ORGANIC LETTERS

2012
Vol. 14, No. 6
1592–1595

Generation of Indeno[1,2-*c*]pyrroles via a Pd-Catalyzed Reaction of 2-Alkynylbromobenzene with Propargylic Sulfonamide

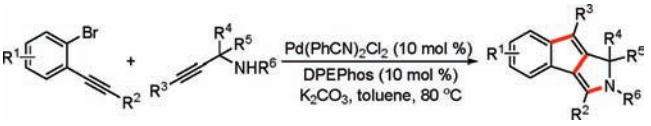
Yong Luo[†] and Jie Wu[*,†,‡]

Department of Chemistry, Fudan University, 220 Handan Road, Shanghai 200433, China, and State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China

jie_wu@fudan.edu.cn

Received February 10, 2012

ABSTRACT



A novel route for the efficient assembly of indeno[1,2-*c*]pyrrole derivatives via a palladium-catalyzed tandem reaction of 2-alkynylbromobenzene with propargylic sulfonamide is reported. The starting materials are easily available, and the reaction proceeds smoothly with good functional group tolerance.

According to the CRC dictionary of natural products, 90% of chemically individual molecules discovered in nature contain either a carbocyclic or a heterocyclic subunit.[1] Among the methods for access to these skeletons, cyclization of alkynes provides an efficient and convenient route.[2] Recently, intramolecular or intermolecular double insertion of triple bonds as a key step has been demonstrated as a powerful strategy for the preparation of heterocyclic or carbocyclic compounds.[3,4] For instance, Lu and co-workers reported the synthesis of 8*H*-acenaphtho[1,2-*c*]pyrroles via a palladium-catalyzed bicyclization of 1,8-diarenynyl naphthalenes and primary amines under air in dimethyl sulfoxide.[3b] We also found that various heterocycles containing an indene skeleton could be synthesized through a palladium-catalyzed double insertion of a triple bond with amine, phenol, or amide.[4] During the process, several side reactions are minimized since the insertion of the triple bond was preferred, compared with the direct C−N or C−O coupling. With these promising results in hand, we further consider expanding the utility of this strategy, with an expectation to introduce more scaffold diversity for different biological evaluations.

Indeno[1,2-*c*]pyrrole with a 6-5-5 scaffold containing a pyrrole core has drawn our attention since remarkable biological activities of these compounds have been reported.[5]

[†] Fudan University.
[‡] Chinese Academy of Sciences.

(1) *Dictionary of Natural Products*, version 14.1; Chapman & Hall/CRC Informa: London, 2005.

(2) Recent reviews: (a) Krüger, K.; Tillack, A.; Beller, M. *Adv. Synth. Catal.* **2008**, *350*, 2153. (b) Balme, G.; Bossharth, E.; Monteiro, N. *Eur. J. Org. Chem.* **2003**, 4101. (c) Guo, L.-N.; Duan, X.-H.; Liang, Y.-M. *Acc. Chem. Res.* **2011**, *44*, 111. (d) Sohel, S.; Md., A.; Liu, R.-S. *Chem. Soc. Rev.* **2009**, *38*, 2269. (e) Yamamoto, Y.; Gridnev, I. D.; Patild, N. T.; Jin, T. *Chem. Commun.* **2009**, 5075. (f) Cacchi, S.; Fabrizi, G.; Goggiamani, A. *Org. Biomol. Chem.* **2011**, *9*, 641. (g) Gilmore, K.; Alabugin, I. V. *Chem. Rev.* **2011**, *111*, 6513. (h) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127.

(3) (a) Chen, X.; Lu, P.; Wang, Y. *Chem.—Eur. J.* **2011**, *17*, 8105. (b) Chen, X.; Jin, J.; Wang, Y.; Lu, P. *Chem.—Eur. J.* **2011**, *17*, 9920.

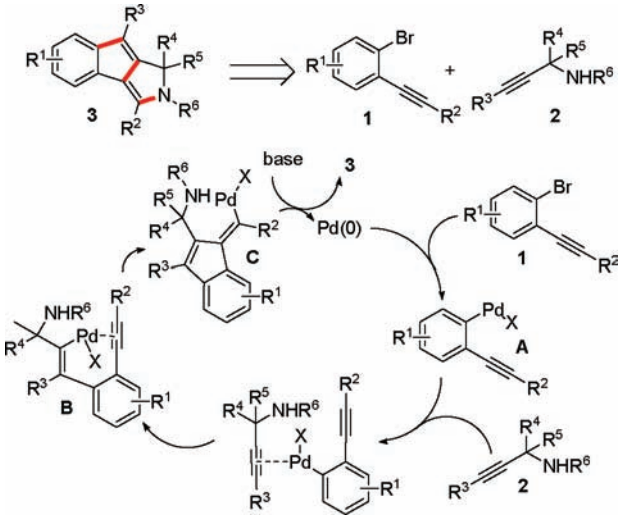
(4) (a) Luo, Y.; Hong, L.; Wu, J. *Chem. Commun.* **2011**, *47*, 5298. (b) Luo, Y.; Pan, X.; Wu, J. *Org. Lett.* **2011**, *13*, 1150. (c) Pan, X.; Luo, Y.; Wu, J. *Chem. Commun.* **2011**, *47*, 8967. (d) Luo, Y.; Wu, J. *Chem. Commun.* **2011**, *47*, 11137. (e) Pan, X.; Luo, Y.; Liu, G.; Pu, S.; Wu, J. *Adv. Synth. Catal.* **2012**, *354*, 171.

(5) (a) Huck, B. R.; Llamas, L.; Robarge, M. J.; Dent, T. C.; Song, J.; Hodnick, W. F.; Crumrine, C.; Stricker-Krongrad, A.; Harrington, J.; Brunden, K. R.; Bennani, Y. L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4130. (b) Qiao, L.; Zhao, L.-Y.; Rong, S.-B.; Wu, X.-W.; Wang, S.; Fujii, T.; Kazanietz, M. G.; Rauser, L.; Savage, J.; Roth, B. L.; Flippen-Anderson, J.; Kozikowski, A. P. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 955. (c) Behler, F.; Habecker, F.; Saak, W.; Klüner, T.; Christoffers, J. *Eur. J. Org. Chem.* **2011**, 4231. (d) Zhou, W.; An, G.; Zhang, G.; Han, J.; Pan, Y. *Org. Biomol. Chem.* **2011**, *9*, 5833.

10.1021/ol300334h
Published on Web 03/05/2012

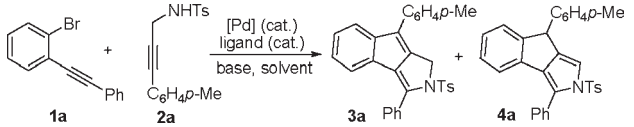
Prompted by the recent results for the generation of cyclic compounds using the strategy[3,4] of palladium-catalyzed double insertion of a triple bond, we envisioned that indeno-[1,2-*c*]pyrrole derivatives could be constructed through a palladium-catalyzed reaction of 2-alkynylbromobenzene with propargylic sulfonamide. The proposed synthetic route is illustrated in Scheme 1. We hypothesized that an oxidative addition of Pd(0) to 2-alkynylbromobenzene **1** would occur first to generate a Pd(II) species **A**. Coordination and insertion to the triple bond of propargylic sulfonamide **2** would result in the formation of intermediate **B**. Then an intramolecular insertion of a triple bond would take place to produce intermediate **C**, which would subsequently undergo a C−N coupling to afford the desired indeno[1,2-*c*]pyrrole **3**. During the reaction process, three bonds would be formed in a tandem sequence. Although it seems feasible theoretically, there are still some challenges that usually appear in the formation of pyrroles using propargylic amides as starting materials:[6−8] (a) the direct C−N coupling seems inevitable under the palladium-catalyzed conditions;[9] (b) a *β*-elimination with the formation of allene often occurs.[10] Encouraged by our recent results,[4] we conceived that all of these side reactions and byproducts might be minimized under suitable conditions. Herein, we disclose our recent efforts for the synthesis of indeno[1,2-*c*]pyrrole derivatives via a palladium-catalyzed tandem reaction of 2-alkynylbromobenzene with propargylic sulfonamide.

Scheme 1. Proposed Synthetic Route to Indeno[1,2-*c*]pyrroles via a Palladium-Catalyzed Reaction of 2-Alkynylbromobenzene with Propargylic Sulfonamides



Our initial attempt was performed for the reaction of 1-bromo-2-(phenylethynyl)benzene **1a** with 4-methyl-*N*-(3-(*p*-tolyl)prop-2-yn-1-yl)benzenesulfonamide **2a** in the presence of $Pd(OAc)_2$ (5 mol %) and K_2CO_3 in 1,4-dioxane under reflux (Table 1). At first, various phosphine ligands were examined (Table 1, entries 1−5). However, only a trace amount of product was detected when DPPP, DPPF, PCy_3, or XantPhos (L1) was used in the reaction. To our surprise, compound **4a** was isolated in 39% yield as an isomer[11] of the desired indeno[1,2-*c*]pyrrole **3a** when DPEPhos (L2) was employed as a ligand (Table 1, entry 5). A comparable result was obtained when the reaction was performed in toluene (Table 1, entry 6). The result was inferior when DMF or DMSO was employed as the solvent (Table 1, entries 7 and 8). A slightly higher yield was generated when the amount of sulfonamide **2a** and $Pd(OAc)_2$ was increased (Table 1, entries 9 and 10). Interestingly, we found that the presence of a weaker base combined with a lower temperature led to the desired product **3a** (Table 1, entries 11−14). The structural

Table 1. Initial Studies for the Palladium-Catalyzed Reaction of 1-Bromo-2-(phenylethynyl)benzene **1a** with 4-Methyl-*N*-(3-(*p*-tolyl)prop-2-yn-1-yl)benzenesulfonamide **2a**[a]

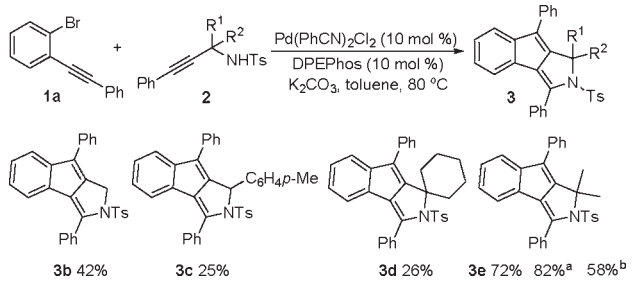


entry	[Pd]	ligand	base	solvent	yield (%)[b]
1	$Pd(OAc)_2$	DPPP	K_2CO_3	dioxane	trace
2	$Pd(OAc)_2$	DPPF	K_2CO_3	dioxane	trace
3	$Pd(OAc)_2$	PCy_3	K_2CO_3	dioxane	trace
4	$Pd(OAc)_2$	L1	K_2CO_3	dioxane	trace
5	$Pd(OAc)_2$	L2	K_2CO_3	dioxane	**4a** (39)
6	$Pd(OAc)_2$	L2	K_2CO_3	toluene	**4a** (40)
7	$Pd(OAc)_2$	L2	K_2CO_3	DMF	trace
8	$Pd(OAc)_2$	L2	K_2CO_3	DMSO	trace
9[c]	$Pd(OAc)_2$	L2	K_2CO_3	toluene	**4a** (43)
10[c,d]	$Pd(OAc)_2$	L2	K_2CO_3	toluene	**4a** (46)
11[c,d]	$Pd(OAc)_2$	L2	Na_2CO_3	toluene	**3a** (32)
12	$Pd(OAc)_2$	L2	Cs_2CO_3	toluene	trace
13	$Pd(OAc)_2$	L2	$^iPr_2NEt$	toluene	trace
14[c,d]	$Pd(OAc)_2$	L2	K_2CO_3	toluene	**3a** (42)[e]
15[c,d]	$Pd(PPh_3)_4$	L2	K_2CO_3	toluene	**3a** (30)[e]
16[e]	$Pd_2(dba)_3$	L2	K_2CO_3	toluene	trace
17[c,d]	$Pd(PhCN)_2Cl_2$	L2	K_2CO_3	toluene	**3a** (55)[e]
18[e]	$[Pd(allyl)Cl]_2$	L2	K_2CO_3	toluene	trace

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), palladium catalyst (5 mol %), ligand (10 mol %), base (0.4 mmol), solvent (2.0 mL). [b] Isolated yield based on 1-bromo-2-(phenylethynyl)benzene **1a**. [c] **2a** (0.3 mmol) was used. [d] In the presence of [Pd] (10 mol %). [e] The reaction occurred at 80 °C. XantPhos (L1): 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene. DPEPhos (L2): 2-(dicyclohexylphosphino)-2′,4′,6′-tri-isopropyl-1,1′-biphenyl.

(6) Yamagishi, M.; Nishigai, K.; Hata, T.; Urabe, H. *Org. Lett.* **2011**, *13*, 4873.
(7) (a) Zhao, L.; Lu, X. *Angew. Chem., Int. Ed.* **2002**, *41*, 4343. (b) Zhang, Q.; Xu, W.; Lu, X. *J. Org. Chem.* **2005**, *70*, 1505.
(8) Ma, S.; Wu, B.; Jiang, X. *J. Org. Chem.* **2005**, *70*, 2588.
(9) Jeong, N.; Seo, S. D.; Shin, J. Y. *J. Am. Chem. Soc.* **2000**, *122*, 10220.
(10) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Parisi, L. M. *J. Organomet. Chem.* **2003**, *687*, 562.
(11) The isomerization could easily happen under basic condition at high temperature: (a) Samet, A. V.; Yamskov, A. N.; Strelenko, Y. A.; Semenov, V. V. *Tetrahedron* **2009**, *65*, 6868. (b) Noland, W. E.; Lanzatella, N. P. *J. Heterocycl. Chem.* **2009**, *46*, 1285. (c) Kim, H. S.; Lee, H. S.; Kim, S. H.; Kim, J. N. *Tetrahedron Lett.* **2009**, *50*, 3154.

Scheme 2. Reactions of 1-Bromo-2-(phenylethynyl)benzene **1a** with Several α-Substituted Propargylic Sulfonamides



[a] 0.5 mL of solvent was used.

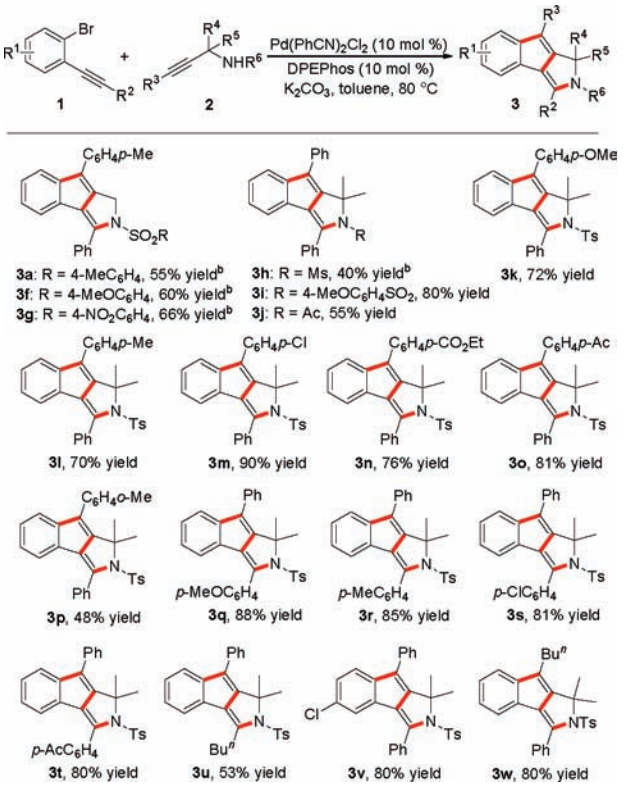
[b] 0.5 mL of solvent and 0.24 mmol of **2e** were used.

elucidation was demonstrated by X-ray diffraction analysis (see the Supporting Information). The reactions were complex when strong bases were employed. Further screening of palladium catalysts revealed that $Pd(PhCN)_2Cl_2$ was the best choice compared with $Pd(OAc)_2$, $Pd(PPh_3)_4$, $Pd_2(dba)_3$, and $[Pd(allyl)Cl]_2$ (Table 1, entries 15−18).

We noticed that, during the reaction process, all of the starting materials were consumed and we did not observe other major byproducts. Since excess sulfonamide was utilized in the reaction, we assumed that the α-unsubstituted propargylic sulfonamide **2a** might generate unstable intermediates, which thus could not complete the reaction cycle. Therefore, several α-substituted propargylic sulfonamides were synthesized and applied to the reaction of 1-bromo-2-(phenylethynyl)benzene **1a** under the optimized conditions highlighted in Table 1 (Scheme 2). From the results, it suggested that the substitutions at the α-carbon of propargylic sulfonamides could have great impact for the outcome. When α-dimethyl-substituted propargylic sulfonamide was employed as a substrate, the reaction provided the corresponding product in 72% yield under the standard condition. After further screening, we found that the effect of starting materials' concentration could not be ignored. When 0.5 mL of solvent was used in this reaction, indeno[1,2-*c*]pyrrole **3e** could be generated in 82% yield.

With these results in hand, we next investigated the scope and generality of this palladium-catalyzed tandem reaction of 2-alkynylbromobenzene with propargylic sulfonamide (Scheme 3). Not only sulfonamides but also amides were all suitable reactants during the transformation. However, the reaction was complex when amine was used. The substituents on the 2-alkynylbromobenzene **1** or propargylic sulfonamide **2** (no matter whether electron-donating or electron-withdrawing) did not obviously affect the formation of the desired products **3**. Additionally, this reaction showed good functional group tolerance because carbonyl (ester and ketone) and nitro groups survived in the conversion. It is also noteworthy that, in all cases,

Scheme 3. Palladium-Catalyzed Tandem Reaction of 2-Alkynylbromobenzene **1** with Propargylic Sulfonamide **2**[a]

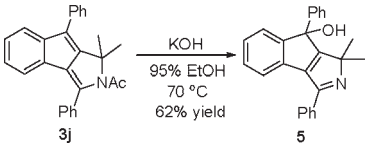


[a] Isolated yield based on 2-alkynylbromobenzene **1**.

[b] 2.0 mL of toluene was used.

no direct coupling or *β*-elimination products were observed. Removal of acetyl group of compound **3j** was tried under different conditions according to literature reports. However, we did not obtain the expected free amine compound. Instead, compound **5** was generated. The best yield (62%) was obtained when the reaction occurred in the presence of KOH (Scheme 4). This phenomenon was also observed in our previous work.[4c]

Scheme 4. Removal of Acetyl Group of Compound **3j**



In conclusion, we have described a novel route for the efficient assembly of indeno[1,2-*c*]pyrrole derivatives via a palladium-catalyzed tandem reaction of 2-alkynylbromobenzene with propargylic sulfonamide. This strategy involving double insertion of triple bonds shows high efficiency with good functional

group tolerance. Currently, using this strategy for the construction of other privileged scaffolds is under investigation in our laboratory.

Acknowledgment. Financial support from National Natural Science Foundation of China (Nos. 21032007 and 21172038) is gratefully acknowledged.

Supporting Information Available. Experimental procedure, characterization data, ^{1}H and ^{13}C NMR spectra of compounds **3**, and a CIF file of compound **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.