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Synthesis of 6-allyl and 6-heteroarylindoles by palladium catalyzed Stille cross-coupling reaction

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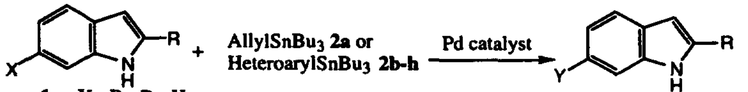
Abstract

Several 6-allyl and 6-heteroarylindoles have been synthesized in high yield by means of palladium catalyzed cross-coupling reactions between tributyltin derivatives and 6-haloindoles to give useful intermediates for the synthesis of analogues of biologically active natural products.

Keywords: heteroarylindoles; Stille cross-coupling; palladium catalysts.

The 2-heteroarylindole motif is of considerable importance in the field of medicinal chemistry since it is a common feature of a number of antibiotics.[1] The related 6- and 7-arylindole systems are also found in natural glycopeptides such as chloropeptins and its analogues which have been reported as antibiotics and CD-4 protein inhibitors.[2]



1a: X= Br, R= H.
1b: X= I, R= H.
1c: X= I, R= CH_2CO_2Me

3a (Y= Allyl)
3b-h (Y= Heteroaryl)

Preparation methods for 6- and 7-arylindole have been reported providing useful intermediates to serve in the syntheses of various natural products.[3] These synthons were obtained in poor-to-moderate yields by application of the classical Suzuki reactions using boronic acid derivatives. We felt that in this series, the Stille[4] cross-coupling reaction should offer real advantages in view of the accessibility and stability of the tin derivatives and the neutral conditions to be employed. In contrast, boronic acids need to be prepared under acidic conditions while basic conditions are necessary for performing Suzuki biaryl cross-coupling reactions. Accordingly, it is not surprising that only a few examples of heteroarylindole

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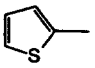
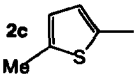
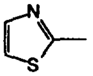
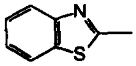
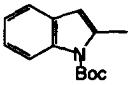
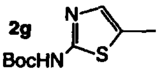
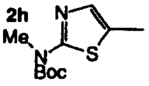
Table 1

Entry	Substrate	Ar	Conditions[a]	Products	Yield[b]
1	**1a**	2a 	80°C, 12h	**3a** (R=H)	89
2	**1b**		60 °C, 0.5h	**3a** (R=H)	92
3	**1c**		60 °C, 0.5h	**3a** ($R=CH_2CO_2Me$)	90
4	**1a**	2b 	80°C, 14h	**3b** (R=H)	81
5	**1b**		60°C, 1h		90
6	**1b**	2c 	60°C, 1h	**3c** (R=H)	83
7	**1b**	2d 	60°C, 0.5h	**3d** (R=H)	77
8	**1b**	2e 	60°C, 0.5h	**3e** (R=H)	87
9	**1b**	2f 	60°C, 0.5h	**3f** (R=H)	93
10	**1a**	2g 	60°C, 48h	**3g** (R=H)	43
11	**1b**		60°C, 3h	**3g** (R=H)	46
12	**1c**		25°C, 16h	**3g** ($R=CH_2CO_2Me$)	61
13	**1a**	2h 	80°C, 12h	**3h** (R=H)	91
14	**1b**		60°C, 0.5h	**3h** (R=H)	88
15	**1c**		60°C, 0.5h	**3h** ($R=CH_2CO_2Me$)	90

[a]Reaction conditions: $Pd(PPh_3)_4$ (0.05 equiv.), CuI (0.2 equiv.), DMF. [b]Yields after purification.

synthesis have been reported. To circumvent this limitation we probed the Stille methodology which, in our hands, gave access to functionalized heteroarylindoles in a convenient manner.

We show (Table 1) that a number of free 6-haloindoles **1a–c** underwent a clean coupling reaction with a variety of tributyltin reagents in DMF in the presence of palladium catalyst to give high yields of the desired 6-substituted derivatives.[5] However, in the case of **2g** the corresponding reaction product **3g** (R=H) was obtained in a moderate yield because of the instability of the organometallic reagent at temperatures higher than 60°C. It is probable that decomposition of the compound occurs by amidic hydrogen transfer on the 5-position, with concomitant tributyltin group elimination. This is in agreement with the following observations: (i) when the reaction was run at room temperature the product was obtained in improved yield (entry 12); whereas (ii) the diprotected derivative **2h** gave the coupling product in high yield under the same conditions (entries 13–15).

In summary, the Stille cross-coupling reaction was applied to give various 6-heteroarylindoles in high yields. The resulting intermediates might serve for the synthesis of heterocyclic derivatives of indoles of potential biological interest.

References

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2. Hegde, V. R.; Dai, P.; Patel, M.; Gullo, V. P. *Tetrahedron Lett.* **1998**, *39*, 5683–5684 and references cited therein.
3. Carbonnelle, A.-C.; Zamora, E. G.; Beugelmans, R.; Roussi, G. *Tetrahedron Lett.* **1998**, *39*, 4467–4470 and references cited therein.

4. Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508–524.
5. Typical reaction procedure: A mixture of 6-haloindole (1 mmol), tributyltin reagent (1.5 mmol) and $Pd(PPh_3)_4$ (0.05 equiv.) ($Pd(PPh_3)_2Cl_2$ gave the same results with longer reaction time) in dry DMF (10 ml) was maintained under an inert atmosphere at the temperature as indicated. The mixture was diluted with EtOAc (50 ml) and filtered over Celite. After removal of the solvent, the residue was purified by flash chromatography (silica gel, EtOAc/heptane) to provide the 6-substituted indoles.