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An Efficient Synthesis of 2-(2-Pyridyl)indoles by Palladium(0)-catalyzed Heteroarylation

Mercedes Amat, Sabine Hadida, and Joan Bosch

Laboratory of Organic Chemistry, Faculty of Pharmacy, University of Barcelona, 08028-Barcelona, Spain

Abstract: A general method for the preparation of 2-(2-pyridyl)indoles based on the palladium(0)-catalyzed coupling of 1-(benzenesulfonyl)-2-indolylzinc chloride with 2-halopyridines is reported.

The 2-(2-pyridyl)indole moiety, either as such or in a reduced form, is present in a large number of indole alkaloids, *e.g.* zwitterionic indolo[2,3-*a*]quinolizine alkaloids[1] or the more complex eburnan- and corynantean-type alkaloids. Although several methods have been reported[2] for the synthesis of this simple structural unit, in most cases their scope is not general or their synthetic utility is restricted by low yields, hardly accessible starting materials, or incompatibility with some functional groups.

We report here an efficient and facile method for the preparation of 2-(2-pyridyl)indoles **3** based on the palladium(0)-catalyzed coupling of a *N*-protected 2-indolylzinc derivative[3,4] **1** with 2-halopyridines **2**.

The required 2-indolylzinc chloride **1** was prepared by treatment of 1-(benzenesulfonyl)indole with LDA followed by metathesis with anhydrous $ZnCl_2$. The reaction of **1** (1.5 equiv.) with 2-bromo-4-methylpyridine (**2a**) in the presence of 2 mol % of a catalyst prepared from $PdCl_2(PPh_3)_2$ and DIBAH (2 equiv.), in refluxing THF under argon for 4 h, led to the corresponding 2-(2-pyridyl)indole **3a** in excellent yield (92 %, Table 1).[5] $Pd(Ph_3P)_4$ also gave good results in the above reaction although it was found less convenient from the experimental standpoint. In all reactions the corresponding 2,2′-biindole was formed in approximately 15 % yield [based on 1-(benzenesulfonyl)indole]. In the absence of Pd(0)-catalyst no reaction was observed, whereas attempted coupling reaction of indole with **2a** or 1-(benzenesulfonyl)indole with **2c** or **2d** in the presence of $Pd(Ph_3P)_4$ (3 mol %) also failed under several reaction conditions.

It is known that the relative rates in the oxidative addition step of aryl halides with Pd(0)-complexes depend on the halogen (I>Br>Cl) and that the process is accelerated by the presence of electron-withdrawing groups on the aryl ring[6]. Accordingly, a similar cross-coupling reaction of indolylzinc **1** with 2-chloropyridine **2b**, having an electron-releasing alkyl group, gave the 2-(2-pyridyl)indole **3b** in lower yield (40 %). However, the unsubstituted 2-chloro- and 2-bromopyridines **2c** and **2d**, respectively, afforded the corresponding pyridylindole **3c** in a similar good yield. The scope of the reaction seems to be quite general as both 2-

bromopyridines **2e**-**2g**, having alkyl or methoxy substituents, and 2-chloropyridines **2i**-**2m**, having strongly electron-withdrawing nitro and ester groups, gave yields ranging from 70 to 97 %.

Worthy of mention are the facts that the organometal indole derivative employed here is compatible with the presence of ester groups and that the reaction also takes place, although in moderate yield (40 %), with 2-bromopyridine **2h**, which incorporates an acidic hydroxy group.

This simple and efficient method deserves interest as provides the most general procedure for the synthesis of 2-(2-pyridyl)indoles, some of which can be envisaged as synthetic precursors of indole alkaloids. Thus, compound **3f** has been previously converted into the zwitterionic alkaloid flavocarpine.[2e]

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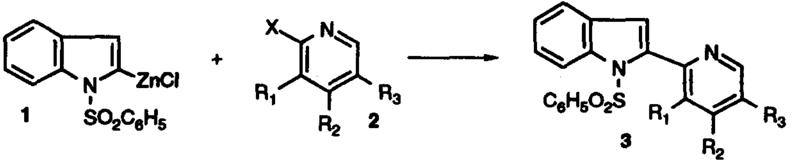

Table 1. The Palladium(0)-catalyzed Coupling of Indolylzinc 1 with Halopyridines 2

	Halopyridine (2)				2-(2-Pyridyl)indole (3)				
	X	R_1	R_2	R_3	Product[a]	R_1	R_2	R_3	Yield(%)[b]
2a	Br	H	Me	H	3a	H	Me	H	92
2b	Cl	H	Me	H	3a	H	Me	H	40
2c	Br	H	H	H	3c	H	H	H	78
2d	Cl	H	H	H	3c	H	H	H	75
2e[a]	Br	Et	Me	H	3e	Et	Me	H	94
2f[a]	Br	H	Me	Et	3f	H	Me	Et	89
2g	Br	OMe	H	H	3g	OMe	H	H	80
2h	Br	OH	H	H	3h	OH	H	H	40
2i	Cl	CO_2Me	H	H	3i	CO_2Me	H	H	83
2j	Cl	H	CO_2Me	H	3j	H	CO_2Me	H	95
2k	Cl	H	H	CO_2Me	3k	H	H	CO_2Me	80
2l	Cl	H	H	NO_2	3l	H	H	NO_2	97
2m	Cl	NO_2	H	NO_2	3m	NO_2	H	NO_2	70

[a] All new products were identified by ^{1}H and ^{13}C NMR, IR, and elemental analysis. [b] Isolated yields (after column chromatography) based on 2-halopyridine.

References and Notes

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3. To our knowledge there is only one report about the use of a 2-indolylzinc derivative in cross-coupling reactions: Vincent, P.; Beaucourt, J. P.; Pichat, L. *Tetrahedron Lett.* **1984**, *25*, 201.
4. a) For a review on transition metal catalyzed reactions of organozinc reagents, see: Erdik, E. *Tetrahedron* **1992**, *48*, 9577. b) For a review on Pd-catalyzed reactions involving heterocycles, see: Kalinin, V. N. *Synthesis* **1992**, 413.
5. A similar reaction using 1-(benzenesulfonyl)-2-indolyltrimethyltin in the presence of Pd(Ph$_3$P)$_4$ (3 mol %) afforded **3a** in 32% yield. Lower yields were obtained from the tri-*n*-butyltin derivative.
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