Sonogashira Coupling Reaction with Diminished Homo Coupling

Arumugasamy Elangovan, Yu-Hsiang Wang and Tong-Ing Ho*

Department of Chemistry, National Taiwan University, Taipei 106, Taiwan R.O.C

Supporting information

Materials:

All the chemicals and reagents were purchased from Acros Organics unless otherwise indicated and used as received. Dicholobis(triphenylphosphine)palladium(II) was either prepared in-house or from commercial source (Acros). Solvents were distilled as per the standard methods and purged with nitrogen before use. Triethylamine (TEA), piperidine and acetonitrile were distilled and purged with a mixture of approximately 1:1 nitrogen and hydrogen before use.

Methods:

Instrumentation:

^1H – NMR spectra of the samples were recorded with 400 MHz Varian instrument and ^{13}C – NMR spectra were recorded with the same instrument at 100.1 MHz operator frequency in CDCl_3 solvent (Merck) with CHCl_3 internal standard ($\delta = 7.24$ ppm for ^1H and 77 ppm, middle of the three peaks, for ^{13}C spectra), unless otherwise specified. Mass spectra were recorded with Jeol SX 102A instrument on nitrobenzylalcohol matrix. TLC was run on Merck precoated aluminium plates (Si 60 F₂₄₅). Column chromatography was run on Merck silica gel (60 -120 mesh) and neutral alumina (Merck) 70 – 230 mesh.

*Correspondence: Prof. Tong-Ing Ho, fax: +886-2-2363-6359. E-mail: hall@ccms.ntu.edu.tw

Synthetic procedures:

I. General procedure for the synthesis of terminal alkynes 3 (Table 1):

A 50 mL round bottom flask was charged with the halide (1 m mol), dichlorobis(triphenylphosphine)palladium(II), the catalyst, (1 mol %) and CuI (1 mol %) along with a magnetic stirring bar and degassed and back-filled three times with a mixture of approximately 10 - 40 % hydrogen and nitrogen/argon filled in a balloon. TEA (8 mL) was introduced into the reaction flask using a syringe under the gaseous mixture atmosphere. Then trimethylsilylacetylene (TMSA) (1.1 m mol) was added to the reaction flask using a syringe with stirring. After required time of stirring, the solvent was evaporated and the residue was shaken with 10 ml saturated aqueous sodium bicarbonate solution and ether/hexane (10 ml). The organic layer was washed with water and then dried over anhydrous sodium sulfate. Evaporation of solvent left a brown residue which was chromatographed on a short neutral alumina column using hexane eluant to get the trimethylsilyl derivative **2**.

Hydrolysis (de-protection of trimethylsilyl group; *cf.* individual cases):

Compound **2** was dissolved in appropriate solvent (8-10 mL) and stirred with > 2 equivalent of base (KOH or K₂CO₃) for required duration with exclusion of air and then the solvent was evaporated to half its original volume, shaken with water (15 - 20mL) and the product was extracted with ether (20 mL + 2x10 mL). The combined ether solutions were washed with brine, dried over anhydrous sodium sulfate and then passed through a short alumina column. Evaporation of the solvent afforded analytically pure **3**

II. General procedure for the synthesis of terminal alkynes 4 (Table 2):

4-Bromopyridine hydrochloride (1 m mol), the palladium catalyst (2 mol %), CuI (1 mol %) and a stirring bar were placed in a two neck round bottom flask fitted with a condenser. The whole set up was degassed and back-filled with gaseous mixture as

before. To the reaction flask was added previously degassed TEA/piperidine (3 eq) using a syringe. The acetylene **3** was dissolved in 8 mL acetonitrile and added to the reaction mixture at about 80 °C. The reaction was stirred at reflux for 8 hrs under the atmosphere of the gas mixture. The solvents were evaporated, saturated aqueous sodium bicarbonate solution (10 mL) was added at room temperature and extracted with ether (20 mL + 2x10 mL). The combined organic layers were washed with water followed by brine before drying and evaporating. The residue after evaporation was chromatographed on silica gel using ethyl acetate – hexane mixture (1:9 – 1:7 – 1:4) to separate the by-product, the butadiyne and the cross-coupled product **4**.

Individual compounds:

2,4-dimethylphenylethyne (**3a**):

Synthesized from 4-iodo-*m*-xylene (**1a**) (Aldrich) (232.1 mg, 1.0 m mol), TMSA (108 mg, 1.1 m mol), palladium catalyst (7 mg, 1mol % based on iodide), CuI (2 mg 1 m mol %) and TEA (8 mL) by stirring for 2 hrs at room temperature. Yield of **2a**: 194 mg (96 %). ¹H NMR (Bruker 300 MHz, CDCl₃; δ, ppm): 7.34 (d, *J*=7.8 Hz, 1H), 6.99 (s, 1H), 6.91 (d, *J*=7.8 Hz, 1H), 2.38 (s, 3H), 2.29 (s, 3H), 0.24 (s, 9H). ¹³C NMR (δ, ppm): 140.3, 138.3, 131.8, 130.0, 126.1, 119.7, 104.2, 97.2, 21.5, 20.6, 0.36. **2a** was dissolved in 7 mL of methanol and stirred with 120 mg of KOH for 3 hrs and then worked-up with water and hexane to get **3a**. Yield: 120 mg (92 %). ¹H NMR (δ, ppm): 7.36 (d, *J*=7.8 Hz, 1H), 7.03 (s, 1H), 6.96 (d, *J*=7.8 Hz, 1H), 3.24 (s, 1H), 2.43 (s, 3H), 2.33m, (s, 3H). ¹³C NMR (δ, ppm): 140.4, 138.7, 132.2, 130.1, 126.2, 118.7, 82.7, 80.2, 21.5, 20.6.

***p*-methoxyphenylacetylene (3b):**

Synthesized from 4-iodoanisole (233 mg, 1 m mol), TMSA (108 mg, 1.1 m mol), palladium catalyst (7 mg, 1mol % based on iodide), CuI (2 mg 1 m mol %) and TEA (8 mL) by stirring for 2 hrs at room temperature. Yield of **2b**: 200 mg (98 %). ^1H NMR (δ , ppm): 7.38 (d, $J=8.8$ Hz, 2H), 6.79 (d, $J=8.8$ Hz, 2H), 3.79, (s, 3H), 0.23 (s, 9H). ^{13}C NMR (δ , ppm): 159.1, 133.0, 114.9, 113.5, 105.0, 92.3, 55.4, 0.7.

2b was dissolved in 10 mL of THF and stirred under reflux for 3 hrs with tetrabutylammonium fluoride hydrate (261 mg 1 m mol). The solvent was then partially evaporated and the remainder was partitioned between ether and water. After the work-up the dry extract was passed through a short alumina column and evaporated to get colorless low melting needles of **3b**. Yield: 125.5 mg (95 %). ^1H NMR (δ , ppm):7.41, (d, $J=8.6$ Hz, 2H), 6.82 (d, $J=8.6$ Hz, 2H), 3.80 (s, 3H), 2.98 (s, 1H). ^{13}C NMR (δ , ppm):160.0, 133.8, 114.4, 114.3, 83.9, 76.1, 55.6.

***p*-*N,N*-dimethylaminophenylethyne (3c):**

From *p*-iodo-*N,N*-dimethylaniline (**1c**, prepared by iodination of *N,N*-dimethylaniline in CHCl_3) (2.47 g, 10 m mol), TMSA (1.08 g, 11 m mol), catalyst (70 mg, 1mol %), CuI, (20 mg, 1 mol %), TEA, (50 mL), by stirring at room temperature for 1 hr. Yield of **2c**: 2.16 g (99.5 %). ^1H NMR (δ , ppm): 7.31 (d, $J=9.0$ Hz, 2H), 6.57(d, $J=9.0$ Hz , 2H), 2.95 (s, 6H), 0.22 (s, 9H). ^{13}C NMR (δ , ppm): 150.01, 132.97, 111.49, 109.79, 106.47, 91.12, 40.25, 0.39.

2c was stirred with 4 g of K_2CO_3 in 75 mL methanol for 2 hrs and then worked-up to get fine low melting needles of **3c** in 95 % yield (1.38 g). 1H NMR (δ , ppm): 7.34 (d, J = 8.8 Hz, 2H), 6.6 (d, J = 8.8 Hz, 2H), 2.957 (s, 1H), 2.952 (s, 6H). ^{13}C NMR (δ , ppm): 150.19, 133.05, 111.58, 108.65, 84.82, 74.75 and 40.25.

***p*-N,N-diethylaminophenylethyne (3d):**

Synthesized from 4-iodo-*N,N*-diethylaniline (**1d**, prepared by iodination of *N,N*-diethylaniline in $CHCl_3$) (275 mg, 1 m mol), TMSA (108 mg, 1.1 m mol), palladium catalyst (7 mg, 1mol % based on iodide), CuI (2 mg 1 m mol %) and TEA (8 mL) by stirring for 2 hrs at room temperature. Yield of **2d**: 244 mg (99.6 %). 1H NMR (δ , ppm): 7.30, (d, J =8.8 Hz, 2H), 6.54, (d, J =8.8 Hz, 2H), 3.33 (q, J = 7.2 Hz, 4H), 1.44 (t, J = 7.2 Hz, 6 H), 0.22 (s, 9H). ^{13}C NMR (δ , ppm): 147.4, 133.2, 110.8, 90.7, 44.5, 12.7, 0.4.

2d was stirred with 100 mg of K_2CO_3 in 10 mL methanol for 2 hrs and then worked-up to get fine low melting needles of **3d** in 94 % yield (163 mg). 1H NMR (δ ppm): 7.22 (d, J = 8.8 Hz, 2H), 6.46 (d, J = 8.8 Hz, 2H), 3.25, (q, J = 7.2 Hz, 4H), 2.86 (s, 1H), 1.06 (t, J = 7.2 Hz, 6H). ^{13}C NMR (δ ppm): 147.2, 133.0, 110.7, 107.2, 85.0, 74.4, 44.5, 12.9.

4-(*m*-xylene)ethynylpyridine (4a):

From **3a** (100 mg, 0.77 m mol), 4-bromopyridine hydrochloride (149.7 mg, 0.77 m mol), TEA (0.3 mL), CH_3CN (10 mL), catalyst (11 mg, 2 mol %) and CuI (1.5 mg, 1

mol %), Yield: 142 mg, (89 %). M.p.: 55-57 °C. R_f : 0.6 (ethyl acetate – hexane 1:9). ^1H , NMR (δ ppm): 8.56 (d, $J=5.6$ Hz, 2H), 7.39 (d, $J= 8.0$ Hz, 1H), 7.36. (dd, $J= 43.1$ Hz, 1.4 Hz, 2H), 6.93 (s, 1H), 6.87 (d, $J= 8.0$ Hz, 1H), 2.34 (s, 3H), 2.21 (s, 3H). ^{13}C NMR (δ , ppm): 149.5, 140.3, 139.4, 131.7, 130.4, 126.4, 125.3, 118.7, 93.3, 889.9, 21.6, 20.7. High mass (m/z): Calculated for $\text{C}_{15}\text{H}_{13}\text{N}$: 207.1048; observed (m/z): 207.1040.

[Di-*m*-xylenylbutadiyne: 4 mg (2 %), R_f : 0.75 (ethyl acetate – hexane 1:9).]

4-*p*-anisylethynylpyridine (4b):

From **3b** (120 mg, 0.907 m mol), 4-bromopyridine hydrochloride (176.5 mg, 0.907 m mol), TEA (0.4 mL), CH_3CN (10 mL), Pd catalyst, (13 mg, 2 mol %) and CuI (1.7 mg, 1 m mol %). Yield: 190 mg (91 %). M.p.: 110-112 °C. R_f : 0.6 (ethyl acetate – hexane 1:4). ^1H NMR (δ , ppm): 8.55 (d, $J=5.8$ Hz, 2H), 7.47 (d, $J=9.2$ Hz, 2H), 7.33 (d, $J=5.8$ Hz), 6.88 (d, $J=9.2$ Hz, 2H), 3.82 (s, 3H). ^{13}C NMR (δ , ppm): 160.1, 149.5, 133.3, 131.7, 125.3, 114.0, 113.9, 94.2, 85.6, 55.4. High mass (m/z): calculated for $\text{C}_{14}\text{H}_{11}\text{NO}$: 209.0841; observed (m/z): M^+ : 209.1010

[Di-*p*-anisylbutadiyne: 5.3 mg (2.2 %), R_f : 0.7 (ethyl acetate – hexane 1:4).]

4-(*p*-*N,N*-dimethylaminophenyl)ethynylpyridine (4c):

From **3c** (145 mg, 1 m mol), 4-bromopyridine hydrochloride (194.5 mg, 1 m mol), piperidine (0.3 mL), CH_3CN (10 mL), Pd catalyst, (14 mg, 2 mol %) and CuI (2 mg, 1 m mol %). Yield: 209 mg (94 %). M.p.: 195-197 °C, R_f : 0.45 (ethyl acetate – hexane 1:4). ^1H NMR. (δ , ppm): 8.52 (d, $J= 6.1$ Hz, 2H); 7.40 (d, $J= 9.0$ Hz, 2H); 7.31 (d, $J= 6.1$ Hz, 2H); 6.64 (d, $J= 9.0$ Hz, 2H); 2.99 (s, 6H). ^{13}C NMR (δ , ppm): 150.48,

149.25, 133.06, 132.43, 125.08, 111.60, 108.36, 96.16, 85.22, 40.19. High mass (m/z): calculated for $C_{15}H_{14}N_2$: 222.1157; observed (m/z): M^+ : 222.123; $M+1$: 223.1322.

[Bis-(*p*-dimethylaminophenyl)butadiyne: 5.8 mg (2 %), R_f : 0.6 (ethyl acetate – hexane 1:4).]

4-(*p*-*N,N*-diethylaminophenyl)ethynylpyridine (4d):

From **3d** (160 mg, 0.923 m mol), 4-bromopyridine hydrochloride (178 mg, 0.923 m mol), piperidine (0.3 mL), CH_3CN (10 mL), Pd catalyst, (13 mg, 2 mol %) and CuI (1.7 mg, 1 m mol %). Yield: 220 mg (95 %). M.p.: 196-199 °C, R_f : 0.45 (ethyl acetate – hexane 1:4). 1H NMR (Bruker 300 MHz; δ , ppm): 5.82 (d, $J=5.4$ Hz, 2H), 7.73 (d, $J=8.8$ Hz, 2H), 7.30 (d, $J=5.4$ Hz, 2H), 6.60, (d, $J=8.8$ Hz, 2H), 3.38 (q, $J=7.1$ Hz, 4H), 1.16 (t, $J=7.0$ Hz, 6H). ^{13}C NMR (δ , ppm): 149.3, 147.9, 133.3, 132.5, 125.1, 110.1, 107.2, 96.4, 85.0, 44.4, 12.7. High mass (m/z): calculated for $C_{17}H_{18}N_2$: 250.147; observed (m/z): M^+ :250.1490, M^++1 : 251.139.

[Bis-(*p*-diethylaminophenyl)butadiyne: 8 mg (2.5 %) R_f : 0.6 (ethyl acetate – hexane 1:4).]

4-phenylethynylpyridine (4e):

From phenylacetylene **3d** (102 mg, 1 m mol), 4-bromopyridine hydrochloride (194 mg, 1 m mol), TEA (0.4 mL), CH_3CN (10 mL), Pd catalyst, (14 mg, 2 mol %) and CuI (2 mg, 1 m mol %). Yield: 157.7 mg (88 %). M.p.: 91-93 °C, R_f : 0.5 (ethyl acetate – hexane 1:9). 1H NMR (δ , ppm): 8.58 (d, $J=5.0$ Hz, 2H), 7.53 (m, 3H), 7.36

(m, 4H), ^{13}C NMR (δ , ppm): 149.1, 131.5, 131.1, 128.8, 128.1, 125.2, 121.7, 93.9, 86.5. High mass (m/z): calculated for $\text{C}_{13}\text{H}_9\text{N}$: 179.0735; observed (m/z): M^+ : 179.072.

[diphenylbutadiyne: 4 mg (2 %) R_f : 0.75 (ethyl acetate – hexane 1:9).]

***p*-tolylethynylpyridine (4f):**

From *p*-tolylacetylene **3d** (Aldrich) (116 mg, 1 m mol), 4-bromopyridine hydrochloride (194 mg, 1 m mol), TEA (0.4 mL), CH_3CN (10 mL), Pd catalyst, (14 mg, 2 mol %) and CuI (2 mg, 1 m mol %). Yield: 164.3 mg (85 %). M.p.: 111-113 °C, R_f : 0.55 (ethyl acetate – hexane 1:9). ^1H NMR (δ , ppm): 8.57 (d, $J=6.0$ Hz, 2H), 7.43 (d, $J=8.4$ Hz, 2H), 7.35 (d, $J=6$ Hz, 2H), 7.17 (d, $J=7.6$ Hz, 2H), 2.37 (s, 3H). ^{13}C NMR (δ , ppm): 149.5, 139.4, 131.6, 131.5, 129.1, 125.4, 118.9, 94.2, 86.1, 21.7. High mass (m/z); calculated for $\text{C}_{14}\text{H}_{11}\text{N}$: 193.0891; observed: M^+ : 193.091.

[Di-*p*-tolylbutadiyne: 5.3 mg (2.3 %) R_f : 0.75 (ethyl acetate – hexane 1:9)].

Synthesis of certain known diarylethynes (Table 3):

Typical procedure:

The haloarene (1 m mol), palladium catalyst (2%), CuI (1%) and a stirring pellet were placed in a flask and degassed and back-filled with the gaseous mixture three times. TEA (10 mL) was introduced into the reaction flask followed by phenylacetylene (1 equivalent) in the atmosphere of N_2+H_2 . DMF (3-5 mL) was also added if applicable. The resulting mixture was stirred at appropriate temperatures for 3 hrs. Then the volatiles were evaporated and the residue chromatographed on silica gel using ethyl acetate and hexane. Yields are of single run isolated pure compounds

2,4-Dimethylphenylethyne (5a):

4-Iodo-*m*-xylene (232 mg), catalyst (14 mg), CuI (4 mg), TEA (10 mL), phenylacetylene (102 mg). Stirred for 3 hrs at 100 °C with added 3 mL DMF. Evaporation of the volatiles and partitioning of the residue between water and ether, then drying and evaporation of ether furnished crude product which was purified by column.

Yield: 198 mg (96%) pale oil (solidifies slowly on standing). R_f : 0.7 (hexane). ^1H NMR (300 MHz): 7.64 (d, 1H, $J=8$ Hz); 7.50-7.52 (m, 2H); 7.30-7.36 (m, 3H); 7.04 (s, 1H); 6.67 (d, 1H, $J=8$ Hz); 2.36 (s, 3H); 2.24 (s, 3H).

4-Methoxydiphenylethyne (5b):

4-Iodoanisole (234 mg), catalyst (14 mg), CuI (2 mg), TEA (10 mL), phenylacetylene (102 mg). Reaction mixture was stirred at RT for 3 hrs. Yield: Diphenylbutadiyne: 4 mg, **5b**: 203.8 mg (98%); mp: 60.62 °C; R_f : 0.77 (10% ethyl acetate / Hexane); ^1H NMR: 7.48 – 7.51 (m, 2H); 7.45 (d, 2H, $J=8.8$ Hz); 7.32 – 7.23 (m, 3H); 6.86 (d, 2H, $J=8.8$ Hz).

Diphenylethyne-4-carbonitrile (5c):

4-Bromobenzonitrile (182 mg), catalyst (14 mg), CuI (2 mg), TEA (10 mL), phenylacetylene (102 mg), DMF (3mL). Reaction mixture was stirred at 100 °C for 3 hrs. Evaporation of the volatiles and partitioning of the residue between water and

ether, then drying and evaporation of ether furnished crude product which was purified by column. Yield: 203.8 mg (98%); mp: 106- 108 °C; R_f : 0.45 (5% ethyl acetate / hexane) ^1H NMR (400 MHz Varian): 7.48 (d, 2H, $J=8.4$ Hz); 7.45 (d, $J=8.4\text{Hz}$), 7.40-7.38 (m, 2H), 7.25-7.11 (m, 3H).

4-Nitrodiphenylethyne(5d):

1-Iodo-4-nitrobenzene (250 mg), catalyst (14 mg), CuI (2 mg), TEA (10 mL), phenylacetylene (102 mg), DMF (3 mL) stirred at 100 °C 3 hrs. Evaporation of the volatiles and partitioning of the residue between water and ether, then drying and evaporation of ether furnished crude product which was purified by column chromatography. Yield: 212 mg (95%), mp: 114-116 °C. ^1H NMR (400 MHz Varian): 8.22 (d, 2H, $J= 8.8$ Hz); 7.36 (d, 2H, $J= 8.8$ Hz); 7.54-7.67 (m, 2H); 7.37-7.41 (m, 3H).

Diphenylethyne-4-carboxaldehyde (5e):

4-Bromobenzaldehyde (185 mg), catalyst (14 mg), CuI (2 mg), TEA (10 mL), phenylacetylene (102 mg), DMF (3 mL). Reaction was stirred at 100 °C for three hours. Evaporation of the volatiles and partitioning of the residue between water and ether, then drying and evaporation of ether furnished crude product which was purified by column. Yield: 102 mg (95%), mp: 98-100 °C; R_f : 0.67 (10%ethyl acetate / hexane). ^1H NMR (400 MHz, Bruker): 10.0 (s, 1H, CHO); 7.84 (d, 2H, $J=8$ Hz); 7.6 (d, 2H, $J=8\text{Hz}$) 7.52-7.54 (m, 2H); 7.24-7.36 (m, 3H).

4-Acetyldiphenylethyne (5f):

4-bromoacetophenone (200 mg), catalyst (14 mg), CuI (2 mg), TEA (10 mL), phenylacetylene (102 mg), DMF (5 mL). Reaction was stirred at 100 °C for three hrs. Evaporation of the volatiles and partitioning of the residue between water and ether, then drying and evaporation of ether furnished crude product which was purified by column. Yield: 211 mg (95.8%), mp: 96-98 °C. R_f : 0.57 (10% ethyl acetate / hexane). ^1H NMR (400 MHz Bruker): 7.92 (d, 2H, $J=8.6$ Hz); 7.59 (d, 2H, $J=8.6$ Hz); 7.52-7.54 (m, 2H); 7.23 – 7.35 (m, 3H).

STANDARD 1H OBSERVE

Pulse Sequence: s2pu1

Pulse Sequence: s2pu1

STANDARD 1H OBSERVE

Pulse Sequence: s2pu1

Pulse Sequence: s2pu1

3b

STANDARD 1H OBSERVE

Pulse Sequence: s2pu1

STANDARD 1H OBSERVE

Pulse Sequence: s2pu1

4a

STANDARD 1H OBSERVE

Pulse Sequence: s2pu1

4c

4e

-0.009

STANDARD 1H OBSERVE

Pulse Sequence: s2pu1

STANDARD 1H OBSERVE

Pulse Sequence: presat