ORGANIC LETTERS

2004
Vol. 6, No. 9
1473−1476

A Highly Efficient Microwave-Assisted Suzuki Coupling Reaction of Aryl Perfluorooctylsulfonates with Boronic Acids

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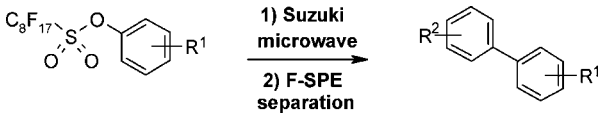
Received February 27, 2004

ABSTRACT



A new strategy to improve the efficiency of Suzuki coupling reactions is introduced by combining fast microwave reaction with easy fluorous separation. Aryl perfluorooctylsulfonates derived from the corresponding phenols are coupled with aryl boronic acids to form biaryls under general microwave conditions. Both intermediates and products are purified by solid-phase extraction over Fluoro*Flash* silica gel. Application of this tagging strategy to multistep synthesis of biaryl-substituted hydantoin is also described.

The palladium-catalyzed cross-coupling of aryl halides with aryl boronic acids (Suzuki coupling) is a powerful reaction for the construction of biaryls.[1] Its scope has been extended through the use of aryl triflates ($ArOSO_2CF_3$) or aryl nonaflates ($ArOSO_2(CF_2)_3CF_3$) as halide equivalents.[2] Aryl perfluoroalkylsulfonates prepared from a wide range of commercially available phenols have shown high reactivity, good stability for room-temperature storage and chromatography, and resistance towards hydrolysis.[3]

Applications of Suzuki coupling reactions for parallel and combinatorial syntheses have been explored by conducting the reaction under microwave irradiation[4] or on solid support[5] with a linker such as perfluoroalkylsulfonyl.[6] However, the microwave reaction does not directly address the separation issue, which is usually the bottleneck of high-throughput synthesis. Microwave-assisted solid-phase reactions have limitations on solvent selection due to resin swelling and thermostability issues.[7] We report here a new strategy that

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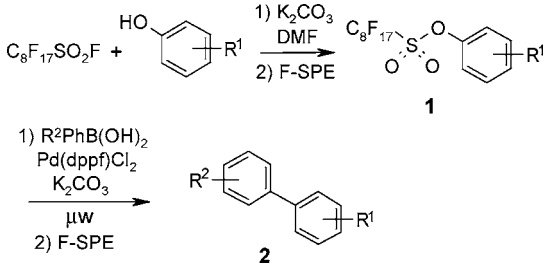
10.1021/ol0496428 CCC: $27.50
Published on Web 03/27/2004

Scheme 1. Fluorous Synthesis of Biaryls



significantly improves the efficiency of Suzuki coupling reactions by combining fast microwave reaction with easy fluorous separation.

Fluorous synthesis unites the attractive features of solution-phase chemistry with the convenient workup of solid-phase chemistry.[8] Molecules attached with a perfluoroalkyl "phase tag" can be easily isolated from the reaction mixture by fluorous separation techniques such as fluorous solid-phase extraction (F-SPE).[9] The fluorous Suzuki coupling reaction employs aryl perfluorooctylsulfonates ($ArOSO_2(CF_2)_7CF_3$) as precursors. The perfluorooctylsulfonyl group has enough fluorines (17) to serve as a fluorous tag for F-SPE. Recently, we reported the use of aryl perfluorooctylsulfonate tag in palladium-mediated cross-coupling reactions for the formation of a C−S bond.[10,11] We now extend the application of this fluorous tag to the synthesis of the C−C bond of biaryls.

A variety of phenols were converted to the corresponding aryl perfluorooctylsulfonates by reacting them with commercially available perfluorooctylsulfonylfluoride under mild conditions, using K_2CO_3 as a base in dimethylformamide (DMF) at 70 °C for 5 h (Scheme 1).[12] The crude aryl perfluorooctylsulfonate **1** has greater than 90% purity and is used directly for the next step reaction. If further purification is needed, this can be accomplished by crystallization from MeOH or by F-SPE purification on Fluoro*Flash*

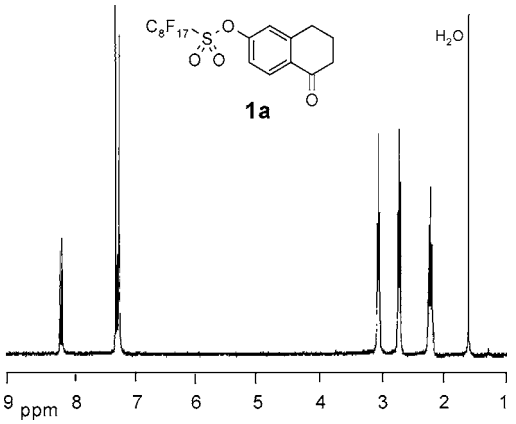


Figure 1. ^1H NMR ($CDCl_3$) of **1a** after F-SPE.

cartridges.[13] Two F-SPE fractions need to be collected; the first elution with 80:20 MeOH/H_2O contains unreacted phenol and other nonfluorous compounds; the second elution with MeOH contains the desired aryl perfluorooctylsulfonate **1**. After F-SPE, the purity is greater than 95% (Figure 1).[14]

Suzuki coupling is a substrate-dependent reaction, which is reflected by numerous publications on the optimization of catalyst, base, solvent, and other reaction conditions.[1,5] The lack of a general procedure suitable for a broad range of substrates limits the application of Suzuki reactions in high-throughput synthesis. As a powerful and easily controllable heating source, microwave irradiation can generate more consistent results than the conventional heating source.[4] In our development of fluorous Suzuki coupling reactions, a literature procedure[15] for the coupling of triflates was adapted for the reaction of aryl perfluorooctylsulfonates.[16] Thus, we used [Pd(dppf)Cl_2] (dppf = 1,1′-bis(diphenylphosphino)ferrocene) as a catalyst, K_2CO_3 as a base, and 4:4:1 toluene/acetone/H_2O as a cosolvent. The reactions were conducted in a sealed-tube under single-mode microwave irradiation at 100−130 °C for 10 min. This general condition is compatible with a range of functionalized aryl perfluorooctylsulfonates with methoxy, aldehyde, ketone, and heterocyclic groups. It is also compatible with a broad range of boronic acids, including sterically hindered *ortho*-isopropoxy-substituted boronic acid and electron-deficient 3,4-dichlorophenylboronic acid (Table 1).[17] The purification of the final product is straightforward; the organic layer of the

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(10) Zhang, W.; Lu, Y.; Chen, C. H−T. *Mol. Diversity* **2003**, *7*, 199.

(11) For early work on microwave-assisted cross-coupling reactions and fluorous liquid−liquid separations, see: (a) Larhed, M.; Hoshino, M.; Hadida, S.; Curran, D. P.; Hallberg, A. *J. Org. Chem.* **1997**, *62*, 5583. (b) Olofsson, K.; Kim, S. Y.; Larhed, M.; Curran, D. P.; Hallberg, A. *J. Org. Chem.* **1999**, *64*, 4539.

(12) **Representative Procedure for the Preparation of Aryl Perfluorooctylsulfonates.** To a mixture of 5-hydroxy-1-tetralone (3.24 g, 20.0 mmol) and K_2CO_3 (2.90 g, 21.0 mmol) in 15 mL of DMF was added perfluorooctylsulfonic fluoride (8.37 g, 16.7 mmol) dropwise through an addition funnel. After heating at 70 °C for 5 h, the mixture was poured onto 100 mL of water and extracted with EtOAc. The organic portion was dried over $MgSO_4$, and the solvent was evaporated under vacuum to give perfluorooctylsulfonate **1a** (9.79 g, 91% yield). The crude product was used for the next step. It can be further purified by recrystallization with MeOH or by F-SPE.

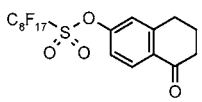
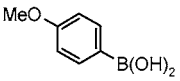
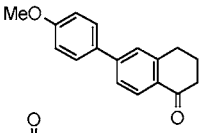
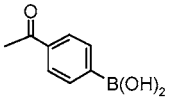
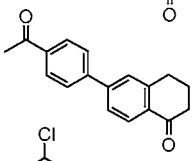
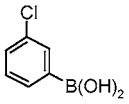
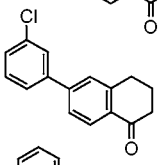
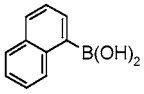
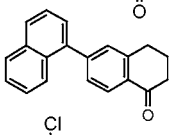
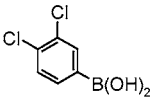
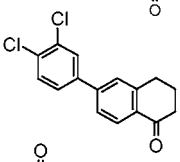
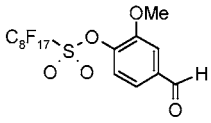
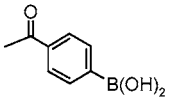
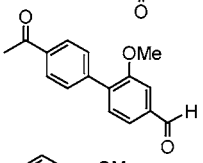
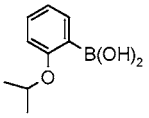
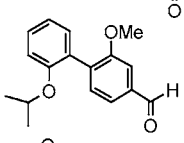
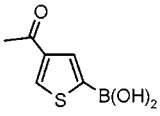
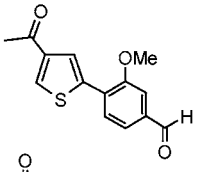
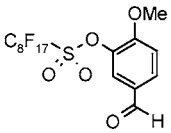
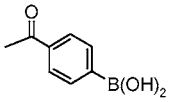
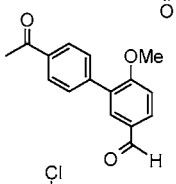
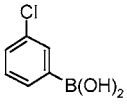
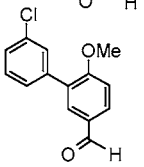
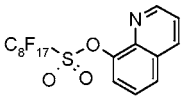
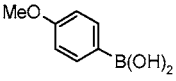
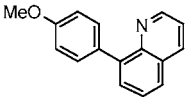
(13) Fluoro*Flash* silica gel charged in the SPE cartridges contains a Si-$(Me)_2C_8F_{17}$ stationary phase. For more information about F-SPE, please log on to http://www.fluorous.com/download/fspe.pdf.

(14) Purities were assessed by ^1H NMR.

(15) Pridgen, L. N.; Huang, G. K. *Tetrahedron Lett.* **1998**, *39*, 8421.

(16) **Representative Procedure for the Suzuki Cross-Coupling Reaction.** A septum-sealed microwave tube charged with aryl perfluorooctylsulfonate **1a** (84.0 mg, 0.13 mmol), 4-methoxyboronic acid (18.9 mg, 0.12 mmol), Pd(pddf)Cl_2 (10.6 mg, 0.013 mmol), and K_2CO_3 (36.0 mg, 0.26 mmol) in 0.8 mL of a 4:4:1 acetone/toluene/H_2O cosolvent was irradiated in a monomode microwave cavity (150W, 130 °C, 10 min). The reaction mixture was washed with 1 mL of H_2O. The organic layer was loaded onto a 5 g Fluoro*Flash* cartridge preconditioned with 80:20 MeOH/H_2O. The cartridge was eluted with 10 mL of 80:20 MeOH/H_2O. The fraction was concentrated to give biaryl **2a** (27.6 mg, 91% yield). The fluorous species were washed from the cartridge with 20 mL of MeOH.

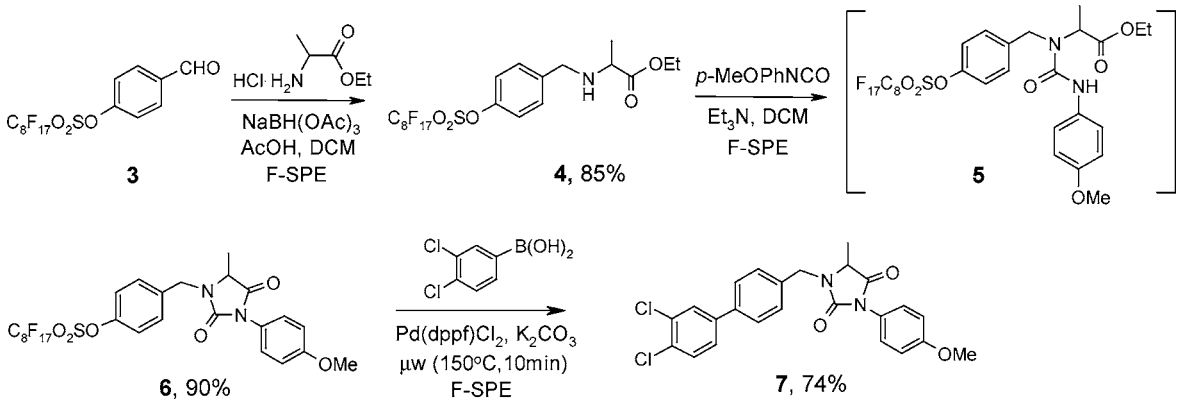
Table 1. Structures and Yields of Biaryls

entry	aryl perfluorooctylsulfonate **1**	boronic acid	biaryl **2**	yield
1	 **1a**		 **2a**	90%
2	**1a**		 **2b**	89%
3	**1a**		 **2c**	93%
4	**1a**		 **2d**	87%
5	**1a**		 **2e**	87%
6	 **1b**		 **2f**	95%
7	**1b**		 **2g**	75%
8	**1b**		 **2h**	78%
9	 **1c**		 **2i**	95%
10	**1c**		 **2j**	88%
11	 **1d**		 **2k**	81%

reaction mixture was directly loaded onto a Fluoro*Flash* SPE cartridge. The biaryl product was collected in the fraction of 80:20 MeOH/H_2O, while the cleaved fluorous tag remained on the cartridge until the wash with MeOH was done. To avoid the coelution of the other organic component in the MeOH/H_2O fraction, boronic acid was used as the limiting agent (~0.95 equiv). After F-SPE, biaryl compounds were isolated in 75−95% yields with purity greater than 90%.[14] No detectable amount of dppf ligand was observed by ^{1}H NMR analysis.[18]

(17) Pd-catalyzed microwave reactions were conducted under a license from Personal Chemistry.

Scheme 2. Fluorous Synthesis of Biaryl-Substituted Hydantoin **7**



We also demonstrated the use of the fluorous sulfonyl tag in a multistep synthesis of a biaryl-substituted hydantoin **7** (Scheme 2). The hydroxyl group of 4-hydroxybenzaldehyde was protected by converting it to a fluorous sulfonate. The tagged benzaldehyde **3** underwent a reductive amination reaction. The resulting amine **4** was treated with an isocyanate to form urea **5**, which spontaneously cyclized to form hydantoin **6**. In the last step, the fluorous sulfonyl group was detagged by the Suzuki coupling reaction to form the C−C bond of biaryl **7**. The efficiency of this multistep synthesis is facilitated by easy F-SPE purification of the reaction intermediates **4** and **6**. The perfluorosulfonyl tag has been demonstrated to be tolerant to reductive amination and isocyanate reactions. The tagged intermediates were also found to be stable during F-SPE separations.

In this fluorous multistep synthesis, the tagging is accomplished at the phenol derivatization and the detagging is conducted at the Suzuki cross-coupling step. No synthetic steps are added just for the sake of putting in and taking off the fluorous tag. In addition to simplifying the intermediate purification, the perfluorosulfonyl group has the functions of protecting the hydroxyl group in the early steps and activating the phenol for cross-coupling at the last step. The high solubility of aryl perfluorooctylsulfonates in common organic solvents and the high thermostability of the perfluorosulfonyl tag render the fluorous molecules good substrates for solution-phase microwave reactions. Other than formation of C−C and C−S bonds, the perfluorooctylsulfonate moiety is amenable to other kinds of cross-coupling reactions to form C−H, C−N, C−O, C−P, and C−CN bonds. We believe this readily available, highly efficient, and synthetically versatile fluorous tag will have broad applications in solution-phase parallel and combinatorial syntheses.

(18) No further quantitative analysis has been attempted to detect the residue of catalyst and ligand in final products.

Acknowledgment. We thank the National Institutes of General Medical Sciences for the SBIR funding (1R43GM-66415-01 and 2R44GM062717-02).

Supporting Information Available: ^{1}H NMR spectra for aryl perfluorooctylsulfonates **1a**−**d**, biaryls **2a**−**k**, compounds **4** and **6**, and biaryl-substituted hydantoin **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0496428