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Divergent Domino Reactions of Prop-2-ynylsulfonium Salts: Access to Sulfur-Containing Benzo-Fused Dioxabicyclo[3.3.1]nonanes and Dihydrofuro[2,3-*c*]chromenes

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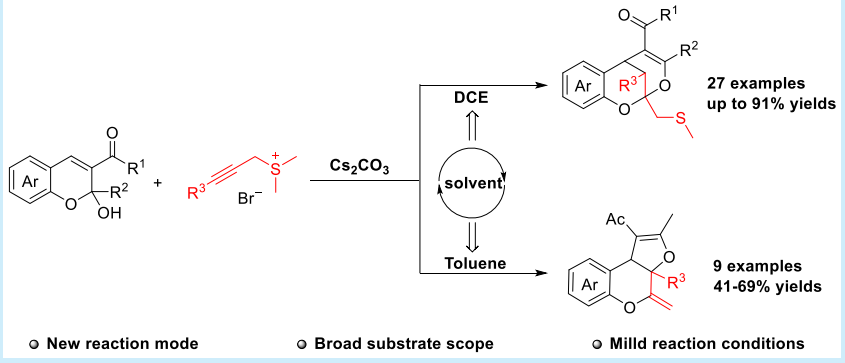

ABSTRACT: Solvent-controlled divergent domino annulation reactions between 2-hydroxy-2-methylchromene derivatives and prop-2-ynylsulfonium salts have been developed. Specifically, a sequential [4 + 2] and [4 + 2] annulation reaction occurred in 1,2-dichloroethane affording sulfur-containing benzo-fused dioxabicyclo[3.3.1]nonanes. In contrast, by changing the solvent to toluene, the reaction course switched to a [4 + 2] and [4 + 1] annulation reaction to afford dihydrofuro[2,3-*c*]chromenes. It is noteworthy that the prop-2-ynylsulfonium salt participates in the transformation with its γ-carbon atom for the first time.

Sulfur ylides, a special type of methylene-transfer reagent, are widely utilized for the construction of epoxide, aziridine, and cyclopropane architectures.[1] Along with the deepening amount of research, sulfur ylides were used to synthesize complex cyclic skeletons beyond three-membered rings.[2] Vinylsulfonium salts, as two-carbon synthons, are a class of good Michael acceptors in organic synthesis.[3] After nucleophilic attack onto the vinylsulfonium species, the transiently formed sulfonium ylide undergoes protonation or a second nucleophilic addition to the electrophilic group to generate intermediate **A**. This step is followed by elimination of the corresponding sulfide or S_N2 substitution to afford different molecules (Scheme 1A, eq 1).

Different from vinylsulfonium salts, prop-2-ynylsulfonium salts[4−6] could isomerize to allenic sulfonium salts under basic conditions and be attacked by a nucleophile at the β-carbon atom first. The obtained zwitterionic intermediate **B** and the resonance structure **B′** can undergo a similar process to access α-regioselective intermediate **C** and γ-regioselective intermediate **D**. The intermediate **D** shows analogous reactivity to vinylsulfonium salts and could be attacked by nucleophiles for the second time at the β-carbon atom (Scheme 1A, eq 2).

Compared with the well-established α-C nucleophilicity, propargylsulfonium salts' γ-C nucleophilicity has been rarely exploited. Only one example has been reported in our previous work, in which the ylide intermediate **B′** undergoes proton transfer followed by ring closure, leading to indole-fused 4*H*-benzo[*e*][1,3]oxazines bearing a thioether moiety.[5] Herein, we develop sequential annulation domino reactions for the production of highly functionalized sulfur-containing benzo-fused dioxabicyclo[3.3.1]nonane derivatives and dihydrofuro-[2,3-*c*]chromene derivatives in a solvent-controlled manner. In these reactions, the β, γ sites of propargylsulfonium salts participated in the transformation rather than α, β sites. It should be noted that intermediate **B′** undergoes intramolecular Michael addition distinguished from protonation (Scheme 1B).

The syntheses of benzo-fused dioxabicyclo[3.3.1]nonane[7] and related bioactive natural products[8] have been reported in numerous literature citations. However, to the best of our knowledge, no sulfur substituent of benzo-fused

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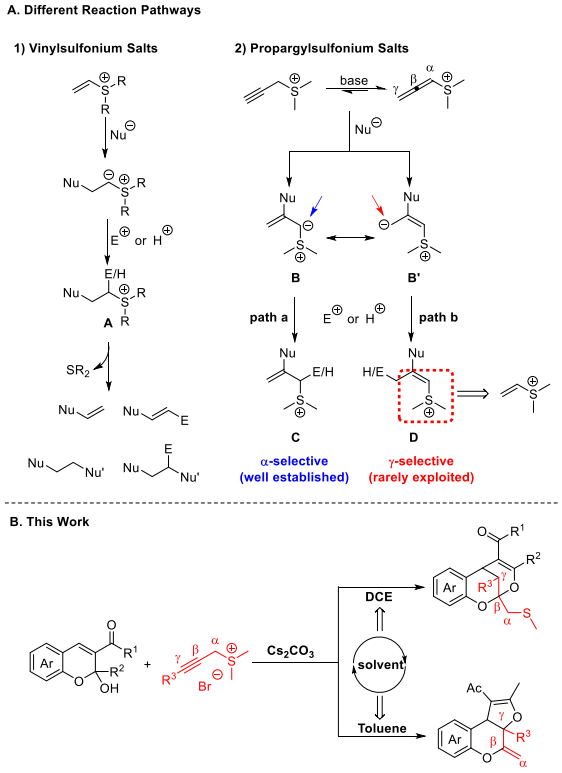
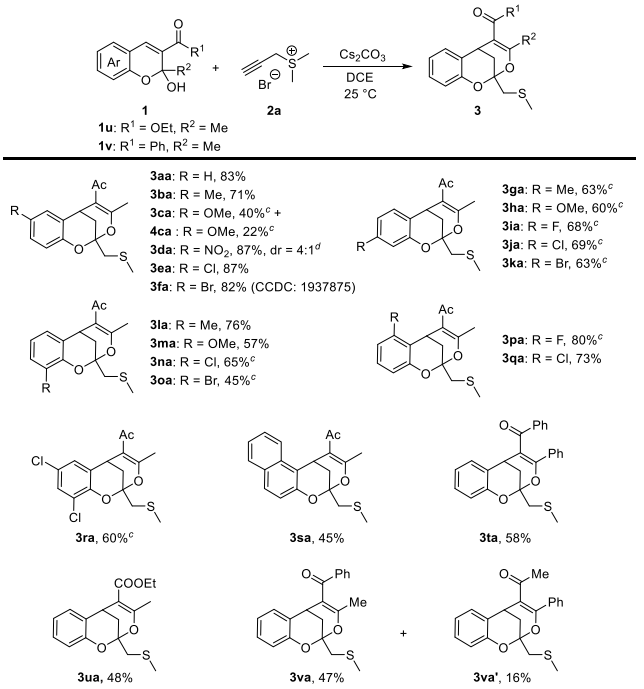
Scheme 1. (A) Different Reaction Pathways for Reactions with Vinylsulfonium Salts and Propargylsulfonium Salts; (B) This Work



Scheme 2. Substrate Scope of Sequential [4 + 2] and [4 + 2] Annulations[a,b]



[a]Reactions of **1** (0.20 mmol) and **2a** (0.40 mmol) were carried out in the presence of Cs_2CO_3 (0.40 mmol) in 1 mL of DCE at 25 °C. [b]Isolated yields are shown. [c]Reaction temperature: 50 °C. [d]Determined by ^1H NMR analysis.

dioxabicyclo[3.3.1]nonane skeleton has been reported. Organosulfur compounds have attracted great attention because of their diversified bioactivity and chemical properties.[9] On the other hand, there are few reports on the synthesis of dihydrofuro[2,3-*c*]chromene frameworks.[10] Therefore, new synthetic approaches for the efficient construction of sulfur-containing benzo-fused bridged dioxabicyclo[3.3.1]nonane and dihydrofuro[2,3-*c*]chromene are highly desirable.

We commenced our investigation by the treatment of 3-acetyl-2-hydroxy-2-methylchromene **1a** and prop-2-ynylsulfonium salt **2a** with 2.0 equiv of Cs_2CO_3 as base in CH_3CN at 25 °C (see the Supporting Information). Gratifyingly, product **3aa** and **4aa** were indeed obtained in 46% and 19% yields. A survey of commonly used solvents revealed that the reaction media exerted a significant influence on the yields. 1,2-Dichloroethane (DCE) turned out to be the best solvent, leading to **3aa** in 83% yield with trace amounts of **4aa**. Interesting, product **4aa** as the major product (41%) was obtained in toluene. Subsequently, screening of inorganic and organic base did not afford better results. After the exploration of temperatures and the ratio of base, **3aa** and **4aa** were finally attained in 83% and 46% yields, respectively.

Having established the optimal reaction conditions, the substrate scope of sequential [4 + 2] and [4 + 2] annulation reaction was first examined. As summarized in Scheme 2, the presence of a methyl group at the C5 position of the aromatic ring afforded the desired product **3ba** in a slightly lower yield. Electron-rich substrate **2c** gave a relatively poor chemoselectivity (**3ca** and **4ca**). In contrast, electron-deficient substrate with NO_2 substitution led to the highest yield of bridged product **3da**, albeit in a comparatively lower diastereoselectivity (4:1 dr). 5-Halogen-substituted substrates did not obviously affect the reaction efficiency, affording the target products **3ea**−**3fa** in 82−87% yields. The structure of **3fa** was unambiguously confirmed by single-crystal X-ray analysis (for the relative stereochemistry, see S-Figure 1). Meanwhile, the tested substrates with a substituent at another position of the aromatic ring also performed well in this process, providing the corresponding products **3ga**−**3qa** in 45−81% yields, whereas **3oa** resulted in reduced yield (45%) likely due to the large steric hindrance. Moreover, an aromatic ring with disubstituted or extended π-framework could be effective for this transformation (**3ra**−**3sa**). Replacement of the methyl group at the R^1 and R^2 positions with phenyl group led to **3ta** in somewhat lower yield (58%). The substituent of the ester group at the R^1 position was also examined, affording **3ua** in 48% yield. The observed lower yield could be attributed to other competing reactions. When R^1 is a phenyl group and R^2 is a methyl group, it can generate the desired products as a pair of regioisomers (**3va**/**3va′**).

To further demonstrate the versatility of this protocol, different propargylsulfonium salts were explored (Scheme 3). Aliphatic substituted and phenyl-substituted sulfonium salts were suitable for the reaction, producing the products **3ab**−**3ad** in excellent yields (74−91%), with low diastereoselective (0.8:1 to 2.4:1). Treatment of diethyl prop-2-ynylsulfonium bromide **2e** afforded the product **4aa** as the major product in 54% yield with **3ae** in 30% yield. When ethyl methyl prop-2-ynylsulfonium bromide **2f** was employed, the product **3ae** was obtained in 15% yield because of the low reactivity of **2f**.

Next, we attempted to examine the scope of the sequential [4 + 2] and [4 + 1] annulation reaction (Scheme 4). The chromenes **1** with electron-donating groups (−Me, −OMe) or electron-withdrawing groups (−Cl, −Br) on the phenyl ring

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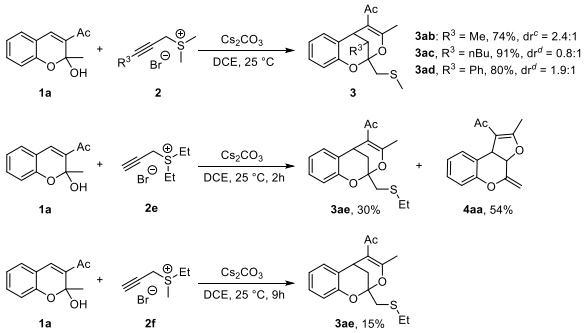
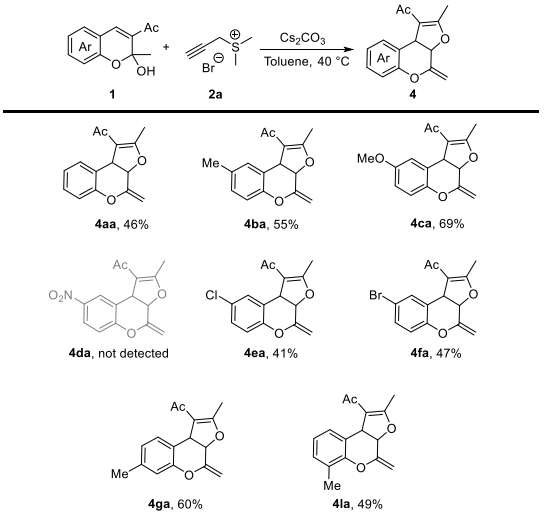
Scheme 3. More Exploration of Propargylsulfonium Salts for Synthesis of Products 3[a,b]



[a]Reactions of **1a** (0.20 mmol) and **2** (0.40 mmol) were carried out in the presence of Cs_2CO_3 (0.40 mmol) in 1 mL of DCE at 25 °C. [b]Isolated yields are shown. [c]Determined by ^1H NMR analysis. [d]The two diastereomers can be separated by column chromatography.

Scheme 4. Substrate Scope of Sequential [4 + 2] and [4 + 1] Annulations[a,b]



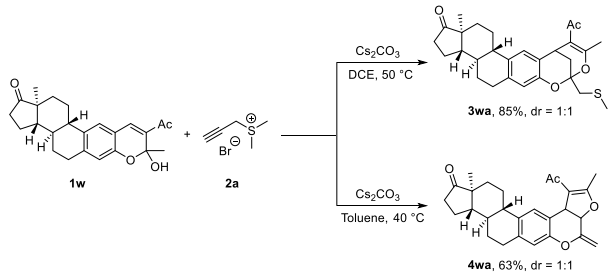
[a]Reactions of **1a** (0.20 mmol) and **2** (0.40 mmol) were carried out in the presence of Cs_2CO_3 (0.40 mmol) in 1 mL of toluene at 40 °C. [b]Isolated yields are shown.

worked smoothly, wherein the desired dihydrofuro[2,3-*c*]chromene derivatives were delivered in moderate yields ranging from 41% to 69%. A small number of byproducts were observed during these reactions. Among them, electron-rich groups at C5-position of the aromatic ring showed better reactivity than electron-poor groups (**4ba**−**4ca** vs **4ea**−**4fa**). Besides, when the 5-NO_2-substituted substrate **1d** was employed in the reaction, we got the bridged product **3da** rather than **4da**, presumably because of the electronic effect.

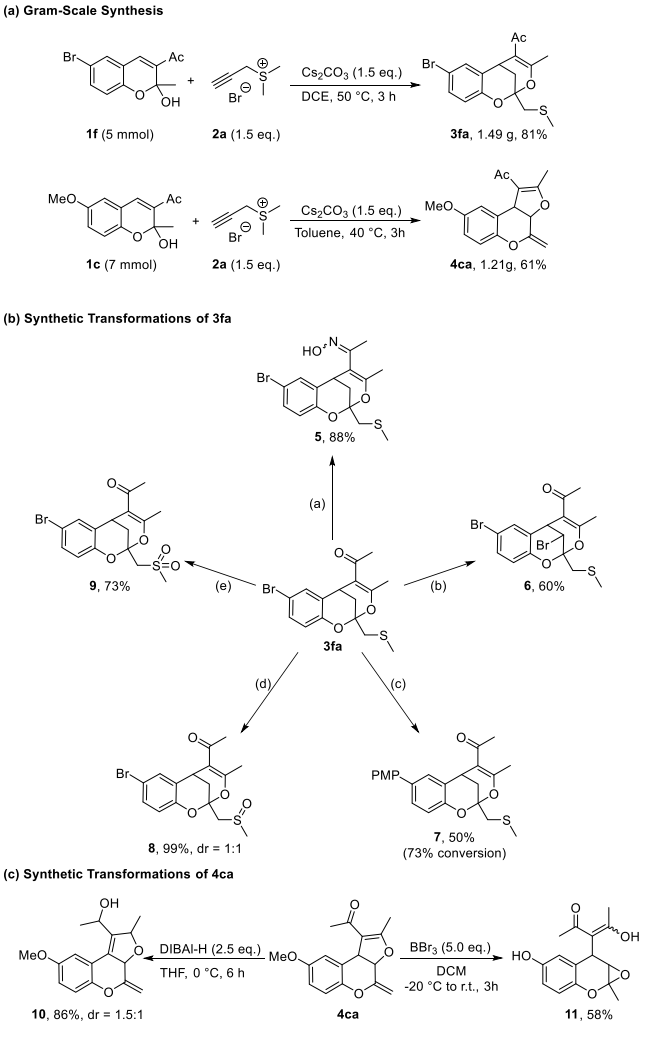
In order to verify the sequential annulation reaction process to late-stage synthetic applications, estrone-derived chromene **1w** was subjected to reaction. To our delight, the desired products **3wa** and **4wa** were obtained in 85% and 63% yields with a 1:1 diastereomeric ratio, respectively (Scheme 5).

To demonstrate the practicability of these transformations, we reduced the amount of prop-2-ynylsulfonium salt **2a** and base in gram-scale synthesis (Scheme 6a). Gratifyingly, the annulation products **3fa** and **4ca** were scaled up without compromising the efficiency. Then several derivatizations were

Scheme 5. Late-Stage Modification of Estrone-Derived Chromene



Scheme 6. Gram-Scale Synthesis and Further Transformation[a]



[a]Reaction conditions: (a) NH_2OH·HCl (3.0 equiv), NaOAc (3.0 equiv), MeOH, 50 °C, 24 h; (b) Br_2 (1.0 equiv), DCM, 0 °C, 40 min; (c) 4-methoxyphenylboronic acid (2.4 equiv), $Pd(PPh_3)$ (4 mol %), CsF (2.4 equiv), DMF, 100 °C, 24 h; (d) *m*-CPBA (1.2 equiv), DCM, rt, 5 min; (e) *m*-CPBA (4.0 equiv), DCM, rt, 10 min.

performed to show the utility of our products. The condensation, bromination, and Suzuki−Miyaura coupling of **3fa** generated the corresponding products **5**−**7**. Moreover, oxidation of sulfone group in the presence of different amounts of *m*-CPBA can readily produce compounds **8** and **9** in excellent yields (Scheme 6b). Next, the carbonyl group of **4ca**

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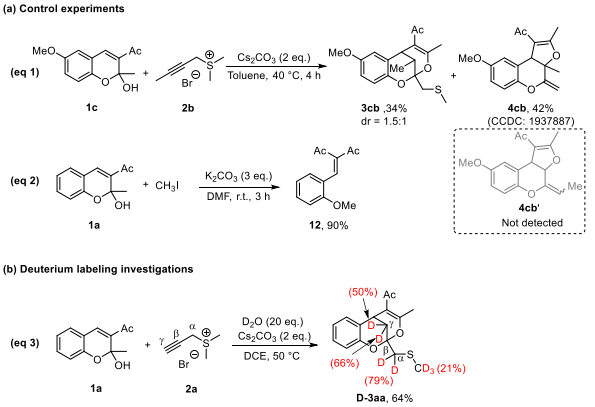
was reduced with DIBAl-H and gave the double-bond isomeric product **10** in 86% yield with 1.5:1 diastereomeric ratio. Furthermore, the product **11** could be obtained via a BBr_3 demethylation strategy in 58% yield (Scheme 6c) (see the Supporting Information for a plausible reaction mechanism).

To gain more insight into these reactions, a series of mechanistic studies were designed and conducted. Treatment of 5-OMe-substituted substrate **1c** with methyl-substituted sulfonium salt **2b** under the standard reaction conditions gave product **3cb** in 34% yield, along with **4cb** in 42% yield. We did not observe the product **4cb′**, suggesting that the propargylsulfonium salts γ site took part in the formation of chemical bonds (Scheme 7a, eq 1). The structure of **4cb** was

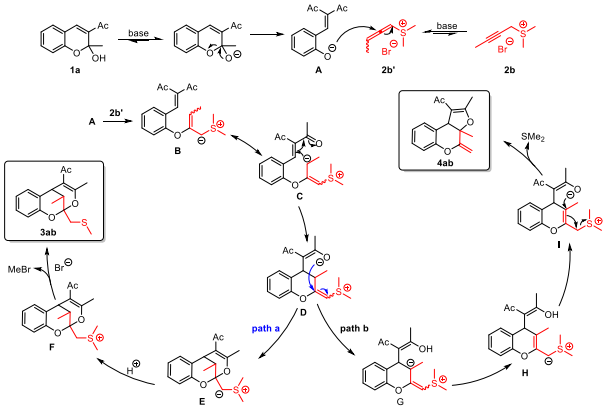
Scheme 7. Mechanistic Studies



confirmed by X-ray analysis (for the relative stereochemistry, see S-Figure 2). Reaction of substrate **1a** with CH_3I afforded the 1,3-dicarbonyl compound **12** in 90% yield after a ring-opening process (Scheme 7a, eq 2). Additionally, the deuterium-labeling experiment provided the deuterated product **D-3aa** in 64% yield, indicating that the possible carbanion intermediates were involved (Scheme 7b, eq 3).

On the basis of these experimental results and our previous reports, plausible pathways for the divergent annulation reactions of **1a** and **2b** are proposed (Scheme 8). In the presence of base, **1a** undergoes a ring-opening process to form intermediate **A** and propargylsulfonium salt **2b** facilely isomerizes to allenic sulfonium salt **2b′**. Next, nucleophilic addition of **A** to the **2b′** forms intermediate **B** and the resonance structure intermediate **C**. Subsequently, intramolecular Michael addition of **C** gives the intermediate **D**, which then proceeds through divergent pathways. For path a, the O anion attacks the β position of sulfur atom generating the intermediate **E**, which can further undergo protonation to give intermediate **F**. Finally, demethylation by attack of the bromide leads to the product **3ab**. On the other hand, path b involves continuous H-shifts to form intermediate **I** via intermediates **G** and **H**. Then, an intramolecular S_N2' reaction of intermediate **I** affords product **4ab**.[11]

Scheme 8. Plausible Reaction Mechanism



In conclusion, we have developed divergent sequential annulation reactions of 2-hydroxy-2-methylchromene derivatives and prop-2-ynylsulfonium salts to efficiently construct sulfur-containing benzo-fused bridged dioxabicyclo[3.3.1]-nonanes and dihydrofuro[2,3-*c*]chromenes. In addition, the methods can be further applied to late-stage modification of estrone-derived chromene. More importantly, we have disclosed the first example of propargylsulfonium salts γ sites participating in the formation of chemical bonds, which further broadens the application of sulfur ylides. Further investigation of the mechanism and synthetic applications to construct other biologically active compounds is ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02025.

Experimental details, characterization data for new compounds, copies of NMR spectra, and X-ray crystal structures of **3fa** and **4cb** (PDF)

Accession Codes

CCDC 1937875 and 1937887 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.

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Notes

The authors declare no competing financial interest.

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