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1-(PHENYLSULFONYL)INDOL-2-YL TRIFLATE: A VERSATILE REAGENT FOR THE SYNTHESIS OF 2-SUBSTITUTED INDOLES.

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Abstract: The palladium-catalysed reaction of 1-(phenylsulfonyl)indol-2-yl triflate **1** with a variety of aryl and heteroaryl boronic acids **2** or vinyl tributylstannane **3** provides a general and an efficient method for the synthesis of 2-substituted indoles **4**.

Despite the low accessibility of 2-aryl and 2-vinyl-*1H*-indoles, they are frequently used as the intermediates for drug and alkaloid syntheses.[1-3] A large number of 2-aryl-*1H*-indoles are prepared by *de novo* construction of the indole nucleus via Fischer indole synthesis. 2-Vinyl-*1H*-indoles have been prepared using Wittig reactions and are often used in Diels-Alder reactions.[4]

Palladium-catalysed coupling reaction is another powerful strategy to introduce miscellaneous groups into indoles at 2-position.[5,6] Most of the reported works dealt with 2-stannylindoles[7,8] or 2-zincindoles species[9,10] due to their easy availability from 2-lithioindoles species. The use of 2-halide derivatives is

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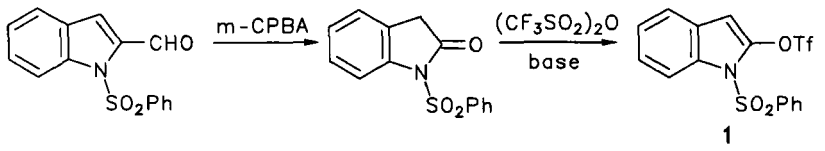


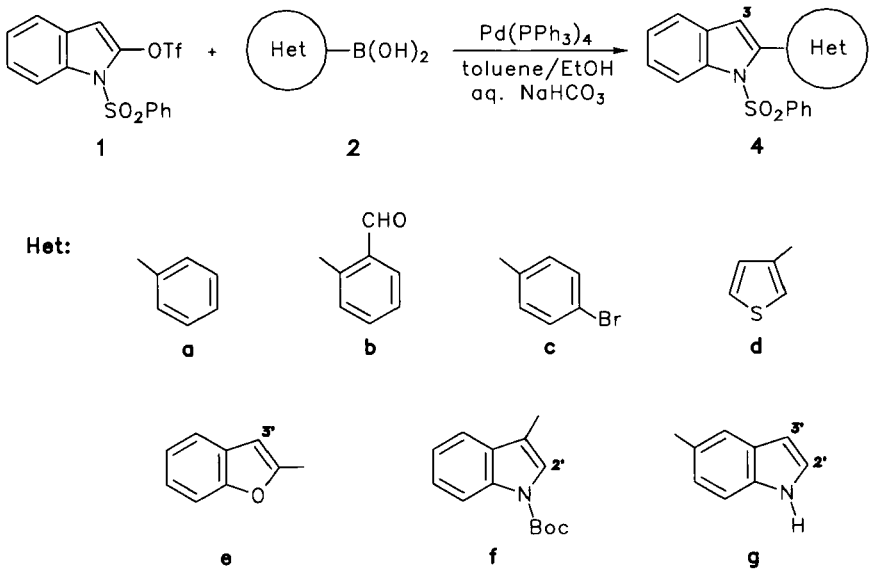
Scheme 1

scarcely described due to the difficulty of obtaining them. Bergman has reported the preparation of 2-bromo or 2-iodoindole[11] which were used in the coupling reactions with stannyl or boronic acid derivatives.[12]

The synthesis and reactivity of indol-3-yl triflate has been reported by Gribble.[13] More recently, we have published a fruitful preparation of 1-(phenylsulfonyl)indol-2-yl triflate in two steps (Scheme 1).[14] 2-formyl-1-(phenylsulfonyl)-1*H*-indole was oxidised with *m*-CPBA and the oxindole obtained was treated with trifluoromethanesulfonic anhydride and diisopropylethylamine to give triflate **1**.

The recent report of Hudkius[15] on palladium-cross coupling reaction of 1-carboxy-2-(tributylstannyl)indole prompted us to present our investigations about the preparation of 2-substituted indoles from indol-2-yl triflate using a Suzuki methodology (Scheme 2).

Preliminary studies were carried out with the commercially available phenyl boronic acid **2a** as a model. The modified protocol, established by G. M. Carrera and G. S. Sheppard,[16] was applied to couple **1** and **2a** using $Pd(PPh_3)_4$, as the catalyst, and aqueous $NaHCO_3$ which hence resulted in complete consumption of the starting material. The 2-phenyl-1-phenylsulfonylindole **4a** was obtained in 90% yield. This protocol was then extended to a variety of aryl and heteroaryl boronic acids **2b-g**. In all cases examined, the coupling reactions furnished the compounds **4b-g** with moderate to excellent yields (Table 1).

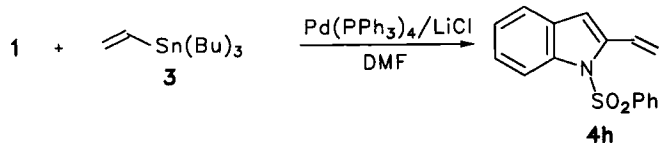


Scheme 2

Table 1: Yields and data for compounds **4**

Compd	Yield (%)	mp (°C)	Molecular Formula[a]	MS (CI, NH_3)
4a	90	103-105 (MeOH)	$C_{20}H_{15}NO_2S$ 333.41	334 $(M+1)^+$
4b	65	gum	$C_{21}H_{15}NO_3S$ 361.42	362 $(M+1)^+$
4c	77	gum	$C_{20}H_{14}BrNO_2S$ 412.31	413 $(M+1)^+$ 415 $(M+3)^+$
4d	60	114-116 (MeOH)	$C_{18}H_{13}NO_2S_2$ 339.44	340 $(M+1)^+$
4e	91	135-137 (MeOH)	$C_{22}H_{15}NO_3S$ 373.43	374 $(M+1)^+$
4f	81	157-159 (Et_2O)	$C_{27}H_{24}N_2O_4S$ 472.57	473 $(M+1)^+$
4g	80	gum	$C_{22}H_{16}N_2O_2S$ 372.45	373 $(M+1)^+$
4h	71	gum	$C_{16}H_{13}NO_2S$ 283.35	284 $(M+1)^+$

[a]Satisfactory microanalysis obtained for compounds **4** C±0.25 H±0.25 N±0.22.



Scheme 3

This methodology gave access to unusual 2,3'- and 2,5'-biindoles, 2,2' and 2,3' heteroarylindoles. Biindoles are known to be important precursors in the synthesis of indolo[2,3-*a*] carbazoles.[17] Compound **4c** can be used, due to the presence of the bromine substituent, as a new starting material to the preparation of biindoles with a phenyl group linker.

In coupling reaction with vinyl stannane **3** (Scheme 3) better yield was obtained in the presence of $Pd(PPh_3)_4$ as catalyst and LiCl in DMF. 2-Substituted indole **4h** was isolated in fair yield. Physical properties and spectroscopic data for compounds **4** are reported in Table 1 and 2.

In summary, we have shown that 1-(phenylsulfonyl)indol-2-yl triflate **1** is a good alternative to 2-halogeno or 2-stannyl indoles in the palladium-catalysed coupling reaction to prepare various and functionnalised 2-substituted-1*H*-indoles.

EXPERIMENTAL

Melting points were determined using a Büchi SMP-20 melting point apparatus and are uncorrected. NMR spectra were recorded at 300°K in $CDCl_3$ on a Bruker Avance DPX 250 (250.13 MHz for ^1H). Chemical shifts are expressed in parts per million and referenced to TMS. Mass spectra were recorded on Nermag-R-10-10C using chemical ionization. Reactions were monitored by thin layer chromatography using Merck silica gel $60F_{254}$ visualized with UV. Column chromatography was performed using Merck silica gel 60 (0.063-0.200 mm).

Table 2: ^{1}H NMR data for compounds **4**.

Compd	^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm), J (Hz)
4a	8.32 (d, 1H, J = 8.3, H_{ar}); 7.51-7.21 (m, 13H, H_{ar}); 6.55 (s, 1H, H_3)
4b	9.74 (s, 1H, CHO), 8.38 (d, 1H, J = 8.4, H_{ar}); 8.04-8.01 (m, 1H, H_{ar}); 7.64-7.25 (m, 11H, H_{ar}); 6.60 (s, 1H, H_3)
4c	8.34 (d, 1H, J = 8.4, H_{ar}); 7.48-7.28 (m, 12H, H_{ar}); 6.56 (s, 1H, H_3)
4d	8.35 (d, 1H, J = 8.4, H_{ar}); 7.47-7.23 (m, 11H, H_{ar}); 6.57 (s, 1H, H_3)
4e	8.31 (d, 1H, J = 8.3, H_{ar}); 7.69-7.63 (m, 3H, H_{ar}); 7.50-7.28 (m, 10H, H_{ar} and $H_{3'}$), 7.00 (s, 1H, H_3)
4f	8.35 (d, 1H, J = 8.4, H_{ar}); 8.20 (d, 1H, J = 8.4, H_{ar}); 7.76 (s, 1H, $H_{2'}$); 7.49-7.15 (m, 11H, H_{ar}); 6.70 (s, 1H, H_3); 1.75 (s, 9H, $(CH_3)_3C$)
4g	8.32 (d, 1H, J = 8.3, H_{ar}); 8.29 (s, 1H, NH); 7.67 (s, 1H, $H_{2'}$); 7.45-7.19 (m, 11H, H_{ar}); 6.60 (dd, 1H, J = 1.0, J = 3.7, $H_{3'}$), 6.53 (s, 1H, H_3)
4h	8.19 (d, 1H, J = 8.4, H_{ar}); 7.77-7.73 (m, 2H, H_{ar}); 7.53-7.19 (m, 7H, H_{ar} and CH=); 6.73 (s, 1H, H_3); 5.71 (dd, 1H, J = 1.5, J = 17.4, $=CH_2$); 5.40 (dd, 1H, J = 1.5, J = 11.1, $=CH_2$)

Boronic acids **2a-e** and stannane **3** were purchased from Lancaster Company and Aldrich Chemical Company. Compounds **3f** and **3g** were obtained using methodologies described by A. R. Martin.[18,19]

General procedure for the synthesis of 2-substituted indoles 4 from boronic acids 2. To a solution of **1** (100 mg, 0.25 mmol) in anhydrous toluene (5 mL) was added *freshly prepared* tetrakis(triphenylphosphine)palladium (5 mol%). The resulting homogeneous solution was stirred for 30 min at room temperature. A boronic acid **2** (1.5 eq.) diluted in absolute ethanol (3 mL) was added, followed immediately by saturated aqueous $NaHCO_3$ (2 mL). This biphasic solution was heated to reflux (1 to 3 h). After cooling, the reaction mixture was poured into brine solution. After separation, the aqueous phase was washed with toluene. The combined organic phases were dried over $MgSO_4$ and evaporated. The crude

product **4** was purified by column chromatography (**4a, 4c, 4d, 4e, 4f**: eluent petroleum ether/CH_2Cl_2 1:1; **4b**: 4:6; **4g**: 1:2).

1-Phenylsulfonyl-2-vinylindole (4h). To a suspension of *freshly prepared* tetrakis(triphenylphosphine)palladium (6 mol%) and LiCl (2.8 eq.) in DMF (2 mL) was added a solution of **1** (100 mg, 0.25 mmol) and vinylstannane **3** (0.11 mL, 0.38 mmol) in anhydrous DMF (2 mL) under argon. The solution was stirred at 90°C for 1h30. After cooling, H_2O (5 mL) and AcOEt (5 mL) were added to the mixture. After extraction, the organic layer was washed with water, then dried over $MgSO_4$ and concentrated under reduced pressure. The crude product **4h** was purified by column chromatography (eluent petroleum ether/AcOEt 9:1).

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