Efficient Synthesis of Unsymmetrical 1,3-Diynes Utilizing a Palladium-Catalyzed Cross-Coupling Reaction Without Homo-Coupling

Boyoung Kim, Sunyoung You, Namgeol Lee, and Sungwook Choi*

*Graduate School of New Drug Discovery and Development, Chungnam National University, Daejon 305-764, Korea. *E-mail: swchoi2010@cnu.ac.kr*

Received July 2, 2014, Accepted September 1, 2014, Published online December 19, 2014

Keywords: Palladium-catalyzed cross-coupling, Conjugated 1,3-diyne

Conjugated 1,3-diynes are important building blocks in the fields of chemistry, biology, and material science because they are found in a variety of natural products,[1–5] pharmaceuticals,[6] electronic and optical materials,[7] and molecular recognition systems.[8] Numerous efficient methods for the construction of conjugated 1,3-diynes have been developed. The Glaser–Hay coupling reaction was the first method used to construct symmetric 1,3-diynes, which were obtained using a Cu-mediated oxidative homo-coupling reaction of two terminal alkynes.[9,10] Later, improved methods, including Cu-catalyzed homo-coupling[11–14] and Pd-catalyzed homo-coupling,[15–21] have been developed for the construction of symmetrical 1,3-diynes. Furthermore, numerous studies have attempted to construct unsymmetrical 1,3-diynes. The method developed by Cadiot and Chodkiewicz has been utilized for the synthesis of unsymmetrical 1,3-diynes via Cu-catalyzed coupling of a 1-haloalkyne and a terminal alkyne.[22] However, the Cadiot–Chodkiewicz coupling showed a limitation in the construction of unsymmetrical 1,3-diynes because of its low selectivity, yielding a mixture of homo-coupled and cross-coupled products. Recently, Cu- and Pd-catalyzed cross-coupling reactions have been reported.[23–27] Although modified coupling methods have been developed for more efficient and selective preparation of unsymmetrical 1,3-diynes, these methods suffer from several drawbacks, such as the generation of undesired homo-coupled by-products and difficulty in isolation of the desired product.

Here, we describe the solid-phase synthesis of various unsymmetrical 1,3-diynes bearing carboxylic acid via Pd-catalyzed cross-coupling reaction. Unsymmetrical 1,3-diyne **5a** was synthesized using the solid-phase route described in Scheme 1. The compound **4**-iodobenzoic acid was attached to commercially available Wang resin using 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and Hydroxybenzotriazole (HOBT) in DMF. The reaction of iodobenzoate **1** with trimethylsilyl acetylene catalyzed by $Pd(PPh_3)_4$ and CuI, followed by desylilation of intermediate **2** with tetrabutylammonium fluoride (TBAF) in Tetrahydrofuran (THF), yielded aryl acetylene **3**. As a starting point for the development of our solid-phase-based method, we chose phenylethynyl bromide to construct unsymmetrical 1,3-diyne **5a**, and the conversion and purity were determined using high-performance liquid chromatography (HPLC) analysis (Table 1). The effects of the catalyst, solvent, and additive were initially investigated for the solid-phase cross-coupling reaction.

As shown in entries 1–4 in Table 1, a variety of palladium catalysts were examined in the presence of CuI at room temperature for 24 h. The use of $Pd_2(dba)_3$ afforded the desired unsymmetrical 1,3-diyne **5a** in 27% overall yield with 86% purity over five steps. Further optimization revealed that the solvent played an important role in this process (Table 1, entries 5–7). The best yield (49% overall yield and 92% purity) was obtained when a catalytic amount of $Pd_2(dba)_3$ and CuI in Et_3N was used (Table 1, entry 6). Based on these results, we next explored the effect of ligands while maintaining constant concentration of $Pd_2(dba)_3$ and CuI in Et_3N (Table 1, entries 8–10). Although the use of PPh_3 and 1,3-bis(diphenylphosphino)propane (Dppp) showed low reactivity, the addition of tri(*o*-tolyl)phosphine (P(o-tol)$_3$) furnished **5a** in 45% yield. Only a trace amount of the cross-coupled product **5a** was detected in the absence of the palladium catalyst, and low conversion was observed with a catalytic amount of $Pd_2(dba)_3$ and CuI in Et_3N at higher temperatures (data not shown).

Using the $Pd_2(dba)_3$-catalyzed system (Table 1, entry 6), we examined the generality and feasibility of our method with a variety of substituted phenylethynyl bromides. All products were isolated via column chromatography and characterized using HPLC and NMR. As shown in Table 2, the solid-phase cross-coupling reaction allowed us to prepare various unsymmetrical 1,3-diynes bearing carboxylic acid with electron-donating groups (Table 2, entries 2, 5, and 6) and electron-withdrawing groups (Table 2, entries 3 and 4) on the benzene ring. In general, electron-deficient phenylethynyl bromide yielded higher amounts of 1,3-diynes compared to electron-rich phenylethynyl bromide. Furthermore, terminal alkynes containing the aminopyridine moiety could be converted into the corresponding unsymmetrical 1,3-diyne scaffold (Table 2, entry 7).

Overall, we developed a simple and robust synthetic approach to prepare unsymmetrical 1,3-diynes bearing carboxylic acid utilizing a variety of substituted phenylethynyl bromides under mild conditions. To the best of our knowledge, this is the first example of unsymmetrical 1,3-diyne prepared by solid-phase synthesis. Although overall yields are

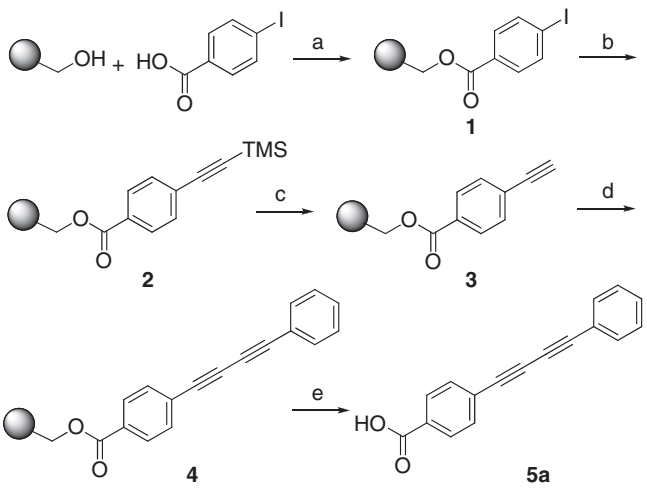
moderate, this approach may be used to synthesize a broad range of unsymmetrical 1,3-diynes bearing carboxylic acid, and may be extended to prepare conjugated triynes or polyynes in natural products or to generate combinatorial chemical libraries.

Experimental

All reactions were run under N_2 atmosphere except especially indicated experiments. Anhydrous solvents were used for most reactions. Solvents were purified by common distillation methods. Some distilled solvents were degassed under N_2 gas flow through the solvent. ^1H and ^{13}C spectra were recorded on BRUKER 300 and 600 MHz spectrometers. Chemical shifts are reported relative to internal $CDCl_3$ (Me_4Si, δ 0.0 for ^1H and $CDCl_3$, 77.16 for ^{13}C) and DMSO-d_6 (δ 2.50 for ^1H and 39.52 for ^{13}C). Analytical reverse-phase HPLC (RP-HPLC) was performed on a Waters Alience 2695 separation module, using a Waters 2487 dual λ absorbance detector (Waters, MA, USA), equipped with Alience 2695 autosampler and a Watchers® 120 ODS-BP Columns (120 Å pore size, 5 μ M particle size, mobile phase A = 0.1% TFA in 95% H_2O + 4.9% MeCN; mobile phase B = 0.1% TFA in 95% MeCN + 4.9% H_2O). Linear gradients were run from 100:0 to 0:100 A:B over 25 min.

General Procedure for the Preparation of 1,3-diynes 5a–5g

The Wang resin (0.9 mmoL/g) was swelled in CH_2Cl_2 for ~10 min. In sequential order, 4-iodobenzoic acid (2 equiv.), Et_3N (1.5 equiv.), EDCI·HCl (2 equiv.), and HOBT (0.3 equiv.) were added to the reaction vessel, and the reaction was stirred for 18 h. The resin was filtered and washed repeatedly with DMF (3×), CH_2Cl_2 (3×), and oxygen-free THF. The resin was then suspended in degassed THF/Et_3N (1:1) and stirred with $Pd(PPh_3)_4$ (0.1 equiv.), CuI (0.1 equiv.), and trimethylsilylacetylene (7 equiv.) for 48 h under a nitrogen atmosphere. The resin was filtered and washed repeatedly with THF (3×), DMF (3×), and THF (2×). This resin was then suspended with THF and stirred with TBAF (1 M in THF, 2 equiv.) for 1 h. The resin was filtered, washed repeatedly with THF (5×) and CH_2Cl_2 (2×), and dried *in vacuo*. Resin-bound alkyne **3** was swelled in degassed Et_3N for 10 min. To this resin were added phenylethynyl bromide (3 equiv.), CuI (0.1 equiv.), and $Pd_2(dba)_3$ (0.1 equiv.). The resin was stirred for 24 h under



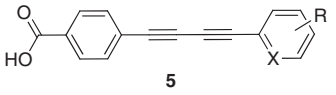
Scheme 1. Synthesis of conjugated 1,3-diynes.

Table 1. Optimization of palladium-catalyzed cross-coupling of polymer-bound alkyne **3** and phenylethynyl bromide.[a]

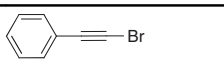
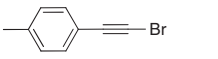
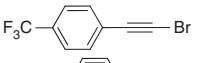
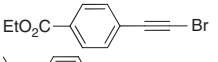
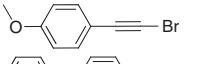
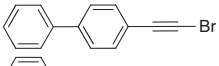
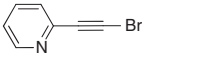
Entry	Catalyst	Additive and solvent	Total yield (%)[b]
1	$Pd(PPh_3)_2Cl_2$	Et_3N (4 equiv.)/DMF	24
2	$Pd(PPh_3)_4$	Et_3N (4 equiv.)/DMF	14
3	$Pd_2(dba)_3$	Et_3N (4 equiv.)/DMF	27
4	$Pd(dba)_2$	Et_3N (4 equiv.)/DMF	26
5	$Pd_2(dba)_3$	Et_3N/DMF (1:1)	10
6	$Pd_2(dba)_3$	Et_3N	49
7	$Pd_2(dba)_3$	*i*-Pr_2NH	37
8	$Pd_2(dba)_3$	PPh_3 (0.2 equiv.)/Et_3N	11
9	$Pd_2(dba)_3$	P(o-tol)$_3$ (0.2 equiv.)/Et_3N	45
10	$Pd_2(dba)_3$	Dppp (0.2 equiv.)/Et_3N	37

[a] Palladium-catalyzed cross-coupling reactions were performed with 0.08 mmol of alkyne **3**, 0.1 equiv. of Pd catalyst, 0.1 equiv. of CuI, additive, and solvent.
[b] Total yields were based on loading of 4-iodobenzoic acid on the Wang resin and determined by HPLC analysis.

Table 2. Palladium-catalyzed cross-coupling of polymer-bound alkyne **3** and a variety of substituted phenylethynyl bromides.[a]



5

Entry	Phenylethynyl bromide	Product	Total yield (%)[b]
1		**5a**	48
2		**5b**	24
3		**5c**	53
4		**5d**	57
5		**5e**	47
6		**5f**	33
7		**5g**	42

[a] Palladium-catalyzed cross-coupling reactions were performed with 0.25 mmoL of polymer-bound alkyne **3**, 0.1 equiv. of $Pd_2(dba)_3$, 0.1 equiv. of CuI, and 3 equiv. of phenylethynyl bromide in 4 mL of degassed Et_3N.
[b] Isolated yield. Total yields were based on loading of 4-iodobenzoic acid on the Wang resin.

a nitrogen atmosphere. The resin was filtered, washed successively with DMF (2×), CH_2Cl_2 (2×), a solution of sodium diethyldithiocarbamate (377 mg) and DIEA (0.33 mL) in DMF, DMF (4×), CH_2Cl_2, and MeOH, and dried *in vacuo*. The final compounds were cleaved from the resin by treatment of TFA/ CH_2Cl_2 (1:1) for 1 h.

5a: ^{1}H-NMR (300 MHz, DMSO-d_6) δ 13.25 (s, 1H), 7.97 (d, J = 8.0 Hz, 2H), 7.7 (d, J = 8.0 Hz, 2H), 7.63–7.66 (m, 2H), 7.43–7.53 (m, 3H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 166.48, 132.57, 132.48, 131.62, 130.24, 129.55, 128.95, 124.65, 120.11, 83.07, 80.87, 75.78, 73.17.

5b: ^{1}H-NMR (300 MHz, DMSO-d_6) δ 7.95 (d, J = 8.7 Hz, 2H), 7.68 (d, J = 8.6 Hz, 2H), 7.52 (d, J = 8.1 Hz, 2H), 7.26 (d, J = 8.1 Hz, 2H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 171.19, 166.67, 140.38, 132.41, 129.58, 129.50, 124.20, 117.10, 83.26, 80.79, 75.71, 72.76, 21.18.

5c: ^{1}H-NMR (300 MHz, DMSO-d_6) δ 7.98 (d, J = 8.4 Hz, 2H), 7.90–7.88 (m, 4H), 7.75 (d, J = 8.4 Hz, 2H); ^{13}C-NMR (150 MHz, DMSO-d_6) δ 166.18, 133.07, 132.46, 131.78, 129.78, 129.57, 129.36, 125.51, 124.46, 124.41, 124.11, 122.65, 81.92, 81.09, 75.20, 75.06.

5d: ^{1}H-NMR (300 MHz, DMSO-d_6) δ 13.25 (s, 1H), 7.97–8.01 (m, 4H), 7.72–7.78 (m, 4H), 4.33 (q, J = 7.1 Hz, 2H), 1.33 (t, J = 7.1 Hz, 3H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 166.44, 164.87, 132.79, 132.76, 131.91, 130.74, 129.55, 129.38, 124.76, 124.27, 82.20, 81.85, 75.68, 75.31, 61.12, 14.06.

5e: ^{1}H-NMR (300 MHz, DMSO-d_6) δ 13.22 (s, 1H), 7.95 (d, J = 8.3 Hz, 2H), 7.69 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 8.9 Hz, 2H), 7.00 (d, J = 8.9 Hz, 2H), 3.80 (s, 3H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 166.99, 161.15, 134.82, 132.93, 131.86, 130.03, 125.47, 115.17, 112.29, 84.09, 80.82, 76.76, 72.61, 55.91.

5f: ^{1}H-NMR (300 MHz, DMSO-d_6) δ 7.97 (d, J = 8.1 Hz, 2H), 7.71–7.78 (m, 8H), 7.39–7.52 (m, 3H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 174.74, 166.50, 141.68, 138.83, 133.16, 132.61, 131.59, 129.59, 129.11, 127.12, 126.81, 124.73, 119.05, 83.07, 81.22, 75.93, 73.90.

5g: ^{1}H-NMR (300 MHz, DMSO-d_6) δ 13.23 (s, 1H), 8.64 (d, J = 4.7 Hz, 1H), 7.98 (d, J = 8.2 Hz, 2H), 7.86–7.92 (m, 3H), 7.74–7.77 (m, 3H), 7.48–7.52 (m, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 166.46, 150.59, 140.52, 137.01, 132.80, 132.02, 129.58, 128.64, 124.75, 124.13, 82.02, 81.44, 75.15, 71.96.

Acknowledgments. This study was financially supported by research fund of Chungnam National University in 2010.

References

1. H. Yun, T.-C. Chou, H. Dong, Y. Tian, Y.-m. Li, S. J. Danishefsky, *J. Org. Chem.* **2005**, *70*, 10375.
2. P. Siemsen, R. C. Livingston, F. Diederich, *Angew. Chem. Int. Ed.* **2000**, *39*, 2632.
3. A. L. K. Shi Shun, R. R. Tykwinski, *Angew. Chem. Int. Ed.* **2006**, *45*, 1034.
4. H. Yun, S. J. Danishefsky, *J. Org. Chem.* **2003**, *68*, 4519.
5. G. Zeni, R. B. Panatieri, E. Lissner, P. H. Menezes, A. L. Braga, H. A. Stefani, *Org. Lett.* **2001**, *3*, 819.
6. A. Stutz, G. Petranyi, *J. Med. Chem.* **1984**, *27*, 1539.
7. F. Diederich, P. J. Stang, R. R. Tykwinski Eds., *Acetylene Chemistry: Chemistry, Biology and Material Science*; WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany **2005**.
8. J. M. Lehn, *Supramolecular Chemistry: Concepts and Perspectives*, VCH, Weinheim, Germany, **1995**.
9. C. Glaser, *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 422.
10. A. Hay, *J. Org. Chem.* **1960**, *25*, 1275.
11. K. Kamata, S. Yamaguchi, M. Kotani, K. Yamaguchi, N. Mizuno, *Angewandte Chemie* **2008**, *47*, 2407.
12. Y. Liao, R. Fathi, Z. Yang, *Org. Lett.* **2003**, *5*, 909.
13. L. Li, J. Wang, G. Zhang, Q. Liu, *Tetrahedron Lett.* **2009**, *50*, 4033.
14. S. Adimurthy, C. C. Malakar, U. Beifuss, *J. Org. Chem.* **2009**, *74*, 5648.
15. R. Rossi, A. Carpita, C. Bigelli, *Tetrahedron Lett.* **1985**, *26*, 523.
16. A. Lei, M. Srivastava, X. Zhang, *J. Org. Chem.* **2002**, *67*, 1969.
17. I. J. Fairlamb, P. S. Bauerlein, L. R. Marrison, J. M. Dickinson, *Chem. Commun.* **2003**, 632.
18. A. S. Batsanov, J. C. Collings, I. J. Fairlamb, J. P. Holland, J. A. Howard, Z. Lin, T. B. Marder, A. C. Parsons, R. M. Ward, J. Zhu, *J. Org. Chem.* **2005**, *70*, 703.
19. J. H. Li, Y. Liang, Y. X. Xie, *J. Org. Chem.* **2005**, *70*, 4393.
20. F. Yang, X. Cui, Y.-n. Li, J. Zhang, G.-r. Ren, Y. Wu, *Tetrahedron* **2007**, *63*, 1963.
21. J. Park, E. Park, A. Kim, S.-A. Park, Y. Lee, K.-W. Chi, Y. H. Jung, I. S. Kim, *J. Org. Chem.* **2011**, *76*, 2214.
22. W. Chodkiewicz, P. Cadiot, *Compt. Rend.* **1955**, *241*, 1055.
23. M. Yu, D. Pan, W. Jia, W. Chen, N. Jiao, *Tetrahedron Lett.* **2010**, *51*, 1287.
24. S. Wang, L. Yu, P. Li, L. Meng, L. Wang, *Synthesis* **2011**, *2011*, 1541.
25. Z. Huang, R. Shang, Z.-R. Zhang, X.-D. Tan, X. Xiao, Y. Fu, *J. Org. Chem.* **2013**, *78*, 4551.
26. Y. Nishihara, K. Ikegashira, K. Hirabayashi, J. Ando, A. Mori, T. Hiyama, *J. Org. Chem.* **2000**, *65*, 1780.
27. W. Shi, Y. Luo, X. Luo, L. Chao, H. Zhang, J. Wang, A. Lei, *J. Am. Chem. Soc.* **2008**, *130*, 14713.

