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SYNTHESIS OF POLYCYCLIC AROMATICS FROM A DIIODOSULTINE BY SUZUKI-MIYAURA CROSS-COUPLING AND DIELS-ALDER REACTION†

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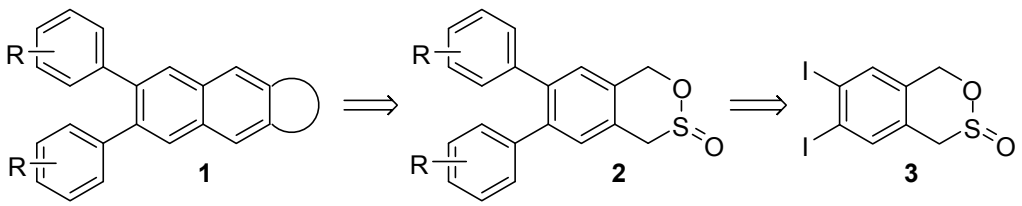
Abstract – A convergent synthesis of polycyclic aromatic compounds by the application of Suzuki-Miyaura cross-coupling and Diels-Alder reaction as key steps is described.

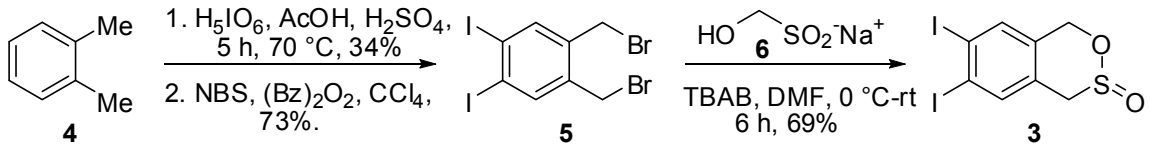
Functionalized polycyclic aromatic systems have found a variety of applications in chemical and pharmaceutical sciences. Linearly fused polycyclic compounds are used as organic semiconductors and luminescence materials. Highly substituted naphthalene derivatives are useful in designing organic electronic materials.[1] To functionalize aromatic systems, the Suzuki-Miyaura (SM) cross-coupling reaction is the one of the efficient method.[2] Now, we report a new strategy for assembling polycyclic aromatic compounds via the application of the Diels-Alder (DA) reaction of highly functionalized sultine derivatives which are generated via SM cross-coupling. The required sultine building block **3** for DA reaction is prepared by using rongalite as a solfoxylate dianion equivalent.[3] The detailed strategy is shown in Figure 1.

Figure 1. Our strategy toward the synthesis of polycyclic compounds



†This paper is dedicated to Prof. Dr. Albert Eschenmoser on the occasion of his 85th birthday.

Toward the synthesis of polycyclics, the known diiodosultine **3**[3] was employed (Scheme 1). To this end, compound **3** was prepared from readily available starting material such as *o*-xylene **4**. Thus, treatment of *o*-xylene **4** with periodic acid in presence of acetic acid and concentrated sulfuric acid afforded 1,2-diiodo-4,5-dimethylbenzene as a white solid in 34% yield which was further subjected to radical bromination reaction (side-chain bromination) using NBS in presence of catalytic amount of benzoyl peroxide as a radical initiator to generate 1,2-diiodo-4,5-bis(bromomethyl)benzene **5** as a white solid in 73% yield (Scheme 1).[3-5]



Scheme 1. Synthesis of 5,6-diiodo-1,4-dihydro-2,3-benzoxathiin-3-oxide **3**

Having the dibromo compound **5** in our hand, the next goal was to prepare sultine derivative **3**. To this end, dibromide **5** was reacted with rongalite **6** in presence of tetrabutylammonium bromide as phase-transfer catalyst, and the desired diiodosultine **3** was obtained in 69% yield as a white solid. Next, the diiodosultine **3** was subjected to SM cross-coupling with $(Ph_3P)_4Pd$ and PEPPSI catalysts. Under the examined conditions, however, no cross-coupling product was obtained. At higher temperature (~80 °C) sultine derivatives rearrange to sulfone derivatives, and therefore, it is desirable to perform the coupling reaction at lower temperature to avoid sulfone formation during the coupling sequence. Later, we found that in the presence of a Buchwald ligand **7**[8-9] (Figure 2) in combination with palladium catalyst **9** was suitable for the cross-coupling reaction. Treatment of the sultine derivative **3** with phenylboronic acid **8a** under the conditions gave the cross-coupling product **2a** in 26% yield. Along similar lines, 3-(trifluoro-methyl)phenylboronic acid **8b** furnished the cross-coupling product **2b** in 31% yield (Scheme 2).[5-7]

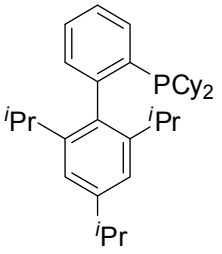
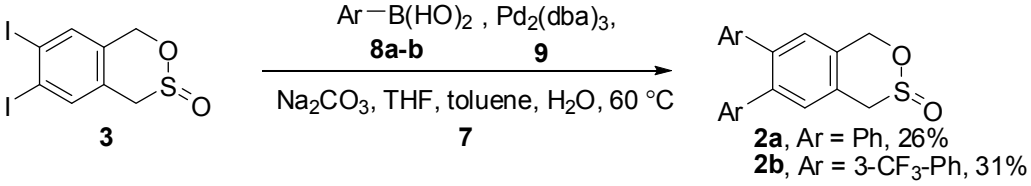
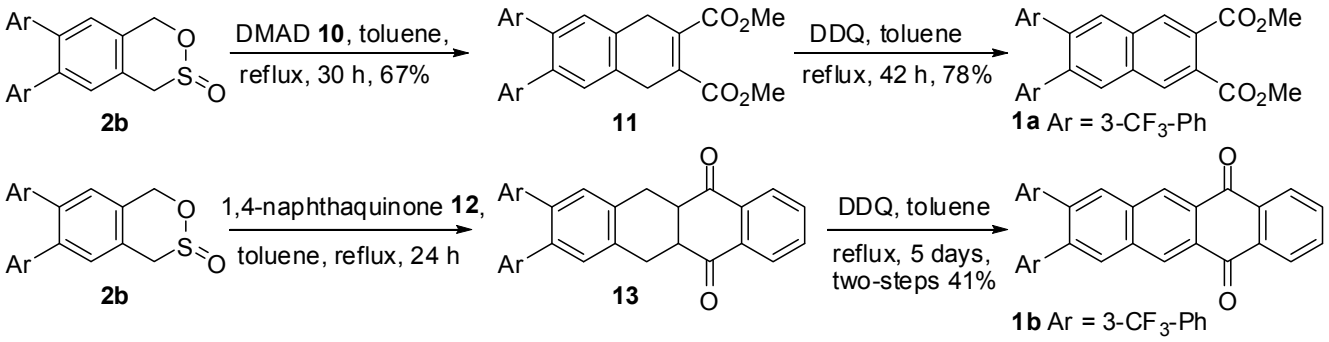


Figure 2. Electron-rich Buchwald ligand **7**



Scheme 2. Synthesis of SM cross-coupling products **2a-b**

The next task was the realization of the DA reaction with the sultine derivatives **2**. In this regard, we previously found that the DA reaction starting with various sulfone derivatives[5] and dimethyl acetylenedicarboxylate (DMAD) **10** under different conditions (toluene reflux and *o*-dichlorobenzene reflux) failed to deliver the desired cycloadducts. Due to this reason we chose the sultine building block **2** which is expected to undergo DA reaction at lower temperature. Toward this goal, the coupling product **2b** was reacted with DMAD **10** under toluene reflux conditions to give the cycloadduct **11** as a white solid in 67% yield. Similarly, the sultine **2b** was treated with another dienophile, 1,4-naphthaquinone **12** under the same reaction conditions to give the corresponding cycloadduct **13**. Later, the DA products **11** and **13** were directly subjected to aromatization sequence using DDQ. Thus, treatment of DA adducts **11** and **13** with DDQ in refluxing toluene afforded the corresponding aromatized compounds **1a-b** in 78% and 41% respectively (Scheme 3).



Scheme 3. Synthesis of functionalized polycyclic aromatics **1a-b**

We have demonstrated a convergent route for the synthesis of polycyclic compounds via SM cross-coupling and DA reaction as key steps. Here, rongalite is used to prepare the required sultine derivative.

EXPERIMENTAL PROCEDURE

Preparation of the cross-coupling product (2a)

To a solution of diiodosultine **3** (50 mg, 0.12 mmol) in THF (2 mL) and toluene (2 mL) were added phenylboronic acid **8a** (75 mg, 0.6 mmol), phosphine-ligand **7** (6 mg, 0.01 mmol) under N_2 and then a solution of sodium carbonate (64 mg, 0.6 mmol) in H_2O (2 mL) was added. The resultant mixture was degassed for 15 min, and later tris(dibenzylideneacetone)dipalladium(0) **9** (2 mg, 0.001 mmol) was added. Then, the reaction mixture was heated at 60 ºC for 15 h. At the completion of the reaction (TLC monitoring), the reaction mixture was quenched with H_2O (5 mL) and then extracted with EtOAc (3 × 10 mL), the organic layer was washed with aqueous sodium hydrogencarbonate solution (10 mL), dried over anhydrous Na_2SO_4, filtered and evaporated to dryness under reduced pressure. The crude product obtained was purified by column chromatography. Elution of the column with 6% EtOAc/petroleum ether mixture gave **2a** as a white solid (10 mg, 26%). mp 168-170 °C. IR (thin film): 3057, 3024, 2924, 1479, 1107, 1023, 763, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.29 (s, 1H, ArH), 7.27 (s, 1H, ArH), 7.20-7.22 (m, 6H, ArH), 7.09-7.12 (m, 4H, ArH), 5.41 (d, *J* = 13.5 Hz, 1H), 5.07 (d, *J* = 13.6 Hz, 1H), 4.46 (d, *J* = 15.5 Hz, 1H), 3.68 (d, *J* = 15.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.2, 140.5, 132.4, 132.1, 129.9, 129.8, 128.2, 127.8, 127.0, 124.9, 62.6, 56.3. HRMS (TOF MS ES^+): m/z: (M+H) calcd. for $C_{20}H_{17}O_2S$: 321.0942; found: 321.0949.

Preparation of the cross-coupling product (2b)

To a solution of diiodosultine **3** (100 mg, 0.24 mmol) in THF (3 mL), toluene (3 mL) were added 3-(trifluoromethyl)phenylboronic acid **8b** (213 mg, 1.14 mmol), phosphine-ligand **7** (10 mg, 0.02 mmol) under N_2 and then a solution of sodium carbonate (127 mg, 1.1 mmol) in H_2O (1.5 mL) was added. The resultant reaction mixture was degassed for 15 min, and later tris(dibenzylideneacetone)dipalladium(0) **9** (4 mg, 0.003 mmol) was added. Then, the reaction mixture was heated at 60 ºC for 15 h. At the completion of the reaction (TLC monitoring), the reaction mixture was quenched with H_2O (10 mL) and then extracted with EtOAc (3 × 10 mL), washed with aqueous sodium hydrogencarbonate solution (15 mL), dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The crude product obtained was purified by column chromatography. Elution of the column with 6% EtOAc/petroleum ether mixture gave **2b** (33 mg, 31%) as a white solid. mp 120-122 °C. IR (thin film): 3004, 2924, 1537, 1454, 1275, 1260, 1021, 764, 749 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.51 (s, 1H, ArH), 7.49 (s, 1H, ArH), 7.35-7.31 (m, 6H, ArH), 7.25-7.22 (m, 2H, ArH), 5.43 (d, *J* = 14.0 Hz, 1H), 5.10 (d, *J* = 14.0 Hz, 1H), 4.45 (d, *J* = 15.5 Hz, 1H), 3.73 (d, *J* = 15.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.6, 139.6, 139.1, 133.3, 133.1, 132.1, 131.0, 130.7, 128.9, 127.7, 126.6, 126.0, 124.1, 62.3, 55.8. HRMS (TOF MS ES^+): m/z: (M+H) calcd. for $C_{22}H_{15}O_2F_6S$: 457.0697; found: 457.0693.

Preparation of the DA adduct (11)

To a solution of the coupling product **2b** (42 mg, 0.093 mmol) in dry toluene (10 mL) was added DMAD **10** (0.04 mL, 0.32 mmol) was added. Then, the reaction mixture was refluxed for 30 h under N_2. At the completion of the reaction (TLC monitoring), the solvent was removed at reduced pressure to deliver the crude product which was purified by silica-gel column chromatography. Elution of the column with 10% EtOAc/petroleum ether mixture gave the desired cycloaddition product (33 mg, 67%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (s, 1H, ArH), 8.01 (s, 1H, ArH), 7.55-7.46 (m, 2H, ArH), 7.34-7.29 (m, 6H, ArH), 3.85 (s, 6H, 2-OMe), 3.82 (s, 4H, 2-CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1 [C=O], 141.2, 138.0, 133.3, 133.1, 132.1, 130.5, 130.1, 129.6, 128.7, 126.7, 123.8, 52.7, 31.3. The DA adduct was directly subjected to aromatization reaction without further purification.

To a solution of DA adduct **11** (30 mg, 0.057 mmol) in toluene (10 mL) was added DDQ (26 mg, 0.1 mmol) in small portions, and then refluxed for 42 h. At the completion of the reaction (TLC monitoring), the reaction mixture was quenched with water, and extracted with EtOAc (3 × 10 mL). The organic layer was washed with aqueous 2% KOH solution, water, brine and dried over anhydrous Na_2SO_4, filtered. Evaporation of the solvent at reduced pressure gave the crude product which was purified by silica-gel column chromatography. Elution with 10% EtOAc/petroleum ether mixture gave the desired product **1a** (24 mg, 78%) as a white solid. mp 148-150 ºC. IR (thin film): 3054, 2986, 1712, 1605, 1421, 1265, 896, 740 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (s, 2H, ArH), 8.01 (s, 2H, ArH), 7.55-7.53 (m, 2H, ArH), 7.42-7.34 (m, 6H, ArH), 3.98 (s, 6H, 2-OMe). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.0 [C=O], 140.7, 140.2, 133.2, 133.0, 131.0, 130.7, 130.4, 130.1, 129.6, 128.9, 126.8, 124.3, 53.0. HRMS (TOF MS ES$^+$): m/z: (M+H) calcd. for $C_{28}H_{19}O_4F_6$: 533.1176; found: 533.1188.

Aromatization of the DA adduct (13)

To a solution of coupling product **2b** (30 mg, 0.093 mmol) in dry toluene (10 mL) was added 1,4-naphthaquinone **12** (14.7 mg, 0.093 mmol). Then, the reaction mixture was refluxed for 24 h under N_2. At the completion of the reaction (TLC monitoring), the solvent was removed at reduced pressure to deliver the crude cycloaddition product **13** as a yellow solid which was subjected to DDQ oxidation without further purification.

To a solution of the DA adduct **13** (56 mg, 0.057 mmol) in dry toluene (10 mL) was added DDQ (26 mg, 0.1 mmol) in portionwise, and then the reaction mixture was refluxed for 5 days. At the completion of the reaction (TLC monitoring), the reaction mixture was quenched with water, and extracted with EtOAc (3 × 10 mL). The organic layer was washed with aqueous 2% KOH solution, water, brine and dried over anhydrous Na_2SO_4, filtered. Evaporation of the solvent at reduced pressure gave the crude product which was purified by silica-gel column chromatography. Elution with 10% EtOAc/petroleum ether mixture gave the desired product **1b** (41% two-steps) as a yellow solid. mp >260 °C. IR (thin film):

3031, 1668, 1589, 1577, 715, 701 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.95 (s, 2H, ArH), 8.44-8.41 (m, 2H, ArH), 8.20 (s, 2H, ArH), 7.87-7.85 (m, 2H, ArH), 7.58-7.56 (m, 2H, ArH), 7.44 (s, 2H, ArH), 7.42-7.34 (m, 4H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.9 [C=O], 141.1, 140.6, 134.7, 134.6, 134.5, 133.1, 131.8, 130.8, 129.6, 129.0, 127.7, 126.8, 124.5, HRMS (TOF MS ES^+): m/z: (M+H) calcd. for $C_{32}H_{17}O_2F_6$: 547.1111; found: 547.1133.

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