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# Fe-Catalyzed Domino Intramolecular Nucleophilic Substitution of 4-Hydroxychromen-2-one and Pyran-2-one/Ring Opening of Activated Arene: An Easy Access to 2,3-Disubstituted Furo[3,2,-*c*]coumarins and Furo[3,2,-*c*]pyran-4-ones via Nonsymmetric Triarylmethanes

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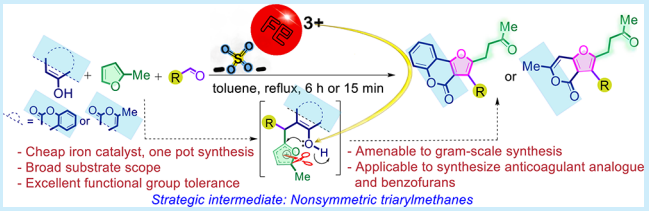
**ABSTRACT:** A one-pot synthesis of functionalized 2,3-disubstituted furo[3,2,-*c*]coumarins and furo[3,2,-*c*]pyran-4-ones under hydrated ferric sulfate catalysis was performed. It was revealed that the reaction proceeds with intramolecular cyclofunctionalization of nonsymmetric triarylmethanes via ring opening of 2-methylfuran followed by recyclization, resulting in the selective formation of desired products. The versatility of this method was demonstrated via the succinct synthesis of an anticoagulant agent analogue and 2,3-disubstituted benzofurans.




Furo[3,2,-*c*]coumarins and furo[3,2,-*c*]pyran-4-ones are privileged oxygen-containing heterocyclic structural motifs and have emerged as some of the most recognized scaffolds, existing in a wide range of natural products and pharmaceuticals (Figure 1, **1**−**5**).[1,2] These heterocyclic scaffolds have

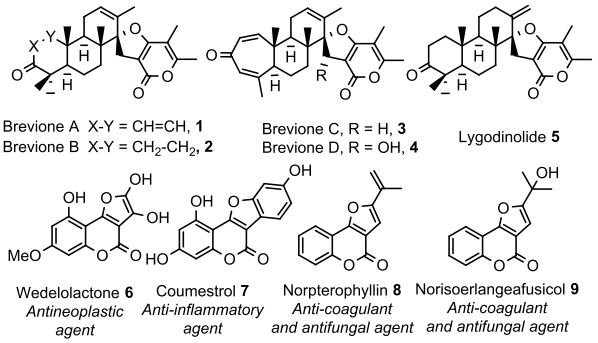



**Figure 1.** Selected natural products and drug molecules containing furo[3,2,-*c*]coumarins and furo[3,2,-*c*]pyran-4-ones scaffolds.

attracted remarkable attention of both pharmacologists and chemists due to a wide spectrum of essential biological properties (Figure 1, **6**−**9**).[3] For this reason, a fervent effort has been made toward developing an innovative synthetic method for these compounds.[4,5]

Many methods have been developed for the synthesis of substituted coumarins and pyranones (Scheme 1). Huang et al. employed a Michael−oxa-Michael−aromatization protocol of nitroallylic acetates with 1,3-dicarbonyls and activating ketones, by Feist−Benary addition−elimination to give 3,5-alkyl/aryl-2-carboxylate-4-keto/cyano-functionalized furans.[6] Raffa and co-workers developed a method that uses Pd-catalyzed cyclofunctionalization of 3-alkynyl-4-methoxycoumarins with aryl halides to obtain selective formation of 3-arylfuro[3,2,-*c*]coumarins.[7] Yoshida's group demonstrated the regiocontrolled construction of furo[3,2,-*c*]pyran-4-one derivatives by Pd-catalyzed cyclization of propargylic carbonates with 4-hydroxy-2-pyrones.[8] DABCO-promoted intermolecular cyclization between enols and nitrostyrenes was illustrated by Ghosh et al. for the regioselective synthesis of angularly fused furan derivatives.[9] Lee's group developed new types of highly functional phosphorus zwitterions via tandem three-component reactions between corresponding functional alkanes, aldehydes, and tributylphosphine to synthesize polysubstituted furo[3,2,-*c*]coumarins.[10]

Despite the significance of these approaches, most of these strategies utilize expensive catalysts and prefunctionalized substrates or require multiple steps. Highly versatile and effective synthesis of 2,3-disubstituted furo[3,2,-*c*]coumarins and furo[3,2,-*c*]pyran-4-ones from readily available starting materials remains a long-standing challenge and is quite a prerequisite. To the best of our knowledge, the functionaliza-

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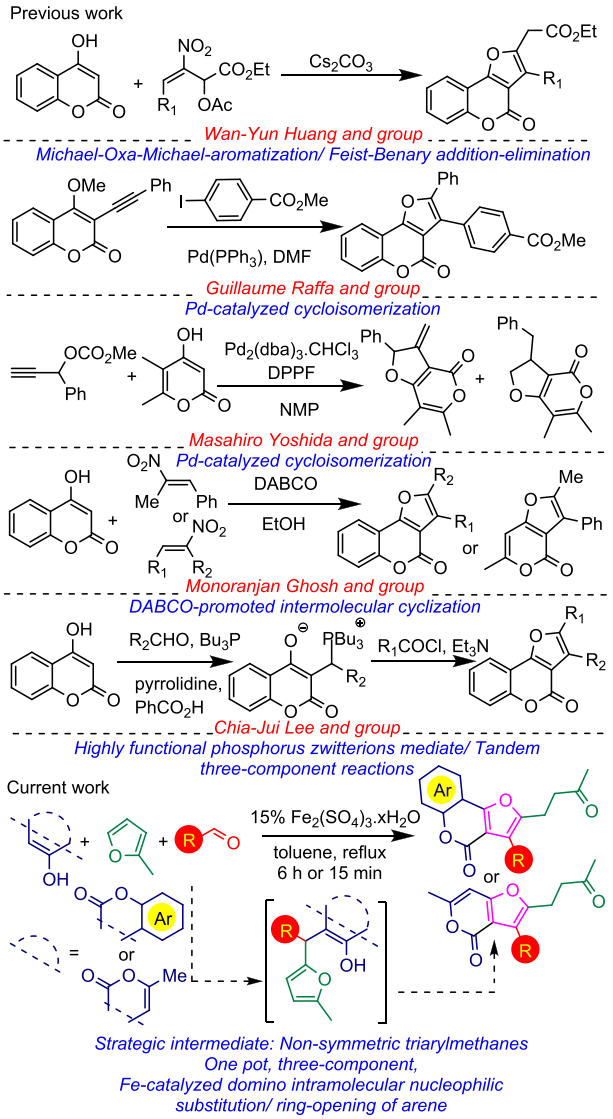
**Scheme 1. Diverse Synthetic Routes to Functionalized Furo[3,2,-*c*]coumarins and Furo[3,2,-*c*]pyran-4-ones**




tion of 2,3-disubstituted furo[3,2,-*c*]coumarins and furo[3,2,-*c*]pyran-4-ones through an iron-catalyzed domino reaction for the synthesis of annulated heterocycles is not yet reported. In this communication, we report a convenient and efficient domino synthesis of Fe-catalyzed 2,3-disubstituted furo[3,2,-*c*]coumarins and furo[3,2,-*c*]pyran-4-ones via nonsymmetric triarylmethanes as a strategic intermediate (Scheme 1).

Intrigued by the initial results, optimization of the reaction conditions was pursued by modifying parameters such as solvent, temperature, catalyst, and reaction time (Table 1). We began our investigation using commercially available 4-hydroxycoumarin **10** (1 mmol), 2-methylfuran **11** (1 mmol), and benzaldehyde **12a** (1 mmol), with $Fe_2(SO_4)_3{\cdot}xH_2O$ (5 mol %, 20 mg) in toluene at room temperature for 24 h. The desired product, 2,3-disubstituted furo[3,2,-*c*]coumarin **13a**, was isolated in 46% yield (Table 1, entry 2). Significant improvement in yield (87%) was achieved by increasing the amount of $Fe_2(SO_4)_3{\cdot}xH_2O$ to 15 mol % in toluene under reflux conditions (Table 1, entry 4).

Several Brønsted and Lewis acids were used to study the transformation. Among them, a metal triflate catalyst $Sc(OTf)_3$ provided moderate yield of **13a** (Table 1, entry 10). Aiming at the identification of a more cost-effective and readily accessible catalytic system, we tested various Fe-derived salts such as $Fe_2(SO_4)_3{\cdot}xH_2O$, $FeCl_3$, $FeBr_3$, and $Fe_2O_3$. Gratifyingly, 15 mol % of $Fe_2(SO_4)_3{\cdot}xH_2O$ in toluene at reflux delivered the desired product in the best isolated yield of 87% in 6 h (Table 1, entry 4). Changing the reaction solvent from toluene to ethyl acetate and chloroform showed a detrimental effect on the yield (Table 1, entries 16 and 18). However, interesting transformations happened when ethanol and THF were used. In ethanol, the detected product was mostly a 1:2 condensation bisfuran product **16** (Scheme 2), whereas in THF, the isolated product was a nonsymmetric triarylmethane **14a** (Table 2). Due to its high reactivity, stability, natural abundance, and cost-effectiveness, $Fe_2(SO_4)_3{\cdot}xH_2O$ was chosen as a prominent catalyst for this work instead of the closely competent but quite expensive $Sc(OTf)_3$. Finally, the optimized reaction conditions were selected as follows: benzaldehyde (1 mmol), 2-methylfuran (1 mmol), and 4-hydroxycoumarin (1 mmol) with $Fe_2(SO_4)_3{\cdot}xH_2O$ (15 mol %) in toluene at reflux for 6 h. A plausible mechanism for the above transformation has been included in the Supporting Information (Scheme S1).

Having optimized the reaction conditions, we consequently expanded the substrate scope to the synthesis of several 2,3-disubstituted furo[3,2,-*c*]coumarins **13a**−**n** (Table 2). Aryl aldehydes having electron-donating *p*-methyl **13b**, *p*-methoxy **13c**, or electron-withdrawing *p*-$NO_2$ **13d** gave the sole furo[3,2,-*c*]coumarins in good yields. Electronegative functional *o*-bromo- and *p*-fluoro-substituents were also found to be suitable for this domino reaction of **13e** and **13f**. A range of linear and branched alkyl aldehydes, such as propionaldehyde, butyraldehyde, valeraldehyde, and isobutyraldehyde, afforded the corresponding products **13g**−**j** in moderate to good yield.

The versatility of the Fe-catayzed domino reaction was further explored with a sterically hindered aromatic aldehyde, 1-napthaldehyde, and a cyclic aldehyde, cyclohexanaldehyde. Both aldehydes underwent intramolecular ring opening smoothly to afford the furo[3,2,-*c*]coumarin products **13k** and **13l**. In addition, heteroaryl rings such as thiophene and piperonal (heliotropin) were also found to be suitable for this domino reaction to afford corresponding products **13m** and **13n** in notable yield. The structure of the furo[3,2,-*c*]coumarin products was confirmed through the internally consistent spectral data and single-crystal X-ray structure determination for **13d** (see Supporting Information, Figure S1).

Under the optimized condition, reaction of **10**, **11**, and **12a**−**n** undergoes a domino reaction to give furo[3,2,-*c*]coumarins via unisolable nonsymmetric triarylmethanes. However, we were able to isolate nonsymmetric triarylmethanes using THF contrary to toluene as a solvent (Table 2). Triarylmethanes are prevalent molecular frameworks in material science, organic chemistry, and medicinal chemistry.[11] These scaffolds are often encountered in natural compounds and biologically active synthetic products. Thus, we decided to explore the synthesis of nonsymmetric triarylmethanes **14a**−**n**. Aldehydes bearing alkyl and aryl substitution, cyclic and polycyclic, and electron-rich heteroaromatics underwent 1:2 condensation reactions smoothly to give desired products **14a**−**n** in moderate to good yields.

To confirm the mechanistic pathway for the synthesis of furo[3,2,-*c*]coumarin via nonsymmetric triarylmethanes, a couple of controlled experiments were performed (Scheme


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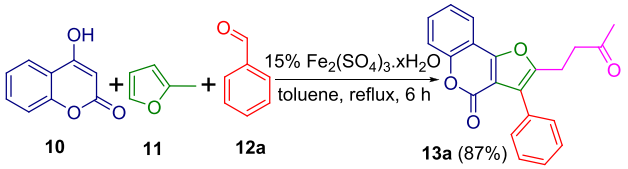
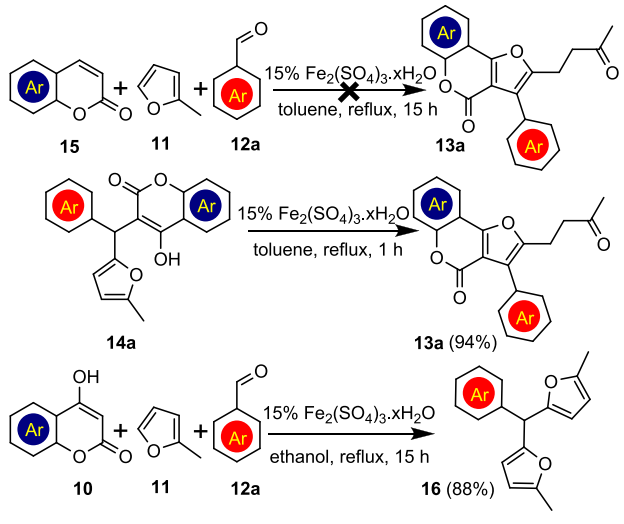
**Table 1. Optimization of Fe-Catalyzed Domino Reaction**[a]




| entry | catalyst | catalyst load[b] (mol %) | solvent | temp (°C) | time (h) | yield[c] (%) |
|---|---|---|---|---|---|---|
| 1 | $Fe_2(SO_4)_3{\cdot}xH_2O$ | 0 | PhMe | reflux | 24 | 0[d] |
| 2 | $Fe_2(SO_4)_3{\cdot}xH_2O$ | 5 | PhMe | rt | 24 | 46 |
| 3 | $Fe_2(SO_4)_3{\cdot}xH_2O$ | 10 | PhMe | reflux | 6 | 66 |
| 4 | $Fe_2(SO_4)_3{\cdot}xH_2O$ | 15 | PhMe | reflux | 6 | 87 |
| 5 | $Fe_2(SO_4)_3{\cdot}xH_2O$ | 20 | PhMe | reflux | 6 | 69 |
| 6 | $Fe_2(SO_4)_3{\cdot}xH_2O$ | 25 | PhMe | reflux | 6 | 40 |
| 7 | $Fe_2O_3$ | 15 | PhMe | reflux | 24 | 6 |
| 8 | $FeCl_3$ | 15 | PhMe | reflux | 24 | 23 |
| 9 | $FeBr_3$ | 15 | PhMe | reflux | 24 | 10 |
| 10 | $Sc(OTf)_3$ | 15 | PhMe | reflux | 24 | 67 |
| 11 | $CH_3COOH$ | 15 | PhMe | reflux | 24 | 22 |
| 12 | $CF_3COOH$ | 15 | PhMe | reflux | 24 | 25 |
| 13 | HCl | 15 | PhMe | reflux | 24 | 10 |
| 14 | $Fe_2(SO_4)_3{\cdot}xH_2O$ | 15 | EtOH | reflux | 24 | 0[d] |
| 15 | $Fe_2(SO_4)_3{\cdot}xH_2O$ | 15 | DCM | reflux | 24 | 0[d] |
| 16 | $Fe_2(SO_4)_3{\cdot}xH_2O$ | 15 | EtOAc | reflux | 24 | 35 |
| 17 | $Fe_2(SO_4)_3{\cdot}xH_2O$ | 15 | THF | reflux | 24 | 0[d] |
| 18 | $Fe_2(SO_4)_3{\cdot}xH_2O$ | 15 | $CHCl_3$ | reflux | 24 | 45 |

[a]Reaction condition: 4-hydroxycoumarin (1 mmol), 2-methylfuran (1 mmol), and benzaldehyde (1 mmol). [b]Based on electrophile. [c]Isolated yields of 2-alkyl-3-arylfuro[3,2,-*c*]coumarin **13a**. [d]No desired product was observed.

**Scheme 2. Control Experiments to Predict the Reaction Pathway for Furo[3,2,-*c*]coumarins via Nonsymmetric Triarylmethanes**




2). First, an attempt to synthesize furo[3,2,-*c*]coumarin from coumarin **15** instead of 4-hydroxycoumarin was made. As expected, the reaction did not proceed to give the desired product. Second, a domino reaction was studied using 4-hydroxy-3-((5-methylfuran-2-yl)(phenyl)methyl)-2*H* chromen-2-one **14a**, a nonsymmetric triarylmethane as a starting material. With this, we were able to obtain **13a** which gave us concrete evidence that the furo[3,2,-*c*]coumarin was formed through Fe-catalyzed domino intramolecular nucleophilic substitution of 4-hydroxychromen-2-one/ring opening of 2-methylfuran.

Under the established reaction conditions, we next examined 4-hydroxy-6-methyl-2-pyrone **17** for the intramolecular substitution/ring opening reactions with arene and substituted aldehydes to construct furo[3,2,-*c*]pyran-4-ones (Table 3). Apart from 4-hydroxy-2*H*-chromen-2-one, strikingly, an enol such as 4-hydroxy-6-methyl-2-pyrone **17** also proved to be a distinctive reactive partner in producing good yields of furo[3,2,-*c*]pyran-4-ones **19a–j** in shortened reaction time (15 min). Under the optimized condition (see Supporting Information, Table S1), the aryl aldehydes bearing electron-donating or electron-withdrawing substituents on the aromatic rings were very compatible, rendering the target products **19d,e** in satisfactory yields. Replacing the aryl aldehydes with alkyl aldehydes such as propanal and hexanal does not hamper the reaction, furnishing the desired products **19f** and **19g** in good yields. The method showed compatibility with heteroaldehydes such as piperonal, 5-methyl-2-thiophene carboxaldehyde, and 5-methylfurfurylaldehyde to afford furo-[3,2,-*c*]pyran-4-ones **19h,j**.

Next, we illustrated the utility of this approach in the synthesis of Phenprocoumon analogue. Phenprocoumon **20** is a long-acting oral anticoagulant drug, has a long elimination half-life,[12] and produces a stable and reliable hypoprothrombinemic.[13] Thus, modification of **20** focusing on the phenyl ring would be an attractive method to investigate structure–activity relationships and find more potent analogues. As shown in Scheme 3, Phenprocoumon analogue **23** can be prepared from the one-pot reaction of 4-hydroxycoumarin **10**, propionaldehyde **21** with 1,3,5-trimethoxybenzene **22**, a highly active arene through Fe-catalyzed reaction in good yield. Based on this straightforward one-pot procedure, a wide variety of bio-


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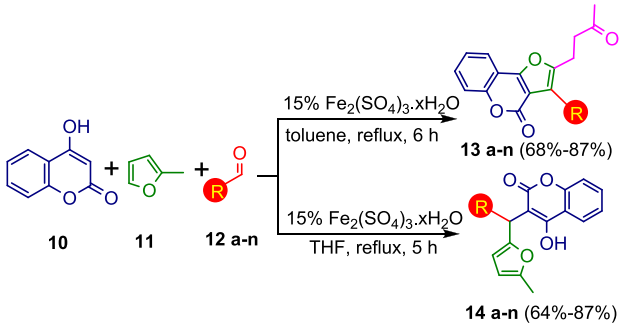
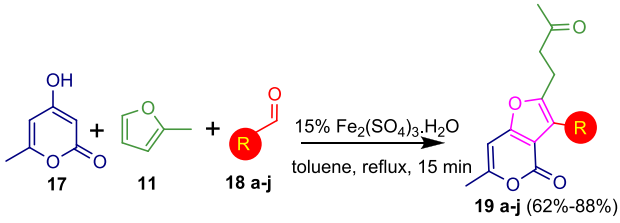
**Table 2. Synthesis of Furo[3,2,-*c*]coumarins 13a−n and Nonsymmetric Triarylmethanes 14a−n**




| entry | aldehyde | R | compound[a] | yield[b] (%) | compound[c] | yield[d] (%) |
|---|---|---|---|---|---|---|
| | | | with aryl aldehydes | | | |
| 1 | **12a** | Ph | **13a** | 87 | **14a** | 87 |
| 2 | **12b** | 4-MePh | **13b** | 78 | **14b** | 82 |
| 3 | **12c** | 4-OMePh | **13c** | 84 | **14c** | 84 |
| 4 | **12d** | 4-$NO_2$Ph | **13d** | 80 | **14d** | 80 |
| 5 | **12e** | 2-BrPh | **13e** | 76 | **14e** | 84 |
| 6 | **12f** | 4-FPh | **13f** | 77 | **14f** | 74 |
| | | | with straight and branched alkyl aldehydes | | | |
| 7 | **12g** | Et | **13g** | 83 | **14g** | 76 |
| 8 | **12h** | Pr | **13h** | 82 | **14h** | 78 |
| 9 | **12i** | Bu | **13i** | 87 | **14i** | 85 |
| 10 | **12j** | *i*-Pr | **13j** | 84 | **14j** | 81 |
| | | | with cyclic, polycyclic, and heterocyclic aldehydes | | | |
| 11 | **12k** | cyclohexyl | **13k** | 68 | **14k** | 64 |
| 12 | **12l** | naphthyl | **13l** | 79 | **14l** | 78 |
| 13 | **12m** | 5-methyl-2-thienyl | **13m** | 71 | **14m** | 77 |
| 14 | **12n** | piperonyl | **13n** | 82 | **14n** | 73 |

[a]2,3-Disubstituted furo[3,2,-*c*]coumarins. [b]Isolated yields of 2,3-disubstituted furo[3,2,-*c*]coumarins. [c]Nonsymmetric triarylmethanes. [d]Isolated yields of nonsymmetric triarylmethanes.

**Table 3. Synthesis of Furo[3,2,-*c*]pyranones 19a−j**

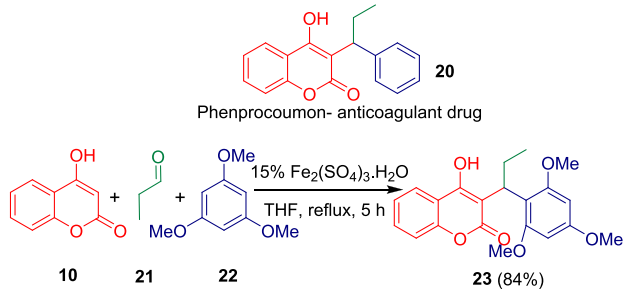



| entry | aldehyde | R | compound[a] | yield[b] (%) |
|---|---|---|---|---|
| | | with aryl aldehydes | | |
| 1 | **18a** | Ph | **19a** | 88 |
| 2 | **18b** | 4-MePh | **19b** | 85 |
| 3 | **18c** | 4-OMePh | **19c** | 83 |
| 4 | **18d** | 4-$NO_2$Ph | **19d** | 82 |
| 5 | **18e** | 4-FPh | **19e** | 85 |
| | | with straight alkyl aldehydes | | |
| 6 | **18f** | Et | **19f** | 81 |
| 7 | **18g** | pent | **19g** | 86 |
| | | with heterocyclic aldehydes | | |
| 8 | **18h** | piperonyl | **19h** | 74 |
| 9 | **18i** | 5-methyl-2-thienyl | **19i** | 62 |
| 10 | **18j** | 5-methyl-2-furanyl | **19j** | 67 |

[a]2,3-Disubstituted furo[3,2,-*c*]pyran-4-ones. [b]Isolated yields.

logically active non-symmetric triarylmethanes should be accessible.

**Scheme 3. Synthetic Application: Anticoagulant Agent Analogue 23**




To explore the more synthetic utility of this method, we demonstrated the synthesis of 2,3-disubstituted benzofurans (Table 4). Benzofurans are ubiquitous building blocks in many bioactive natural products and primary structural motifs in several pharmaceuticals, molecular electronics,[14] and drug discovery.[15] To examine the applicability of the proposed method, 2-methylfuran **11** and a variety of salicylaldehyde derivatives **24a−f** were subjected to the domino intramolecular nucleophilic substitution/ring opening reaction with 1,3,5-trimethoxybenzene **22**, an electron-rich aromatic compound, under the optimized reaction conditions (see Supporting Information, Table S2). We were able to isolate the desired product in moderate yield in toluene. A substantial gain in yield (90%) was observed in **25a** by switching the solvent from toluene to the more polar solvent ethanol.


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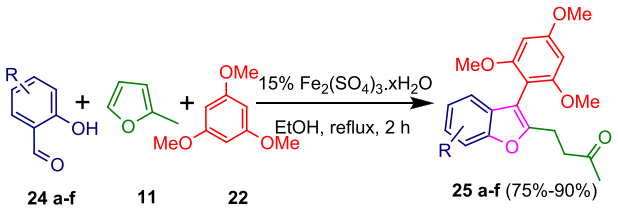
**Table 4. Synthetic Application: 2,3-Disubstituted Benzofurans 25a–j**




| entry | aldehyde | R | compound[a] | yield[b] (%) |
|---|---|---|---|---|
| 1 | **24a** | H | **25a** | 90 |
| 2 | **24b** | 5-$NO_2$ | **25b** | 81 |
| 3 | **24c** | 5-Br | **25c** | 78 |
| 4 | **24d** | 3-OMe | **25d** | 85 |
| 5 | **24e** | 4,6-di-*t*-Bu | **25e** | 75 |
| 6 | **24f** | 5-Me | **25f** | 83 |

[a]2,3-disubstituted benzofurans. [b]Isolated yields.

Generally, the reactions afforded 2,3-disubstituted benzofurans **25a–f** in good yields (75–90%) (Table 4). Based on these results, the domino transformation was well tolerated with the various functionalities. The yields of products were not significantly affected by the electron-donating *o*-OMe and *p*-$CH_3$ salicylaldehydes. A slight decrease in the yield was observed when an electron-withdrawing $-NO_2$ group was introduced. A highly hindered 3,5-di-*tert*-butyl group promoted the transformation, providing **25e** in moderate yield. The presence of the electronegative group −Br at the para position furnished 2,3-disubstituted benzofurans in good yield.

Indeed, reactions described in aforementioned scopes appeared scalable, and as a demonstration, **13a**, **14a**, **19a**, and **25a** were easily prepared on a gram scale, enabling exploration of potentially useful domino transformations (see Supporting Information, Schemes S2–S5).

In summary, we have developed a contemporary general synthesis for polyfunctional 2,3-disubstituted furo[3,2,-*c*]-coumarins and furo[3,2,-*c*]pyran-4-ones from 4-hydroxy-2*H*-chromen-2-one and 4-hydroxy-6-methyl-2*H*-pyran-2-one with 2-methylfuran, an activated arene, and substituted aldehydes under hydrated ferric sulfate catalysis. The reaction proceeds through a domino intramolecular nucleophilic substitution of 4-hydroxychromen-2-one and pyran-2-one/ring opening of activated arene steps, affording the final product. The straightforwardness, one-pot operation, and good yields marked this methodology for wider exploitation in targeting more embellished anticoagulant agent analogues and benzofurans. This finding holds potential for accessing polycyclic heteroaromatic and complex natural products based on these motifs. Further application of the current catalyst system on functionalized ketones/arenes is under investigation and will be reported in due course.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00123.

Experimental procedures, characterization of new compounds, X-ray crystallographic data of **13d**, and copies of NMR spectra (PDF)

### Accession Codes

CCDC 1961601 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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