1,3,5-Tripyridylbenzenes *via* Threefold Stille Couplings [1]

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Novel 1,3,5-tripyridylbenzenes are synthesized using a threefold Stille coupling as the strategic reaction.

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We have been looking at the synthesis of polycyclic triamines for use as recognition domains in molecular hosts and catalysts [2]. Tripyridylbenzenes exemplify such domains, distinctive in part for the multiple ways that the pyridyl moieties can be arranged around the central stage (Figure 1). A fully symmetrical 1,3,5-arrangement might best be constructed by way of a threefold Stille coupling [3]. We describe here the preparation of new 1,3,5-tripyridylbenzenes by the Stille-based approach.

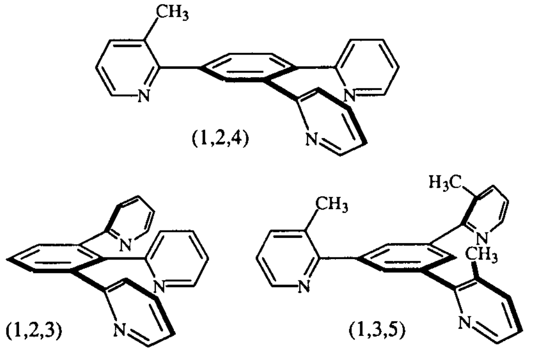

Figure 1. Substitution patterns of tripyridylbenzenes.

Our first target was obtained as shown in Figure 2. We prepared 2-bromo-3-picoline **1** by a literature procedure [4] from 2-amino-3-picoline (Aldrich), then converted it to the corresponding trimethylstannylpicoline **2** [5]. Attempts to couple **2** with 1,3,5-tribromobenzene (Aldrich) resulted in the desired compound **5**, but only in low yields based on **3**. Products resulting from incomplete reaction and homocoupling of the stannane were usually observed. The yield of **5** could not be made to exceed 20% without a resubjection of isolated intermediates, and resubjection did not help greatly.

A much better yield of **5** was obtained by the combination of **2** with triiodobenzene **4** [6]. This improvement was expected from the generally superior performance of iodoarenes in Stille couplings [3a,b]. The observed variability in the yield is not unreasonable in retrospect. To an extent, it should represent a multiplication of the variability inherent in a corresponding "onefold" coupling experiment.

We next examined ways of including functionality for the attachment of such tripyridyl domains to other host components. Because of three pyridyl groups being present, any post-Stille pyridyl functionalizations would need to be particularly efficient, just as with the Stille coupling itself. Figure 3 outlines our best attempts to convert **5** to suitable analogs. An oxidation of the nitrogens with *m*-chloroperoxybenzoic acid was followed by acetylation/rearrangement (to the tris(6-acetoxy) species) and a final methanolysis. This afforded tris(hydroxypyridyl)benzene **7**. Both **6** and **7** are extremely water-soluble. Isolated yields of **6** were rather variable, as with **2** + **4** → **5** above, and they depended strongly on perseverance in the extraction procedure. Some bis(*N*-oxide) was usually isolated along with **6** and simply resubjected to the oxidation conditions. Compound **7** could be converted to the corresponding trichloro analog **8** with phosphorus oxychloride. The best overall yield of **8** from **5** was only 12% after much effort at optimization. Attempts to convert **7** to the tribromo analog **9** with phosphorus tribromide were also mildly successful. The low net yields are attributed to an evident instability of **7** during purification and to the threefold aspect of each of four successive reactions.

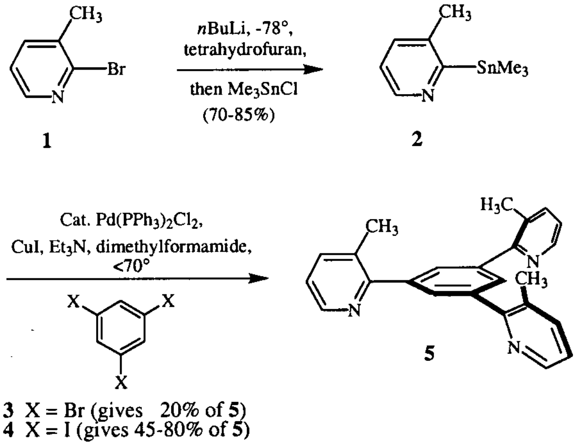

Figure 2. Synthesis of **5**.

The conversion of **5** to **8** seemed likely to improve, but other experiments in progress showed the 6-chloropyridyl moiety as unpromising for subsequent desired transformations. At the same time, 6-bromopyridyl was behaving well. A tris(bromopyridyl) domain therefore became the goal of choice. We ultimately arrived at the new target and concise reaction sequence presented in Figure 4. The

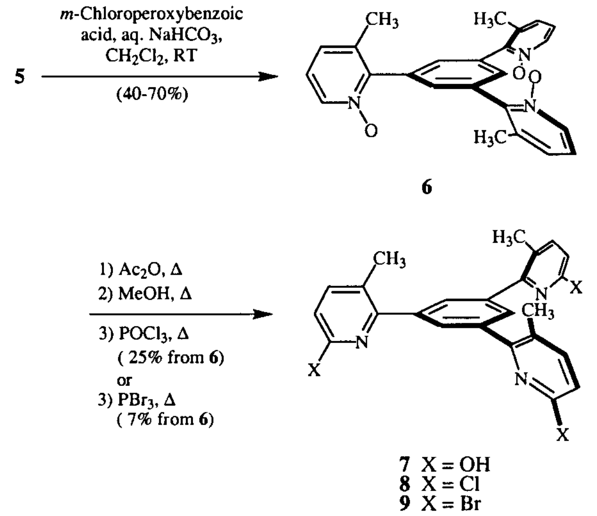

Figure 3. Synthesis of **8** and **9**.

idea was to install auxiliary bromines prior to the Stille reaction in a convenient and "Stille-resistant" fashion. The known 2,6-dibromo-3,5-lutidine (**10**) is easily prepared [7], and because of its symmetry it would avoid the issue of regioselectivity during stannylation. We expected its extra methyl group to frustrate side-reactions during the Stille coupling by virtue of steric hindrance. The Stille is notably the only threefold reaction here.

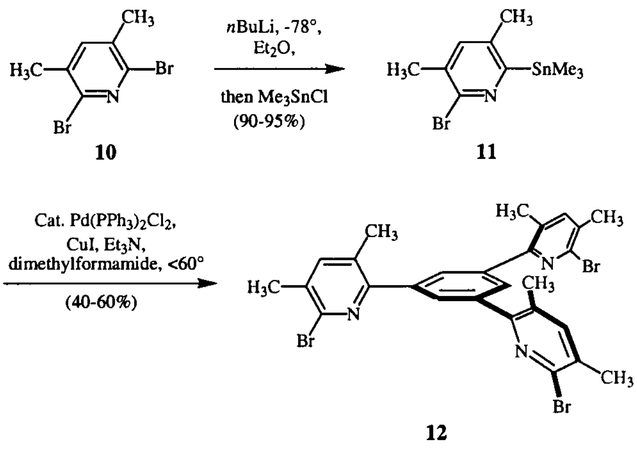

Figure 4. Synthesis of **12**.

We obtained very favorable results with this two-step sequence. Lutidine **10** suffered metal/halogen exchange and stannylation in high yield. The stannane was in turn a good partner for the Stille coupling. Target **12** is easily prepared on multi-gram scale and has since proven itself a good to excellent substrate for Sonogashira coupling [8] to other prospective host components.

In summary, we have prepared 1,3,5-tripyridylbenzenes **5** and **12**. Analogs **8** and **9** have also been achieved, but far less efficiently so.

EXPERIMENTAL

Melting points were determined on a Meltemp apparatus from Laboratory Devices and are uncorrected. The infrared spectra were taken from chloroform solutions unless otherwise noted, and recorded on a Nicolet 520 FT-IR spectrometer using chloroform solutions unless otherwise specified. The 300 MHz ^{1}H spectra were taken from deuteriochloroform solutions and recorded on a Varian Gemini 300 FT-NMR spectrometer. The high resolution mass spectra were recorded on a VG Instruments 70-SE mass spectrometer. Elemental analyses were performed by Robertson Microlit Laboratories, Inc., Madison, NJ, and by Atlantic Microlab, Inc., Norcross, GA.

3-Methyl-2-trimethylstannylpyridine (**2**).

A solution of 2-bromo-3-methylpyridine (1.02 g, 5.90 mmoles) in dry tetrahydrofuran (10 ml) was cooled to -78°. *n*-Butyllithium in hexanes (2.5*M*, 2.60 ml, 6.5 mmoles) was added dropwise with stirring over 15 minutes. The resulting orange mixture was stirred at -78° for 1 hour. A solution of trimethyltin chloride in tetrahydrofuran (1.0*M*, 6.50 ml, 6.5 mmoles) was then added dropwise over 15 minutes. The cold bath was removed and the mixture was stirred for 2 hours. The mixture was then poured into ether and washed with water. The ether phase was dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was distilled in a Kugelrohr apparatus to yield **2** (1.25 g, 82%) as a slightly yellow liquid; ir (neat): 3038, 2982, 2917, 1556, 1569, 1436, 1395, 772, 712 cm^{-1}; ^{1}H nmr: δ 8.56 (d, 1H, J = 3.8 Hz), 7.37-7.35 (m, 1H), 7.08-7.05 (m, 1H), 2.39 (s, 3H), 0.26 (s, 9H); hrms: 257.0230 (M$^+$ Calcd. for $C_9H_{15}NSn$: 257.0226).

2,2',2"-(1,3,5-Benzenetriyl)tris[3-methylpyridine] (**5**).

1,3,5-Triiodobenzene (3.22 g, 7.06 mmoles) and 3-methyl-2-trimethylstannylpyridine (**2**, 8.14 g, 31.8 mmoles) were dissolved in dry dimethylformamide (60 ml), and bis(triphenylphosphine)palladium(II) chloride (248 mg, 0.35 mmole, 5 mole-%) and copper(I) iodide (109 mg, 0.57 mmole) were added. The mixture was purged with nitrogen gas before heating for 24.5 hours (60°C sand bath). The reaction was then diluted with 10% aqueous potassium fluoride (50 ml) and extracted with chloroform. The combined extracts were washed with water several times and concentrated *in vacuo*. Flash column chromatography (tetrahydrofuran/hexane, 2:1) and concentration of product fractions gave **5** as a pale yellow powder (1.75 g, 70%), mp 145.5-147.5°; ir: 3053, 2983, 1593, 1565, 1453, 1405, 1118, 799 cm^{-1}; ^{1}H nmr: δ 8.54 (d, 3H, J = 3.3 Hz), 7.77 (s, 3H), 7.60 (d, 3H, J = 7.5 Hz), 7.19 (dd, 3H, J = 3.3, 7.5 Hz), 2.44 (s, 9H); hrms: 351.1701 (M$^+$ Calcd. for $C_{24}H_{21}N_3$: 351.1735).

Anal. Calcd. for $C_{24}H_{21}N_3$: C, 82.01; H, 6.02; N, 11.96. Found: C, 81.71; H, 5.82; N, 11.85.

2,2',2"-(1,3,5-Benzenetriyl)tris[3-methylpyridine *N*-Oxide] (**6**).

Compound **5** (1.12 g, 2.85 mmoles) and *m*-chloroperoxybenzoic acid (50-60%, 3.27 g, >12 mmoles) were dissolved in dichloromethane (16 ml). A saturated aqueous solution of sodium bicarbonate (160 ml) was added and the mixture was stirred vigorously at room temperature for 6 hours. The mixture was then extracted several times with chloroform, after which aqueous sodium hydroxide (5*N*, 160 ml) was added to the aqueous phase and the mixture was extracted several more times. All extracts were concentrated *in vacuo*, and the residue was subjected to flash column chromatography (methanol). Product fractions were concentrated *in vacuo*, redissolved in chloroform, filtered, and reconcentrated to give **6** as a colorless powder (0.88 g, 69%), mp >265.5° dec; ir: 3433, 3085, 2916, 2857, 1682, 1459, 1417, 1281, 1230, 1044, 806 cm^{-1}; ^1H nmr: δ 8.20 (d, 3H, *J* = 6.3 Hz), 7.60 (s, 3H), 7.22-7.13 (m, 6H), 2.33 (s, 9H); hrms: (FAB) 400.1687 (M+H Calcd. for $C_{24}H_{22}N_3O_3$: 400.1661).

Anal. Calcd. for $C_{24}H_{21}N_3O_3$: C, 65.72; H, 5.49; N, 9.73. Found: C, 65.75; H, 5.50; N, 9.37.

2,2',2"-(1,3,5-Benzenetriyl)tris[6-hydroxy-3-methylpyridine] (**7**).

Tris(*N*-oxide) **6** (118 mg, 0.30 mmole) was dissolved in acetic anhydride (10 ml) and heated at reflux under nitrogen for 64.5 hours. The reaction mixture was then cooled and concentrated *in vacuo*, and a mixture of methanol (6 ml) and ethyl acetate (12 ml) was added to the residue. The new mixture was heated at reflux for 43 hours, then cooled and concentrated *in vacuo*. The desired product was somewhat unstable to silica gel chromatography. Most of the impurities could be removed by a rapid chromatography, eluting first with tetrahydrofuran and then with methanol. Methanolic product fractions were concentrated *in vacuo*, redissolved in chloroform, filtered, and reconcentrated to give **7** (127 mg) as an impure solid that was satisfactory for use in subsequent reactions, mp >201.5° dec; ir: 3136, 2983, 2865, 1671, 1620, 773 cm^{-1}; ^1H nmr: δ 7.67 (s, 3H), 7.40 (d, 3H, *J* = 9.3 Hz), 6.81 (d, 3H, *J* = 9.3 Hz), 2.27 (s, 9H).

2,2',2"-(1,3,5-Benzenetriyl)tris[6-chloro-3-methylpyridine] (**8**).

The sample of compound **7** from the above procedure was divided into two approximately equal portions, and each was added to phosphorus oxychloride (1 ml portions). The two mixtures were heated at reflux under nitrogen for 26 hours. After cooling, they were poured into a single separatory funnel containing ice and water. The resulting mixture was basified with aqueous sodium hydroxide (5*N*), then extracted with dichloromethane. Combined extracts were washed with brine and concentrated *in vacuo*. Flash column chromatography (hexane/ethyl acetate, 1:1) and concentration of product fractions gave **8** as a colorless powder (33 mg, 25% from **6**), mp 179.5-180.5°; ir: 2968, 2926, 1642, 1575, 1557, 1151, 1109, 905 cm^{-1}; ^1H nmr: δ 7.77 (s, 3H), 7.57 (d, 3H, *J* = 7.8 Hz), 7.24 (d, 3H, *J* = 8.1 Hz), 2.41 (s, 9H); hrms: 453.0525 (M^+ Calcd. for $C_{24}H_{18}N_3Cl_3$: 453.0566).

Anal. Calcd. for $C_{24}H_{18}N_3Cl_3$: C, 63.40; H, 3.99; N, 9.24. Found: C, 63.07; H, 3.97; N, 9.12.

2,2',2"-(1,3,5-Benzenetriyl)tris[6-bromo-3-methylpyridine] (**9**).

Compound **7** (0.99 g, 2.5 mmoles) was dissolved in phosphorus tribromide (6 ml), and the mixture heated at reflux for 18 hours. After cooling, the mixture was poured onto ice. The resulting mixture was basified with ice-cold aqueous sodium hydroxide (6*N*), then extracted with dichloromethane. Combined extracts were washed with brine and concentrated *in vacuo*. Flash column chromatography (ether/hexane, 4:3) and concentration of product fractions gave **9** as a colorless powder (115 mg, 7% from 1.105 g of **6**), mp 204.0-206.5°; ir: 2980, 2960, 2920, 1571, 1553, 1452, 1414, 1104, 887, 834, 754 cm^{-1}; ^1H nmr: δ 7.76 (s, 3H), 7.47 (d, 3H, *J* = 8.1 Hz), 7.38 (d, 3H, *J* = 8.1 Hz), 2.39 (s, 9H); hrms: 584.9033 (M^+ Calcd. for $C_{24}H_{18}N_3Br_3$: 584.9051).

Anal. Calcd. for $C_{24}H_{18}N_3Br_3$: C, 49.01; H, 3.08; N, 7.14. Found: C, 48.88; H, 3.04; N, 7.05.

6-Bromo-3,5-dimethyl-2-trimethylstannylpyridine (**11**).

A solution of 2,6-dibromo-3,5-dimethylpyridine (13.50 g, 50.9 mmoles) in dry ether (390 ml) was cooled to -78°. *n*-Butyllithium in hexane (1.7*M*, 36 ml, 61 mmoles) was then added slowly over several minutes. The mixture was stirred at -78° for a further 35 minutes, after which was added a solution of trimethyltin chloride in tetrahydrofuran (1.0*M*, 61 ml, 61 mmoles). The cold bath was removed and the mixture was stirred for 2.5 hours. After concentration of the mixture *in vacuo*, the residue was redissolved in ether, insoluble solids were filtered and the filtrate was reconcentrated. Flash column chromatography (triethylamine/hexane, 1:40) and concentration of product fractions gave **11** as an oil (16.14 g, 91%), ir (neat): 2980, 2927, 1381, 1085, 979, 775 cm^{-1}; ^1H nmr: δ 7.19 (s, 1H), 2.30 (app s, 6H), 0.36 (s, 9H); hrms: 348.9493 (M^+ Calcd. for $C_{10}H_{16}NBrSn$: 348.9488).

2,2',2"-(1,3,5-Benzenetriyl)tris[6-bromo-3,5-dimethylpyridine] (**12**).

1,3,5-Triiodobenzene (3.19 g, 6.99 mmoles) and stannane **11** (9.75 g, 28.0 mmoles) were dissolved in dry dimethylformamide (146 ml), after which bis(triphenylphosphine)palladium(II) chloride (247 mg, 0.35 mmoles, 5 mole %) and copper(I) iodide (108 mg, 0.57 mmoles) were added. The mixture was purged with nitrogen gas before heating for 22 hours (60° sand bath). The reaction was diluted with 10% aqueous potassium fluoride (100 ml), then extracted with chloroform (3 x 100 ml). The combined extracts were washed with water (3 x 100 ml), dried over sodium sulfate, and concentrated *in vacuo*. Flash column chromatography (ether/hexane, 1:1) and concentration of product fractions gave **12** as a pale yellow powder (2.42 g, 55%), mp 238.5-239.5°; ir 2979, 2693, 2925, 1536, 1459, 1406, 1006, 761 cm^{-1}; ^1H nmr: δ 7.71 (s, 3H), 7.42 (s, 3H), 2.40 (s, 9H), 2.35 (s, 9H); hrms: 626.9579 (M^+ Calcd. for $C_{27}H_{24}N_3Br_3$: 626.9520).

Anal. Calcd. for $C_{27}H_{24}N_3Br_3$,: C, 51.45; H, 3.84; N, 6.67. Found: C, 51.65; H, 3.84; N, 6.52.

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REFERENCES AND NOTES

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