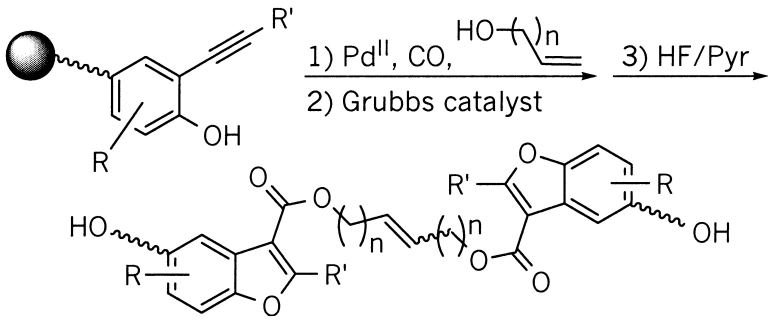
JOURNAL OF combinatorial CHEMISTRY

Review

Convergent Solid-Phase Synthesis of Symmetrical Benzo[*b*]furan's Dimerizer

Yun Liao, Reza Fathi, and Zhen Yang

J. Comb. Chem., **2003**, 5 (2), 79-81• DOI: 10.1021/cc020049w • Publication Date (Web): 28 December 2002



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 2 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

Journal of Combinatorial Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

JOURNAL OF combinatorial CHEMISTRY

Volume 5, Number 2 March/April 2003

Reports

Convergent Solid-Phase Synthesis of Symmetrical Benzo[*b*]furan's Dimerizer

Yun Liao,* Reza Fathi, and Zhen Yang

VivoQuest, Inc. 711 Executive Blvd. Valley Cottage, New York 10989

Received July 15, 2002

Introduction

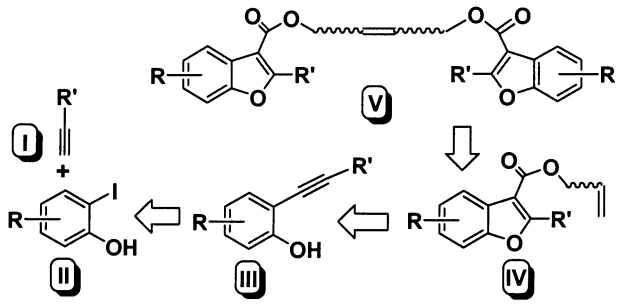
In pursuit of identifying small molecule ligands for studying biological function as well as potential candidates as a lead compound,[1] we have explored efficient methodologies for the combinatorial synthesis of natural-product-like molecules on solid support.[2] One of the scaffolds of remarkable importance is the dimeric molecule[3] because of its unique function of either activating cellular processes[4] or increasing the binding affinity of ligands to their binding sites by providing an extra binding domain.[5]

Recently, Schreiber[6] described an approach for exploiting site−site interaction on solid support[7] to generate dimeric molecules. Herein, we would like to describe our recent efforts to explore a general synthetic approach for constructing benzo[*b*]furan-based dimeric molecules by employing the Sonogashira reaction (from **I** and **II** to **III**, Scheme 1),[2e] palladium-mediated carbonylative annulation (**III** to **IV**, Scheme 1),[2a,f] and olefin cross-metathesis (**IV** to **V**, Scheme 1)[8] as the key steps on high-capacity (1−2 mmol), lightly cross-linked (1% DVB), and silyl-linker-based polystyrene macrobeads.[9]

From the standpoint of biological effects, we considered that it is important for the molecular libraries to possess the natural-product-like structural features. We preferred benzo[*b*]furan as our scaffold because of its frequent occurrence in nature and its wide range of biological activity.[10]

As is shown in the retrosynthetic analysis in Scheme 1, dimeric molecule **V** could be derived from two identical modular building blocks **IV** via ruthenium-catalyzed site−site olefin metathesis. This modular construction approach, which takes advantage of commercially available aryl iodides and acetylenes through intermediate **III**, is intended to allow convenient construction of diversified library members. Here, we demonstrate this synthetic strategy in the following examples in which eight different substituted benzo[*b*]furans and 5-hexen-1-ol as tether to link the two homo substructures were employed.

Scheme 1. Retrosynthetic Scheme for the Synthesis of Symmetric Dimeric Molecules V



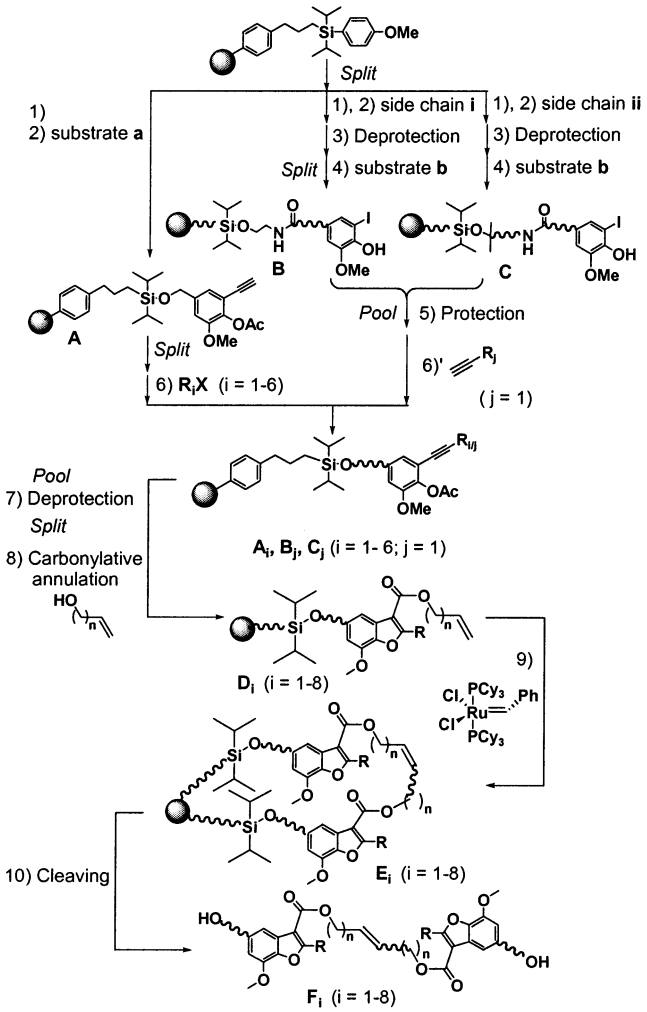
With the objective of constructing a relatively large dimeric molecular library in the future, we sought to apply our proposed strategy by using IRORI MicroKans with radio frequency encoding tags[11] in a split-pool format in order to gain sufficient experience to guide our later study.

The internal acetylenes $\mathbf{A}_i$, $\mathbf{B}_j$ and $\mathbf{C}_j$ were generated as illustrated in Scheme 2. Synthetically on-bead *o*-alkynylphenol acetates $\mathbf{A}_i$, $\mathbf{B}_j$, $\mathbf{C}_j$ were prepared by three different approaches. In the first one, substrate **a** (see Table 1) was directly loaded onto the beads to give the intermediate **A**, which was then split into six pools, followed by the Sonogashira reaction to couple with six aryl iodides ($\mathbf{R}_i\mathbf{X}$,

* To whom correspondence should be addressed. E-mail: y.liao@vivoquest.com.

10.1021/cc020049w CCC: $25.00
Published on Web 12/28/2002

Scheme 2. Diagram of Split-Pool Synthesis of Symmetric Dimeric Molecules



Conditions: (1) Me_3SiCl, imidazole, CH_2Cl_2, rt, 2 h; TfOH, CH_2Cl_2, rt, 1.5 h. (2) 2, 6-lutidine, CH_2Cl_2, rt, 4 h. (3) piperidine, DMF, rt, 1 h. (4) Py-BOP, NMM, DMF/THF 1/2, rt, 12 h. (5) LiCl, CH_2Cl_2, rt, 10 h. (6) X = OTf, $Pd(PPh_3)_4$, CuI, DIPEA, DMF/THF 1/1, rt, 24 h; X = I, fresh Pd^0 (0.3 equiv), CuI, DIPEA, DMF/THF 1/1, rt, 24 h, or $Pd_2(dba)_3$ (5%), CuI, NEt_3, rt, 48 h. (6)′ $Pd(PPh_3)_2Cl_2$ (0.3 equiv), CuI, DIPEA, CH_3CN, rt, 24 h. (7) NH_2NH_2/THF, (0.1 M). (8) CO, R^2OH, $Pd(PPh_3)_2Cl_2$-dppp (1.2 eq), CsOAc, DMF, 45 °C, 48 h. (9) Grubbs catalyst (0.1 equiv), CH_2Cl_2, 40 °C, 24 h. (10) HF/Py 5% in THF, rt, 1 h; TMSOMe, 0.5 h.

Table 1. Building Blocks for Scheme 2

Side Chains	i	ii
Substrates	a	b
R_i^1X	1	2	3	4	5	6
R_j^1	CN	
	HO	

Table 1) to give the corresponding six phenylacetylenes ($\mathbf{A}_i$). The second approach primarily involved the loading of a Fmoc protected hydroxylamine (side chain **i**, Table 1) onto the beads, then deprotection to remove the Fmoc, followed by Py-BOP-mediated coupling of the acid (substrate **b**) to afford on-bead iodophenol **B**, whereas the third approach for the synthesis of on-bead **C** started with a tertiary alcohol-based Fmoc-protected amine (side chain **ii**, Table 1) as a spacer in order to test the stability of the corresponding silyl ether (vs on-beads **A**−**B**), followed by deprotection and coupling with substrate **b**. Therefore, these two on-bead iodophenols (**B** and **C**) were pooled, then protected as their corresponding acetates, and coupled with an acetylene to give on-bead phenylacetylenes ($\mathbf{B}_j$, $\mathbf{C}_j$).

All eight of these phenylacetylenes ($\mathbf{A}_i$, $\mathbf{B}_j$, and $\mathbf{C}_j$) were subsequently pooled, followed by deprotection to remove the acetate, and then underwent the palladium-mediated cascade carbonylative annulations with the terminal alkenyl alcohol to give on-bead 2,3-disubstituted benzo[*b*]furans $\mathbf{D}_i$ (i = 1−8). The presence of a terminal olefin leads to an assembling of two benzo[*b*]furan-based modules into a symmetric dimeric molecule. Thus, treatment of these on-bead benzo[*b*]furans $\mathbf{D}_i$ with Grubbs catalyst finally afforded the dimeric molecules $\mathbf{E}_i$. All homo dimers were released from beads by HF−Py solution to give the final products $\mathbf{F}_i$ (Table 2).

The structures of all intermediates (**A**, **B**, **C**, $\mathbf{A}_i$, $\mathbf{B}_j$, $\mathbf{C}_j$, and $\mathbf{D}_i$) and final products ($\mathbf{F}_i$) were fully confirmed by both ^{1}H NMR and HPLC/MS (APCI or ESP). On the basis of analytical data, conversions and purities of 80−95% for all

Table 2. Synthesized Symmetrical Dimeric Molecules

Symmetrical dimeric products	*Z*/*E*[a]	Conversions/ Purities[a,b] (%)
F_1	1/2	75
F_2	2/3	80
F_3	1/1	75
F_4	1/10	80
F_5	1/10	80
F_6	1/10	80
F_7	1/1	80
F_8	2/1	75

[a] Estimated by ^{1}H NMR integration. [b] Estimated by LC-MS.

intermediates and those around 70−80% for final symmetric products were estimated directly after cleaving the samples from the beads, followed by evaporation without further purification. As expected,[6] in most cases, *E* isomers dominated the final symmetric product mixtures from olefin metathesis, as shown in Table 2.

Conclusion

We have efficiently synthesized homo-dimeric molecules of benzo[*b*]furan on high-loading polystyrene macrobeads using copper, palladium, and ruthenium chemistry by means of a split-pool methodology. This protocol provides direct access to a range of dimeric molecules that are ideal for high-throughput screening of protein−protein interactions in a cell-based assay system. Further efforts related to generation of a larger library of these interesting molecules are underway in our laboratory.

Supporting Information Available. Experimental procedures and ^{1}HNMR, LCMS spectra for all compounds are available as Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) (a) Mitchison, T. J. *Chem. Biol*. **1994**, *1*, 3−6. (b) Mayer, T. U.; Kapoor, T. M.; Haggarty, S. J.; King, R. W.; Schreiber, S. L.; Michison, T. J. *Science* **1999**, *286*, 971−974. (c) Haggarty, S. J.; Mayer, T. U.; Miyamoto, D. T.; Fathi, R.; King, R. W.; Mitchison, T. J.; Schreiber, S. L. *Chem. Biol*. **2000**, *7*, 275−286. (d) Nicolaou, K. C.; Pfefferkorn, J. A.; Schulaer, F.; Roecker, A. J.; Cao, G.-Q.; Casida, J. E. *Chem. Biol*. **2000**, *7*, 979−992.

(2) (a) Nan, Y.; Miao, H.; Yang, Z. *Org. Lett*. **2000**, *2*, 297−299. (b) Miao, H.; Yang, Z. *Org. Lett*. **2000**, *2*, 1765−1768. (c) Hu, Y.-H.; Yang, Z. *Org. Lett*. **2001**, *3*, 1387−1390. (d) Wu, J.; Liao, Y.; Yang, Z. *J. Org. Chem*. **2001**, *66*, 3642−3645. (e) Liao, Y.; Fathi, R.; Reitman, M.; Zhang, Y.; Yang, Z. *Tetrahedron Lett*. **2001**, *42*, 1815−1818, and references therein. (f) Liao, Y.; Reitman, M.; Zhang, Y.; Fathi, R.; Yang, Z. *Org. Lett*. **2002**, *4*, 2607−2609.

(3) Clemons, P. A. *Curr. Opin. Chem. Biol*. **1999**, *3*, 112−115.

(4) Diver, S. T.; Schreiber, S. L. *J. Am. Chem. Soc*. **1997**, *119*, 5106−5109 and references therein.

(5) Nicolaou, K. C.; Hughes, R.; Cho, S.-Y.; Winssinger, N.; Smethurst, C.; Labischinski, H.; Endermann, R. *Angew. Chem., Int. Ed*. **2000**, *39*, 3823−3828 and references therein.

(6) Blackwell, H. E.; Clemons, P. A.; Schreiber, S. L. *Org. Lett*. **2001**, *3*, 1185−1188.

(7) (a) Rapoport, H.; Crowley, J. I. *Acc. Chem. Res*. **1976**, *9*, 135−144. (b) Yan, B.; Sun, Q. *J. Org. Chem*. **1998**, *63*, 55−58. (c) Lindsley, C. W.; Chan, L. K.; Goess, B. C.; Joseph, R.; Shair, M. D. *J. Am. Chem. Soc*. **2000**, *122*, 422−423.

(8) (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450. (b) Fürstner, A. *Angew. Chem., Int. Ed*. **2000**, *39*, 3012−3043. (c) Blackwell, H. E.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. A.; Bussman, D. A.; Grubbs, R. H. *J. Am. Chem. Soc*. **2000**, *122*, 58−71 and references therein.

(9) Tallarico, J. A.; Depew, K. M.; Pelish, H. E.; Westwood, N. J.; Lindsley, C. J.; Shair, M. D.; Schreiber, S. L.; Foley, M. A. *J. Comb. Chem*. **2001**, *3*, 312−318.

(10) For examples, see: (a) Engler, T. A.; LaTessa, K. O.; Lyengar, R.; Chai, W.; Agrios, K. *Bioorg. Med. Chem*. **1996**, *4*, 1755−1769. (b) Pieters, L.; Van Dyck, S.; Gao, M.; Bai, R.; Hamel, E.; Vlietinck, A.; Lemiere, G. *J. Med. Chem*. **1999**, *42*, 5473−5481. (c) Vishnu, V. R. K.; Ashok, D. *Book of Abstracts*, Proceedings of the 219th ACS National Meeting, San Francisco, CA, March 26−30, 2000.

(11) Nicolaou, K. C.; Pfefferkorn, J. A.; Mitchell, H. J.; Roecker, A. J.; Barluenga, S.; Cao, G.-Q.; Affleck, R. L.; Lillig, J. E. *J. Am. Chem. Soc*. **2000**, *122*, 9954−9967.CC020049W

CC020049W