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Convenient Synthesis of *Bis*(3-indolyl)acetylene via Sonogashira Coupling

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Abstract: We describe the synthesis of bis(3-indolyl) acetylene 6 via a Pd-catalyzed cross-coupling reaction of iodoindole 8 and 3-indolylacetylene 9, followed by deprotection of 14 to furnish 6.

Keywords: (indolyl)acetylenes, iodoindoles, Pd-catalyzed reaction

Bis(3-indolyl)acetylenes (1) constitute a potentially important class of molecules because of their possible use as building blocks in heterocycle synthesis. The phenyl analog of 1, diphenylacetylene (2, tolan), has been widely used in organic synthesis. Huang and Larock have extensively utilized the triple bond of 2 in the palladium-catalyzed synthesis of substituted phenanthrenes, indenones, β -naphthylamines, indoles, naphthalenes, β - and γ -carbolines, coumarins, isocoumarins, α -pyrones, fluorenes, tetraarylolefins, carbazoles, isoquinolines, dihydroisoquinolines, pyridines, benzofurans, and benzopyrans.^[1] Takahashi et al. used **2** in the zirconium-mediated synthesis of substituted pyridines, pyridones, iminopyridines, and arylcyclobutanes and palladium-catalyzed synthesis of pentasubstituted fulvenes.^[2] Satoh et al. demonstrated the palladium-catalyzed synthesis of highly substituted 1,3-butadienes and rhodium-catalyzed synthesis of 2,3-diphenyl-1indenones using 2.^[3] Tobisu et al. have used 2 for the ruthenium-catalyzed synthesis of functionalized γ -butyrolactones.^[4] Chang et al. also used 2 in cobalt- and nickel-catalyzed synthesis of substituted indenol, indenes, and substituted cyclobutenes.^[5] Diphenylacetylene (2) was also used by others to synthesize various substituted heterocycles.^[6] However, *bis*(3-

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indolyl)acetylenes are relatively unexplored, and only one synthesis of this class of molecules has been reported to date.



R, R' = H, alkyl, aryl, protecting group

The aforementioned sole synthesis of **6** was reported by Kamenskii and coworkers; they obtained an 8% yield of the desired product from 3-indolyl skatyl ketone (1,2-di-1*H*-indol-3-yl-ethanone, **5**) (Scheme 1).^[7] Their synthesis of **5** involved the use of highly unstable indole-3-acetyl chloride (**3**), which needs to be used immediately after preparation from indole-3-acetic acid. The indolyl Grignard **4** was generated from indole and ethylmagnesium bromide.

A direct synthesis of $1 (R, R' = SO_2Ph)$ involving a Sonogashira reaction as the key step in which two indole fragments are combined seemed very attractive. Toward this goal, we synthesized 3-iodo-1-(phenylsulfonyl)indole (8) and 3-ethynyl-1-(phenylsulfonyl)indole (9). The known 3-iodo-1-(phenylsulfonyl)indole (8) was prepared from indole in 61% yield via iodination followed by *N*-protection (Scheme 2).

To synthesize 3-ethynyl-1-(phenylsulfonyl)indole (9), we protected 3-formylindole (10) with the phenylsulfonyl group to give 11, which was then converted to 12 using the Corey–Fuchs procedure (Scheme 3).^[8]



Scheme 2.

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Dibromide **12** was first treated with lithium hexmethyldisilazide (LiHMDS) to generate bromoalkyne **13**, which was subjected to the next reaction without any further purification. Treatment of crude bromoalkyne **13** with *sec*-BuLi gave the alkyne **9** in 60% yield in two steps.^[9] Alkyne **9** can also be prepared from **12** directly using two equivalents of *n*-BuLi albeit in lower yield.

Having the required components in hand, we coupled them using a Sonogashira reaction with $Pd(PPh_3)_4$ as the catalyst in the presence of



Scheme 4.

catalytic CuI. To our delight, the desired compound **14** was produced in 86% yield (Scheme 4). Compound **14** can be conveniently deprotected by 2.5 M NaOH (aq) in ethanol to furnish the unprotected compound **6** in 70% yield (85% yield based on recovered starting material).

In summary, we describe a convenient synthesis of phenylsulfonylprotected and unprotected *bis*(3-indolyl)acetylenes. The chemistry of these internal alkynes is ongoing in our laboratory and will be reported in due course.

EXPERIMENTAL

Melting points were determined with a Mel-Temp Laboratory Device apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 600 series FTIR spectrophotometer. ¹H and ¹³C NMR spectra were recorded on either a Varian XL-300 or a 500 Fourier transform NMR spectrometer. Both lowand high-resolution mass spectra were carried out at the Mass Spectrometry Laboratory, School of Chemical Sciences, University of Illinois at Urbana– Champaign. Elemental analyses were performed by Atlantic Microlab Inc., Norcross, GA. All experiments were performed under a nitrogen atmosphere. Anhydrous THF and CH₂Cl₂ were prepared on a solvent purification system. All other solvents (analytical grade) including anhydrous solvents and reagents were used as received.

3-Iodo-1-(phenylsulfonyl)indole (8)

To a stirred solution of indole (1.76 g, 15 mmol) in DMF (25 mL) at rt, freshly powdered KOH (88%, 2.10 g, 33 mmol) was added. The mixture was stirred at rt for 1 h. Then a solution of iodine (3.88 g, 15.3 mmol) in DMF (25 mL) was added dropwise. After the addition was complete, the solution was stirred at rt for 2 h. It was then poured into ice-cold water (400 mL) containing aqueous ammonium hydroxide (10 mL) and sodium metabisulfite (1g). The solid precipitate was allowed to settle, filtered, washed well with ice-cold water, airdried, and redissolved in dichloromethane (50 mL). Freshly powdered NaOH (1.8 g, 45 mmol) and tetra-n-butylammonium hydrogen sulfate (0.25 g, 0.75 mmol) were added. After stirring the mixture for 15 min at rt, benzenesulfonyl chloride (2.3 mL, 18 mmol) was added dropwise and stirred for 6 h. The reaction mixture was then washed with brine (50 mL), water (3 \times 50 mL), and then again with brine (50 mL). The organic phase was dried (MgSO₄) and concentrated in vacuo. The residue was dissolved in minimum amount of dichloromethane and subjected to purification by column chromatography on silica gel (petroleum ether-ether 4:1) followed by recrystallization from ethyl acetatehexanes to yield the desired product (3.51 g, 61%) as a colorless solid: mp 127-129°C (lit.^[10] 125-127°C): ¹H NMR (CDCl₃): δ 7.97-7.99 (m, 1H),

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7.90–7.92 (m, 2H), 7.72 (s, 1H), 7.55–7.58 (m, 1H), 7.45–7.48 (m, 2H), 7.38–7.41 (m, 2H), 7.31–7.34 (m, 1H); 13 C NMR (CDCl₃): δ 138.0, 134.5, 134.3, 132.6, 129.8, 129.6, 127.0, 125.9, 124.2, 122.2, 113.5, 67.4.

1-(Phenylsulfonyl)indole-3-carbaldehyde (11)

To a stirred solution of commercially available 3-formylindole (Aldrich, 5.81 g, 40 mmol) in dichloromethane (50 mL) at 0°C, freshly powdered NaOH (4.64 g, 116 mmol) and tetra-*n*-butylammonium hydrogen sulfate (0.54 g, 1.6 mmol) were added. The mixture was stirred at the same temperature for 15 min, and then a solution of benzenesulfonyl chloride (6.2 mL, 48 mmol) in dichloromethane (5 mL) was added dropwise. The mixture was stirred at 0°C for 1 h and then at rt for 2 h. Water (100 mL) was added to the reaction mixture. The separated organic layer was washed with water (3 × 100 mL) and brine (100 mL) and dried (Na₂SO₄). The solvent was evaporated, and the residue was purified by recrystallization from dichloromethane–hexanes to yield **11** (10.95 g, 96%) as a white solid: mp 156–158°C (lit.^[111] 156–157°C); ¹H NMR (CDCl₃): δ 10.11 (s, 1H), 8.26–8.27 (m, 2H), 7.96–7.99 (m, 3H), 7.06–7.63 (m, 1H), 7.50–7.53 (m, 2H), 7.40–7.44 (m, 1H), 7.36–7.39 (m, 1H); ¹³C NMR (CDCl₃): δ 185.5, 137.5, 136.4, 135.4, 134.9, 129.9, 127.3, 126.6, 126.4, 125.3, 122.8, 122.7, 113.4.

3-(2,2-Dibromoethenyl)-1-(phenylsulfonyl)indole (12)

To a stirred solution of carbon tetrabromide (6.63 g, 20 mmol) in dichloromethane (75 mL) at 0°C, triphenylphosphine (10.5 g, 40 mmol) was added in portions. After stirring the mixture at the same temperature for 1 h, a solution of 11 (2.85 g, 10 mmol) in dichloromethane (35 mL) was added dropwise. The mixture was stirred at 0°C for an additional 5 h and then poured into hexanes (500 mL) with vigorous stirring. Stirring was continued for 1 h. The precipitate was filtered off and washed thoroughly with hexanes $(3 \times 100 \text{ mL})$. The combined filtrate was concentrated in vacuo, and the residue was purified by column chromatography on silica gel (hexanes-ethyl acetate 9:1) to yield 12 (4.27 g, 97%) as a white solid: mp 160-162°C; IR (thin film): 1446, 1366, 1175, 1132, 1093, 971, 756 cm⁻¹; ¹H NMR (CDCl₃): δ 8.32 (s, 1H), 8.01-8.03 (m, 1H), 7.92-7.94 (m, 2H), 7.52-7.58 (m, 3H), 7.45-7.49 (m, 2H), 7.36-7.40 (m, 1H), 7.28-7.31 (m, 1H); ¹³C NMR (CDCl₃): δ 138.0, 134.3, 134.2, 129.6, 129.5, 127.1, 127.0, 126.9, 125.7, 125.1, 123.9, 119.1, 117.7, 113.8, 90.7; LRMS (EI): m/z 441, 400, 300 (100%), 221, 194, 140, 113, 77; HRMS (EI): m/z calcd. for C₁₆H₁₁NO₂SBr₂: 438.8877, found: 438.8886. Anal. calcd. for C16H11NO2SBr2: C, 43.56; H, 2.51; N, 3.18; S, 7.27; Br, 36.23. Found: C, 43.72; H, 2.42; N, 3.35; S, 7.30; Br, 36.43.

3-Ethynyl-1-(phenylsulfonyl)indole (9)

Using LiHMDS followed by sec-BuLi

To a stirred solution of **12** (2.21 g, 5 mmol) in THF (40 mL) at -78° C, lithium *bis*(trimethylsilyl)amide (11 mL, 1 M solution in THF, 11 mmol) was added dropwise. After the addition was complete, the reaction mixture was stirred at the same temperature for 30 min and then quickly quenched by the rapid addition of saturated aqueous ammonium chloride solution (75 mL). It was extracted with ethyl acetate (3 × 50 mL) and dried (Na₂SO₄). The solvent was evaporated, and the solid residue was subjected to prolonged drying. After complete drying, it was redissolved in THF (40 mL), cooled to -78° C, and *sec*-butyllithium (5.4 mL, 1.4 M in cyclohexane, 7.5 mmol) was added dropwise. The mixture was stirred at -78° C for 15 min, and then saturated aqueous NH₄Cl solution was rapidly added. The mixture was evaporated, and the residue was purified by column chromatography on silica gel (dichloromethane–hexanes 1:1) to furnish the desired product (0.84 g, 60% in two steps) as a yellowish brown solid.

Using n-BuLi

To a stirred solution of 12 (0.13 g, 0.3 mmol) in tetrahydrofuran (3 mL) at -78°C, n-butyllithium (0.26 mL, 2.5 M in hexanes, 0.65 mmol) was added dropwise. The mixture was stirred at the same temperature for 1 h, then allowed to warm to rt, and stirred for 45 min. The reaction was quenched by the dropwise addition of cold water and extracted with *n*-pentane (50 mL). The organic phase was washed with brine (100 mL) and dried (Na_2SO_4). The solvent was evaporated, and the residue was purified by column chromatography (dichloromethane-hexanes 1:1) to yield 9 (31 mg, 37%) as a yellowish brown solid: mp 83-85°C; IR (thin film): 3287, 1446, 1374, 1177, 1132, 1097, 967, 745 cm⁻¹; ¹H NMR (CDCl₃): δ 8.00 (d, 1H, J = 8.3 Hz), 7.92 (d, 2H, J = 7.8 Hz), 7.81 (s, 1H), 7.66 (d, 1H, J = 7.8 Hz), 7.56 (t, 1H, J = 7.1 Hz), 7.47 (t, 2H, J = 7.6 Hz), 7.38 (t, 1H, J = 7.6 Hz), 7.32 (t, 1H, J = 7.6 Hz), 3.28 (s, 1H); ¹³C NMR (CDCl₃): δ 137.9, 134.4, 134.2, 130.9, 130.1, 130.0, 129.6, 127.1, 125.9, 124.1, 120.7, 113.7, 104.5, 81.9, 75.0; LRMS (EI): m/z 281 (M⁺), 140 (100%), 113, 77; HRMS (EI): m/z calcd. for C₁₆H₁₁NO₂S: 281.0510, found: 281.0502.

1-(Phenylsulfonyl)-3-[[1-(phenylsulfonyl)indolyl]ethynyl]indole (14)

To a mixture of alkyne **9** (0.17 g, 0.6 mmol), iodoindole **8** (0.19 g, 0.5 mmol), Pd (PPh₃)₄ (24 mg, 0.02 mmol), and cuprous iodide (2 mg, 0.01 mmol) in anhydrous DMF (2 mL), triethylamine (1.4 mL, 10 mmol) was added. The

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reaction mixture was stirred at rt for 20 h. It was then poured into 0.1 M HCl (100 mL) and extracted with ethyl acetate (2×50 mL). The combined organic phase was washed with water (50 mL), brine (50 mL), and dried (Na₂SO₄). The solvent was evaporated, and the residue was dissolved in a minimum amount of dichloromethane, purified by column chromatography (hexanes-ethyl acetate = 2:1), and followed by recrystallization from ethyl acetate to furnish 14 (0.23 g, 86%) as a white solid: mp 249-251°C (dec); IR (thin film): 1446, 1372, 1175, 1128, 980, 748 cm⁻¹; ¹H NMR (DMSO d_6): δ 8.34 (s, 2H), 8.07–8.10 (m, 4H), 8.02 (d, 2H, J = 8.1 Hz), 7.71–7.78 (m, 4H), 7.60–7.65 (m, 4H), 7.37–7.50 (m, 4H); 13 C NMR (DMSO-d₆): δ 136.5, 135.1, 133.5, 130.0, 129.8, 126.9, 126.0, 124.4, 120.3, 113.5, 104.2, 84.6; LRMS (EI): m/z 536 (M⁺), 400, 395, 383, 277, 254, 242, 141, 127, 115, 73 (100%); HRMS (EI): m/z calcd. for $C_{30}H_{20}N_2O_4S_2$: 536.0865, found: 536.0850. Anal. calcd. for C30H20N2O4S2 · 1/6H2O: C, 66.77; H, 3.80; N, 5.19; S, 11.88. Found: C, 66.50; H, 3.64; N, 5.10; S, 11.71. Extensive drying did not remove the water present in the sample, which was found to be present in the ¹H NMR spectrum.

3-[(Indolyl)ethynyl]indole (6)

To a stirred solution of **14** (107 mg, 0.2 mmol) in ethanol (3 mL), 2.5 M NaOH (0.8 mL, 2 mmol) were added. The mixture was stirred for 48 h. Water (25 mL) was added. It was extracted with ether (2 × 50 mL). The aqueous layer was acidified with 1 N HCl (25 mL) and extracted with ethyl acetate (25 mL). The combined organic phase was dried (Na₂SO₄) and purified by column chromatography on silica gel (dichloromethane) to yield **6** (36 mg, 70%) as a white solid (24 mg, 22% of the starting material was recovered): mp 253–255°C (dec) (lit.^[7] 268–270°C, dec); IR (thin film): 3383, 742 cm⁻¹; ¹H NMR (DMSO-d₆): δ 11.44 (s, 2H), 7.71 (s, 2H), 7.66–7.68 (m, 2H), 7.44–7.46 (m, 2H), 7.17–7.21 (m, 2H), 7.12–7.15 (m, 2H); ¹³C NMR (DMSO-d₆): δ 135.4, 128.6, 128.1, 122.1, 119.8, 118.9, 112.0, 97.3, 84.2; LRMS (EI): m/z 256 (100%), 236, 199, 128, 77; HRMS (EI): m/z calcd. for C₁₈H₁₂N₂: 256.1001, found: 256.1004.

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