**C–O/C–S difunctionalized benzene derivatives via multicomponent coupling of tetrynes†**

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C–O/C–S difunctionalization of fused highly substituted benzene derivatives was conducted via the multicomponent coupling reaction of tetrynes, sulfoxides, and cyclopropenones. This reaction is associated with several bond cleavage and formation reactions in one pot, and also features exquisite regioselectivity and excellent yields. Preliminary mechanistic studies reveal that the reaction possibly proceeds in a sequential [2 + 2] cycloaddition, ring-opening of the cyclopropenone, protonation and dealkylation pathway.

Carbon–heteroatom bond formation is one of the most important tools used in pharmaceutical chemistry, medicinal chemistry, and materials sciences.1 One-step synthesis of Csp–O and Csp–S bonds is an important and challenging task for chemists. Xiao and Chen disclosed the first case of arylene insertion into the S=O bond of sulfoxide for the direct synthesis of 1,2-O,S-disubstituted arenes.2 Wang’s group developed a synthesis technique for ortho-aryloxydiaryl sulfoxides in the absence of an external electrophile.3 Li and co-workers reported tandem arylene S==O bond insertion/C–H functionalization, featuring arene 1,2,3-trisubstitution from a relatively simple aryl allyl sulfoxide.4 Peng and co-workers synthesized o-aryloxytriaryl sulfonium salts instead of thioethers via arene insertion into diaryl sulfoxides.5 Studer and his group designed a new protocol for the direct synthesis of O-arylsulfenyl aryl vinyl ethers by using arylene and aryl vinyl sulfoxides via arene insertion into the S–O σ-bond and concomitant stereospecific S–O vinyl migration.6 Gogoi’s group designed an interesting three-component reaction for 2-[(o-methylthio)aryl]oxy] substituted dialky maleate derivatives by using arylene, dimethyl sulfoxide and activated alkynes.7 Many o-oxygen substituted aryl sulfides have been synthesized via arene insertion into the S=O bond of sulfoxides. Two or more substituted o-alkylthio aryl esters are the important structural units in biologically active molecules and medicines, such as cox-2 inhibitors,8 boldine,9 and antitumor metabolites10 (Scheme 1a). Therefore, an efficient strategy is desirable to be developed for the C–O/C–S difunctionalization of fused highly substituted benzene derivatives.

Demonstrated by Hoye’s group in 2012,11 the hexahydrodiels-Alder (HDDA) reaction, a new strategy to produce benzyne intermediates, can assemble three consecutive functional groups on a benzene ring in a “one-pot” process, and is compatible with various reagents and functional groups.12 These benzyne intermediates are suitable for versatile transformations, thereby greatly expanding the fields of arylene chemistry and drug synthesis.13 As part of our ongoing research on the efficient construction of polysubstituted arenes via HDDA-derived benzene chemistry,14 we envisioned that different tetryne substrates can be used as HDDA-derived benzyne precursors to form the C–O/C–S difunctionalized and concomitant o-alkylthio aryl ester core structure benzene derivatives by inserting benzyne into the S==O bond and opening the ring of cyclopropenone (Scheme 1b). To the best of our knowledge, this hypothesis has not been verified by using benzyne intermediates. Thus, exploring the resultant intermediate could provide a novel platform to incorporate sulfide and ester groups into valuable aromatic compounds.

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**Scheme 1**  Bioactivity with the ortho-alkylthio aryl ester core structure and our work.
A multicomponent coupling reaction of HDDA-derived benzynes, cyclopropenones, and sulfoxides was performed to produce various C–O/C–S difunctionalized benzene derivatives in good to excellent yields. The process of introducing sulfide and ester moieties into an aromatic ring can be achieved in the absence of catalysts, bases, or oxidants and therefore could provide a broad range of construction methods for fully functionalized arenes. Synthesis chemists can achieve the rapid synthesis of drug molecules and other high-value compounds.

**Results and discussion**

Inspired by the preliminary result, tetrayne 1a was used as a HDDA-derived benzyne precursor and 2,3-diphenylcycloprop-2-enone 2a in DMSO at 90 °C to optimize the reaction conditions. Screening results revealed that the optimal yield could be obtained at 120 °C in DMSO at the 1 : 1.1 ratio of tetrayne to cyclopropenone in an 8 h reaction. It was verified that DMSO played a crucial role in this multicomponent coupling reaction. The optimal conditions were as follows: 1.0 equiv. of tetraynes reacted with 1.1 equiv. of cyclopropenones in DMSO at 120 °C for 8 h.

The scope of tetrayne substrates was investigated under the optimized conditions. As depicted in Table 1, various products (4a–4q) were readily isolated with good to excellent yields (ranging from 69% to 89%) from the reactions of tetraynes 1 with 2,3-diphenylcycloprop-2-enone 2a in DMSO. The effect of different tetraynes on the product yield was also examined. When tolerated, tetrayne substrates bearing different esters (OMe, OEt, and OiPr) gradually increased in yields (4a (82%), 4d (85%), and 4j (89%)). By contrast, the substituent groups in the aryl rings of tetraynes bearing electron-donating groups, including p-Me, m-Me, and p-Et (4k, 4l, and 4m), exhibited higher yields than the electron-withdrawing groups, such as p-F and p-Cl (4n and 4o) possibly because the electron-withdrawing groups decreased the reactivity. Compound 4j had the highest isolated yield (89%) among the examined products.

Furthermore, 2,3-di-p-tolylcycloprop-2-enone and 2,3-bis(4-fluorophenyl)cycloprop-2-enone can participate in the reaction to afford good yields (4p (85%) and 4q (74%)). The structures of 4a and 4m were confirmed through X-ray diffraction.15

As shown in Table 2, 68%–82% yields were obtained from the reactions of tetraynes 1 with 2,3-diphenylcycloprop-2-enone 2a in n-butyl sulfoxide. The carboxylates of the tetraynes with OPr, OEt and OMe provided minimal impact, providing 4r (79%), 4s (80%), and 4w (82%), respectively. The yields of benzene ring-containing tetraynes with alkyl groups as electron donors were slightly higher than those of tetraynes directly bearing halogen atoms as electron-withdrawing groups. For example, the yields of 4t and 4u were 74% and 76%, respectively, and that of 4v was only 68%. These results revealed the potential of the multicomponent coupling reaction of current HDDA-derived benzynes with cyclopropenones and sulfoxides for the synthesis of C–O/C–S difunctionalized benzene derivatives.

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**Table 1** Preparation of fully functionalized o-(methylthio)phenyl acrylates

| Tetrayne  | Cyclopropenone | Sulfoxide | Conditions | Yield (%) |
|---------|---------------|----------|------------|----------|
| 1a      | 2a            | H2O      | 1 : 1.1, DMSO, 120 °C, 8 h | 89%      |
| 1b      | 2b            | H2O      | 1 : 1.1, DMSO, 120 °C, 8 h | 82%      |
| 1c      | 2c            | H2O      | 1 : 1.1, DMSO, 120 °C, 8 h | 79%      |
| 1d      | 2d            | H2O      | 1 : 1.1, DMSO, 120 °C, 8 h | 85%      |

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*a Conditions: tetraynes 1 (0.5 mmol), cyclopropenones 2 (1.1 equiv), H2O (1.0 equiv), DMSO (2 mL), stirred at 120 °C for 8 h. *b Yield of the isolated product after flash column chromatography.*
Labeling and control experiments were performed to gain insight into the reaction mechanism (Scheme 2). DMSO-$d_6$ was used instead of DMSO for the synthesis of 4d under the optimized reaction conditions (Scheme 2, eqn (1)). The deuterium-labeled product d-4d was isolated in 83% yield. $^1$H NMR analysis confirmed the complete deuterium incorporation at the “CH₃” moiety, indicating that DMSO serves as the “SMe” source. Another independent experiment was performed in which D₂O was used instead of H₂O with 1d, and 2a in DMSO-$d_6$ to further investigate the reaction mechanism (Scheme 2, eqn (2)). The expected product d-4d′ was formed in 84% yield with complete deuterium incorporation at the vinylic position. These results suggest that our reaction proceeded via the [2 + 2] cycloaddition of a HDDA-derived benzyne with DMSO solvent, and that H₂O served as the proton source (details are in the Experimental section and ESI†).

A possible mechanism underlying the formation of C–O/C–S difunctionalized benzene derivatives was proposed on the basis of the above results and previous literature²,⁷,¹⁶ (Scheme 3). First, the HDDA-derived benzyne intermediate A underwent [2 + 2] cycloaddition insertion into the S–O bond of dimethyl sulfoxide to form a four-membered ring intermediate B. Owing to the ring strain, this intermediate exhibited ring opening to afford an o-quinone intermediate C. Zwitterion D, a resonance form of C, also experienced nucleophilic attack and ring opening to activate the cyclopropenone 2a. This phenomenon leads to the formation of zwitterion E, which was further protonated in the presence of residual water to form intermediate F. Finally, the resultant hydroxide anion from H₂O abstracted the methyl cation of intermediate F to generate the product d-4d′.

Conclusions

In conclusion, we have developed a multicomponent coupling reaction of HDDA-derived benzynes, cyclopropenones and sulfoxides for the direct synthesis of C–O/C–S difunctionalized benzene derivatives. This reaction strategy has been accomplished through several bond cleavage and formation reactions in a one-pot procedure. Compared with previous work, this strategy introduces sulfide and ester moieties at the adjacent positions of an arene ring with the C–O and C–S bonds and derivatives thereof. The reaction does not require a transition
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metal catalyst but exhibits excellent regioselectivity and produces all types of highly substituted fused benzene derivatives under mild conditions with good to excellent yields. Further work on the applications and scope extension of this protocol is on-going in our laboratory.

Conflicts of interest

There are no conflicts to declare.

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CCDC 1571270 (4a) and 1571269 (4m) contain the supplementary crystallographic data for this paper.†

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