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Rapid Communication

A new and simple synthetic approach to functionalized sulphone derivatives by the Suzuki–Miyaura cross-coupling reaction†

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Synthesis of various highly functionalized sulphone derivatives are reported via the *bis* Suzuki–Miyaura (SM) cross-coupling reaction as a key step. In this regard, the dibromo sulphone **8**, prepared from the corresponding sultine derivative **7** by thermal rearrangement has been used as a key building block to prepare various highly functionalized aromatic sulphone derivatives.

Keywords: Sulphones, Suzuki-Miyaura reaction, cross-coupling, rongalite, sultine

IPC: Int.Cl.[7] C 07 D

Sulphones have proved to be useful building blocks in organic synthesis[1]. For example substituted 3-sulpholenes are latent source of conjugated dienes and valuable in Diels–Alder reaction **(Scheme I)** [2]. In addition they are useful precursors for the Ramberg–Backlund reaction[3]. Molecules containing SO_2 moiety are intricate templates for a variety of synthetic transformations because SO_2 can be eliminated either thermally and photochemically from the target molecule as and when desired. In view of varied applications, sulphone derivatives are useful starting materials for diversity oriented synthesis. Therefore, development of new methods or improvement of the existing methods for the preparation of various sulphones is highly desirable.

Despite of their extensive use in organic synthesis, only a handful of methodologies are available for the construction of highly functionalized sulphones[4]. Most of these methods start from sulfides, prepared by multi-step synthetic sequence, followed by oxidation of the sulfides to the corresponding sulphones[5].

In connection with our interest in developing new methodologies related to metathesis[6], benzocyclobutane chemistry[7] and SM cross-coupling reaction[8], we require benzo-annulated sulphones of different substitution pattern **(Scheme II)**. In this regard, a persual of literature indicated that there is no simple and unified approach for the preparation of sulphones that can deliver a variety of substitution pattern.

Herein, we report a useful methodology for the preparation of various functionalized benzo-annulated sulphones by reacting the readily available *o*-xylene dibromide derivative with rongalite (sodium hydroxy methanesulfinate)[9] to generate sulphone and the subsequent SM cross-coupling reaction with a variety of boronic acid derivatives.

Towards this goal, tetrabromo derivative **6** was prepared from the readily available starting material, *o*-xylene by two-step synthetic sequences as shown in **Scheme III**. In this regard, we found that the traditional conditions for benzylic bromination (NBS/AIBN or benzoyl peroxide) of **4** to generate the corresponding tetrabromo derivative **6** did not result in a synthetically useful yield. Also, it was observed that unwanted polybrominated compounds formed during the reaction are difficult to purify. Therefore, a stepwise procedure was adapted to generate the required tetrabromide **6**. Thus, benzylic bromination of **4** under photochemical condition gave **6** via **5**. It is necessary to perform this reaction in a stepwise fashion and the product was purified at each stage by column chromatography to obtain the desired compound **6**.

Later on, the tetrabromo compound **6** was reacted with rongalite[9] in the presence of tetrabutyl-ammonium bromide (TBAB) in DMF at 0°C **(Scheme IV)**. The sultine derivative **7** was obtained in 49% yield. Rearrangement of sultine derivative **7** under thermal conditions (sealed tube/toluene/120°C) gave the corresponding sulfone **8**.

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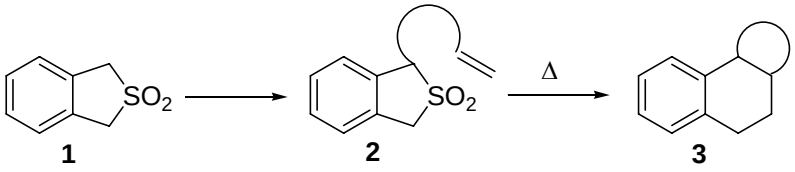
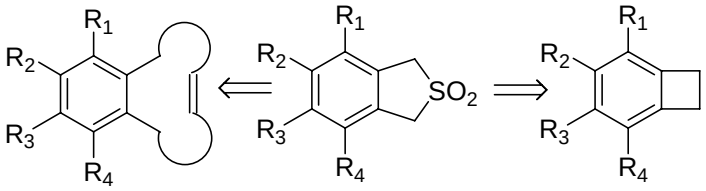
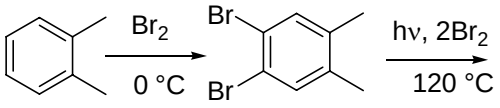


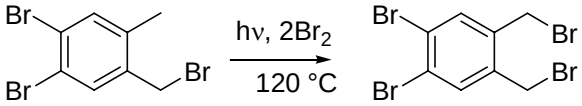
Scheme I



Scheme II

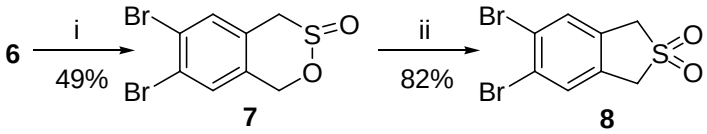


4, 70%



5, 65% **6**, 62%

Scheme III

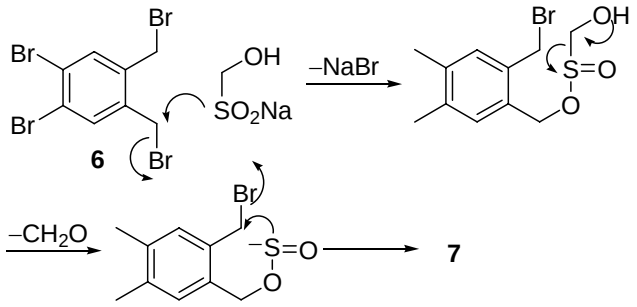


Reagents and Conditions (i) rongalite, TBAB, DMF, 0 °C, (ii) sealed tube, toluene 130 °C.

Scheme IV

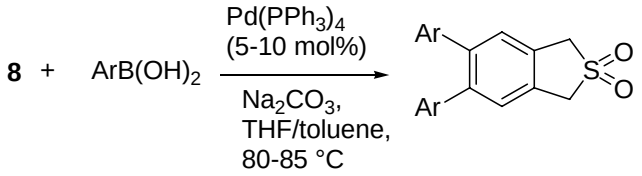
A possible mechanism for the formation of sultine derivative **7** from tetrabromo compound **6** using rongalite is shown in **Scheme V**. Here, the formaldehyde molecule is eliminated from the rongalite. It is interesting to note that rongalite is a useful source of SO_2^{-2}.

Having prepared the dibromo sulphone **8**, next we examined the SM cross-coupling reaction under Pd(0) catalyst conditions **(Scheme VI)**. Although, there are several methods available to effect the aryl-aryl cross-coupling reaction, we have chosen the SM cross-coupling reaction as a key steps in our strategy because the side products formed during the SM coupling reaction can be isolated with ease. A typical experimental procedure for the SM coupling reaction involves reacting the sulphone derivative **8** with the required boronic acid under the influence of Pd(0) catalyst in THF/toluene/water solvent system. At the conclusion of reaction (TLC monitoring), the reaction mixture was worked up by usual procedure and crude product was charged on a silica gel column. Elution of the column with ethyl acetate-pet. ether (b.p. 60-80°C) mixture gave the required cross-coupling product. All the cross-coupling products **9-18 (Table I)** are well characterised by high field ^{1}H NMR and ^{13}C NMR



Possible mechanism for the sultine formation

Scheme V

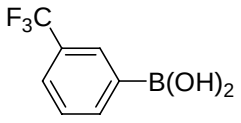
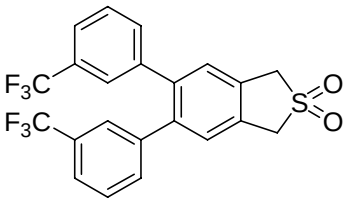
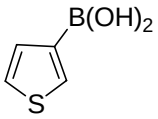
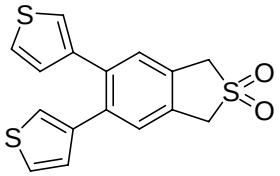
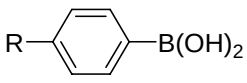
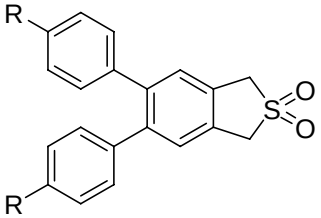


Scheme VI

spectral data[10,11]. The symmetry present in the individual coupling products is evident from the number of ^{13}C NMR spectral lines. Additional functional groups present in the cross-coupling products may serve as a useful handle for further synthetic manipulation. The major attraction of this approach is: (i) utilization of the readily available starting materials; (ii) short synthetic sequence and (iii) commercial availability of diverse boronic acids as coupling partners.

In conclusion, it has been shown that the dibromo sulphone **8** obtained by the rearrangement of the sultine derivative **7** under thermal reaction conditions is a useful precursor for the preparation of highly functionalized cyclic sulphone derivatives by SM cross-coupling reaction. The operational simplicity makes this route as an attractive strategy for the combinatorial synthesis of various sulphones. The strategy reported here for different sulphone building blocks is likely to play an

Table I — List of various functionalised sulphone derivatives prepared by the SM cross-coupling reaction with dibromo sulphone **8**

S. No.	Boronic acid	Coupling product	Yield (%)
1			96
2			98
3			

a	R= H	**a**	R=H	**11**	98
b	R= Me	**b**	R=Me	**12**	99
c	R= OMe	**c**	R=OMe	**13**	91
d	R= CHO	**d**	R=CHO	**14**	95
e	R= Ac	**e**	R=Ac	**15**	98
f	R= CN	**f**	R=CN	**16**	99
g	R= F	**g**	R=F	**17**	97
h	R= Ph	**h**	R=Ph	**18**	96

important role in advanced organic synthesis and also in the preparation of biologically active molecules[12].

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10 General procedure for the SM cross-coupling reaction of arylboronic acids with 5,6-dibromo-1,3-dihydro-benzo[c]thiophene 2,2-dioxide **(8).** A mixture of the dibromo compound **8** (1 equiv.), arylboronic acid (4-5 equiv.), $(PPh_3)_4Pd$ (~ 5-10 mole%), Na_2CO_3 (4 equiv.) in water / THF / toluene and the reaction mixture was heated at 80 ^oC under N_2. At the conclusion of the reaction (TLC monitored), the reaction mixture was diluted with water (5 mL) and extracted with diethyl ether. The combined organic layer was washed with water, brine and dried over $MgSO_4$. The solvent was evaporated and the crude product was charged on a silica gel column. Elution of the column with ethyl acetate-pet. ether gave the desired cross-coupling product.

11 All new compounds are characterized by their spectral data. ^{13}C NMR spectral data and melting point of all new compounds are given here. **8** m.p. 197-98°C; ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 56.2, 125.4, 131.1, 132.0. **9** m.p. 172-73°C; ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 56.8, 122.0, 124.2 (J = 3.8 Hz), 126.0, 126.5 (J = 3.8 Hz), 128.0, 128.9, 130.9 (J = 32.5 Hz), 131.6, 133.0, 140.3 (J = 3.8 Hz). **10** m.p. 235-36°C; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 57.0, 123.7, 125.4, 127.8, 128.7, 130.5, 136.5, 141.0. **11** m.p. 217-18°C; ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 56.9, 127.1, 128.0, 128.1, 129.7, 130.4, 140.2, 141.6. **12** m.p. 237-38°C; ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 21.2, 56.9, 128.0, 128.9, 129.5, 130.0, 136.8, 137.4, 141.5. **13** m.p. 186-87°C; ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 55.3, 57.0, 113.6, 128.0, 130.0, 130.8, 132.8, 141.1, 158.7. **14** m.p. 228-29°C; ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 56.8, 128.1, 129.8, 130.4, 131.8, 135.2, 140.3, 145.9, 191.7. **15** m.p. 219-20°C; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 26.8, 56.9,128.2, 128.5, 130.0, 131.6, 136.0, 140.6, 144.8, 197.8. **16** m.p. 265-66°C; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 56.9, 111.9, 118.4, 128.3,

130.5, 132.4, 139.8, 144.3. **17** m.p. 224-25°C; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 56.8, 115.3 (*J* = 21.5 Hz), 128.0, 130.7, 131.3 (*J* = 8.4 Hz), 136.0, 140.6, 162.0 (*J* = 246.9 Hz). **18** m.p. 227-28°C; ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 56.9, 126.9, 127.0, 127.5, 128.1, 128.9, 130.2, 130.5, 139.2, 139.9, 140.4, 141.2. *Values in parentheses are ^{13}C, ^{19}F coupling constant in Hertz.

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