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INDOLYLZINC IODIDES BY OXIDATIVE ADDITION OF ACTIVE ZINC TO IODOINDOLES

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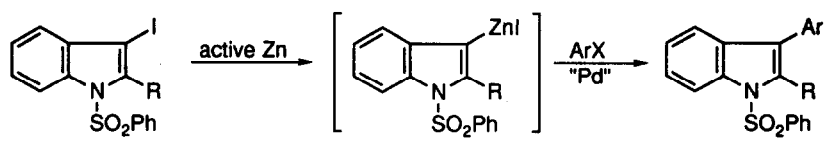
Abstract: Indolylzinc derivatives were prepared by the oxidative addition of active zinc to iodoindoles, which coupled with aromatic halides in the presence of palladium catalyst to give arylated indoles.

Organozinc derivatives have been used for the palladium-catalyzed cross-coupling reaction to perform chemoselective carbon-carbon bond formation.[1] Arylzinc derivatives have been used for functionalization of aromatic rings, and direct preparation of arylzinc derivatives by the oxidative addition of active zinc to haloaromatics was recently reported.[2] The method is considered to have wide applicability to many aromatic compounds, but the application of this method on the heteroaromatics is known only for pyridines.[3]

2-Indolylzinc derivatives can be prepared by transmetallation of 2-indolyllithium with zinc chloride,[4] but the transmetallation of 3-indolyllithium[5] with zinc chloride was unsuccessful.[6] In order to develop practical method to prepare 3-indolylzinc derivatives, the oxidative addition of active zinc to 3-iodoindoles was investigated.

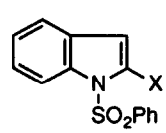
3-Iodo-1-(phenylsulfonyl)indole (**1a**) was treated in tetrahydrofuran with active zinc *at room temperature* to give 1-(phenylsulfonyl)-3-indolylzinc iodide (**2a**) which coupled with iodobenzene in the presence of tetrakis-(triphenylphosphine)palladium at room temperature to afford 3-phenyl-1-(phenylsulfonyl)indole (**3a**) in 83% yield.[7] 3-Indolylzinc iodide **2a** was also reacted with 2-bromopyridine and 2-iodothiazole to give the corresponding coupling products (**3b** and **3c**) in excellent yields as shown in Table I.



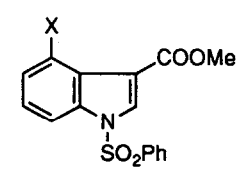
1a: R=H
1b: R=COOEt

2a: R=H
2b: R=COOEt

3a-e



4a: X=I
4b: X=Ph
4c: X=2-pyridyl



5a: X=I
5b: X=Ph

Ethyl 3-iodo-1-phenylsulfonyl-2-indolecarboxylate (**1b**) reacted with active zinc smoothly to give the corresponding indolylzinc iodide (**2b**) which was subjected to palladium-catalyzed cross-coupling reaction with iodobenzene and 2-bromopyridine to give **3d** and **3e** in moderate yields.

Table I. Palladium-Catalyzed Arylation of Indolylzinc Iodides Derived from Iodoindoles

Substrate	ArX	Reaction conditions	Product	Yield (%)
1a	iodobenzene	room temp., 18 h	**3a**	83
1a	2-bromopyridine	room temp., 18 h	**3b**	76
1a	2-iodothiazole	room temp., 18 h	**3c**	73
1b	iodobenzene	reflux, 18 h	**3d**	44
1b	2-bromopyridine	reflux, 18 h	**3e**	44
4a	iodobenzene	room temp., 18 h	**4b**	57
4a	2-bromopyridine	room temp., 18 h	**4c**	45
5a	iodobenzene	room temp., 18 h	**5b**	41

Similarly, 2-iodo-1-(phenylsulfonyl)indole (**4a**) and ethyl 4-iodo-1-(phenylsulfonyl)-3-indolecarboxylate (**5a**) were converted into zinc derivatives by the oxidative addition of active zinc, and the subsequent palladium-catalyzed cross-coupling reaction was carried out with no difficulty.

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6 Transmetallation of 3-indolyllithium with $ZnCl_2$ at –40°C gave a 1:1 mixture of 2- and 3-indolylzinc derivatives.

7 3-Phenyl-1-(phenylsulfonyl)indole: All operations were performed under argon atmosphere. A mixture of naphthalene (3.7 g, 29 mmol) and lithium (83 mg, 12 mmol) in dry THF (5 ml) was stirred at room temperature for 18 h, followed by addition of an 1M THF solution of $ZnCl_2$ (6.3 ml, 6.3 mmol). The mixture was centrifuged (2,500 rpm, 20 min), and the supernatant was discarded. The remained active zinc was suspend ed in dry THF followed by addition of 3-iodo-1-phenylsulfonylindole (766 mg, 2 mmol). The mixture was stirred at room temperature for 2 h. The mixture was centrifuged (2,500 rpm, 20 min), and the supernatant was added to a THF solution (2 ml) of iodobenzene (410 mg, 2 mmol) and $Pd(PPh_3)_4$ (0.05 mmol). The whole mixture was stirred at room temperature for 18 h, and filtrated with Celite. The filtrate was extracted with $CHCl_3$ (25 ml x 3), dried over $MgSO_4$, and evaporated *in vacuo*. The crude product was purified by silica gel column chromatography using hexane-AcOEt (9:1) as an eluent to give 3-phenyl-1-(phenylsulfonyl)indole as colorless needles (hexane-AcOEt) (550 mg, 83%). mp 141-143°C. ^{1}H-NMR ($CDCl_3$) δ: 7.28-7.63 (10H, m), 7.70 (1H, s), 7.78 (1H, d), 7.93 (2H, dt, *J*8.1, 1.7Hz), 8.06 (1H, d, *J*8.1Hz).

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