JOC*Note*

Generation of Substituted Styrenes via Suzuki Cross-Coupling of Aryl Halides with 2,4,6-Trivinylcyclotriboroxane

Fergal Kerins and Donal F. O'Shea*

Centre for Synthesis and Chemical Biology, Conway Institute, Department of Chemistry, University College Dublin, Belfield, Dublin 4, Ireland

donal.f.oshea@ucd.ie

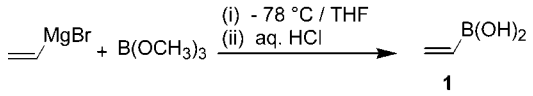
Received January 30, 2002

Abstract: The synthesis of functionalized styrene derivatives can be readily achieved utilizing a Suzuki cross-coupling protocol between aryl halides and 2,4,6-trivinylcyclotriboroxane−pyridine complex. The scope and limitations of the procedure were demonstrated by investigation of an array of ortho-substituted aryl halides.

Functionalized styrenes are of considerable synthetic importance for the generation of new polymeric materials and as key synthetic intermediates. Specifically, ortho-substituted styrenes act as intermediates for the synthesis of benzo-fused ring systems such as indenes,[1] indoles,[2] 2,3-dihydroindoles,[3] quinolines,[4] and isocoumarins.[5] Traditional methods for the generation of styrenes require dehydration under acidic conditions or an elimination under basic conditions to generate the double bond. Several palladium-catalyzed methods have been developed that utilize aryl halides as starting materials in reaction with a variety of reagents to provide the alkene functional group; the Heck[6] methodology uses ethene under high pressures, and the Stille[7] procedure exploits a tributyl(vinyl)tin reagent. Vinylmagnesium bromide,[8] vinyltrimethylsilane,[9] and vinylpolysiloxanes[10] have also been demonstrated as viable reagents utilizing aryl iodides as starting reagents. To date, the Heck and Stille methodologies have possibly been the most widely exploited in general synthetic procedures. We required an efficient method for the generation of ortho-substituted styrenes as a key step of an indole synthesis. We found tributyl(vinyl)tin effective for the desired conversion but had considerable difficulty in removing all of the toxic organotin residues from the styrene products. As this is a known drawback of organotin reagents, it is perhaps surprising that an equivalent vinylboronic acid derivative has not previously been described for the generation of styrenes. A review of the literature shows that only vinylboronate esters have been investigated and reported to give mixtures of Heck- and Suzuki-type products under various conditions.[11] As a result, we undertook an investigation to develop a synthetic equivalent boronic acid for tributyl(vinyl)tin.

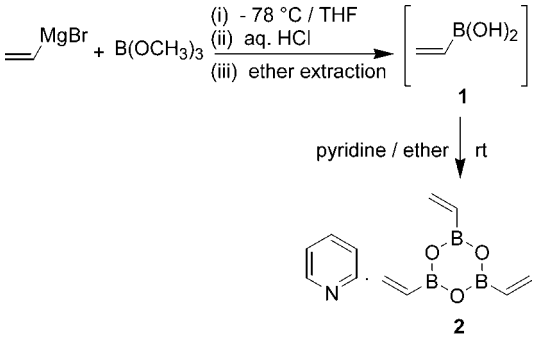
The synthesis of vinylboronic acid **1** from vinylmagnesium bromide and trimethyl borate was first reported by Matteson,[12] who described the compound as undergoing uncontrollable polymerization during the final stages of isolation (Scheme 1). Following the described procedures, we found that vinylboronic acid could be isolated

SCHEME 1



but the reaction had very poor reproducibility and did indeed on several attempts spontaneously polymerize. Even when successfully isolated, it always degraded over a time period of several days. This was not acceptable for use as a general synthetic reagent, and we sought to convert the vinylboronic acid into a bench stable form, which would still be capable of undergoing Suzuki-type couplings.[13] The conversion of the **1** into its anhydride form by stirring in pyridine has been reported to yield a bench stable solid.[14] From this earlier report, we have devised a modified direct synthetic procedure to the anhydride form, 2,4,6-trivinylcyclotriboroxane−pyridine complex **2** (Scheme 2). The synthesis of **2** was achieved

SCHEME 2



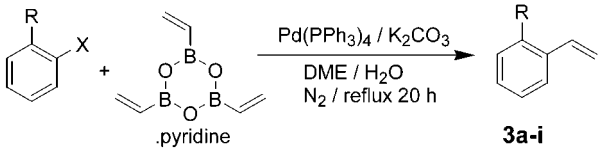
reproducibly by the reaction of vinylmagnesium bromide and trimethyl borate at −78 °C in dry THF followed by acid hydrolysis to the boronic acid and in situ conversion to the cyclic anhydride **2** by stirring with pyridine, resulting in a 79% isolated yield (Scheme 2). The isolated

(1) Brase, S.; Rumper, J.; Voigt, K.; Albecq, S.; Thurau, G.; Villard, R.; Waegell, B.; de Meijere, A. *Eur. J. Org. Chem*. **1998**, 671.
(2) (a) Harrington, P. J.; Hegedus, L. S. *J. Org. Chem*. **1984**, *49*, 2657. (b) Krolski, M. E.; Renaldo, A. F.; Rudisill, D. E.; Stille, J. K. *J. Org. Chem*. **1988**, *53*, 1170. (c) Larock, R. C., Hightower, T. R.; Hasvold, L. A.; Peterson, K. P. *J. Org. Chem*. **1996**, *61*, 3584. (d) Soederberg, B. C.; Shriver, J. A. *J. Org. Chem*. **1997**, *62*, 5838. (e) Ucciani, E.; Bonfand, A. *Chem. Commun*. **1981**, 82. (f) Yamaguchi, M.; Arisawa, M.; Hirama, M. *Chem. Commun*.**1998**, 1399.
(3) Larock, R. C.; Pace, P.; Yang, H.; Russell, C. E.; Cacchi, S.; Fabrizi, G.; *Tetrahedron* **1998**, *54*, 9961.
(4) Hibino, S.; Sugino, E. *Heterocycles* **1987**, *26*, 1883.
(5) Izumi, T.; Nishimoto, Y.; Kohei, K.; Kasahara, A. *J. Heterocycl. Chem*. **1990**, *27*, 1419.
(6) Plevyak, J. E.; Heck, R. F., *J. Org. Chem*. **1978**, *43*, 2454.
(7) McKean, D. R.; Parrinello, G.; Renaldo, A. F.; Stille, J. K. *J. Org. Chem*. **1987**, *52*, 422.
(8) Bumagin, N. A.; Luzikova, E. V. *J. Organomet. Chem*. **1997**, *532*, 271.
(9) Jeffery, T. *Tetrahedron Lett.* **1999**, *40*, 1673.
(10) (a) Denmark, S. E.; Wang, Z. *Synthesis* **2000**, 999. (b) Denmark, S. E.; Wang, Z. *J. Organomet. Chem*. **2001**, *624*, 372.
(11) Hunt, A. R.; Stewart, S. K.; Whiting, A. *Tetrahedron Lett*. **1993**, *34*, 3599.
(12) Matteson, D. S. *J. Am Chem. Soc*. **1960**, *82*, 4228.
(13) Suzuki A. *Pure Appl. Chem*. **1994**, *66*, 213.
(14) Matteson, D. S. *J. Org. Chem*. **1962**, *27*, 3712.

10.1021/jo020074o CCC: $22.00
Published on Web 05/23/2002

product is bench stable for prolonged periods and can be obtained analytically pure by vacuum distillation. The 1:1 ratio of pyridine to trivinylcyclotriboroxane was confirmed by ^{1}H NMR, and the single observed ^{11}B NMR signal was consistent with a rapid ligand exchange process between the pyridine nitrogen and the three borons of the boroxane ring.[15] It is known that boronic anhydrides are converted into their corresponding acids in the presence of water. As a result, our expectation was that with the commonly used coupling solvent conditions of 1,2-dimethoxyethane (DME)/water, it would be possible to generate the vinylboronic acid in situ. To test the suitability of **2** as a viable reagent, a model set of conditions were employed for all reactions with aryl halides as follows: tetrakis(triphenylphosphine)palladium-(0) as catalyst, potassium carbonate as base, and DME/water (3:1) as solvent, under reflux for 20 h (Scheme 3). Reaction conversions were determined by GC−MS and ^{1}H NMR.

SCHEME 3



Our first model aryl bromide, 2-bromo-6-methoxynaphthalene, gave an excellent result of a 100% conversion of starting aryl bromide and an isolated purified product yield of 76%, utilizing 1.0 mol % catalyst (Table 1, entry 1). As sterically hindered couplings are reported to be the most challenging to achieve,[13] we tested the scope of the reaction with a range of ortho-substituted aryl halides with varying electronic and steric properties. We discovered that as with other boronic acid couplings the reaction was tolerant of a wide range of sensitive functional groups, which enabled the generation of a diverse array of ortho-substituted styrenes **3a**−**i** (Scheme 3, Table 1). The reactivity followed was as expected for a Suzuki coupling with electron-withdrawing substituents on the aryl halide achieving better conversions than electron donating substituents. The steric factors of the ortho substituents did not appear to significantly impede the reactions. Entries 2−8 were all fully converted in the reaction time with 1 mol % catalyst and gave good isolated yields. The tolerance of nitro **3a**, amide **3b**, nitrile **3c**, aldehyde **3d**, and carbamic ester **3e** functional groups to the reaction conditions being demonstrated. The coupling reaction proved successful for aryl bromides and iodides, entries 2 and 3. The carbamic acid *tert*-butyl ester derivative **3g** (entries 9 and 10) gave only 25% conversion with 1 mol % catalyst, but the reaction could be driven to completion by increasing the catalyst ratio to 5 mol %. The aryl halides with ortho-electron-donating methyl (entries 11 and 12) and methoxy (entry 13) groups also gave improved conversions at increased catalyst levels. Currently, there is an increasing demand for achieving palladium-catalyzed coupling reactions using aryl chlorides as starting reagents. We examined 1-chloro-2-nitrobenzene under our model reaction conditions with 1 and 5 mol % catalyst (entries 14 and 15). Although the conversions to styrene **3a** were low (3%, 12%, respectively) it does show the potential for use of **2** with reported specialized catalyst ligands to achieve improved conversions.[16]

In summary, we have described a facile method for the generation of substituted styrene derivatives using 2,4,6-trivinylcyclotriboroxane−pyridine complex in a Suzuki cross-coupling protocol, which has the potential to become a new versatile synthetic reagent for the vinylation of aryl halides. A direct synthesis of the key vinylation reagent is described.

Experimental Section

Materials. All commercially available solvents and reagents were used as supplied unless otherwise stated. Tetrakis(triphenylphosphine)palladium(0) was supplied by Aldrich Chemical Co. and used without any modification. 1,2-Dimethoxyethane was passed through a bed of aluminum oxide immediately before use.

Analysis. GC−MS was recorded using a ThermoQuest Trace MS 2000. ^{1}H and ^{13}C NMR were recorded on a 300 MHz instrument and were referenced to tetramethylsilane (TMS). ^{11}B NMR spectrum was recorded on a 270 MHz instrument and referenced to $BF_3{\cdot}OEt_2$. Melting points are uncorrected.

2,4,6-Trivinylcyclotriboroxane−Pyridine Complex (2). A solution of trimethyl borate (10 mL, 89.2 mmol) in dry THF (75 mL) was cooled to −78 °C under N_2 in a dry ice−acetone bath. Vinylmagnesium bromide (50 mL of a 1.0 M solution in THF, 50.0 mmol) was added dropwise over 1 h and the reaction stirred for a further 1 h. Hydrochloric acid (1 M, 25 mL) was added over 5 min and the solution removed from the cooling bath and allowed to warm to room temperature. Brine (20 mL) was added, the solution was extracted with diethyl ether (4 × 50 mL), and the combined extracts were washed with water (50 mL) and brine (50 mL), dried over sodium sulfate, and concentrated under reduced pressure to 25 mL. The diethyl ether solution was treated with pyridine (10 mL) and stirred at room temperature for 4 h. The solvents were evaporated under reduced pressure to give a pale yellow oil. Distillation under reduced pressure (75−85 °C, 0.1 Torr) gave the product as a white solid 3.2 g, 79%, mp 46−48 °C. Samples were routinely stored in a sample bottle, under air, at 0 °C, which showed no deterioration by ^{1}H NMR over a 4 week period. ^{1}H NMR ($CDCl_3$) δ: 5.78−5.86 (m, 3H), 5.93−6.07 (m, 6H), 7.54−7.59 (m, 2H), 7.94−8.01 (m, 1H), 8.79−8.81 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 125.3, 131.5, 138.0 (broad) 140.1, 145.1. ^{11}B NMR ($CDCl_3$) δ: 17.68. EI-MS: *m*/*z* 242 (3) 161 (30), 79 (100). IR (KBr) cm^{-1}: 1620, 1442. Anal. Calcd for $C_{11}H_{14}B_3NO_3$: C, 54.90; H, 5.86; N, 5.82. Found: C, 54.76; H, 5.83; N, 5.75.

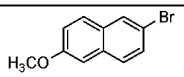
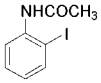
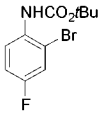
General Suzuki Coupling Procedure. Aryl halide (1.25 mmol) was dissolved in DME (10 mL), treated with tetrakis-(triphenylphosphine)palladium(0) (0.0125 or 0.0625 mmol), and stirred at room temperature under N_2 for 20 min. Potassium carbonate (1.25 mmol), water (3 mL), and **2** (1.25 mmol) were added, and the reaction was heated under reflux under N_2 for 20 h. The reaction mixture was cooled to ambient temperature, extracted with ether (25 mL), dried over sodium sulfate, and diluted with hexane (25 mL). The solution was passed through a short aluminum oxide column, solvent evaporated, and analyzed by GC, GC−MS, and ^{1}H NMR. If required, further purification by column chromatography on silica, eluting with hexanes/diethyl ether, was performed.

Analytical data for new compounds is shown in Table 1.

(15) Comparison to ^{11}B NMR data of $(CH_3)_3B_3O_3$·L. Beckett, M. A.; Brassington, D. S.; Owen, P.; Hursthouse, M. B.; Light, M. E.; Abdul Malik, K. M.; Sukumar Varma, K. *J. Organomet. Chem.* **1999**, *585*, 7.

(16) (a) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413. (b) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3387. (c) Bei, X.; Turner, H. W.; Weinberg, W. H.; Guram, A. S.; Petersen, J. L. *J. Org. Chem.* **1999**, *64*, 6797.

TABLE 1. Cross-Coupling Experiments of Aryl Halides with 2,4,6-Trivinylcyclotriboroxane Pyridine[a]

entry	aryl halide	mol% Pd	product	% conversion[b]	% yield[c]
1		1		100	76
2		1	**3a**	100	74
3		1	**3a**	100	77
4		1	**3b**	100	73
5		1	**3c**	100	79
6		1	**3d**	100	77
7		1	**3e**	98	84
8		1	**3f**	100	78
9		1	**3g**	25	-
10		5	**3g**	94	80
11		1	**3h**	40	-
12		5	**3h**	98	68
13		5	**3i**	100	70
14		1	**3a**	3	-
15		5	**3a**	12	-

[a] Reaction times are not minimized. [b] Average of two or more runs. [c] Isolated yield.

4-Fluoro-2-vinylphenylcarbamic Acid *tert*-Butyl Ester 3f. Mp: 70−71 °C. ^{1}H NMR ($CDCl_3$) δ: 1.50 (s 9H), 5.42 (dd, J = 1.0, 11.0 Hz, 1H), 5.65 (dd, J = 1.0, 17.4 Hz), 6.27 (bs, 1H), 6.76 (1H, m), 6.94 (1H, m), 7.1 (1H, m), 7.63 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 28.5, 80.9, 111.8 (d, J_{CF} = 22.9 Hz), 114.1 (d, J_{CF} = 22.1 Hz), 114.6, 117.4, 123.7, 129.9 (d, J_{CF} = 2.3 Hz), 130.4 (d, J_{CF} = 1.5 Hz), 152.3, 158.6 (d, J_{CF} = 242.6 Hz). IR (KBr disk) cm^{-1}: 3268, 2948, 1768. EI-MS: *m*/*z* 237.3. HRMS: calcd for $C_{13}H_{16}FNO_2$ 237.1165, found 237.1160. Anal. Calcd for $C_{13}H_{16}FNO_2$: C, 65.81; H, 6.80; N, 5.90. Found: C, 65.6; H, 6.78; N, 5.90.

(2-Vinylphenyl)carbamic Acid *tert*-Butyl Ester 3g. Mp: 47−48 °C. ^{1}H NMR ($CDCl_3$) δ: 1.51 (s, 9H), 5.36 (dd, J = 1.3, 11.0 Hz, 1H), 5.61 (dd, J = 1.3, 17.3 Hz, 1H), 6.44 (bs, 1H), 6.80 (dd, 1H), 7.05 (m, 1H), 7.25 (m, 1H), 7.24 (m, 1H), 7.77 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 28.5, 80.7, 118.0, 122.0, 124.2, 127.1, 128.7, 129.1, 132.5, 135.3, 153.3. IR (KBr disk) cm^{-1}: 3327, 2990, 1689. EI-MS: *m*/*z* 219.1. HRMS: calcd for $C_{13}H_{17}NO_2$ 219.1259, found 219.1259. Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 70.95; H, 7.80; N, 6.25.

Acknowledgment. We gratefully acknowledge Enterprise Ireland for financial support.

Supporting Information Available: ^{1}H, ^{13}C, and ^{11}B NMR spectral characterization of 2,4,6-trivinylcyclotriboroxane pyridine complex **2**. ^{1}H and ^{13}C NMR spectra for the new compounds **3f** and **3g**. This material is available free of charge via the Internet at http://pubs.acs.org

JO020074O