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Preparation of Vinylogous 2-Sulfonylindolines by the Palladium-Catalyzed Cyclization of 1-Sulfonyl-1,3-dienes with N-Cbz-*o*-Iodoanilines

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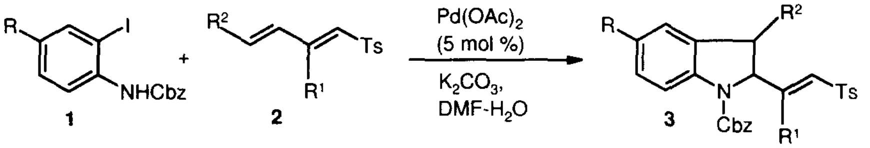
Abstract: N-Cbz-*o*-Iodoanilines undergo $Pd(OAc)_2$-catalyzed coupling and cyclization with 1(-*p*-toluenesulfonyl)-1,3-dienes to afford 2-(2- *p*-toluenesulfonylvinyl)-indolines under mild conditions.

The palladium-catalyzed coupling of aryl or vinyl halides with olefins via the Heck reaction[1] provides a powerful method for C-C bond formation between two sp^2-hybridized centers.[2] When the reaction is performed with a conjugated diene in the presence of a nucleophile such as a secondary amine, incorporation of the latter takes place via displacement of palladium from a π-allyl palladium complex.[1a,1b] Although variously substituted olefins have been employed as substrates, unsaturated sulfones[3] have rarely been exploited in Heck or related palladium-catalyzed coupling reactions.[4] We now report that the $Pd(OAc)_2$-catalyzed coupling of N-Cbz-*o*-iodoanilines **1** with 1-(p-toluenesulfonyl)-1,3-dienes **2** affords the corresponding 2-substituted indolines **3** as shown in eqn 1. The products are potential intermediates for synthetic routes to a variety of biologically interesting target compounds containing the indoline or, after oxidation, the corresponding indole moiety.



(eqn 1)

The anilines **1**[5] and sulfonyldienes **2**[6] were easily obtained by literature procedures and the results of the coupling reactions are shown in Table 1. The reaction tolerates both electron-donating (entries 4 and 8) and withdrawing groups (entry 7) at the 4-position of the aniline, although the most rapid rate was observed with the electron-withdrawing ester substituent. The 2-methyl-substituted sulfonyldiene (entries 2, 5 and 9) afforded lower yields than the corresponding unsubstituted diene (cf. entries 1, 4 and 8), while the 4-methyl analogue failed to cyclize to the corresponding product **3** (entries 3 and 6). No improvement was noted when triphenylphosphine was added to the reaction mixtures.[1] Attempts to perform the reactions at elevated temperatures gave lower yields and more complex product mixtures than at room temperature. The presence of the Cbz group was essential for the successful formation of **3**.

These experiments show that 1-sulfonyldienes can be effectively employed in Heck reactions and, when used in conjunction with *o*-iodoanilines, provide access to indolines containing potentially useful vinyl sulfone[3] moieties at the 2-position.

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Table 1. Preparation of Indolines 3

	Aniline **1**	Diene **2**		Reaction	Isolated
Entry	R	R^1	R^2	time (days)^a	Yield of **3** (%)^b
1	H	H	H	5	83
2	H	Me	H	6	66
3	H	H	Me	16	-
4	Me	H	H	8	81
5	Me	Me	H	12	53
6	Me	H	Me	19	-
7	CO_2Me	H	H	0.5	73
8	OMe	H	H	12	78
9	OMe	Me	H	11	25

a) All reactions were performed at room temperature in DMF-water
b) All products were characterized by their IR, ^{1}H-NMR and mass spectra; all gave either satisfactory combustion analyses or ^{13}C-NMR and high-resolution mass spectra

Typical experiment (entry 1): N-Cbz-*o*-iodoaniline (0.51 mmol), (*E*)-1-(*p*-toluenesulfonyl)-1,3-butadiene(1.03 mmol), potassium carbonate (0.51 mmol) and palladium acetate (0.025 mmol) were stirred in 6 mL of DMF-H_2O (10:1) under argon for 5 days at room temperature. After removal of the solvent, the product was triturated with ether, filtered, washed with brine, dried and purified by flash chromatography (silica-gel, hexane-ethyl acetate 2:1) to afford 83% of the product **3** (R, R^1, R^2 = H), mp 145.5-146.5°C (from benzene). The large coupling constant of the olefinic protons J_{trans}= 15.2 Hz confirmed the *E*-configuration.

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5. The anilines **1** were prepared from the following known compounds by standard methods. *o*-iodoaniline: commercially available (Aldrich Co.); *o*-iodo-*p*-toluidine: Kajigaeshi, S.; Kakinami, T.; Yamasaki, H.; Fujisaki, S.; Okamoto, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 600-602; 4-amino-3-iodobenzoic acid: Hill, M.L.; Raphael, R.A. *Tetrahedron Lett.* **1986**, *27*, 1293-1296; 4-amino-3-iodophenol: Kvalnes, D.E. *J. Am. Chem. Soc.* **1934**, *56*, 667-670.
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