Parallel Synthesis of Tamoxifen and Derivatives on Solid Support via Resin Capture

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Estrogen analogs can be used to prevent and treat breast cancer, osteoporosis, and other conditions that affect women. Since estrogen receptors are found in a variety of tissues, there is a need for analogs that are tissue selective.[1,2] Tamoxifen (Figure 1) is used clinically to treat estrogen dependent breast cancer because it acts as an estrogen antagonist in breast tissue.[3] However, it acts as a partial agonist in the uterus which increases a woman's risk for endometrial cancer. A more selective analog could be used to prevent breast cancer without undesirable side effects in the uterus. Combinatorial chemistry can facilitate the search for ligands that can make distinctions among a family of receptors.[4] A focused library can access many structural variants of a particular pharmacophore in a relatively short time. Using a combinatorial approach, it may be possible to develop drugs that are specific for a number of estrogen-mediated disorders.

Recently, we reported the synthesis of substituted ethylenes on solid support via resin capture.[5] In this communication, we demonstrate how this chemistry can be used in the parallel synthesis of triphenylethylene derivatives based on tamoxifen where each position about the ethylene core can be modified. We also report a novel silicon linker with an increased rate of TFA cleavage.

The 25-member library was synthesized using 5 alkynes, 5 aryl halides, and a polymer bound aryl iodide as inputs. The alkynes were converted into bis(boryl)alkenes **A**−**E** in solution by a platinum-catalyzed reaction developed by Ishiyama and co-workers[6,7] (Scheme 1). The crude intermediates **A**−**E** were used in solution Suzuki reactions with an excess of aryl halide to generate **6** (Scheme 2). Since the aryl halide could react at either side of the bis(boryl)alkene, intermediates **6** were produced as a mixture of two possible regioisomers. When all of the bis(boryl)alkene was consumed, the reaction mixture was introduced to the resin **7** and the reaction continued on solid support. Through resin capture, only **6** participated in the second Suzuki reaction on solid support. Side reactions such as deboration or Suzuki reactions of **6** with the solution aryl halide gave products that remained in solution and were washed away during workup. Suzuki reactions are typically run at elevated temperatures. Using our modified conditions, however, these reactions proceeded at reasonable rates at room temperature[8] which simplified the reaction setup for the library. The products are cleaved from the polymer as amine salts of trifluoroacetic acid. Filtering the salts through a plug of basic alumina gave **1A**−**5E** as free amines in >90% purity. The yields of the products varied from 13−68% depending upon the input as shown in Table 1.[9,10]

Resin capture is a versatile strategy for combinatorial synthesis. By initiating the library in solution, there was

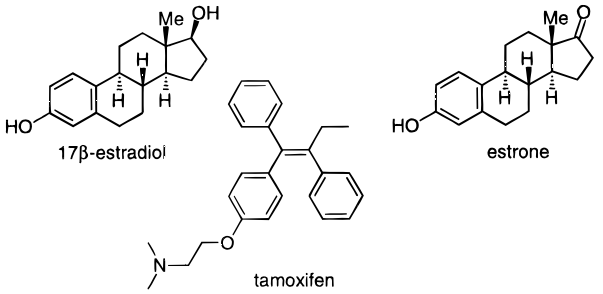
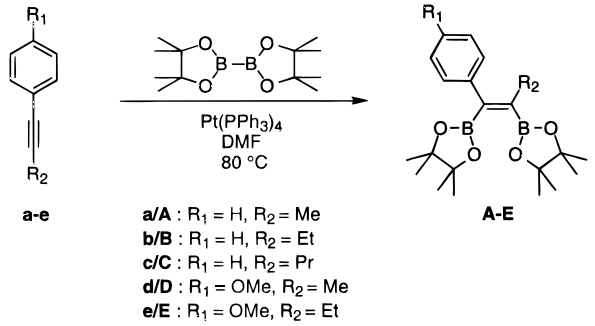
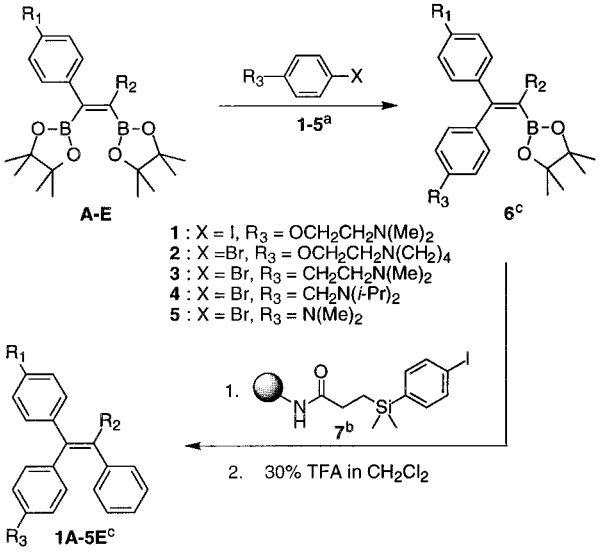


Figure 1. Tamoxifen and natural estrogens 17β-estradiol and estrone.

Scheme 1



Scheme 2



[a] Bis(boryl)alkene (10 equiv), aryl halide (15 equiv), Pd(dppf)Cl_2 (0.5 equiv), 3,5-dimethoxyphenol (50 equiv), 6 M KOH (50 equiv), DME, 25 °C, 18 h. [b] **7** (1 equiv), 6 M KOH (100 equiv), 25 °C, 18 h. [c] For simplicity, only one of two possible regioisomers is shown.

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(8) For other room temperature Suzuki conditions on solid support, see Guiles, J. W.; Johnson, S. G.; Murray, W. V. *J. Org. Chem.* **1996**, *61*, 5169−5171.
(9) For **1B**, ^{1}H NMR indicates the *trans*-isomer, tamoxifen, is the major isomer. See Collins, D. J.; Hobbs, J. J.; Emmens, C. W. *J. Med. Chem.* **1971**, *14*, 952.

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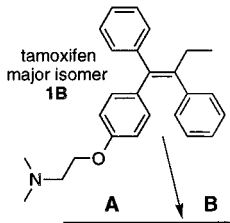
Table 1. Yields and Isomeric Ratios for Triarylethylene Derivatives Obtained through Parallel Synthesis on Solid Support via Resin Capture[10]



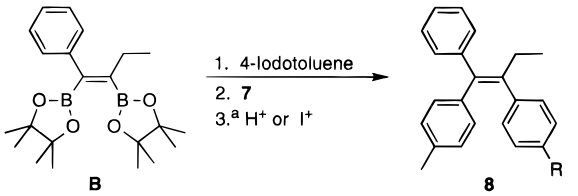
Aryl Halides	Boronates A	B	C	D	E
1	59% 1 isomer	57% 4:2:1	48% 2:1	54% 1:1	52% 4:3:1
2	55% 1:1	46% 3:1	45% 4:1	64% 3:2:1	68% 2:1
3	54% 2:1	59% 3:1	57% 3:1	64% 2:1	68% 2:1
4	27% 2:1	13% 2:1	19% 3:1	19% 3:1	31% 1:1
5	59% 3:2:1	64% 7:3:1	54% 9:4:1	61% 5:3:3:1	44% 7:3:1

no need to optimize diboration (Scheme 1) for solid support. Including solution reactions in the synthetic scheme also prevents side products from building up on the polymer. A major side product in the Suzuki reactions was deboration.[11] Since diboronates **A**−**E** and boronate intermediates **6** were in solution, there was no resin-bound boronate which could decompose via deboration. Both of the solution reactions were performed sequentially without the need for purification. As long as all of the initial diboronate was consumed in the solution Suzuki reaction (Scheme 2), none of the side products could react with **7**. After resin capture, the advantages of solid phase synthesis were realized. The resin was isolated by filtration and purified by washing. At that point, we could cleave the products from the resin or continue the synthesis on solid support. Resin capture combines the flexibility of traditional solution synthesis with the purity of products on solid support.

This synthetic strategy provides access to a wide variety of triphenylethylenes. The alkyl side chain R_2 and phenyl substituent R_1 can be varied readily with the appropriate choice of alkyne. Commercially available aryl halides provide a large selection of R_3 substituents. Although the final input, resin **7**, was not varied in this synthesis, the silicon linker offers some advantages over more traditional benzyl linkers. **7** may be cleaved in "traceless" fashion as in the present work, or it may be cleaved with alternative conditions to obtain more diversity in the final product.

Plunkett and Ellman first reported the use of a traceless linker in which no functional group in the product remained to testify to its former attachment to the polymer.[12,13] This method relies on electrophilic *ipso*-substitution of arylsilanes.[14] When the electrophile is an acid, the silyl group is replaced with hydrogen. Several other groups have also employed silicon linkers in various solid-supported syntheses.[15−17] A drawback to these linkers is the relative difficulty of acid cleavage in comparison to other linkers such as Rink or Wang. The reported cleavage conditions require exposure of the silicon linkers to 100% TFA for 8−24 h. To increase the rate of TFA cleavage, we prepared resin **7**.[18] The linker was synthesized in solution as a carboxylic acid and was coupled to ArgoGel amine resin according to standard conditions.[19] The presence of the β-amide exerts a remarkable rate enhancement to protodesilation. Products attached to **7** were cleaved efficiently in less than 10 min upon exposure to 30% TFA in CH_2Cl_2 (Scheme 3). In Suzuki reactions where the coupling efficiency was less than 100%, reduced or unreacted sites on the polymer were cleaved off as benzene or iodobenzene, which were removed under vacuum. Therefore, products were obtained in high purity even in the cases with low coupling efficiencies. Han and co-workers[16] have demonstrated that silicon linkers are cleaved with a variety of electrophiles including Br^+ and I^+. This feature can be used to introduce additional diversity in an otherwise static input by varying the cleavage conditions. Accordingly, we obtained **8b** upon cleavage with ICl (Scheme 3).

Scheme 3



[a] H^+: 30% TFA in CH_2Cl_2, 10 min; I^+: ICl (3 equiv) in CH_2Cl_2, 30 min. [b] Obtained in greater than 90% purity after cleavage. [c] Purified by preparative TLC after cleavage to remove small amounts of 1,4-diiodobenzene that result from unreacted sites on the polymer.

We have described a parallel synthesis of triphenylethylene derivatives on solid support. This strategy relies upon resin capture and a novel silicon linker to obtain products that resemble tamoxifen, an estrogen antagonist. Using this strategy, each position about the ethylene core can be modified by the appropriate choice of alkyne, aryl halide, and cleavage conditions. An investigation into the cleavage mechanism of **7** is currently in progress.

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

Supporting Information Available: Experimental procedures and copies of ^1H NMR and ^{13}C NMR spectra as well as lists of IR absorbances and results of mass spectrometric analysis for compounds **e**, **A**−**E**, **1**, **3**, **1A**−**5E**, **7**, **8a**, and **8b**. Compound **d** was synthesized as described previously[20] (82 pages).

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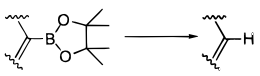
(10) For some products with electron rich π-systems, additional isomers are present due to facile isomerization of the double bond. See Murphy, C. S.; Parker, C. J.; McCague, R.; Jordan, V. C. *Mol. Pharmacol.* **1991**, *39*, 421 and references contained within.

(11)



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(18) While this work was in progress, **7** was presented at a conference, but no examples of its application or utility were given: Veber, D. F. Presented at the Second Winter Conference on Medicinal and Bioorganic Chemistry, Steamboat Springs, CO, January 1997.

(19) The synthesis of **7** is detailed in the Supporting Information.

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