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One-Pot Allylation−Intramolecular Vinylogous Michael Addition−Isomerization Cascade of *o*-Hydroxycinnamates and Congeners: Synthesis of Substituted Benzofuran Derivatives

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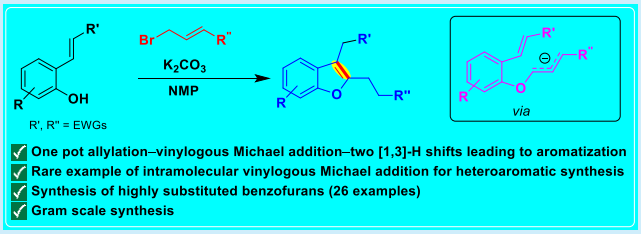
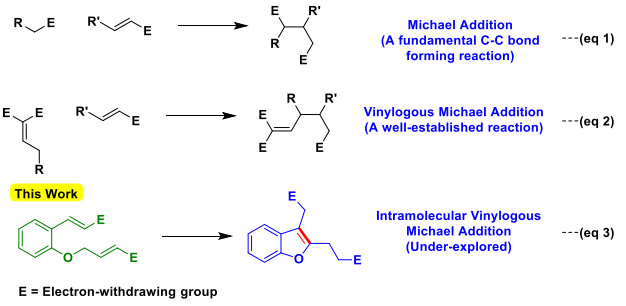
Supporting Information

ABSTRACT: A unique intramolecular vinylogous Michael addition leading to the synthesis of heterocycles has been disclosed. Base-promoted one-pot sequential *O*-allylation of *o*-hydroxy-cinnamates or -cinnamonitrile or -chalcones with γ-bromocrotonates followed by an intramolecular conjugate addition of vinylogous Michael donors resulted in the formation of highly substituted benzofuran derivatives in good to excellent yields. The intramolecular event followed by two [1,3]-H shifts leading to aromatization appears to be the key to the success of this unprecedented transformation.



The development of efficient approaches for C−heteroatom, C−C bond formations leading to the construction of heterocycles has been one of the most sought after research areas for organic chemists.[1] Michael reaction (conjugate addition) is among the most fundamental, classical C−C and C−heteroatom bond forming reactions in organic synthesis (Scheme 1, eq 1).[2] The vinylogous variant of the

Scheme 1. Michael Addition and Its Vinylogous Variants



Michael reaction has attracted considerable attention since it can provide the product with the retained C−C double bond from the vinylogous partner (Scheme 1, eq 2).[3] The olefin functionality is usually intact and can be useful for further/deliberate organic transformations. Though the intermolecular version of this reaction has been well-studied, the intramolecular vinylogous Michael addition (intra-VMA) reaction remains underexplored (Scheme 1, eq 3).[4] In many ring-forming events, the key VMA is intermolecular.[3k−o] In some cases, the ring closure of an intra-VMA to the carbo- or heterocyclic ring features a 1,6-conjugate addition of non-vinylogous donors.[4a−f] In rare cases, intra-VMA of vinylogous donors is operative.[4g,h]

Benzofurans are one of the "privileged" scaffolds in medicinal chemistry and drug discovery research programs. Several of the molecules containing a benzofuran core have shown potential biological activities, and many have become marketed drugs while few of them are on the World Health Organization's List of Essential Medicines.[5] In particular, 2,3-disubstituted benzofurans are among the important benzofuran derivatives that have exhibited excellent biological and therapeutic activities.[5] Hence, there has been significant attention from organic chemists to access these scaffolds.[5] However, direct methods to access 2,3-disubstituted benzofuran derivatives have been less explored, obviating the use of transition metals.[6] One of the traditional ways to access benzofurans is based on the century-plus-old Rap−Stoermer reaction, which is essentially a base-meditated reaction of salicylaldehydes/*o*-hydroxyphenyl ketones and α-haloketones involving an intramolecular aldol-type reaction.[7] Herein, we report the development of a base-mediated intra-VMA−isomerization cascade to access 2,3-disubstituted benzofuran derivatives.

In continuation of our research program for the development of novel methods leading to the synthesis of fused heterocycles,[8] we envisaged and considered an opportunity to develop intra-VMA to generate useful heterocyclic scaffolds. We have designed *o*-*O*-allyl cinnamate derivative **1a** as a model substrate to test the intra-VMA hypothesis. Initially, the reaction of **1a** with a base such as K_2CO_3 was performed.

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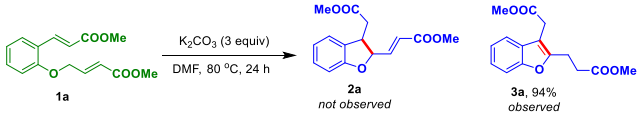
Org. Lett. XXXX, XXX, XXX−XXX

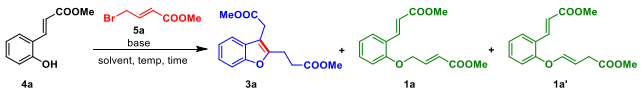
Gratifyingly, we have observed the formation of the corresponding 2,3-disubstituted benzofuran derivative **3a** in excellent yield, while the possible 2,3-dihydrobenzofuran derivative **2a** was not detected (Scheme 2). This reaction appears to go through intra-VMA. However, we did not observe a Dieckmann condensation product of **3a** under the reaction conditions.

Scheme 2. Base-Mediated Intra-VMA



We next performed a one-pot sequential allylation followed by intra-VMA using methyl *o*-hydroxycinnamate **4a** and methyl 4-bromocrotonate **5a** as precursors. Delightfully, this sequential transformation provided the corresponding 2,3-disubstituted benzofuran **3a** in 72% yield. Interestingly, in this one-pot reaction, we have also observed the formation of *O*-alkenyl derivative[9] **1a′** in 23% yield, which is an isomer (tautomer) of the allylated product **1a** (Table 1, entry 1). We then conducted

Table 1. Optimization Study[a]



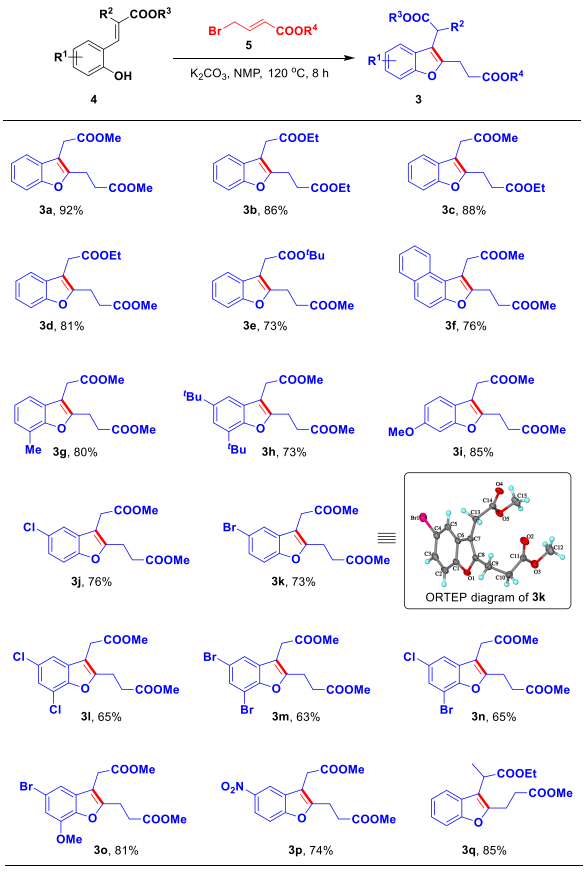
entry	base	solvent	temp (°C)	time (h)	% yield of **3a**[b]	% yield of **1a**[b]	% yield of **1a′**[b]
1	K_2CO_3	DMF	80	24	72		23
2	K_3PO_4	DMF	80	24	49		21
3	DBU	DMF	80	24	62		17
4	NaH	DMF	80	24		34	
5	K_2CO_3	NMP	80	24	78		8
6	K_2CO_3	CH_3CN	80	24		24	39
7	K_2CO_3	^{t}BuOH	80	24			67
8	K_2CO_3	NMP	100	24	84		6
9	K_2CO_3	NMP	120	8	92		5
10		NMP	120	8			

[a]Reaction conditions: **4a** (0.5 mmol), **5a** (0.75 mmol), base (1.5 mmol), solvent (3 mL). [b]Isolated yields.

an optimization study for this one-pot transformation by varying the base, solvent, and reaction conditions in order to find suitable conditions to obtain benzofuran **3a** in high yields (Table 1; also see Supporting Information for an extensive optimization survey). Use of K_3PO_4 and DBU provided moderate yields of **3a**, while the formation of **1a′** was also observed in low yields (Table 1, entries 2 and 3). However, sodium hydride gave only *O*-allyl derivative **1a** in 34% yield (Table 1, entry 4). When we used NMP as a solvent, the desired product **3a** was obtained in good yield (Table 1, entry 5). Other solvents like acetonitrile and *tert*-butyl alcohol were not effective in this transformation to provide the benzofuran **3a** (Table 1, entries 6 and 7). To our delight, an increase in the temperature provided an excellent yield of **3a** (Table 1, entries 8 and 9). As expected, this transformation failed in the absence of base (Table 1, entry 10).

We next sought to evaluate the scope of this transformation using the optimized reaction conditions (Scheme 3). Initially, *o*-hydroxycinnamates **4** and 4-bromocrotonates **5** containing

Scheme 3. Synthesis of 2,3-Disubstituted Benzofurans[a,b]



[a]Reaction conditions: **4** (0.5 mmol), **5** (0.75 mmol), K_2CO_3 (1.5 mmol), NMP (3 mL). [b]Isolated yields.

different alkyl groups on their ester parts have been subjected to the sequential allylation−intra-VMA (Scheme 3). Although the corresponding benzofuran derivatives **3a−e** were obtained in good to excellent yields, the precursors bearing methyl esters were found to provide the highest yield of the benzofuran, **3a**. We then used differently substituted methyl *o*-hydroxycinnamates **4** and methyl 4-bromocrotonate **5a** in this sequential transformation. Methyl (*E*)-3-(2-hydroxynaphthalen-1-yl)-acrylate as a substrate provided the corresponding naphthofuran **3f** in good yield. Methyl *o*-hydroxycinnamates containing electron-donating groups produced the corresponding benzofuran derivatives **3g−i** in good yields. Halogen-substituted *o*-hydroxycinnamates furnished the corresponding benzofuran derivatives **3j−n** in slightly lower yields, which may be attributed to the lower electron density on the OH group of **4** to undergo *O*-allylation. The structure of the benzofuran **3k** was further confirmed by an X-ray crystal structure in addition to the standard spectroscopic methods. *o*-Hydroxycinnamate bearing both halogen and electron-donating substituents gave the corresponding benzofuran derivative **3o** in high yields. An electron-withdrawing group such as a nitro group on *o*-hydroxycinnamate was well tolerated and afforded the corresponding benzofuran derivative **3p** in 74% yield. Introduction of an α-substituent such as a methyl group on the α,β-unsaturated ester part of **4** was also well tolerated and produced the corresponding benzofuran derivative **3q** in 85% yield.

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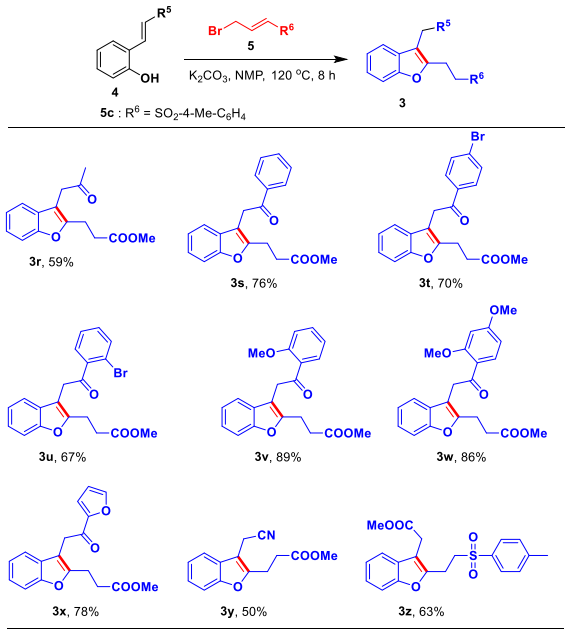
Org. Lett. XXXX, XXX, XXX−XXX

We next turned our focus to study the scope of the electron-withdrawing groups on the alkene moieties of **4** and **5** (Scheme 4). Reaction of (*E*)-4-(2-hydroxyphenyl)but-3-en-2-one and

Scheme 4. Synthesis of 2,3-Disubstituted Benzofurans[a,b]



[a]Reaction conditions: **4** (0.5 mmol), **5** (0.75 mmol), K_2CO_3 (1.5 mmol), NMP (3 mL). [b]Isolated yields.

methyl 4-bromocrotonate **5a** provided the corresponding benzofuran derivative **3r** in reasonable yield. Different salicylaldehyde-derived chalcones proved to be good substrates in the base-mediated sequential *O*-allylation−intra-VMA and provided the corresponding benzofuran derivatives **3s−x** in moderate to high yields. The reaction of *o*-hydroxycinnamonitrile and **5a** provided the corresponding benzofuran derivative **3y** in moderate yield. However, *o*-hydroxy *β*-nitrostyrene was found to be an unsuitable substrate, which decomposed under the reaction conditions. Instead of an ester group on **5**, we have also used different electron-withdrawing group such as a sulfone group on the allyl bromide partner **5**. Accordingly, the reaction of **4a** and (*E*)-((3-bromoprop-1-en-1-yl)sulfonyl)-benzene **5c** was performed to obtain the corresponding benzofuran derivative **3z** in good yield.

We have monitored the present sequential reaction at different time intervals to follow the kinetics (Figure 1). After 1 h of reaction time, the benzofuran product **3a** was isolated in 51% yield while the intermediates **1a** and **1a′** were formed in

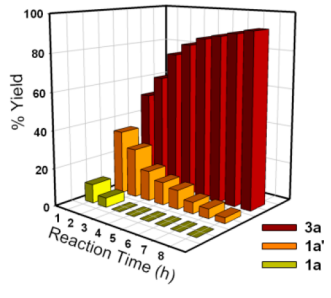
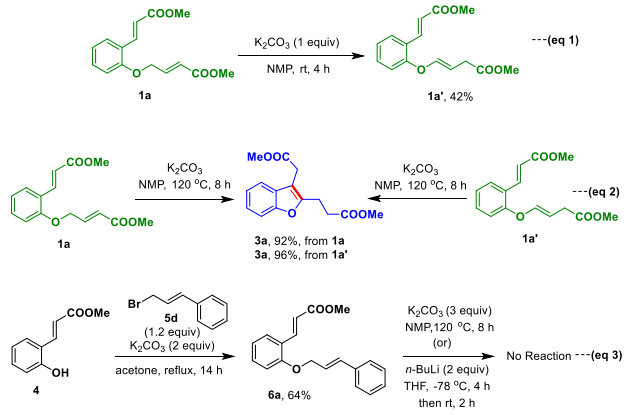


Figure 1. Kinetics of the reaction.

10% and 34% yields, respectively. After 2 h, the yield of **3a** was increased to 64%, and there was a decrease in the yields of **1a** and **1a′**. As the time increased, the intermediate **1a** was not observed and yield of intermediate **1a′** dropped significantly. At the end of 8 h, the yield of **3a** reached 92%, and only traces of intermediate **1a′** were observed. This study suggests that the formation of benzofuran **3a** occurred via the intermediates **1a** (or) **1a′**.

We have conducted some experiments to gain insights into the reaction mechanism. Since we have observed both allylated product **1a** and its isomer **1a′** in the one-pot transformation (Table 1) and also at different time intervals (Figure 1) in the reaction of *o*-hydroxycinnamate **4a** and 4-bromocrotonate **5a**, we thought **1a** and **1a′** could be in equilibrium. We have conducted a reaction of **1a** in the presence of 1 equiv of base and monitored the reaction to obtain **1a′** (Scheme 5, eq 1). It

Scheme 5. Mechanistic Studies



was observed that either **1a** or **1a′** lead to the formation of **3a** in excellent yields in the presence of base (Scheme 5, eq 2). From this result, it is reasonable to think that **1a** or **1a′** can be the intermediates in the present transformation. The use of cinnamyl bromide **5d**, instead of 4-bromocrotonate, in the one-pot reaction did not proceed to completion to provide the corresponding benzofuran derivative, while only *o*-*O*-cinnamyl product **6a** was obtained. When we subjected the *O*-cinnamyl cinnamate **6a** to the optimized reaction conditions, however, the reaction did not proceed. *o*-*O*-Cinnamyl cinnamate **6a** did not prove to be a substrate for the present transformation even with the use of a strong base like *n*-butyllithium (Scheme 5, eq 3). These results suggest that there is a requirement of an electron-withdrawing group on the allylic halide substrate to direct the key intramolecular vinylogous Michael reaction.

On the basis of the control experiments and literature reports,[4] a plausible mechanism can be proposed for the present one-pot transformation leading to 2,3-disubstituted benzofurans (Scheme 6). Initially, *O*-allylation of *o*-hydroxycinnamate **4a** with 4-bromocrotonate **5a** takes place to provide intermediate **1a**, which can be in equilibrium with its tautomer **1a′**. In the presence of base, **1a**/**1a′** would provide anionic intermediate **I** that can undergo intramolecular vinylogous Michael (conjugate) addition to provide the 2,3-dihydrobenzofuran intermediate **II**. The intermediate **II** would then undergo two consecutive [1,3]-H shifts leading to aromatization to furnish 2,3-disubstituted benzofuran product **3a**.

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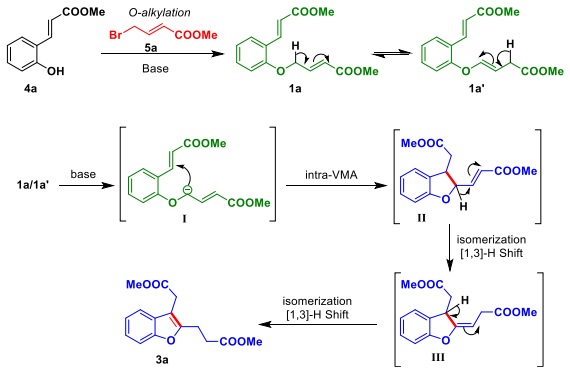
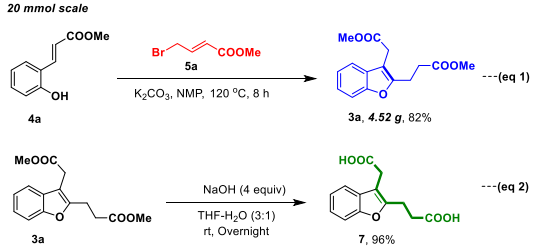
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 6. Plausible Reaction Mechanism



To demonstrate the practicality and scalability of the present one-pot transformation, a model reaction of **4a** and **5a** was performed on a multigram scale to afford **3a** in high yields (Scheme 7, eq 1). We have subjected the benzofuran derivative

Scheme 7. Gram-Scale Synthesis of 3a and Hydrolysis of Ester Groups of 3a



3a to base-mediated ester hydrolysis to obtain benzofuran bearing 1,7-dicarboxylic acid **7** in excellent yield (Scheme 7, eq 2). Seven-membered linear 1,7-dicarboxylic acids have been established as key precursors in the biosynthesis of essential compounds.[10]

In conclusion, an unprecedented intramolecular vinylogous Michael addition−isomerization has been demonstrated. The reaction of *o*-hydroxy-cinnamates/-cinnamonitrile/-chalcones and *γ*-bromocrotonates provided 2,3-disubstituted benzofuran derivatives. This one-pot transformation occurred via intermolecular *O*-allylation and intramolecular C−C bond formation followed by isomerization. It was established that *O*-allylated or *O*-vinylated intermediates can lead to the formation of the title compounds via a vinylogous Michael addition−isomerization cascade. Variously substituted benzofuran derivatives tethered with electron-withdrawing groups have been synthesized in good to excellent yields. Efforts are underway to develop and explore the applications of the underexplored intramolecular vinylogous Michael addition for the synthesis of biologically important and targeted heterocyclic and carbocyclic compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00414.

Experimental data, optimization data, characterization information, and NMR spectra (PDF)

Accession Codes

CCDC 1887439 contains 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.

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Notes

The authors declare no competing financial interest.

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