Synthesis of Tetrasubstituted Ethylenes on Solid Support via Resin Capture

S. David Brown and Robert W. Armstrong*

Department of Chemistry and Biochemistry
University of California
Los Angeles, California 90095

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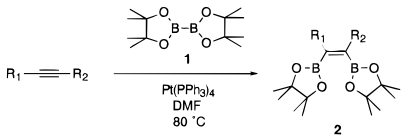
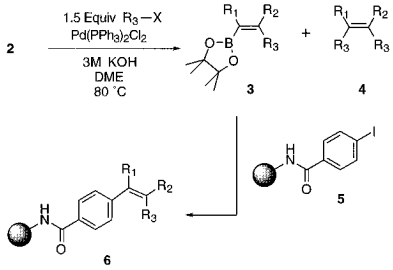
Combinatorial chemistry has sparked a great deal of interest due to its potential to accelerate the drug discovery process.[1] The majority of libraries described to date have used a solid support matrix for multiple-step syntheses.[2] Fewer libraries have been generated in solution due to the difficulty in isolating pure products, although elegant strategies to address this issue have been recently reported.[3] Described herein is a method for initiating the synthesis of a library in solution and subsequently transferring the material to solid support for further transformation. This strategy, which we refer to as resin capture,[4] offers some advantages over a single-phase synthesis. Using resin capture, we have synthesized a number of tetrasubstituted ethylenes in which all four substituents can be modified. This synthesis provides a route to antiestrogenic triphenylethylene derivatives[5] like tamoxifen,[6] which is used to treat breast cancer.[7]

Recently, Miyaura and Suzuki described the platinum-catalyzed diboration of alkynes to give bis(boryl)alkenes, **2**, with very high cis selectivity[8] (Scheme 1). We felt that **2** was an attractive starting material because the bis-boronate esters could be differentiated to introduce two additional substituents. **2** could be monoalkylated in a solution Suzuki reaction with alkyl or aryl halides. A second Suzuki reaction with a resin-bound aryl halide would result in the synthesis of substituted ethylenes involving three distinct components in a single-pot transformation. Several groups have reported success in coupling aryl boronic acids to polymer-bound aryl halides.[9] However, resin capture allows us to exploit the full range of Suzuki substrates in solution: methyl, benzyl, allyl, vinyl, and aryl halides.[10] The large number of commercially available alkynes also provides access to a variety of bis(boryl)alkenes through diboration.

Scheme 1



Scheme 2



Following Miyaura and Suzuki's procedure, we have diborated a variety of alkynes to give **2** in good to excellent yield. Isolation of **2** is unnecessary because the starting alkyne is unreactive in the following Suzuki reaction as required by our resin capture strategy. Crude **2** is reacted with 1.5 equiv of organohalide to give the monoaddition product **3**[11] along with the diaddition product **4** (Scheme 2). The first coupling is fast in comparison to the second coupling which produces **4**; thus, most of **2** is consumed in the reaction**.** The mixture of **3** and **4** is combined with Rink resin-bound aryl iodide **5** to initiate a second Suzuki reaction *without* any further addition of palladium catalyst. Only **3** is captured on solid support to produce **6**, because **4** and other impurities cannot react with **5**. Of a number of bases (NaOH, KOH, K_2CO_3, $Ba(OH)_2$, and K_3PO_4) and solvents (THF, DME, DMA, DMF, dioxane, and toluene), a combination of aqueous KOH in DME gives the best results in these reactions. We have found that although both $Pd(PPh_3)_4$ and $PdCl_2(PPh_3)_2$ work equally well, $PdCl_2(PPh_3)_2$ is easier to work with when setting up a number of reactions in a library synthesis.[12,13]

We have synthesized a number of tetrasubstituted ethylenes, including several triphenylethylenes as described in Table 1. Using the symmetrical aryl−aryl and alkyl−alkyl boronates **8**[8] and **9** (Figure 1), we obtained products in high yield and purity after TFA cleavage. We note that this methodology also provides sterically hindered tetraphenylethylenes in high yield (See Table 1).

When using unsymmetrical bis(boryl)alkenes, regioisomers are produced. When **10** is reacted with **5**, a 2.3 to 1 ratio of **11a** to **11b**[14] is obtained in >95% yield. We have also found that the reaction of **10** with 4-iodo-(2-(*N*,*N*-dimethylamino)-ethoxy)benzene gives the tamoxifen benzamide **12b** in a 2.5 to 1 ratio with its regioisomer **12a** in a >95% yield (Figure 2).

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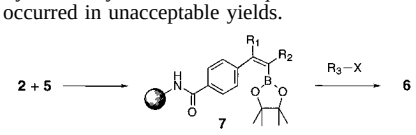
(11) Regioisomers are produced when $R_1 \neq R_2$.

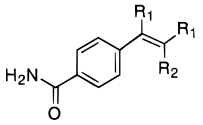
(12) Our general procedure is as follows: A small test tube is charged with **2** (10 equiv), organohalide (15 equiv), $PdCl_2(PPh_3)_2$ (0.3 equiv), 3 M KOH (20 equiv), and enough DME to bring the concentration of **2** to 0.5 M. The test tube is covered with a septum and flushed with N_2. The reaction mixture is heated overnight in a sand bath under N_2. Another test tube is charged with 100 equiv of KOH and 1 equiv of **5** and flushed with N_2. The DME/KOH solution is syringed into the tube containing the polymer and heated overnight. The polymer is filtered out of the solution and washed successively with H_2O, MeOH, ethyl acetate, and CH_2Cl_2. The products are cleaved from the polymer with 30% TFA in CH_2Cl_2.

(13) The opposite order of addition of halides produced resin-bound boronate **7** very efficiently. However, subsequent condensation with solution aryl halides occurred in unacceptable yields.



S0002-7863(96)01203-6 CCC: $12.00

Table 1



R_1	R_2	% yield
phenyl	methyl	>95
phenyl	2-methyl-1-propenyl	78[a]
phenyl	2-propenyl	>95[c]
phenyl	benzyl	>95
phenyl	4-tolyl	83[a]
ethyl	methyl	>95
ethyl	2-methyl-1-propenyl	75[b]
ethyl	2-propenyl	>95[a]
ethyl	benzyl	83[b]
ethyl	4-tolyl	85[a]

[a] Contains a small percentage of 4-iodobenzamide. [b] Contains a small percentage of deborated material.[17] [c] Partial isomerization to conjugated diene.

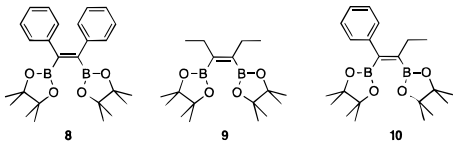


Figure 1.

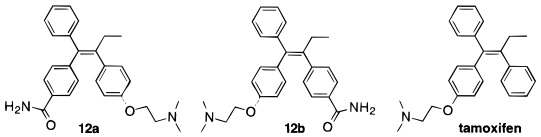
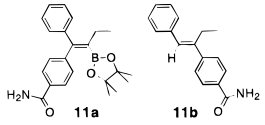


Figure 2.

After resin capture, further synthetic transformations may be carried out. For instance, the use of 2-(4-bromophenoxy)ethanol in the condensation with **8** and **5** affords tetraphenylethylene **13** with an additional reactive functional group. Condensation of **13** with 3,5-dimethylphenol using Mitsunobu conditions[15] leads to the formation of **14** after resin cleavage (Scheme 3). Reagent **1** has also been reported to facilitate the conversion of aryl halides to aryl boronic esters.[16] Thus, Pt-catalyzed reaction of **5** with reagent **1** afforded aryl boronic ester **15** which could

(14) **11b** is the result of hydrolytic deboration of **7** during the Suzuki reaction (see ref 13). Resin capture minimizes the amount of deborated material that collects on the polymer since it avoids resin-bound vinyl boronates like **7**.



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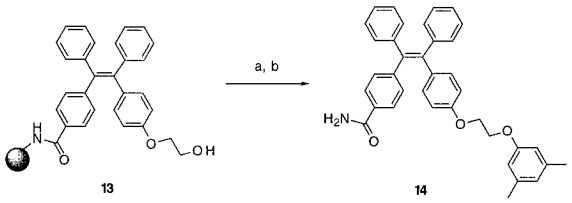
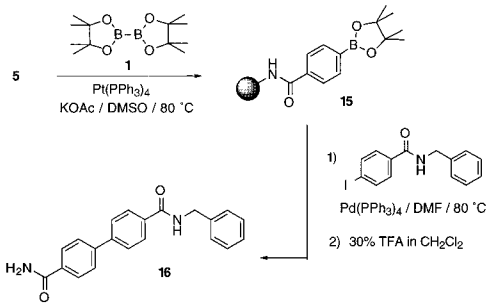
Scheme 3[a]



[a] (a) 3,5-dimethylphenol, diisopropylazodicarboxylate, triphenylphosphine, *N*-ethylmorpholine, 16 h; (b) 30% TFA in CH_2Cl_2; >95% yield based on loading of polymer.

Scheme 4



be coupled to *N*-benzyl-4-iodobenzamide in >95% yield (Scheme 4).[10] Thus, in contrast to resin-bound vinyl boronates, the resin-bound aryl boronates readily react with aryl halides in solution.[13]

We have reported an efficient synthesis of tetrasubstituted ethylenes using a solution/solid support strategy. The solution step allows us to use a broad range of Suzuki substrates and prevents side products from building up on the polymer,[14] while resin capture purifies the solution product after a multistep synthesis. The tandem Suzuki reactions are carried out without recharging the reaction mixture with catalyst, which simplifies the reaction procedure. We are currently working on a library of triphenylethylenes based on tamoxifen, and our results will be reported in due course.

Acknowledgment. This work was supported by the National Institutes of Health (GM-51095).

Supporting Information Available: Experimental procedures and copies of ^{1}H NMR and ^{13}C NMR spectra for new compounds as well as lists of IR absorbances and results of mass spectrometric analysis (41 pages). See any current masthead page for ordering and Internet access instructions.

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(17) This material is the result of unreacted **2** coupling to the resin followed by deboration of the intermediate **7** (see ref 14).