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Efficient synthesis of 5- and 6-tributylstannylindoles and their reactivity with acid chlorides in the Stille coupling reaction

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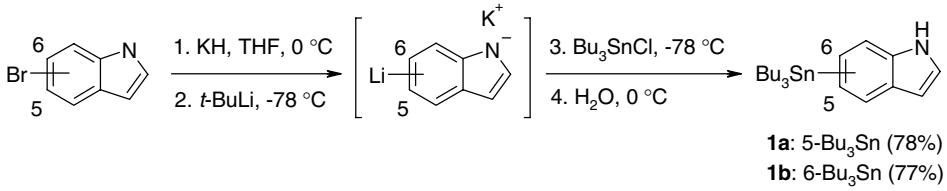
Abstract—Several 5- and 6-acylindoles have been synthesized in good yield by means of palladium catalyzed cross-coupling reactions between acid chloride derivatives and 5- or 6-tributylstannylindoles to give useful intermediates for the synthesis of analogues of biologically and pharmacologically active molecules.

5- or 6-Acylindoles are useful intermediates for the synthesis of a large range of biologically and pharmacologically active molecules.[1] Two main approaches have been utilized in the synthesis of such compounds: either the construction of a suitably functionalized benzenoid ring followed by annulation of the pyrrole portion to generate the indole system[2] or direct introduction of acyl substituents onto an already constructed indole.[3]

One of the common methods to prepare 5- or 6-acylindoles employs a halogen–metal exchange strategy from 5- or 6-bromoindoles. The resulting indolyl organometallic derivatives react with a variety of electrophiles as Weinreb amides, potassium carboxylic salts,[4] dimethylacetamide[5] or trifluoroacetic anhydride[6] to give pure acylated indoles. But this method contains one limitation due to lack of ability to incorporate a variety of substituents such as acid chlorides. Few examples of Pd-catalyzed cross-coupling reactions with acid chlorides can be found in the literature. Stille and co-workers were first to employ acyl chlorides and organostannanes in the Pd-catalyzed formation of unsymmetrical ketones.[7] Interestingly, stannylindole species and their implication in the Stille coupling have previously received very little attention in organic synthesis.[5,8] We report here the synthesis of 5- and 6-tributylstannylindoles and their reactivity with acid chlorides in the Stille coupling reaction.

Reaction of 5- or 6-bromoindole[9] with potassium hydride in THF at −78 °C allowed abstraction of the indole NH and gave a homogeneous solution of the potassium salt, which upon treatment with *tert*-butyllithium underwent rapid and efficient lithium–halogen exchange. The metallated species was then reacted with tributyltin chloride as electrophile to afford 5- and 6-tributylstannylindoles in, respectively, 78% and 77% yields[10] (Scheme 1). Yang and co-workers described



Scheme 1. Synthesis of 5- and 6-tributylstannylindoles.

Keywords: Tributylstannylindole; Acylation; Stille coupling reaction.
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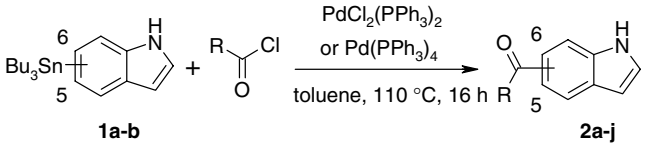
the synthesis of 5-trimethylstannylindole in 37% yield.[5] This low yield can be explained by the cleavage of Sn–C bond due to treatment with an acidic aqueous solution of the reaction mixture. We obtained high yields of stannylindoles by hydrolysis with ice cold water and purification on silica gel previously neutralized with triethylamine, which avoided cleavage of the Sn–C bond.

The stannanes **1a**,**b** were then reacted with a variety of acid chlorides under the Stille-type cross-coupling conditions.[7,11] We found that the best results of ketone formation from cyclopropanoyl chloride were obtained with 1.3 equiv of stannylindole **1a**, 5% dichlorobis(triphenylphosphine)-palladium II or tetrakis(triphenylphosphine)palladium in toluene at 110 °C for 16 h and afforded **2a** in 70% yield.[12] The use of less than 1.3 equiv of stannylindole **1a** led to the formation of a mixture of 5-cyclopropanoylindole and 1,5-dicyclopropanoylindole. We were pleased to find that 5- and 6-tributylstannylindoles **1a,b** underwent a clean coupling reaction with a variety of acid chlorides (Table 1) such as cycloalkylcarbonyl, arylcarbonyl and heteroarylcarbonyl chlorides in 70–82% yields.

Coupling of **1a** or **1b** with cyclopropanoyl or cyclohexanoyl chloride gives the corresponding acylindoles **2a,b,h** in 70% yield (Table 1, entries 1, 2, 8) when the acylium ion is unstable under the Friedel–Craft conditions and the reaction cannot be performed. The reaction proceeds equally well with benzoyl chloride derivatives substituted with electron rich or withdrawing groups (entries 3–6, 9) or heteroarylcarbonyl chlorides (entries 7, 10).

In summary, we have developed a general, simple and effective procedure for the synthesis of 5- and 6-tributylstannylindoles by halogen–metal exchange method followed by the addition of tributyltin chloride as electrophile. Under Stille conditions, 5- and 6-tributylstannylindoles react with acid chlorides to give 5- and 6-acylindoles in good isolated yields. The mild reaction conditions of the indole acylation by Stille coupling and the tolerance of the substituent nature make this method an attractive alternative to existing methodologies. The resulting intermediates might serve for the synthesis of heterocyclic derivatives of indoles with potential biological interest.

Table 1. Stille coupling of compounds **1a**,**b** with acyl chlorides



1a-b **2a-j**

Entry	Position of tributyltin	R	Products (yield[a]) (%)
1	5	Cyclopropyl	**2a** (70)
2	5	Cyclohexyl	**2b** (71)
3	5	4-Fluorophenyl	**2c** (77)
4	5	4-Tolyl	**2d** (79)
5	5	4-Cyanophenyl	**2e** (75)
6	5	4-Methoxyphenyl	**2f** (79)
7	5	2-Thienyl	**2g** (82)
8	6	Cyclohexyl	**2h** (70)
9	6	4-Fluorophenyl	**2i** (77)
10	6	2-Thienyl	**2j** (80)

[a] Isolated yield.

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Supplementary data

Spectroscopic data and elemental analysis are provided for compounds **2b–j**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.06.084.

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9. 5-Bromoindole is commercially available, 6-bromoindole was prepared by the Batcho-Leimgruber Indole synthesis from the 4-bromo-2-nitrotoluene in 62% overall yield,

please see for references: Clarck, R. D.; Repke, D. B. *Heterocycles* **1984**, *22*, 195–221, and Ref. 4.

10. *General procedure for the synthesis of 5- and 6-tributylstannylindoles:* A solution of 3.98 g (20 mmol) of 5- or 6-bromoindole in 40 mL of anhydrous THF was added to 2.29 g of KH dispersion in mineral oil (35%, 20 mmol) in 40 mL of anhydrous THF at 0 °C. After 15 min the solution was cooled to −78 °C and *tert*-butyllithium (40 mmol, 1.5 M in pentane) precooled to −78 °C was added via a cannula. A white precipitate immediately formed and, after 10 min, 13 g of tributyltin chloride (40 mmol) dissolved in 10 mL of anhydrous THF was added. The reaction mixture was allowed to slowly warm to room temperature and the suspension was poured into 150 mL of ice cold water. The organic layer was separated and the aqueous layer was extracted twice with diethyl ether. The ether extracts were combined, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was chromatographed on silica gel (40–63 mesh) previously neutralized with triethylamine, eluting with petroleum ether/triethylamine 99:1 then petroleum ether/ethyl acetate/triethylamine 90:9:1 to give compounds **1a**,**b** as a colourless oil. Compound **1a**: IR (KBr) ν (cm^{-1}): 3412, 2956, 2925, 2870, 2852, 1605, 1510, 1454; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.89 (t, $J = 7.3$ Hz, 9H), 1.07 (m, 6H), 1.34 (m, 6H), 1.55 (m, 6H), 6.55 (m, 1H), 7.17 (m, 1H), 7.27 (d, $J = 8.4$ Hz, 1H), 7.40 (d, $J = 8.4$ Hz, 1H), 7.76 (t, $J = 22$ Hz, 1H), 8.16 (NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 9.8 (t, $J = 166$ Hz, 3C), 13.9 (3C), 27.7 (t, $J = 27$ Hz, 3C), 29.4 (t, $J = 10$ Hz, 3C), 102.0, 111.2 (t, $J = 22$ Hz), 123.9, 128.4, 129.0 (t, $J = 17$ Hz), 129.5 (t, $J = 18$ Hz), 130.5, 136.1. Anal. Calcd for $C_{20}H_{33}NSn$: C, 59.14; H, 8.19; N, 3.45. Found: C, 59.48; H, 8.11; N, 3.51. **1b**: IR (KBr) ν (cm^{-1}): 3410, 2952, 2926, 2873, 2855, 1606, 1510, 1455; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.90 (t, $J = 7.3$ Hz, 9H), 1.08 (m, 6H), 1.36 (m, 6H), 1.57 (m, 6H), 6.54 (m, 1H), 7.18–7.23 (m, 2H), 7.52 (t, $J = 22$ Hz, 1H), 7.65 (d, $J = 7.9$ Hz, 1H), 8.10 (NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 9.7 (t, $J = 169$ Hz, 3C), 13.7 (3C), 27.4 (t, $J = 27$ Hz, 3C), 29.2 (t, $J = 10$ Hz, 3C), 103.4, 118.8 (t, $J = 18$ Hz), 120.3 (t, $J = 23$ Hz), 123.6, 127.3 (t, $J = 17$ Hz), 127.8, 133.6, 136.2. Anal. Calcd for $C_{20}H_{33}NSn$: C, 59.14; H, 8.19; N, 3.45. Found: C, 59.39; H, 8.05; N, 3.58.
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12. *General procedure for Stille coupling:* Dichlorobis-(triphenylphosphine) palladium (140.4 mg, 0.2 mmol) was added to a solution of the appropriate acid chloride (10 mmol) in anhydrous toluene (40 mL) under argon. The mixture was stirred at room temperature for 10 min and 5- or 6-tributylstannylindole (5.3 g, 13 mmol) in 10 mL of toluene was added. The reaction mixture was stirred and heated at 110 °C for 16 h. After conversion was complete (checked by TLC), the solvent was evaporated under reduced pressure and the oily mixture was treated with ethyl acetate and 1 M solution of potassium fluoride at room temperature for 30 min to precipitate the formed tributyltin fluoride. The resulting solution was filtered through a Celite pad and extracted with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The crude products were chromatographed on silica gel (petroleum ether/ethyl acetate 95:5 then petroleum ether/ethyl acetate 80:20) to afford compounds **2a**–**j**. For example: Compound **2a**: Mp: 114–116 °C; IR (KBr) ν (cm^{-1}): 3264, 2912, 2846, 1643, 1593, 1565, 1500; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.05 (m, 2H), 1.27 (m, 2H), 2.82 (m, 1H), 6.69 (m, 1H), 7.30 (m, 1H), 7.44 (d, $J = 8.8$ Hz, 1H), 7.93 (dd, $J = 8.8$ Hz, $J = 1.7$ Hz, 1H), 8.44 (d, $J = 1.7$ Hz, 1H), 8.51 (NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 11.2 (2C), 16.9, 104.0, 111.1, 121.9, 122.5, 125.9, 127.4, 130.4, 138.5, 201.2; Anal. Calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 78.03; H, 6.04; N, 7.47.