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One-pot synthesis of aryl biaryl sulfones

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ABSTRACT

Synthesis of aryl biaryl sulfones **3** with good yields is described. The one-pot efficient synthetic route is carried by the NaH-mediated tandem [C3+C3] annulations of cinnamaldehydes **1** and propargylic sulfones **2** under the boiling THF conditions.

Introduction

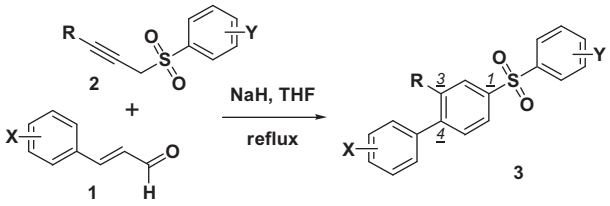
Construction of diaryl sulfones with different functional groups has drawn much attention since they constitute useful building blocks in organic and medicinal chemistry.[1] Their biological activities and chemical properties have emerged as key targets since the sulfonyl substituent has been used as the main constituent of many drugs, such as nonsteroidal anti-inflammatory drugs (DuP-697, SC-58125, MK 966),[2] selective COX-2 inhibitors (Vioxx),[3] useful prostaglandin D_2 antagonist (MK-0524),[4] and other potential pharmaceutical molecules.[5] There are a number of processes available to generate the structural skeleton of diaryl sulfones,[6–10] but they are generally synthesized by the oxidation of the resulting aryl sulfides,[6a] the electrophilic aromatic substitution of arenes with arenesulfonic acids in the presence of strong acids[7] or with arenesulfonyl halides,[8] the reaction of carbon electrophiles with sulfinate salts,[9] and the reaction of organometallic compounds with sulfinate or sulfonate ester.[10]

Although a number of diaryl sulfones and their derivatives with this specific substitution pattern have been developed by almost all multi-step reactions, new methods for their novel and efficient preparation are needed. In continuation of our previous investigations on one-pot synthesis of monocyclic cyclohexanes,[11a] tricyclic benzo[*g*]indazoles and tetrahydrocyclobuta[*a*]naphthalenes,[11b,c] and polycyclic azahomoisotwistanes and tetrahydrobenzo[*j*]fluoranthen-12-ones,[11d,e] a transition-metal free and one-pot expeditious cascade methodology[12,13] for establishing the framework of aryl biaryl sulfones **3** was developed via the NaH-mediated treatment of commercially available cinnamaldehydes **1** with substituted propargylic sulfones **2** under the boiling THF conditions.

Results and discussion

As shown in Scheme 1, aryl biaryl sulfones **3** can be prepared via NaH-mediated one-pot annulation of cinnamaldehydes **1** with propargylic sulfones **2** in good yields. Skeleton **2** is synthesized using nucleophilic substitution of propargylic bromides with sulfinic sodium salts with 45–85% yields. For investigating one-pot reaction conditions, we found that treatment of model compound **1a** (X = H) with compound **2a** (Y = R = Me) provided compound **3a** as a sole isomer in a 75% yield in the presence of NaH (3.0 equiv) in boiling THF, which was better than $NaNH_2$ (70%) or DBU (68%). This is an efficient synthetic route to achieve the structural skeleton of aryl biaryl sulfones (sulfonyl biaryls), and its sulfonyl group can also be introduced with a specific site-selectivity during the annulation procedure.

With the result in hand, one-pot preparation of substituted skeleton **3** was further examined. By changing X, Y, and R groups



Scheme 1. The synthetic route of aryl biaryl sulfones **3**.

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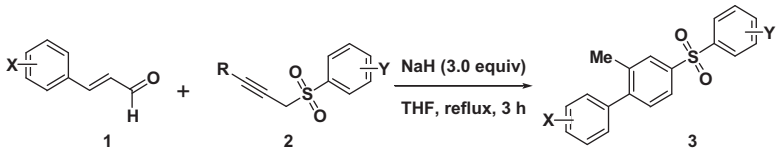
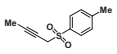
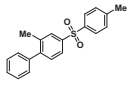
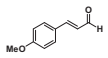
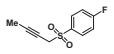
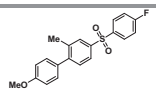
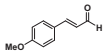
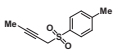
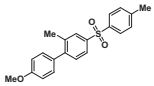
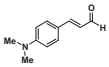
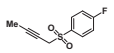
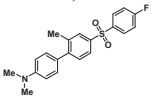
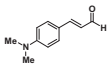
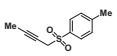
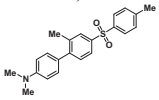
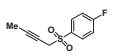
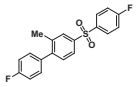
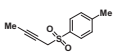
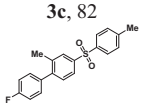
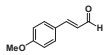
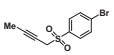
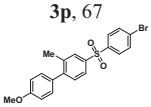
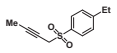
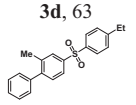
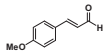
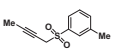
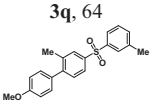
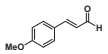
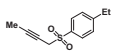
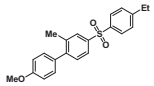
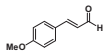
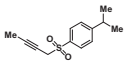
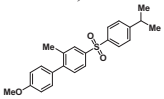
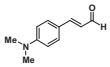
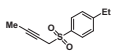
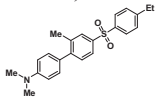
Table 1
Synthesis of aryl biaryl sulfones **3**[a]



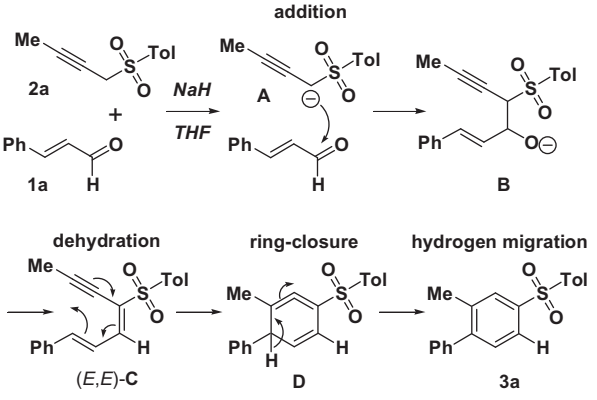
Entry	cinnamaldehydes **1**	sulfones **2**	product **3**, yield (%)	Entry	cinnamaldehydes **1**	sulfones **2**	product **3**, yield (%)
1	 **1a**	 **2a**	 **3a**, 75	14	 **1b**	 **2d**	 **3n**, 85
2	 **1b**	 **2a**	 **3b**, 78	15	 **1c**	 **2d**	 **3o**, 74
3	 **1c**	 **2a**	 **3c**, 82	16	 **1d**	 **2d**	 **3p**, 67
4	 **1d**	 **2a**	 **3d**, 63	17	 **1b**	 **2e**	 **3q**, 64
5	 **1a**	 **2b**	 **3e**, 74	18	 **1b**	 **2f**	 **3r**, 72
6	 **1b**	 **2b**	 **3f**, 75	19	 **1b**	 **2g**	 **3s**, 75
7	 **1c**	 **2b**	 **3g**, 82	20	**1b**	**2h**	**3t**, 76
8	**1d**	**2b**	**3h**, 86	21	**1b**	**2i**	**3u**, 81
9	**1a**	**2c**	**3i**, 80	22	**1e**	**2a**	**3v**, --[b]
10	**1b**	**2c**	**3j**, 74	23	**1a**	**2j**	**3w** / 82
11	**1c**	**2c**	**3k**, 78	24	**1b**	**2j**	**3x** / 80
12	**1d**	**2c**	**3l**, 76	25	**1c**	**2j**	**3y** / 76
13	**1a**	**2d**	**3m**, 82	26	**1d**	**2j**	**3z** / 76

[a] For the best one-pot reaction conditions: (i) substituted cinnamaldehydes **1** (1.0 mmol), propargylic sulfones **2** (1.0 mmol), NaH (60% in oil, 120 mg, 3.0 mmol), THF (15 mL), reflux, 3 h.
[b] Unknown mixture was obtained.

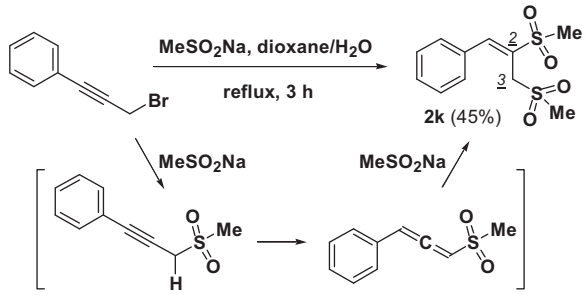
in the aryl substituent of skeletons **1** and **2**, the diversified aryl biaryl sulfones (3-alky-4-aryl-1-arylsulfonyl benzenes) **3a**–**z** were isolated in good yields by one-pot domino methodology with the expected compound **3v**; they are summarized in Table 1.[14] The *o*-nitrophenyl substituent of compound **1e** should inhibit the formation of compound **3v**. The skeletons **3** were confirmed through spectral analysis, including ^{1}H and ^{13}C NMR and HRMS spectra. The structures of compounds **3b**, **3j**, **3l**, and **3w** were determined by single-crystal X-ray crystallography.[15]

Compared with the isolated yields of products **3**, it was found that there was no obvious interference from different kinds of substituents (e.g., electron-withdrawing oxygen-containing groups; electron-donating fluoro-containing groups) in the product yields using the one-pot domino [C3+C3] reaction route. This is a novel, high-yield, and one-pot cascade route to the framework of functionalized sulfonyl biphenyls **3**. As shown in Scheme 2, a plausible explanation for preparing compound **3a** should be that intermediate **A** of sodium α-sulfonyl carbanion was first generated via a NaH-mediated deprotonation of compound **2a** in refluxing THF. Under the thermodynamic condition, intermediate **C**, with a (*E*,*E*)-conjugated configuration, was afforded from 1,2-addition of intermediate **A** followed by sequential dehydration of intermediate **B**. If the dehydration occurred from antiperiplanar orientation between hydrogen group and hydroxyl group, the ratio of (*E*,*E*) and (*E*,*Z*)-isomers would be determined by threo/erythro intermediate of β-hydroxyl sulfone. Under our one-pot condition, no isolation of (*Z*,*E*)-isomer was observed. It should be easy to form due to a stronger repulsion with steric hindrance than intermediate **C** had. According to Ogura reports,[6b] the similar isomer with (*E*)-orientation had been formed as the sole product via the *n*-BuLi-mediated dehydration of α-sulfonyl carbanion and cinnamaldehyde. Therefore, we believed that the dehydration should occur from the planar sp^2-like sulfonyl carbanion. Next, the formation of compound **3a** was observed via the stepwise ring-closure of intermediate **C** followed by the sequential hydrogen migration of intermediate **D** (an aromatization process).

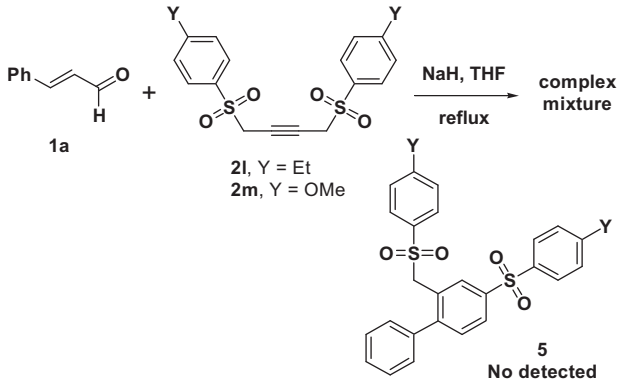
To further evaluate the synthetic scope of skeleton **2**, the terminal alkyl group (R = Me or Et) was changed to phenyl group (R = Ph) and the arylsulfonyl group (Ar) was changed to methylsulfonyl group (Me), as shown in Scheme 3. Especially, treatment of 1-bromo-3-phenyl-2-propyne with methylsulfinic sodium salt ($MeSO_2Na$) afforded compound **2k** in 45% yield. This is a facile route for synthesizing 2,3-bis-sulfonylpropenes.[16] From the experimental results, the reaction pathway included a double nucleophilic addition and the formation of sulfonyl allene intermediate. The structure of compound **2k** was determined by single-crystal X-ray crystallography.[15] For the shown yields in Table 1, different aryl or aliphatic functionalities of these substrates provided the skeleton of biphenyl with good yields and excellent regioselectivity.



Scheme 2. A possible mechanism to compound **3a**.



Scheme 3. Synthesis of compound **2k**.



Scheme 4. Reaction of compound **2l** or **2m** with compound **1a**.

To explore other biphenyls with sulfonyl groups, compounds **2l** and **2m** with two sulfonyl groups and one alkyne motif were further examined to establish the skeleton of bis-sulfonyl biphenyls **5**. When the methyl group of 2-butynyl arylsulfone was changed to methylsulfonyl substituent, one-pot reaction of compound **2l** or **2m** with compound **1a** afforded a complex mixture under the above mentioned conditions (Scheme 4).

Conclusion

In summary, we have successfully presented a synthetic route for the synthesis of sulfonyl biphenyls **3** via NaH-mediated domino annulations of cinnamaldehydes **1** with propargylic sulfones **2** in refluxing THF. The structures of key products were confirmed by X-ray crystal analysis. The one-pot transition metal-free synthetic approach begins with simple starting materials and reagents, and provides a potential methodology for the synthetic research and biological activities of sulfonyl biphenyls. Further studies regarding one-pot cascade synthesis of multi-functionalized carbocycles will be conducted and published in due course.

Acknowledgment

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Supplementary data

Supplementary data (experimental procedures, characterization data and scanned photocopies of ^{1}H and ^{13}C NMR of skeletons **2**–**3**, and crystallographic data of compounds **3b**, **3j**, **3l** and **3w**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.10.067.

References and notes

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14. *A representative synthetic procedure of skeleton* ***3*** *is as follows:* Sodium hydride (NaH, 60% in oil, 120 mg, 3.0 mmol) was added to a solution of propargylic sulfones **2** (1.0 mmol) in THF (8 mL). A solution of cinnamaldehydes **1** (1.0 mmol) in the THF (7 mL) was added to the reaction mixture at rt. The reaction mixture was stirred at reflux for 3 h. The reaction mixture was cooled to rt. Water (1 mL) was added to the reaction mixture at 0 °C. The solvent was concentrated under reduced pressure. The residue was diluted with water (10 mL) and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product. Purification on silica gel (hexanes/EtOAc = 10/1–6/1) afforded skeleton **3**. For **3j**: Yield = 74% (272 mg); mp = 162–163 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++1) calcd for $C_{21}H_{21}O_4S$ 369.1161, found 369.1165; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, J = 9.2 Hz, 2H), 7.79 (d, J = 1.6 Hz, 1H), 7.74 (dd, J = 1.6, 8.0 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.19 (d, J = 8.8 Hz, 2H), 6.98 (d, J = 9.2 Hz, 2H), 6.95 (d, J = 8.8 Hz, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.29, 159.16, 146.37, 140.45, 137.04, 133.45, 132.44, 130.67, 129.98 (2×), 129.84 (2×), 128.90, 124.69, 114.48 (2×), 113.75 (2×), 55.62, 55.30, 20.66. Single-crystal X-ray diagram: crystal of **3j** was grown by slow diffusion of EtOAc into a solution of **3j** in CH_2Cl_2 to yield colorless prisms. The compound crystallizes in the triclinic crystal system, space group P-1 , a = 8.2608(9) Å, b = 10.2952(12) Å, c = 11.2990(13) Å, V = 900.77(18) Å^3, Z = 2, d_{calcd} = 1.358 g/cm^3, F(000) = 388, 2θ range 1.90–26.39°, R indices (all data) $R1$ = 0.0650, $wR2$ = 0.1735. For **3l**: Yield = 76% (271 mg); mp = 133–135 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++1) calcd for $C_{20}H_{18}FO_3S$ 357.0961, found 357.0968; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, J = 8.8 Hz, 2H), 7.80 (d, J = 2.0 Hz, 1H), 7.72 (dd, J = 2.0, 8.0 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.24–7.19 (m, 2H), 7.14–7.09 (m, 2H), 6.99 (d, J = 8.8 Hz, 2H), 3.85 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.35 (d, J = 245.6 Hz), 163.37, 145.61, 141.09, 137.05, 136.07, 133.28, 130.62, 130.43 (d, J = 7.6 Hz, 2×), 129.89 (2×), 128.94, 124.76, 115.35 (d, J = 21.2 Hz, 2×), 114.52 (2×), 55.63, 20.53. Single-crystal X-ray diagram: crystal of **3l** was grown by slow diffusion of EtOAc into a solution of **3l** in CH_2Cl_2 to yield colorless prisms. The compound crystallizes in the triclinic crystal system, space group P-1, a = 7.6155(3) Å, b = 10.3670(18) Å, c = 11.226(2) Å, V = 835.7(3) Å^3, Z = 2, d_{calcd} = 1.416 g/cm^3, F(000) = 372, 2θ range 1.90–26.56°, R indices (all data) $R1$ = 0.0395, $wR2$ = 0.0838.
15. CCDC 965537 (**2k**), 936536 (**3b**), 947226 (**3j**), 948270 (**3l**) and 965538 (**3w**) contain the supplementary crystallographic data for this paper. This data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).
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