Synthesis Of 2-Aryl- and 2-Vinyl-1*H*-indoles *via* Palladium-Catalyzed Cross-Coupling of Aryl and Vinyl Halides with 1-Carboxy-2-(tributylstannyl)indole

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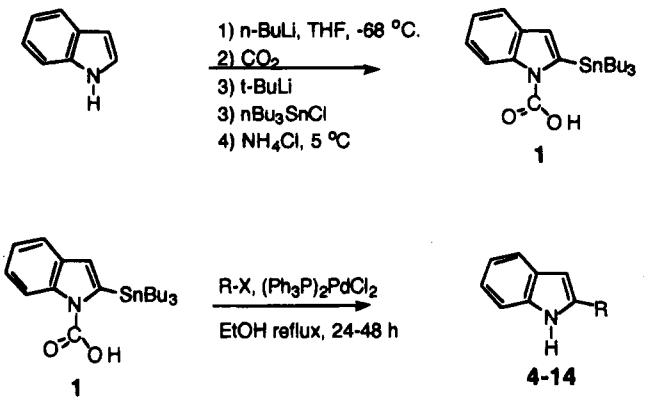
Introduction

Despite their difficulty of preparation, 2-aryl- and 2-vinyl-1*H*-indoles frequently occur as subunits in intermediates for drug and alkaloid synthesis.[1] 2-Vinyl-1*H*-indoles have been prepared using Wittig related olefination reactions on 2-formyl- or 2-ketoindoles,[1cd,2] and by treatment of indol-2-ylmethyltriphenylphosphoranes or -diethylphosphonates with carbonyl compounds.[3] 2-Aryl-1*H*-indoles are most often prepared by *de novo* construction of the indole nucleus from the phenylhydrazones of the appropriate aryl or heteroaryl methyl ketones.[4] Palladium-catalyzed coupling of organotin compounds with vinyl and aryl halides is an effective method for the formation of carbon–carbon bonds (Stille reaction).[5] The 2-stannyl-1*H*-indole species has previously received little attention in organic synthesis. While this work was in progress, initial reports on the palladium-catalyzed cross-coupling using a 2-stannylindole derivative were described in the literature.[6] Preliminary accounts on the preparation and coupling reactions using the 1-methyl-, 1-BOC-, and 1-SEM- protected 2-stannylindoles were reported.[6,7] The 1-BOC protected indole reportedly gave poor yields in the formation of the 1-BOC-2-stannyl intermediate (due to stability) and also low yields of coupled products.[6a] The 1-SEM protecting group was reportedly difficult to remove and often gave low yields of the coupled products.[6a] In one report the 1-SEM-2-substituted indoles were not successfully deprotected.[6b] Attempts to use 1-(benzenesulfonyl)-2-(trimethylstannyl)-indole to prepare 2-(2-pyridyl)indole was unsuccessful.[8] However, carbon dioxide has been previously described as a source of protection of the indole NH and as an α-carbanion stabilizing group.[9] This paper reports on the preparation and reactions of a new reagent, 1-carboxy-2-(tributylstannyl)indole (**1**) (1-CSI) for the synthesis of 2-substituted-1*H*-indoles in high yield *via* palladium-catalyzed coupling with aryl and vinyl halides.

Scheme 1



Chemistry Results and Discussion

The Katritzky method utilizing carbon dioxide for the simultaneous protection of the indole NH and activation of the 2-position and subsequent 2-lithiation has been successful with a number of electrophiles to give 2-substituted-1*H*-indoles.[9,10] The synthesis of a 2-stannylindole by this method has not been previously described. In general, the CO_2 protecting group is generated *in situ* and readily decarboxylates in the reaction or workup. However, it has been reported that the 1-carboxy-2-substituted indoles may be isolated in certain cases.[9] Indole was lithiated with butyllithium in THF at −68 °C followed by the addition of excess carbon dioxide gas. After removal of excess carbon dioxide, lithio indole-1-carboxylate was metalated with *tert*-butyllithium to generate lithio 2-lithioindole-1-carboxylate. Treatment of this species with tributyltin chloride followed by an aqueous workup and neutralization (ammonium chloride) at 0–5 °C gave 1-carboxy-2-(tributylstannyl)indole (**1**) in near quantitative yield as a clear mobile oil. Reagent **1** was unstable to acidic or basic conditions and was found to readily decarboxylate in toluene at reflux. Indole-1-carboxylic acid readily decarboxylates above 100–120 °C[9] and slowly decarboxylates at room temperature.[11] In certain cases small quantities of pure **1** could be obtained after silica gel chromatography although purifying the reagent proved to be difficult and was not attempted further. Stannane **1** was stored under nitrogen at −20 °C and is stable for periods of up to one month. Slow decarboxylation occurs at room temperature or extended periods at low temperature. This is followed by rearrangement to 1-(tributylstannyl)indole (**2**).

The stannane **1** reacted with a variety of aryl halides in the presence of 5 mol % of bis(triphenylphosphine)-palladium(II) chloride under nitrogen in ethanol at reflux

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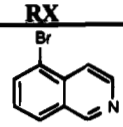
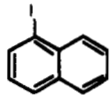
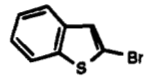
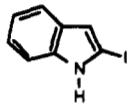
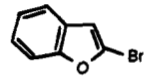
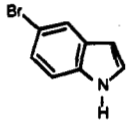
Table 1. Coupling Reactions of 1-Carboxy-2-(tributylstannyl)indole (1-CSI)

Entry	RX	% Yield	Entry	RX	% Yield
4	PhCH=CHBr	86	9		92
5		88	10		75
6		73	11		70
7		75	12		70
8		80	13	C_6H_5I	80
			14[a]	C_6H_5I	86

[a] 1-Carboxy-5-chloro-2-(tributylstannyl)indole was used in this example.

after 24-48 h producing high yields of 2-aryl-1*H*-indoles (Scheme 1). The desired products could be readily isolated after filtration of insoluble materials, concentrating the solvent and purifying the product by either recrystallization or, in some cases, by column chromatography. The arylvinyl, 2-styryl-1*H*-indole (**4**) was prepared from stannane **1** and β-bromostyrene in 86% yield, a marked improvement over the literature method (57%).[12b]

A number of aryl and heteroaryl halides undergo the reaction (Table 1). Iodobenzene and iodonaphthylene gave 2-phenyl- (**13**) and 2-naphthyl-1*H*-indole (**5**) in 80% and 88% yield, respectively. Heteroaryl moieties such as indole, pyridine, isoquinoline, thiophene, benzothiophene, and benzofuran gave good to excellent yields of the 2-substituted products. 2,2′-Biindole (**6**) is an important intermediate in routes toward the synthesis of indolo[2,3-*a*]carbazoles.[13] The literature reports methods for the preparation of **6** in <20% yield,[14] whereas stannane **1** coupled with 2-iodoindole[10] to give biindole **6** in 73% yield.

A number of coupling partners have been used successfully in the Stille reaction. Stannane **1** may serve as a method to incorporate a variety of functionality at the 2-position of indoles. In addition to aryl and vinyl halides, benzyl and allylic halides,[5a,15a] organic triflates,[5a,15b] organic sulfonates,[5a,15c] and acid chlorides[5a] have been used to couple with aryl tin reagents. A variety of substitutents on the indole moiety may also be compatible in the formation of a 1-carboxy-2-stannyl reagent. 5-Chloro-2-phenyl-1*H*-indole (**14**) was prepared from 1-carboxy-5-chloro-2-(tributylstannyl)indole (**3**) and iodobenzene in 86% yield.

In summary, a new reagent, 1-carboxy-2-(tributylstannyl)indole has been prepared and demonstrated to be an efficient method to synthesize 2-substituted-1*H*-indoles by palladium-catalyzed cross-coupling with aryl and vinyl halides. An advantage of the CO_2 protecting group for indoles compared to BOC, SEM, or benzenesulfonyl is the *in situ* formation of the N1 carboxy group which is readily cleaved during the reaction or workup thereby eliminating steps involving protection–deprotection. The problems associated with the removal of protecting groups such as SEM or benzenesulfonyl from indoles have been well documented. The stannane reagent was readily prepared on a multigram scale and could be used for up to one month when stored at −20 °C. The mild reaction conditions and high yields make this method an attractive alternative to existing methodologies for 2-substituted-1*H*-indoles.

Experimental Section

Melting points were determined in open capillary tubes and are uncorrected. Proton NMR spectra were recorded in the solvent indicated with TMS as an internal standard. FAB mass spectra (MS) were obtained using a cesium ion gun to generate ions. Elemental analyses were performed by Quantitative Technologies, Whitehouse, NJ. Column chromatography was

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performed on silica gel 60 (230–400 mesh). Reagents were purchased from Aldrich Chemical Co. and used as received.

1-Carboxy-2-(tributylstannyl)indole (1). To a solution of indole (10 g, 86 mmol) in THF (200 mL, −68 °C, nitrogen atmosphere) was added BuLi (34 mL of 2.5 M solution in hexanes, 86 mmol) dropwise over 30 min. After stirring for 30 min, CO_2 gas was passed through the solution for 10 min. The clear solution was allowed to warm to rt. The excess CO_2 was removed under vacuum at rt while the solvent was concentrated to ca. 125 mL. An additional 100 mL of THF was added and the solution cooled to −68 °C. To this mixture, t-BuLi (50 mL of 1.7 M solution in pentane, 86 mmol) was added dropwise over a 30 min period, and the mixture was stirred for 2 h at −68 °C. Tributyltin chloride (29.4 g, 24.5 mL, 90 mmol) was added dropwise over 10 min. After stirring for 1.5 h the cold solution was poured over crushed ice–water (300 g), and saturated NH_4Cl was added to acidic pH by litmus. The aqueous solution was extracted with Et_2O (2 × 200 mL), dried ($MgSO_4$), and concentrated to give 40 g of a clear mobile oil. This compound was stored under nitrogen at −20 °C and used directly without further purification (contains 5% tributyltin chloride): ^{1}H NMR ($CDCl_3$) δ 0.92–1.10 (m, 15H), 1.30–1.50 (m, 12H), 6.64 (s, 1H), 7.15–7.28 (m, 2H), 7.53 (d, J = 7.2 Hz, 1H), 8.12 (d, J = 7.3 Hz, 1H); IR (neat) 1640, 1480, 1380 cm^{-1}.

1-Carboxy-5-chloro-2-(tributylstannyl)indole (3). This compound was prepared by the same procedure as **1** using 5-chloroindole to give **3** as a clear mobile oil. This compound was stored under nitrogen at −20 °C and used directly without further purification: ^{1}H NMR ($CDCl_3$) δ 0.90–1.00 (m, 9H), 1.30–1.40 (m, 12H), 1.45–1.55 (m, 6H), 6.52 (s, 1H), 7.05 (d, J = 7 Hz, 1H), 7.45 (d, J = 7.2 Hz, 1H), 7.55 (s, 1H); IR (neat) 1630, 1510, 1380 cm^{-1}.

1-(Tributylstannyl)indole (2): ^{1}H NMR ($CDCl_3$) δ 0.80–0.90 (m, 9H), 1.30–1.42 (m, 6H), 1.55–1.62 (m, 6H), 1.63–1.78 (m, 6H), 7.02 (bs, 1H), 7.25–7.46 (m, 3H), 7.60–7.75 (m, 1H), 8.36 (d, J = 6Hz, 1H); IR (KBr) 1560, 1390 cm^{-1}.

General coupling procedure: 2-(2-styryl)indole (4). A mixture of 1-carboxy-2-(tributylstannyl)indole (**1**) (4.0 g, 8.9 mmol), β-bromostyrene (825 mg, 4.5 mmol), and bis(triphenylphosphine)palladium(II) chloride (300 mg, 0.4 mmol) in EtOH (40 mL) was maintained at reflux 48 h. The mixture was cooled to rt, filtered through a pad of Celite, and concentrated at reduced pressure. The crude solid was recrystallized from cyclohexane to give 850 mg (86%): mp 208–210 °C (lit.[12a] mp 202 °C); ^{1}H NMR (DMSO-d_6) δ 6.58 (s, 1H), 6.97 (t, J = 7 Hz, 1H), 7.09 (t, J = 7.1 Hz, 1H), 7.12–7.42 (m, 6H), 7.49 (d, J = 7.7 Hz, 1H), 7.55 (d, J = 7 Hz, 2H), 11.39 (s, 1H); MS (FAB) m/z = 219 (M$^+$). Anal. Calcd for $C_{16}H_{13}N$: C, 87.64; H, 5.98; N, 6.39. Found: C, 87.71; H, 5.97; N, 6.19.

2-(1-Naphthyl)indole (5): yield 88%, mp 109–110 °C (hexane); ^{1}H NMR (DMSO-d_6) δ 6.73 (s, 1H), 7.06 (t, J = 7.0 Hz, 1H), 7.15 (t, J = 7.0 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.57–7.73 (m, 5H), 7.98–8.05 (m, 2H), 8.31, 8.33 (dd, J = 3.5 Hz, 3.5 Hz, 1H), 11.58 (s, 1H); MS (FAB) m/z = 243 (M$^+$). Anal. Calcd for $C_{18}H_{13}N$: C, 88.86; H, 5.39; N, 5.76. Found: C, 88.44; H, 5.34; N, 5.64.

2-(2-Indolyl)indole (6): yield 73%, mp 310–312 °C (lit.[14] mp 311–314 °C) (EtOH); ^{1}H NMR (DMSO-d_6) δ 6.92 (s, 2H), 7.00 (t, J = 8.1 Hz, 2H), 7.10 (t, J = 8.1 Hz, 2H), 7.40 (d, J = 8.5 Hz, 2H), 7.60 (d, J = 8.5 Hz, 2H), 11.55 (s, 2H); MS (FAB) m/z = 232 (M$^+$). Anal. Calcd for $C_{16}H_{12}N_2$: C, 82.73; H, 5.21; N, 12.06. Found: C, 82.87; H, 4.95; N, 11.94.

2-(5-Indolyl)indole (7). Purification by column chromatography (silica gel, EtOAc:hexane 1:3): yield 75%, mp 217–218 °C; ^{1}H NMR (DMSO-d_6) δ 6.50 (s, 1H), 6.77 (s, 1H), 6.96–7.07 (m, 2H), 7.36–7.50 (m, 4H), 7.61 (d, J = 8.5 Hz, 1H), 8.05 (s, 1H), 11.21 (s, 1H), 11.43 (s, 1H); MS (FAB) m/z = 232 (M$^+$). Anal. Calcd for $C_{16}H_{12}N_2$: C, 82.73; H, 5.21; N, 12.06. Found: C, 82.83; H, 5.19; N, 11.80.

2-(2-Pyridyl)indole (8). Purification by column chromatography (silica gel, EtOAc:hexane 1:3): yield 80%, mp 155.5–156.5 °C (lit.[4a] mp 145–147 °C); ^{1}H NMR (DMSO-d_6) δ 7.01 (t, J = 7.6 Hz, 1H), 7.09–7.14 (m, 2H), 7.31 (dd, J = 4.9, 1.6 Hz, 1H), 7.46 (d, J = 8.1 Hz, 1H), 7.57 (d, J = 7.9 Hz, 1H), 7.86 (t, J = 6.1 Hz, 1H), 8.01 (d, J = 8.0 Hz, 1H), 8.62 (d, J = 4.7 Hz, 1H), 11.69 (s, 1H); MS (FAB) m/z = 195 (M + 1)$^+$. Anal. Calcd for $C_{13}H_{10}N_2$: C, 80.39; H, 5.19; N, 14.42. Found: C, 80.10; H, 5.15; N, 14.55.

5-(2-Indolyl)isoquinoline (9). Purification by column chromatography (silica gel EtOAc:hexane 1:3): yield 92%, mp 234–235.5 °C; ^{1}H NMR (DMSO-d_6) δ 6.87 (d, J = 1.4 Hz, 1H), 7.11 (t, J = 7.2 Hz, 1H), 7.16 (t, J = 7.2 Hz, 1H), 7.47 (d, J = 8.1 Hz, 1H), 7.64 (d, J = 8.1 Hz, 1H), 7.78 (t, J = 7.3 Hz, 1H), 7.87 (t, J = 7.2 Hz, 1H), 8.24 (d, J = 8.0 Hz, 1H), 8.36 (d, J = 8.5 Hz, 1H), 8.72 (s, 1H), 9.36 (s, 1H), 11.72 (s, 1H); MS (FAB) m/z = 245 (M + 1)$^+$. Anal. Calcd for $C_{17}H_{12}N_2$: C, 83.58; H, 4.95; N, 11.47. Found: C, 83.51; H, 4.85; N, 11.41.

2-(2-Benzothienyl)indole (10). Purification column chromatography, silica gel EtOAc:hexane 1:3: yield 75%, mp 275–276 °C; ^{1}H NMR (DMSO-d_6) δ 6.82 (d, J = 1.5 Hz, 1H), 7.05 (t, J = 7.4 Hz, 1H), 7.15 (t, J = 7.9 Hz, 1H), 7.35–7.43 (m, 3H), 7.56 (d, J = 7.8 Hz, 1H), 7.82 (s, 1H), 7.86 (d, J = 7.2 Hz, 1H), 7.97 (d, J = 8.1 Hz, 1H), 11.81 (s, 1H); MS (FAB) m/z = 250 (M + 1)$^+$. Anal. Calcd for $C_{16}H_{11}NS$: C, 77.08; H, 4.45 N, 5.62. Found: C, 77.20; H, 4.48; N, 5.35.

2-(2-Benzofuryl)indole (11): yield 70%, mp 213–214 °C (cyclohexane); ^{1}H NMR (DMSO-d_6) δ 6.98 (s, 1H), 7.07 (t, J = 7.7 Hz, 1H), 7.17 (t, J = 7.3 Hz, 1H), 7.27–7.36 (m, 3H), 7.45 (d, J = 7.8 Hz, 1H), 7.58–7.65 (m, 2H), 7.71 (d, J = 7.2 Hz, 1H), 11.86 (s, 1H); MS (FAB) m/z = 233 (M$^+$). Anal. Calcd for $C_{16}H_{11}NO{\cdot}0.15H_2O$: C, 81.44; H, 4.83; N, 5.94. Found: C, 81.58; H, 4.60; N, 5.49.

2-(2-Thienyl)indole (12): yield 70%, mp 167–168 °C (hexane); ^{1}H NMR (DMSO-d_6) δ 6.67 (s, 1H), 7.00 (t, J = 6.9 Hz, 1H), 7.08 (d, J = 7.7 Hz, 1H), 7.12–7.16 (m, 1H), 7.37 (d, J = 7.6 Hz, 1H), 7.48–7.54 (m 3H), 11.56 (s, 1H); MS (FAB) m/z = 199 (M$^+$). Anal. Calcd for $C_{12}H_9NS{\cdot}0.05C_6H_{12}$: C, 72.57; H, 4.80; N, 6.88. Found: C, 72.94; H, 4.46; N, 6.92.

2-Phenylindole (13): yield 80%, mp 191–192 °C (EtOH) (lit.[4b] mp 187 °C); ^{1}H NMR (DMSO-d_6) δ 6.92 (s, 1H), 7.02 (t, J = 7.4 Hz, 1H), 7.10 (t, J = 7.6 Hz, 1H), 7.33 (t, J = 7.4 Hz, 1H), 7.38–7.54 (m, 4H), 7.87 (d, J = 7.8 Hz, 2H), 11.54 (s, 1H); MS (FAB) m/z = 194 (M + 1)$^+$. Anal. Calcd for $C_{14}H_{11}N$: C, 87.01; H, 5.74; N, 7.25. Found: C, 86.68 H, 5.80; N, 7.81.

5-Chloro-2-phenylindole (14): yield 86%, mp 197–198 °C (cyclohexane); ^{1}H NMR (DMSO-d_6) δ 6.90 (s, 1H), 7.10 (d, J = 7.1 Hz, 1H), 7.33–7.42 (m, 2H), 7.50 (t, J = 7.5 Hz, 2H), 7.56 (s, 1H), 7.86 (d, J = 7.9 Hz, 2H), 11.76 (s, 1H); MS (FAB) m/z = 227 (M$^+$). Anal. Calcd for $C_{14}H_{10}ClN$: C, 73.85; H, 4.43; N, 6.15; Cl, 15.57. Found: C, 73.89; H, 4.32; N, 6.17; Cl, 15.47.

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