STILLE AND SUZUKI CROSS COUPLING REACTIONS OF *o*-NITROPHENYL TRIFLATES: A VERSATILE ROUTE TO A VARIETY OF HETEROCYCLES

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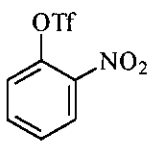
Abstract- The cross coupling reactions of selected *o*-nitrophenyl triflates with arylstannane and arylboron substrates are reported. The resultant 2-nitrobiphenyls provide ready access to a variety of substituted heterocycles.

We recently reported the versatility of *o*-nitrophenyl triflates as intermediates in the synthesis of 2-hydroxyquinolines.[1] Their success as substrates for palladium catalysed Heck reactions prompted us to investigate their potential in Stille and Suzuki cross coupling reactions as the mechanisms proceed *via* the same initial palladium insertion step.[2] The three *o*-nitrophenyl triflates (**1-3**) which were selected for the study were readily prepared from the corresponding *o*-nitrophenols[3] and include appropriate functionality to compare the effects of electron donating and withdrawing groups on the cross coupling reactions.



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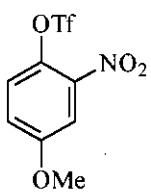

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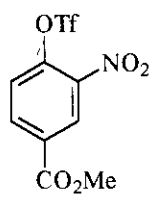

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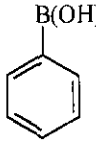
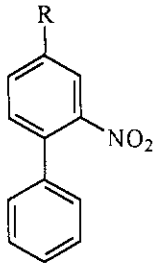
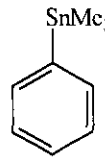
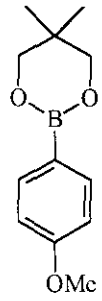
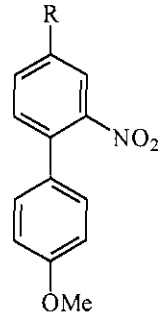
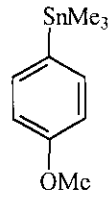
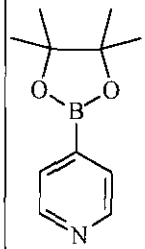
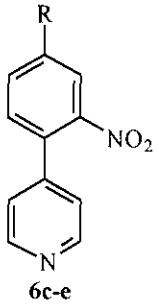
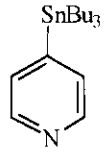
Preliminary investigations employing phenylboronic acid (**4a**) and *o*-nitrophenyl triflate (**1**) as simple substrates indicated that optimal conditions for the Suzuki cross coupling of these substrates involved the use of $Pd(PPh_3)_4$ as catalyst, K_3PO_4 as base and DME as solvent. However, in the corresponding Stille reaction employing phenyltrimethyltin, $Pd(PPh_3)_4$ was found to afford poorer results than the $Pd_2dba_3.CHCl_3/P(o\text{-tol})_3$ catalyst system. Dioxane was employed as the solvent, and as is standard in Stille reactions involving triflates,[2b] lithium chloride was employed as an additive.

Table 1 compares the results of the Stille and Suzuki reactions of triflates (**1-3**) with a selection of arylstannanes and arylboron compounds under these standard conditions. Substrates (**4a**) and (**4b**) were purchased, while substrates (**5a**) and (**5b**) were obtained from 4-iodoanisole *via* halogen exchange (*n*-BuLi, THF, -78°C) followed by treatment with $B(OMe)_3$ and Me_3SnCl respectively. In the case of **5a**, the crude boronic acid was isolated, characterised and further reacted after conversion to the 2,2-dimethyl-propanediol derivative. The preparation of 4-substituted pyridines (**6a-b**) was accomplished using the method of Coudret.[4] He recently reported a vastly improved synthesis of 4-iodopyridine *via* a Sandmeyer reaction, from which compound (**6a**) was prepared *via* halogen exchange, treatment with $B(OMe)_3$, hydrolysis and derivatisation with pinacol. We extended this method to the preparation of 4-pyridyl(tri-*n*-butyl)stannane (**6b**). Under identical halogen exchange conditions, 4-iodopyridine was converted into **6b** by treatment of the corresponding organolithium species with tri-*n*-butyltin chloride. The use of ether as solvent appears to be crucial to the success of this reaction. Reactions carried out in THF failed, as did attempts to prepare the trimethylstannane derivative upon addition of Me_3SnCl (purchased as a 1 M solution in THF). However, the addition of neat Bu_3SnCl resulted in the desired product.

As can be seen in Table 1, the Suzuki couplings afforded superior results to those obtained from the corresponding Stille reactions. In addition, while the Suzuki reactions generally proceeded cleanly and rapidly to one product, reactions of the arylstannanes were slower, and significant homocoupling was observed in the reactions of arylstannane (**5b**). As expected,[2] the better reactions were those involving the more electron deficient triflates and/or the more electron rich arylstannanes and boron compounds. This is evidenced by the good yields obtained for products (**4e**) and (**5e**)[6] and the poorer results obtained with substrates (**6a-b**). Under the standard conditions, direct comparison of the Suzuki reactions of commercially available 2-bromonitrobenzene and 4-bromo-3-nitroanisole with those of the corresponding triflates (**1**) and (**2**) revealed little or no difference in reaction rate or yields. However, it is important to note one important limitation of *o*-nitrophenyl triflates. In our previous communication we noted the tendency of certain *o*-nitrophenyl triflates to hydrolyse under basic Heck conditions,[1] and the unsuitability of certain bases for Suzuki couplings of triflates has been reported.[5] Except for K_3PO_4, most other bases traditionally employed in Suzuki reactions led to immediate hydrolysis of our *o*-nitrophenyl triflates to the corresponding phenol. This problem is exacerbated when the *o*-nitrophenyl triflate has additional electron withdrawing groups and in the case of slow cross couplings – in the reaction of triflate (**3**) with substrate (**6a**) significant amounts of the corresponding phenol were detected (10-20%). While K_3PO_4 generally afforded good results for both *o*-nitrophenyl triflates and the corresponding bromides, where couplings are slow, little can be done to improve reaction rate in the case of the triflates. For example, the coupling of

Table 1. Cross coupling of selected arylstannane and boron compounds with *o*-nitrophenyl triflates

Substrate	Yields (time) [a]	Triflate → Product	Yields (time) [b]	Substrate
 **4a**	**4c**: 98% (2.5 h) **4d**: 82% (10 h) **4e**: 95% (1.5 h)	**1** → **4c** (R=H) **2** → **4d** (R=OMe) **3** → **4e** (R=CO_2Me)  **4c-e**	**4c**: 93% (8 h) **4d**: 80% (12 h) **4e**: 89% (8 h)	 **4b**
 **5a**	**5c**: 89% (2.5 h) **5d**: 85% (3 h) **5e**: 94% (3 h)	**1** → **5c** (R=H) **2** → **5d** (R=OMe) **3** → **5e** (R=CO_2Me)  **5c-e**	**5c**: 52%[c] (15 h) **5d**: 31%[c] (15 h) **5e**: 45%[c] (15 h)	 **5b**
 **6a**	**6c**: 65% (10 h) **6d**: 60% (18 h) **6e**: 64% (10 h)	**1** → **6c** (R=H) **2** → **6d** (R=OMe) **3** → **6e** (R=CO_2Me)  **6c-e**	**6c**: 58% (10 h) **6d**: 41% (18 h) **6e**: 59% (10 h)	 **6b**

a) 1.00 mmol aryl boronic acid/ester, 0.80 mmol aryl triflate, 10 mol % $Pd(PPh_3)_4$, 0.66 mmol K_3PO_4, DME, 85°C.

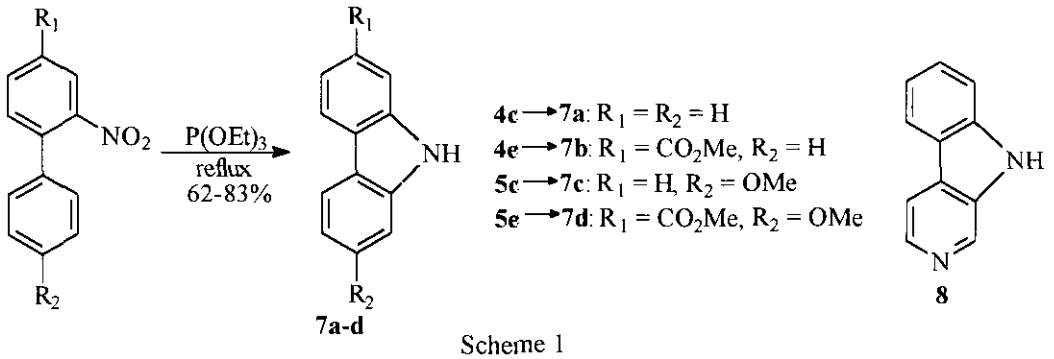
b) 1.00 mmol arylstannane, 0.80 mmol aryl triflate, 5 mol % $Pd_2dba_3.CHCl_3$), 40 mol % P(*o*-tol)$_3$, 2.40 mmol LiCl, dioxane, 85°C.

c) In these cases significant amounts (20-30%) of the product of arylstannane homocoupling were isolated as the major byproduct.

phenylboronic acid (**4a**) with both 4-methoxy-2-nitrophenyl triflate (**2**) and 4-bromo-3-nitroanisole took 10 hours to reach completion when employing K_3PO_4 as base. However, in the case of the bromide the reaction time was significantly decreased (2.5 h) when employing KO^{t}Bu.

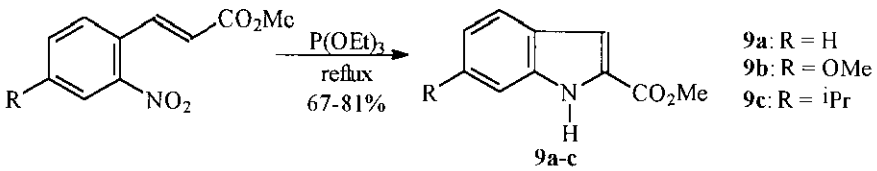
The products obtained above provide access to a variety of substituted carbazoles *via* reductive cyclisation in the presence of triethyl phosphite. In this regard, carbazoles (**7a-d**)[6] were prepared in good yields

following the method of Cadogan *et al.*[7] This entailed stirring the *o*-nitrobiphenyl substrates in triethyl phosphite at reflux temperature under nitrogen until TLC indicated total consumption of the starting material (Scheme 1). Likewise, the azacarbazole norharman (**8**) was prepared from **6c**. However, the product was obtained in low yields (*ca.* 40%) due to competing thermal decomposition of the starting material. Lower temperatures did not effect an improvement, but higher yields (70-80%) could be obtained by stopping the reaction at an early stage (*ca.* 40% conversion) and recovering starting material.



Scheme 1

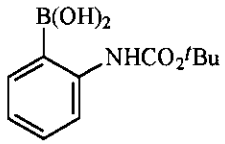
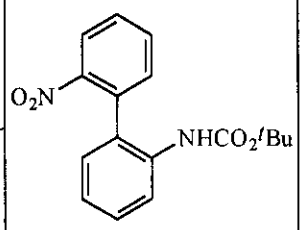
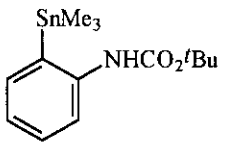
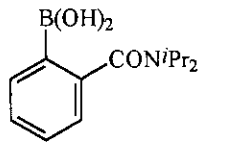
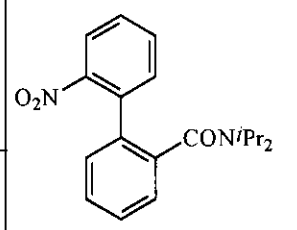
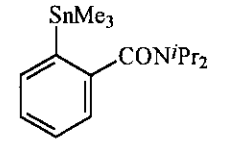
While carrying out this work, we realised that the Heck products derived from *o*-nitrophenyl triflates (which we previously used as precursors to 2-hydroxyquinolines)[1] could also be employed to afford substituted indoles. Thus indoles (**9a-c**) were prepared from the corresponding methyl 2-nitrocinnamates employing $P(OEt)_3$ at 160°C (Scheme 2).



Scheme 2

The cross coupling reactions of *o*-nitrophenyl triflate (**1**) with substrates (**12a-b**) and (**13a-b**) were also investigated (Table 2). Substrates (**12a-b**) were prepared from the corresponding iodide *via* halogen exchange (*n*-BuLi, THF, -78°C) and treatment with $B(OMe)_3$ (followed by hydrolysis) and Me_3SnCl respectively, while substrates (**13a-b**) were prepared *via* direct deprotonation of the carboxy amide (*n*-BuLi, TMEDA, -78°C, 2 h), followed by similar treatments with $B(OMe)_3$ and Me_3SnCl. Reasonable to good results were obtained for both substrates, and the couplings of the arylstannanes were comparable to those of the corresponding boronic acids. The longer reaction times can be ascribed to the increased steric hindrance. When employing 2-bromonitrobenzene, substrates (**12a-b**) afforded slightly improved yields of product (**12c**)[8] whereas yields of **13c** were comparable to those obtained with the triflate. Yields obtained for the Suzuki coupling of **13a** with 2-bromonitrobenzene were in accordance with published results.[9]

Table 2. Further *o*-nitrophenyl triflate cross couplings

Substrate	Yield (time)	Product
 **12a**	58% (24 h)[a]	 **12c**
 **12b**	65% (24 h)[b]	
 **13a**	78% (8 h)[a]	 **13c**
 **13b**	76% (8 h)[b]	

a) 1.00 mmol aryl boronic acid, 0.80 mmol aryl triflate, 10 mol % $Pd(PPh_3)_4$, 0.66 mmol K_3PO_4, DME, 85°C.
b) 1.00 mmol arylstannane, 0.80 mmol aryl triflate, 10 mol % Pd (as $Pd_2dba_3.CHCl_3$), 40 mol % P(*o*-tol)$_3$, 2.40 mmol LiCl, dioxane, 85°C.

Compounds such as **13c** hold great potential for the synthesis of a variety of substituted heterocycles. Reduction of the nitro group followed by acid-catalysed cyclisation would afford phenanthridinones, which in turn could be converted to the corresponding phenanthridines.[9] Alternatively, reduction of the nitro group followed by conversion to the iodide (Sandmeyer reaction) provides access to substituted fluorenones *via* metallation.[10]

These results further indicate the versatility of *o*-nitrophenyl triflates as intermediates in heterocycle synthesis. They are readily prepared from the corresponding phenols and provide a larger selection of substrates than the generally less accessible and environmentally unfavourable halides. They are good substrates for both Stille and Suzuki cross coupling reactions and the results obtained are comparable to those of the corresponding aryl bromides under the same conditions. The biphenyl products which are obtained provide ready access to a variety of heterocycles, including carbazoles and phenanthridinones. In addition, substituted indoles can be prepared from the Heck products described previously.

ACKNOWLEDGEMENTS

We thank the FRD (South Africa), AECI and SASOL for funding.

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2. For general reviews: a) A. de Meijere and F. E. Meyer, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 2379; b) S. P. Stanforth, *Tetrahedron*, 1998, **54**, 263; c) N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457; d) V. Farina, *Pure & Appl. Chem.*, 1995, **68**, 73.
3. Compound (**1**) was obtained *via* triflation (Tf_2O/2,4,6-collidine/CH_2Cl_2/0°C) of 2-nitrophenol. Compound (**2**) was prepared from 4-methoxyphenol *via* nitration ($NO_2^+BF_4^-$/DME/-50°C, C. L. Dwyer and C. W. Holzapfel, *Tetrahedron*, in press), followed by triflation. Compound (**3**) was prepared from 4-hydroxybenzoic acid methyl ester *via* nitration using a two-phase system (HNO_3-AcOH in CH_2Cl_2, using the method of E. M. Hindmarsh, I. Knight, and R. Robinson, *J. Chem. Soc.*, 1917, **110**, 943), followed by triflation.
4. C. Coudret, *Synth. Commun.*, 1996, **26**, 3543.
5. T. Oh-e, N. Miyaura, and A. Suzuki, *Synlett.*, 1990, 221.
6. Representative physical data: **5e**: ^{1}H NMR (300 MHz, $CDCl_3$): 8.41 (1H, d, J=1.5 Hz), 8.20 (1H, dd, J=8.1 Hz, 1.5 Hz), 7.50 (1H, d, J=8.1 Hz), 7.25 (2H, A of A_2B_2 system, J=8.1 Hz), 6.94 (2H, B of A_2B_2 system, J=8.1 Hz), 3.95 (3H, s), 3.82 (3H, s), ^{13}C NMR (300 MHz, $CDCl_3$): 165.0, 160.3, 149.3, 139.9, 132.7, 132.1, 129.8, 129.1 (2C), 128.4, 125.2, 114.4 (2C), 55.3, 52.6, MS: *m/z* 287 (M^+, 100%); **7d**: ^{1}H NMR (300 MHz, $CDCl_3$): 8.10 (1H, br s), 8.09 (1H, d, J=1.5 Hz), 7.96 (1H, d, J=7.2 Hz), 7.95 (1H, d, J=8.1 Hz), 7.89 (1H, dd, J=7.2 Hz, 1.5 Hz), 6.91 (d, 1H, J=1.5 Hz), 6.87 (1H, dd, J=8.1 Hz, 1.5 Hz), 3.94 (3H, s), 3.89 (3H, s), ^{13}C NMR (300 MHz, $CDCl_3$): 168.0, 160.2, 142.3, 138.8, 127.4, 125.9, 122.0, 121.0, 119.0, 116.4, 112.1, 109.2, 94.5, 55.6, 52.1, MS: *m/z* 255 (M^+, 100%).
7. J. I. G. Cadogan, M. Cameron-Wood, R. K. Mackie, and R. J. G. Searle, *J. Chem. Soc.*, 1965, 4831.
8. **12c**: ^{1}H NMR (300 MHz, $CDCl_3$): 7.98 (1H, dd, J=8.1 Hz, 1.2 Hz), 7.89 (1H, d, J=8.4 Hz), 7.66 (1H, td, J=7.8 Hz, 1.2 Hz), 7.55 (1H, td, J=7.8 Hz, 1.5 Hz), 7.39 (1H, dd, J=7.5 Hz, 1.5 Hz), 7.37 (1H, td, J=7.5 Hz, 1.8 Hz), 7.10 (1H, td, J=7.8 Hz, 1.2 Hz), 7.04 (1H, dd, J=7.5 Hz, 1.8 Hz), ^{13}C NMR (300 MHz, $CDCl_3$): 152.9, 149.5, 135.5, 135.0, 133.1 (2C), 132.8, 129.3, 129.1, 128.9, 124.5, 123.9, 121.9, 80.6, 28.1, MS: *m/z* 314 (M^+, 27%), 258 (41%), 214 (68%).

Received, 16th April, 1998