Pergamon

Tetrahedron Letters 42 (2001) 1815–1818

TETRAHEDRON
LETTERS

Optimization study of Sonogashira cross-coupling reaction on high-loading macrobeads using a silyl linker

Yun Liao, Reza Fathi, Mike Reitman, Yan Zhang and Zhen Yang*

Institute of Chemistry and Cell Biology, Harvard University, 250 Longwood Avenue, SGM 604, Boston, MA 02115-5731, USA

Received 27 November 2000; revised 8 January 2001; accepted 9 January 2001

Abstract—Two types of Sonogashira reactions were systematically evaluated on silyl linker based high-loading polystyrene macrobeads, this study paves the way for their future application in the combinatorial syntheses of some natural product-like molecules. © 2001 Elsevier Science Ltd. All rights reserved.

Benzo[*b*]furan with diversified functional groups have both important and broad ranging research and clinical applications.[1] Synthetic strategies toward benzofurans focuses primarily on either generating benzofurans for subsequent incorporation into their corresponding complex natural products[2] or modifying benzofurans by attaching different substitutions.[3] The former involves multiple synthetic and purification steps to the desired benzofurans, which proves a highly labor-intensive process, and the latter does provide different substituted benzofurans; however, the diversity of this library is limited to only a few scaffolds. Consequently, there is a need for new and powerful methods that offer greater flexibility and synthetic ease to diversity-oriented synthesis[4] (DOS) of benzofuran's library.

We reported previously our novel synthetic method for the synthesis of 2,3-disubstituted benzo[*b*]furans (Scheme 1), and diversified benzofurans have been synthesized in solution phase.[5]

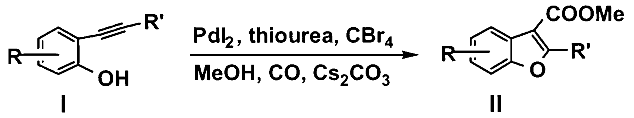
In this communication, we present our recent efforts on a systematic evaluation of the Sonogashira reaction for synthesizing the key intermediate **I** (Scheme 1) on a solid support to enable future combinatorial synthesis of a 2,3-disubstituted benzo[*b*]furan library.

The Sonogashira reaction is a versatile tool for carbon–carbon bond formation,[6] and has become a powerful method in the combinatorial chemistry, one such elegant demonstration is the application of this reaction in Shikimic acid library synthesis.[7]

In our benzofuran's library synthesis, we preferred to use silyl linker[8] based high-capacity polystyrene macrobeads[9] as a solid support in order to realize a 'one bead, one compound' concept[10] by using a split-pool strategy.[11] The advantages of using these beads are (1) high-capacity (up to 1.4 mmol/g) macrobeads (450–500 μm) will provide sufficient material from a single bead for a multiple assay;[12] (2) the silyl linker will allow compounds generated on-beads to be released by utilizing volatile cleavage reagents (such as HF/pyridine and trimethylsilylmethanol in our case), therefore, the compounds can go directly into assays without purification.

However, the macrobeads create a number of new challenges, which include (a) how to overcome the problem of permissibility in the macrobeads; (b) how to develop a synthetic strategy which will be compatible with an acid-sensitive silyl linker; (c) how to prevent the large beads from breakage.

Although significant progress in the Sonogashira reaction on solid supports has been made,[7,13] to the best of our knowledge, an evaluation of this reaction on silyl linkers based high-capacity macrobeads has not been reported yet. In order to address the above challenges, we, therefore, started to systematically evaluate this reaction on these beads in order to synthesize diversified *o*-hydroxyaryl acetylenes **I** (Scheme 1).

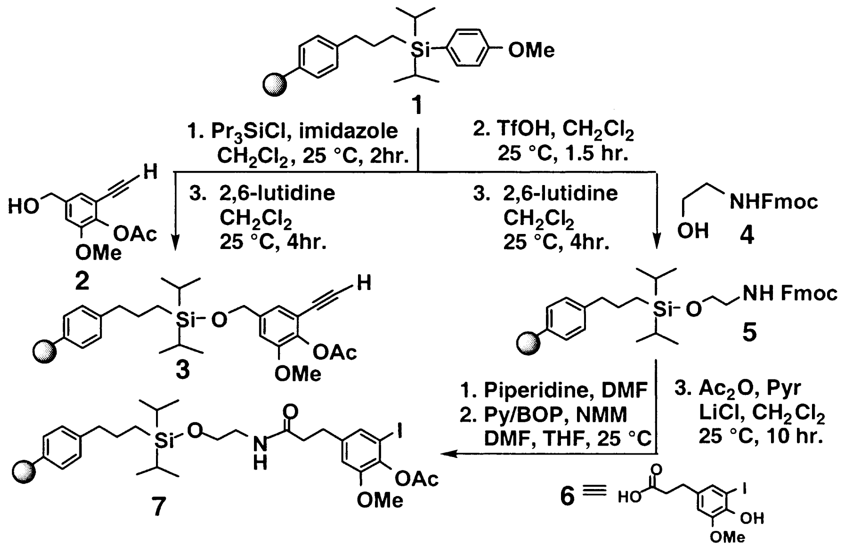


Scheme 1. Palladium-catalyzed carbonylative heteroannulation to synthesize benzo[*b*]furans.

---

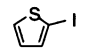
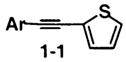
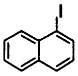
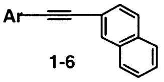
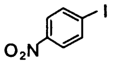
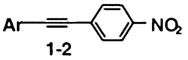
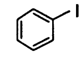
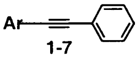
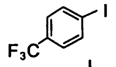
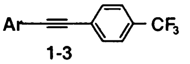
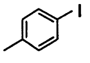
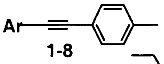
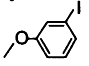
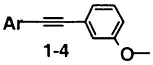
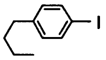
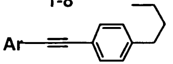
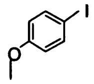
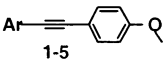
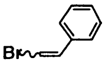
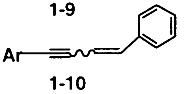
* Corresponding author.

PII: S0040-4039(01)00052-1

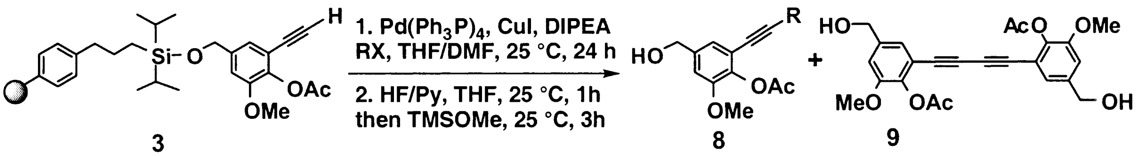


Scheme 2. Synthesis of the on-bead substrates **3** and **7**.

Table 1. Sonogashira cross-coupling between the on-bead terminal alkyne **3** and aryl/vinyl halides

entry	RX	coupling product **8**	conversion/purity[a]	dimer **9**	entry	RX	coupling product **8**	conversion/purity[a]	dimer **9**
1		 1-1	> 90%	< 10%	6		 1-6	> 85%	<15%
2		 1-2	> 95%	< 5%	7		 1-7	> 90%	< 10%
3		 1-3	> 95%	< 5%	8		 1-8	> 90%	< 10 %
4		 1-4	> 95%	< 5%	9		 1-9	> 90%	< 10%
5		 1-5	> 95%	< 5%	10		 1-10	> 90%	< 10%

[a]conversion and purity were obtained by calculating the individual intergration of the corresponding NMR peak. Ar represents the core of compound **8**.



Scheme 3. Sonogashira reaction of on-bead alkyne **3** with aryl/vinyl halides or aryl/vinyl triflates.

After an extensive investigation in solution phase, we selected compounds **2** and **6** (Scheme 2) as test substrates for the Sonogashira reaction. The synthetic sequence described in Scheme 2 gave excellent results to prepare the on-bead phenyl acetylene **3** and phenyl iodide **7** (see the supporting information). Because a large amount of terminal acetylenes and aryl/vinyl halides or triflates are commercially available or synthetically accessible, coupling them with their corresponding partners will generate a large amount of diversified *o*-hydroxyaryl acetylenes **I** (Scheme 1).

At the beginning, substrate **3** was coupled with the iodides (entries 1–10 in Table 1) under Pd(Ph$_3$P)$_4$/CuI catalysis. The coupling reactions turned out to be too slow to generate the desired product **8** (Scheme 3). However, on increasing Pd(Ph$_3$P)$_4$/CuI to stoichiometric amount, the homo-coupling product **9** (Scheme 3) was generated predominately.

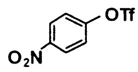
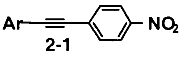
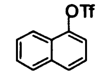
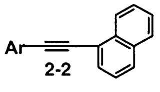
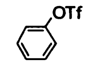
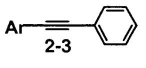
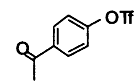
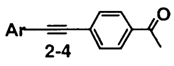
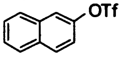
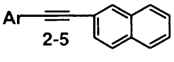
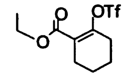
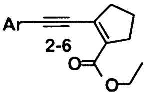
We speculated that **9** might be generated by the Eglinton–Glaser reaction[14] due to the high-loading level of our macrobeads. In order to test this notion, we set up a reaction under the condition listed in Scheme 3 without $Pd(Ph_3P)_4$. More than 30% of **9** was formed under such conditions (RX as ArI, vinyl bromide or ROTf from Tables 1 and 2). Therefore, using an excess amount of $Pd(Ph_3P)_4$/CuI to drive the reactions to completion seems to be incompatible with our high loading macrobeads.

$Cl_2Pd(Ph_3P)_2$ can be reduced to $Pd^0(PPh_3)_2$ (the putative active catalyst) through sequential CuI-mediated bis-alkynylation and reductive elimination reaction.[6] Therefore, we designed a novel procedure to generate the $Pd^0(PPh_3)_2$ by pre-treatment of a catalytic amount of $Cl_2Pd(Ph_3P)_2$ with 2.5 equivalents of phenyl acetylene in the presence of catalytic amount of CuI and DIPEA (di*iso*propylethylamine) at room temperature for 2 h. Coupling of the on-bead acetylene **3** with aryl iodides or vinyl bromide in a co-solvent (THF/DMF = 1/1) followed. This solvent system eventually proved to be very critical to maintain the macrobeads entirety. To our delight, all the selected organic halides coupled with **3** to give the desired product **8** in high yields under these reactive conditions listed in Scheme 3, and only a small amount of dimer **9** was formed (see Table 1).

Interestingly, the catalytic system discussed above did not give good results when aryl triflates were used as electrophiles. Satisfactory results were eventually obtained only by using $Pd(Ph_3P)_4$ as a catalyst under these reactive conditions listed in Scheme 3, and the results are listed in Table 2.

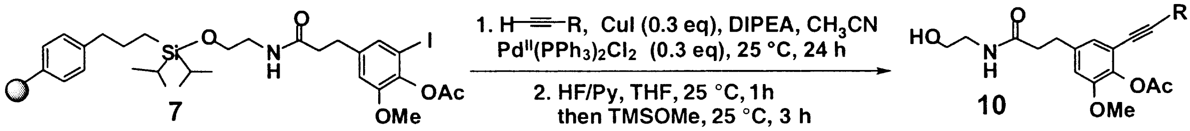
The coupling reaction between the on-bead phenyl iodide **7** (Scheme 2) with terminal acetylenes (entries 1–12 in Table 3) gave much better results than expected, since the generated alkyne dimers only stay in solution phase, and can be easily removed by washing the beads with solvents. These reactions were carried out in acetonitrile to prevent the macrobeads from breakage, and 0.3 equivalents of $Cl_2Pd(Ph_3P)_2$/CuI were used to promote these couplings. The results are listed in Table 3.

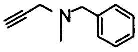
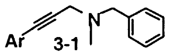
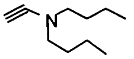
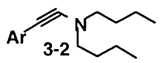
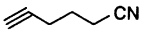
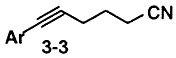
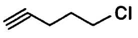
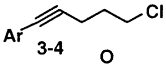
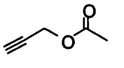
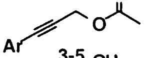
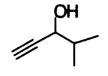
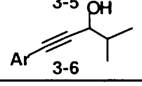
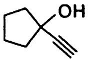
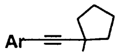
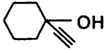
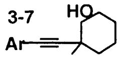
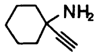
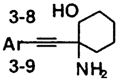
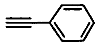
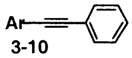
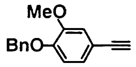
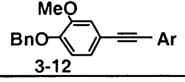
Table 2. Sonogashira cross-coupling between the on-bead terminal alkyne **3** and aryl/vinyl triflates

entry	ROTf	coupling product 8	conversion/purity[a]	dimer 9
1		 2-1	> 92%	< 8%
2		 2-2	> 92%	< 8%
3		 2-3	> 90%	< 10%
4		 2-4	> 97%	< 3%
5		 2-5	100%	0%
6		 2-6	> 94%	< 6%

[a]conversion and purity were obtained by calculating the individual intergration of the corresponding NMR peak. Ar represents the core of compound **8**.

Table 3. Sonogashira cross-coupling between the on-bead aromatic iodide with terminal acetylenes



entry	H—≡—R	product	conversion/purity (%)[a]
1		 3-1	> 95
2		 3-2	> 95
3		 3-3	> 95
4		 3-4	> 95
5		 3-5	> 95
6		 3-6	> 95
7		 3-7	> 95
8		 3-8	> 95
9		 3-9	> 95
10		 3-10	> 95
11		 3-11	> 95
12		 3-12	> 95

[a]conversion and purity were obtained by calculating the individual intergration of the corresponding NMR peak. Ar represents the core of compound **10**.

In conclusion, we have optimized the Sonogashira reaction for synthesis of the *o*-acetoxyphenyl-acetylenes on the silyl linker based high-capacity macrobeads. The original challenges associated with the macrobeads have been resolved by proper selection of reaction conditions and solvents. Thus, this investigation has paved a credible way for its application on combinatorial synthesis of a 2,3-disubstituted benzo[*b*]furan library, which is currently in progress in our lab and will be reported in due course.

Acknowledgements

We thank Professors Stuart L. Schreiber and Timothy J. Mitchison and Rebecca Ward for their invaluable advice during the course of this research, and Dr. Micheal Foley's group for their generous providing the silyl linker based high loading macrobeads. Financial support from the NIH grant (#: 1PO1 CA78048), Merck & Co. grant (#: MCI97MITC804) and Merck KGaA is gratefully acknowledged.

References

1. Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Moro, L. *Syntlett* **1999**, *9*, 1432–1434 and references cited therein.
2. (a) Fuerst, D. F.; Stoltz, B. M.; Wood, J. L. *Org. Lett.* **2000**, *2*, 3521–3523; (b) Vedejs, E.; Wang, J. *Org. Lett.* **2000**, *2*, 1031–1034.
3. (a) Yang, Z.; Liu, H. B.; Lee, C. M.; Chang, H. M.; Wong, H. N. C. *J. Org. Chem.* **1992**, *57*, 7248–7257; (b) Mann, I. S.; Widdowson, D. A. *Tetrahedron* **1991**, *47*, 7991–8000.
4. (a) Schreiber, S. L. *Science* **2000**, *287*, 1964–1969; (b) Nicolaou, K. C.; Pfefferkorn, J. A.; Barluenga, S.; Mitchell, H. J.; Roecker, A. J.; Cao, G.-Q. *J. Am. Chem Soc.* **2000**, *122*, 9968–9976.
5. Nan, Y.; Miao, H.; Yang, Z. *Org. Lett.* **2000**, *2*, 297–299.
6. Sonogashira, K.; Tohda, Y; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467–4470.
7. Tan, D. S.; Foley, M. A.; Stockwell, B. R.; Shair, M. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9073–9087.
8. Plunkett, M. J.; Ellman, J. A. *J. Org. Chem.* **1997**, *62*, 2885–2893.
9. Tallarico, J. A.; Depew, K. M.; Westwood, N.; Pelish, H.; Athanasopoulos, J.; Lindsley, C.; King, R. W.; Schreiber, S. L.; Shair, M. D.; Foley, M. A., unpublished results.
10. Lam, K. S.; Salmon, S. E.; Hersh, E. M.; Hruby, V. J.; Kazmierski, W. M.; Knapp, R. J. *Nature* **1991**, *354*, 82–84.
11. Furka, A.; Sebestyen, F.; Asgedom, M.; Dibo, G. *Int. J. Pept. Protein Res.* **1991**, *37*, 487–493.
12. (a) Stockwell, B. R.; Haggarty, S. J.; Schreiber, S. L. *Chem. Biol.* **1999**, *6*, 71–83; (b) Mayer, T. U.; Kapoor, T. M.; Haggarty, S. J.; King, R. W.; Schreiber, S. L.; Mitchison, T. J. *Science* **1999**, *286*, 971–974.
13. (a) Huang, S.; Tour, J. M. *J. Am. Chem. Soc.* **1999**, *121*, 4908–4909; (b) Khan, S. I.; Grinstaff, M. W. *J. Am. Chem. Soc.* **1999**, *121*, 4704–4705 and references cited therein.
14. (a) Haley, M. M.; Pak, J. J.; Brand, S. C. *Top. Curr. Chem.* **1999**, *201*, 81 and references therein; (b) Höger, S.; Bonrad, K.; Karcher, L.; Meckenstock, A.-D. *J. Org. Chem.* **2000**, *65*, 1588–1589.