 23 successful examples are summarized in Table 2. For the *para*-substituents of Ar^1, substrates **1a−f** with either electron-donating or electron-withdrawing groups could smoothly furnish the corresponding products **3a−f** (86−92%) (Table 2, entries 1−6). With the substituent of Ar^1 at the *meta*- and *ortho*-substituents, substrates **1g** and **1h** were also transformed into **3n** and **3o** in the yield of 83 and 82%, respectively, which showed that the steric hindrance had hardly any influence on the reactivity. Compounds **3t** and **3u** were obtained in 80 and 85% yield, respectively, when substrate Ar^1 contained heterocyclic thiophene (Table 2, entries 20 and 21), whereas the substituent of Ar^1 bearing a 1,4-dioxane unit led to somewhat lower yields of 71 and 75%, respectively, of **3v** and **3w** (Table 2, entries 22 and 23). For the R substituents of the chroman unit (Table 2, entries 16−20), substrates **1j−n** with either electron-withdrawing or electron-donating groups could smoothly yield **3p−t** in good yields, which showed good substrate tolerance toward the reaction. Remarkably, a significant substituent effect could be observed, and electron-donating groups had positive impacts on the yields.

Subsequently, the limitation of this reaction was investigated with a variety of electronically and sterically diverse **2** subjected to the optimal conditions. Substrates **2c−e** produced **3h−j** in 85, 82, and 81% yield, respectively. Substrate **2b** with a strong electron-donating group (−OMe) could afford product **3h** in slightly higher yield despite the substituent of Ar^2 at the *ortho*-position. It revealed that the position of substituents and the electronic effect of Ar^2 significantly influence reactivity. The strong electron-donating group of Ar^2 is propitious to the title reaction compared with weak electron-donating and electron-withdrawing groups. The higher yields might be rationalized by the fact that the benzyl carboanion generated in situ could significantly attack the β-position of nitroalkene by the electron-rich aryl groups under basic conditions.

The stereochemistry of representative compounds **3b**, **3c**, and **3u** was confirmed by X-ray crystallography analyses (Figure 1). Remarkably, all benzalations and oximes were stereospecific, which only formed the *Z* form at the more sterically demanding chroman unit.

To rationalize the reaction mechanism, two control reactions were conducted. As it is well-known that 4-benzylidene-oxazol-5(4*H*)-one can be converted to 3-aryl-2-benzamidoacrylic acid under basic conditions via hydrolysis ring opening (Scheme 1),[24] **1b** and 3-aryl-2-benzamidoacrylic acid (**2e**°) were subjected to the optimal conditions to investigate the possibility of the reaction pathway via the intermediate of 3-aryl-2-

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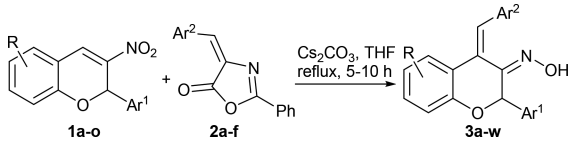
Table 2. Cs_2CO_3-Promoted Synthesis of Chroman-3-one Oximes 3a–w[a]



entry	R	Ar^1	Ar^2	time (h)	yield (%)[b]
1	H	C_6H_5	C_6H_5	5	87 (**3a**)
2	H	4-MeC_6H_4	C_6H_5	5	91 (**3b**)
3	H	4-$MeOC_6H_4$	C_6H_5	5	92 (**3c**)
4	H	4-FC_6H_4	C_6H_5	6	88 (**3d**)
5	H	4-ClC_6H_4	C_6H_5	6	90 (**3e**)
6	H	4-BrC_6H_4	C_6H_5	6	86 (**3f**)
7	H	4-$MeOC_6H_4$	4-MeC_6H_4	7	82 (**3g**)
8	H	4-MeC_6H_4	2-$MeOC_6H_4$	7	85 (**3h**)
9	H	4-MeC_6H_4	3-MeC_6H_4	7	82 (**3i**)
10	H	4-MeC_6H_4	4-ClC_6H_4	7	81 (**3j**)
11	H	4-BrC_6H_4	3-ClC_6H_4	8	80 (**3k**)
12	H	C_6H_5	4-MeC_6H_4	7	84 (**3l**)
13	H	C_6H_5	3-ClC_6H_4	7	80 (**3m**)
14	H	3-MeC_6H_4	4-MeC_6H_4	7	83 (**3n**)
15	H	2-MeC_6H_4	3-ClC_6H_4	7	82 (**3o**)
16	6-Me	4-$MeOC_6H_4$	C_6H_5	6	85 (**3p**)
17	8-EtO	2-ClC_6H_4	C_6H_5	6.5	84 (**3q**)
18	6-Br	4-MeC_6H_4	C_6H_5	8	82 (**3r**)
19	6-Cl	4-ClC_6H_4	C_6H_5	8	81 (**3s**)
20	6-Me	thiophen-2-yl	4-MeC_6H_4	10	80 (**3t**)
21	H	thiophen-3-yl	C_6H_5	9	85 (**3u**)
22	H	3,4-$(CH_2O)_2C_6H_3$	C_6H_5	8	71 (**3v**)
23	H	3,4-$(CH_2O)_2C_6H_3$	4-MeC_6H_4	8	75 (**3w**)

[a]Reaction conditions: **1a–o** (1 mmol), **2a–f** (1.2 mmol), Cs_2CO_3 (2 mmol), THF (10 mL), reflux, 5–10 h. [b]Isolated yield.

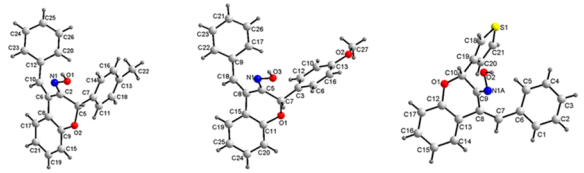
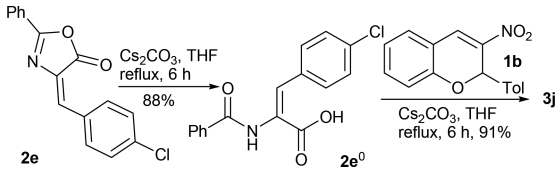


Figure 1. X-ray crystal structure of compounds **3b**, **3c**, and **3u**; non-hydrogen atoms are shown at the 30% probability level.

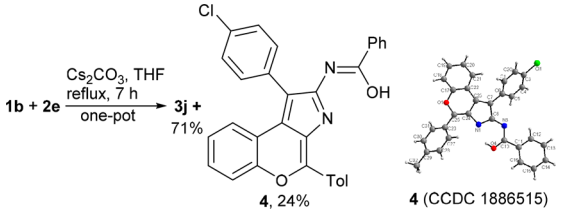
Scheme 1. Two-Step Reactions of 3-Nitrochromene 1b and Phenyloxazol-5(4*H*)-one 2e



benzamidoacrylic acid **2e**^{o} (Scheme 1). The desired product **3j** as the only product was furnished in higher yield; thus, the pathway via 3-aryl-2-benzamidoacrylic acid could be affirmed.

In addition, starting materials **1b** and **2e** were stirred together, and the mixture was employed for the synthesis of **3j** as a one-pot reaction (Scheme 2); surprisingly, **3j** was obtained in 71% yield, and an unexpected product, chromeno[3,4-*b*]pyrrole **4**, was isolated in 24% yield, which was determined unambiguously by single-crystal X-ray crystallography (for the mechanistic rationalization for **4**, see the Supporting Information for details).

Scheme 2. One-Pot Reaction of 3-Nitrochromene 1b and Oxazol-5(4*H*)-one 2e



On the basis of our results and previous reports, a plausible mechanism was proposed (Scheme 3), Initially, **2** undergoes hydrolysis and ring opening under basic conditions to furnish intermediate [**A**], which then attacks C4 of 3-nitro-2*H*-chromenes **1** as a nucleophilic reagent, delivering zwitterionic [**B**], followed by oxime oxide [**C**] being formed via the resonance.[10f] Afterward, the benzoylimino salt core of [**C**] is attacked by water to yield α-hydroxyglycine [**D**]. Finally, [**D**] undergoes sequential deprotonation and dehydration to afford intermediate [**E**], which subsequently undergoes a carbon–carbon bond cleavage to yield **3**. For 3-nitrous chromene intermediate [**E**], due to the higher steric hindrance of the substituted glycine group and the stronger electronic effect, the C_{Ar}–COH bond of intermediate [**E**] would be more readily polarized, followed by consecutive deprotonation and carbon–carbon bond cleavage to furnish **3**, which can elegantly rationalize the stereospecificity of benzalation.

To demonstrate the synthetic potential of the reaction, the intramolecular oxidative coupling reaction[25] of substituted (*Z*)-

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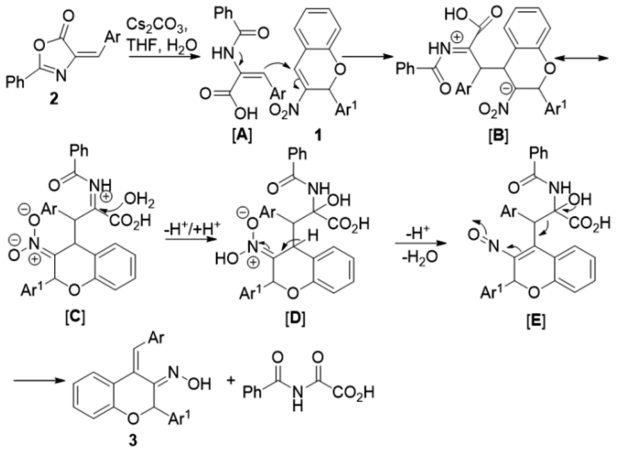
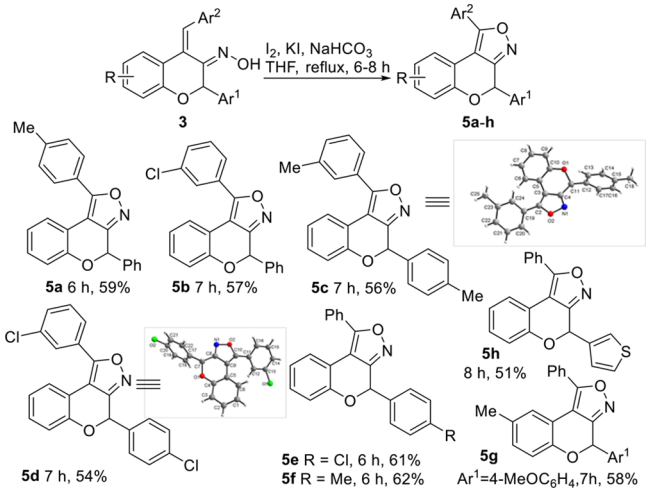
Scheme 3. Mechanistic Rationalization for the Benzalation of Substituted 3-Nitro-2*H*-chromene with 4-Benzylidene-2-phenyloxazol-5(4*H*)-ones



4-((*Z*)-benzylidene)chroman-3-one oxime under the I_2/KI/$NaHCO_3$ system was conducted (Scheme 4). The biologically important 4*H*-chromeno[3,4-*c*]isoxazoles **5a**−**h** were obtained in 51−62% yields. The X-ray crystallography data for **5c** and **5d** have been obtained, which unequivocally confirmed their structures.

Scheme 4. Synthesis of 1,4-Diphenyl-4*H*-chromeno[3,4-*c*]isoxazole[a,b]



[a]Reactions of **3** (1.0 mmol) and I_2 (504 mg, 2 mmol) were carried out in the presence of $NaHCO_3$ (168 mg, 2 mmol) and KI (332 mg, 2 mmol) in 10 mL of THF. [b]Isolated yields are shown.

In summary, we have developed the first example of a divergent domino benzalation reaction with a variety of 2-aryl-3-nitro-2*H*-chromenes and 4-benzylidene-2-phenyloxazol-5(4*H*)-ones in the presence of Cs_2CO_3 to generate substituted (*Z*)-4-((*Z*)-benzylidene)chroman-3-one oxime with moderate to excellent yields. The advantages of the current protocol include readily available starting materials, mild reaction conditions, good functional tolerance, and broad substrate scope. In addition, substituted (*Z*)-4-((*Z*)-benzylidene)chroman-3-one oximes could easily be transformed to the biologically important 4*H*-chromeno[3,4-*c*]isoxazoles with the I_2/KI/$NaHCO_3$ system. We believe the divergent domino benzalation reaction will have the potential to be applied to construct natural products and pharmaceuticals. Further studies on the detailed mechanism and synthetic applications are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00776.

Detailed experimental procedures, X-ray crystallographic data characterization of compounds **3b**, **3c**, **3u**, **4**, **5c**, and **5d**, characterization data of compounds, and copies of NMR spectra (PDF)

Accession Codes

CCDC 1870366−1870367, 1879543, 1885043, 1886515, and 1888928 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: wangcd@yzu.edu.cn.

ORCID

Cunde Wang: 0000-0001-5561-979X

Notes

The authors declare no competing financial interest.

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