ORGANIC LETTERS

2005
Vol. 7, No. 5
843−846

Pentafluorophenyl Sulfonate Ester as a Protecting Group for the Preparation of Biaryl- and Heterobiaryl Sulfonate Esters

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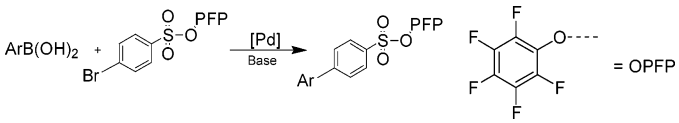
Received December 16, 2004

ABSTRACT



The use of the pentafluorophenyl (PFP) group as a sulfonic acid protecting group has allowed the synthesis of new biaryl- and heterobiaryl-PFP-sulfonate esters by use of the Suzuki–Miyaura reaction. The successful employment of a novel inorganic base, anhydrous sodium tetraborate, was crucial to give the products in excellent yields. The PFP-sulfonate ester has been previously shown to be an excellent alternative to sulfonyl chlorides in the synthesis of sulfonamides.

The palladium-catalyzed Suzuki−Miyaura reaction involves an oxidative addition−transmetalation−reductive elimination mechanism, which has become a general and powerful synthetic method for the C−C cross-coupling of an aryl halide or aryl triflate with a boronic acid.[1−4] This reaction offers a number of advantages, being largely unaffected by the presence of water, tolerating a broad range of functional groups, and proceeding with excellent regio- and stereoselectivity. Recently, Dubbaka and Vogel have reported that arene-, arylmethane, and alk-2-ene-1-sulfonyl chlorides undergo Suzuki−Miyaura cross-coupling reactions with arene-, heteroarene-, and alkeneboronic acids.[5] In these reactions, the sulfonyl chloride moiety behaves as a pseudo-halide leaving group and is lost in the C−C cross-coupling reaction. The same authors have reported the reactivity order of the halide and pseudo-halide leaving groups as ArI > $ArSO_2Cl$ > ArBr ≫ ArCl.[5] Therefore, we sought to find a synthetic equivalent of the sulfonyl chloride moiety that is stable to the basic conditions required for the Suzuki−Miyaura reaction and can then be manipulated for further elaboration.

As reported in the World Drug Index, there are more than 2000 sulfonamides either in clinical trials or already on the market covering a variety of therapeutic targets. Thus, new approaches for the preparation of novel sulfonamides are an increasingly important synthetic goal for pharmaceutical companies to explore.

The pentafluorophenyl (PFP) group has been extensively used as a carboxylic acid activating group, notably for peptide synthesis.[6,7] Recently, the use of the PFP group has been extended to prepare sulfonate esters as a more stable synthetic equivalent than the corresponding sulfonyl chlorides for the preparation of sulfonamides.[8,9] As a result of their stability,

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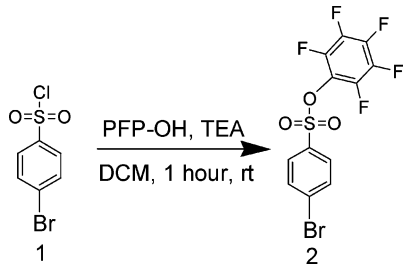
10.1021/ol047422o CCC: $30.25
Published on Web 02/05/2005

the PFP-sulfonate esters are often crystalline in nature and are significantly less reactive to nucleophiles than their sulfonyl chloride counterpart. We have demonstrated that the Suzuki−Miyaura reaction can be performed in the presence of the PFP-sulfonate ester moiety in good yield, thereby providing a convenient route to the synthesis of biaryl and heterobiaryl sulfonate esters. The resulting biaryl product should impart the desired stability, ease of handling, and simple activation for the preparation of sulfonamides.

The PFP-sulfonate ester (**2**) was prepared from 4-bromobenzenesulfonyl-chloride (**1**) in excellent yield, following the conditions reported in Scheme 1. Complete esterification

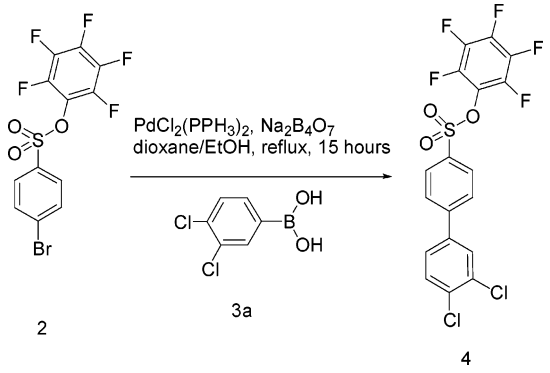
Scheme 1. Pentafluorophenyl Sulfonate Esterification of 4-Bromobenzenesulfonyl Chloride (**1**)



was observed after 1 h at room temperature. This product was then used as a substrate to prepare 4-biaryl- and 4-heterobiaryl-PFP-sulfonate esters (**4**−**8**) using the C−C Suzuki−Miyaura cross-coupling reaction.

Scheme 2 illustrates the general synthetic strategy used to prepare 3′,4′-dichlorobiphenyl-4-sulfonic acid pentafluorophenyl ester (**4**) from the 4-bromobenzene-PFP-sulfonate ester (**2**) in the presence of $PdCl_2(PPh_3)_4$.

Scheme 2. Synthesis of 3′,4′-Dichlorobiphenyl-4-sulfonic Acid Pentafluorophenyl Ester (**4**)



In our search for optimal conditions, we explored the C−C cross-coupling between the electron-deficient, 3,4-dichlorobenzene boronic acid (**3a**) and the 4-bromobenzene-PFP-sulfonate ester (**2**) (see Table 1). A variety of palladium catalysts were tested such as $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, $Pd_2(dba)_3$, $Pd(OAc)_2$, $Pd(PPh_3)_4$, Herrmann's $PdPC_{21}H_{20}$, $PdCl_2(dppf)$, $PdCl_2(CH_3CN)$, and $PdCl_2[P(CH_3C_6H_4)_3]_2$. From the screening experiments, the catalyst that gave the best results was found to be $PdCl_2(PPh_3)_2$ (Table 1, entry 7).

The reactions were carried out in a variety of refluxing solvents (DME, DMF, THF, toluene, and dioxane) and also in single combinations of these solvents with EtOH. In fact, the reaction does not occur without some ethanol being present (Table 1, entries 1, 2, 6, 7). In general, the best results were found with various combinations of dioxane and EtOH (Table 1, entry 7).

As the cross-coupling reaction only occurs in the presence of a moderately strong base, a number of bases were screened for their ability to promote the desired cross-coupling reaction, e.g., K_2CO_3, Cs_2CO_3, Li_2CO_3, Na_2CO_3, $NaHCO_3$, NaF, NaOTf, $NaCF_3CO_2$, Et_3N, and $Na_2B_4O_7$. It is noteworthy that under similar reaction conditions, sodium carbonate (Table 1, entry 2) was infinitely better than potassium carbonate (Table 1, entry 5) in the C−C cross-coupling reaction. Although these two bases would appear to have similar basicities, the presence of a potassium cation appears to significantly accelerate the rate of hydrolysis of the PFP-sulfonate ester (**2**) and presumably any of the desired cross-coupling products (**4**−**8**) shown in Scheme 3. A small but consistent improvement in yield was also observed when the reactions were carried out using conventional heating (Table 1, entry 2) rather than using microwave heating (Table 1, entry 3). Moreover, we were delighted to discover that the use of anhydrous sodium tetraborate ($Na_2B_4O_7$), a reasonably inexpensive and mild base, resulted in a significant improvement in the isolated yield of the target biaryl and heterobiaryl-PFP-sulfonate esters (**4**−**8**) (e.g., Table 1, entry 7). One very notable feature of the employment of this base over sodium carbonate was a significant reduction in the formation of unwanted byproducts derived from bis-boronic acid coupling, reduction of the aryl bromide (**2**), or hydrolysis of the PFP-sulfonate ester (**2**).

In attempting to analyze the effects of different bases in the cross-coupling reaction, there is a balance between promoting the desired cross-coupling reaction and causing undesirable hydrolysis of the PFP-sulfonate ester. The base K_2CO_3, and to a lesser extent Na_2CO_3, was found to promote hydrolysis of the PFP-sulfonate ester. The use of $Na_2B_4O_7$ not only promoted the cross-coupling reaction but also minimized the formation of all unwanted side reactions, allowing much easier isolation of the products (**4**−**8**) (see Scheme 3).

Scheme 3 illustrates the general synthetic strategy used to prepare both 4-biaryl-PFP-sulfonate esters (**4**−**6**) and 4-heterobiaryl-PFP-sulfonate esters (**7**, **8**) from the 4-bromobenzene-PFP-sulfonate ester (**2**) using methods **A** and **D**.

A variety of boronic acids were chosen to determine the scope of the reaction from an electron-deficient example, 3,4-dichlorophenyl boronic acid (**3a**), through more electron-rich examples, including *para*-tolyl boronic acid (**3b**) and

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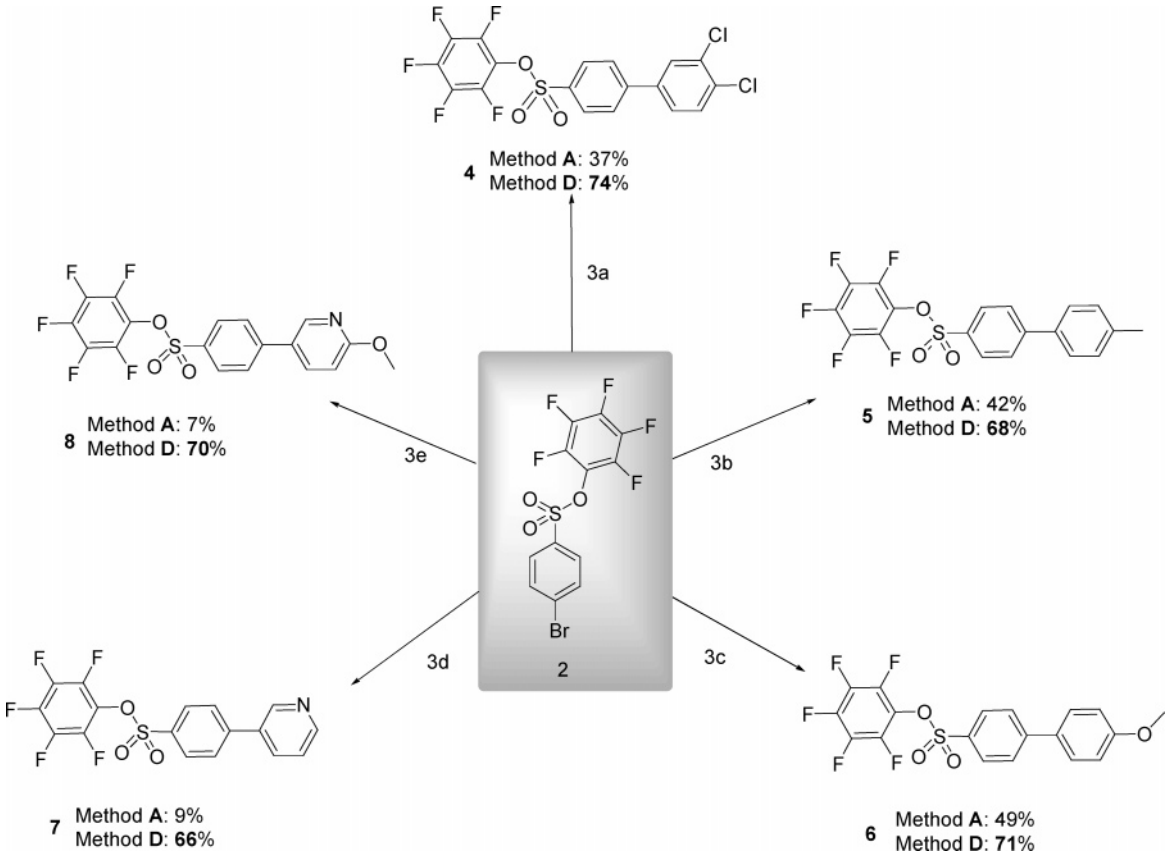
Table 1. Cross-Coupling Conditions of 4-Bromobenzene-PFP-sulfonate Ester (**2**) with 3,4-Dichlorobenzene Boronic Acid (**3a**)

entry	catalyst (3 mol %)	solvent	base (3 equiv)	conditions	yield of **4**[f]
1	$Pd(PPh_3)_4$	toluene	Na_2CO_3	Δ reflux	0[e]
2[a]	$Pd(PPh_3)_4$	toluene/EtOH 5/1	Na_2CO_3	Δ reflux	37
3[b]	$Pd(PPh_3)_4$	dioxane/EtOH 5/1	Na_2CO_3	μW 180 °C, 6 min	30
4	$Pd(PPh_3)_4$	1,4-dioxane	K_2CO_3	Δ reflux	0[e]
5[c]	$Pd(PPh_3)_4$	dioxane/EtOH 5/1	K_2CO_3	Δ reflux	0[e]
6	$PdCl_2(PPh_3)_2$	1,4-dioxane	$Na_2B_4O_7$	Δ reflux	0[e]
7[d]	$PdCl_2(PPh_3)_2$	dioxane/EtOH 5/1	$Na_2B_4O_7$	Δ reflux	74

[a] Method A. [b] Method B. [c] Method C: complete hydrolysis was observed from LC/MS. [d] Method D. [e] LC/MS analysis shows no evidence of product formation. [f] Yields of cross-coupling products determined after medium-pressure chromatography and crystallization from 1,4-dioxane/EtOH.

Scheme 3. Synthesis of 4-Biaryl- and 4-Heterobiaryl PFP-sulfonate Esters (**4**−**8**) Using Methods **A** and **D**[a]



[a] Method D: boronic acids (**3a**−**e**), $PdCl_2(PPh_3)_2$ (3 mol %), $Na_2B_4O_7$ (3 equiv), dioxane/EtOH, reflux. Method A: boronic acids (**3a**−**e**), $Pd(PPh_3)_4$ (3 mol %), Na_2CO_3 (3 equiv), toluene/EtOH, reflux.

4-methoxyphenyl boronic acid (**3c**). Two pyridyl boronic acids, 3-pyridylboronic acid (**3d**) and 4-methoxy-3-pyridyl boronic acid (**3e**), were also selected to further illustrate the applicability of this synthetic approach. Often this heteroaromatic system can prove problematic to either synthesize or isolate. However, when using method D, little difference was observed either in the reactivity of any of the boronic acids reported or in the excellent yields. The reported yields are of analytically pure material, of the total sample, following chromatography and crystallization.

In conclusion, this paper describes the first reported use of anhydrous sodium tetraborate as a base in the C−C Suzuki−Miyaura cross-coupling reaction. The successful employment of this base allowed the preparation of a range of 4-biaryl and 4-heterobiaryl-PFP-sulfonate esters (**4**−**8**).

The PFP-sulfonate ester group behaves as a sulfonic acid protecting group for carrying out chemoselective C−C Suzuki−Miyaura cross-coupling reactions. The resulting 4-biaryl and 4-heterobiaryl-PFP-sulfonate esters were all stable, crystalline solids.

We are currently exploring the scope of this process in respect to both the electronic and steric effects of the aromatic PFP-sulfonate ester. Similarly, we are planning to further exploit the stability of the PFP-sulfonate ester for other

synthetically interesting metal-catalyzed processes requiring mildly acidic or basic reaction conditions. We see the PFP-sulfonate ester group as a way to prepare novel building blocks by a variety of modern synthetic methodologies of which the C−C Suzuki−Miyaura reaction is an extremely powerful example.

Acknowledgment. We thank the EU for the Marie Curie Fellowship to Barbara G. Avitabile. We also acknowledge Douglas Prain for his useful suggestions during the course of this work.

Supporting Information Available: Experimental procedure and characterization for compounds **2** and **4**−**8**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL047422O