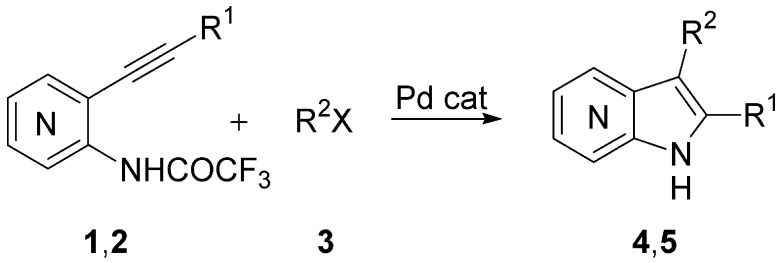
JOURNAL OF combinatorial CHEMISTRY

Report

The Aminopalladation-Reductive Elimination Process as a Tool for the Solution-Phase Synthesis of 2,3-Disubstituted Azaindole Libraries

Sandro Cacchi, Giancarlo Fabrizi, and Luca M. Parisi

J. Comb. Chem., **2005**, 7 (4), 510-512• DOI: 10.1021/cc049821g • Publication Date (Web): 03 May 2005



1,**2** **3** **4**,**5**

More About This Article

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

- Supporting Information
- Links to the 4 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

The Aminopalladation-Reductive Elimination Process as a Tool for the Solution-Phase Synthesis of 2,3-Disubstituted Azaindole Libraries

Sandro Cacchi,* Giancarlo Fabrizi, and Luca M. Parisi

Dipartimento di Studi di Chimica e Tecnologia delle Sostanze Biologicamente Attive, Università degli Studi "La Sapienza", P.le A. Moro 5, 00185 Rome, Italy

Received November 25, 2004

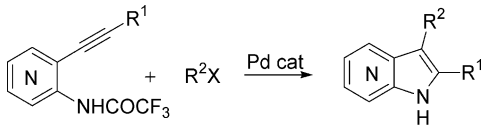
The design of small molecule libraries based on natural products as templates and, hence, the development of procedures that allow for the incorporation of diverse reagents into these molecules are two of the topics of great current interest in combinatorial chemistry.[1] Though azaindoles are relatively scarse as naturally occurring compounds,[2] their bioisosteric relationship with indoles, diffused in a vast number of biologically active natural and unnatural compounds, and their widespread application as pharmaceutical agents[3] make them attractive synthetic targets for the preparation of combinatorial libraries. Traditional methods for the preparation of azaindoles rely on the well-established Fischer, Madelung, and Reissert procedures, which in general require drastic reaction conditions and afford the desired products in modest yields.[4] Recently, transition metal-catalyzed syntheses of this class of compounds have been described. In particular, azaindoles have been prepared from appropriately substituted pyridines and terminal alkynes through a coupling/cyclization process involving palladium or copper catalysis,[5] an intramolecular Heck reaction of enamine derivatives,[3a] and a heteroannulation of internal alkynes[6] according to the procedure developed by Larock for the synthesis of indoles.[7]

Our aminopalladation-reductive elimination procedure[8] revealed a quite general and versatile tool for the synthesis of functionalized indoles and appeared to us particularly suited for introducing diversities in the pyrrole ring incorporated into the azaindole system. Even slightly different aryl or heteroaryl substituents can be expected to be selectively introduced at positions 2 and 3 by using this chemistry, which is not a viable task with other methodologies[6] relying mostly on steric effects for differentiating between the substituents at these two positions. Therefore, as part of our ongoing studies on the preparation of druglike products, we decided to explore the utilization of the aminopalladation-reductive elimination protocol for developing a solution-phase synthesis of free N−H 2,3-disubstituted azaindole libraries according to Scheme 1.

Hereafter, we report the results of this study.

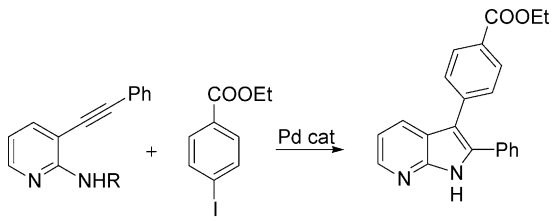
Results and Discussion. Initial attempts examined the reaction of 3-phenylethynyl-2-acetamidopyridine **6** (prepared through the Sonogashira coupling[9] of 3-iodo-2-aminopyridine with phenyl acetylene, followed by the reaction of the resultant coupling product with acetic anhydride) and ethyl *p*-iodobenzoate (Scheme 2).

Scheme 1



1,**2** **3** **4**,**5**

Scheme 2



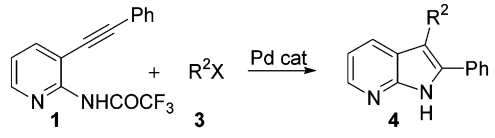
6: R = COMe
1: R = $COCF_3$ **4a**

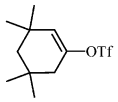
Previous studies[10] showed that the acidity of the nitrogen−hydrogen bond plays a crucial role in the synthesis of indoles via the aminopalladation−reductive elimination process. Using free amino and acetamido derivatives met with failure, and the trifluoroacetamido group was found to be the nitrogen derivative of choice in this type of chemistry. In fact, in addition to favoring the cyclization reaction, it allows for the formation of free N−H indoles (the trifluoroacetyl group is eliminated during the reaction after the formation of the pyrrole ring or the workup), avoiding time-consuming, troublesome, deprotecting steps. In the present case, we surmised that the electron-withdrawing effect due to the pyridine ring might require a weaker electrophile as the activating group. However, when **6** and ethyl *p*-iodobenzoate were treated with 5% of $Pd(PPh_3)_4$ as the Pd(0) source and Cs_2CO_3 as the base in MeCN at 100 °C for 5 h, the desired azaindole derivative **4a** was isolated only in 37% yield, and the starting alkyne was recovered in 49% yield. Although this result shows that the pyridine moiety does play a beneficial role in favoring the formation of the free N−H pyrrole ring if compared with the recovery of the starting alkyne in 98% yield, when *o*-(phenylethynyl)acetanilide was subjected to the same cyclization conditions,[10] it is unsatisfactory from a synthetic standpoint. Therefore, we examined the use of the trifluoroacetamido derivative **1**, which produced the corresponding azaindole **4a** in 83% yield in 3.5 h under the same conditions, confirming the crucial role of the trifluoroacetyl group in this type of cyclization. The use of $Pd(PPh_3)_4$ and Cs_2CO_3 in MeCN at 100 °C as the optimal reaction conditions was suggested by the extensive screening we carried out to explore the role of bases and palladium precatalyst systems (including $Pd(PPh_3)_4$ and $Pd_2(dba)_3$ in conjunction with a variety of phosphine ligands) in the related reaction of *o*-alkynyltrifluoroacetanilides with aryl(heteroaryl) bromides and triflates.[8d,11]

* Corresponding author. E-mail: sandro.cacchi@uniroma1.it.

10.1021/cc049821g CCC: $30.25
Published on Web 05/03/2005

Table 1. Palladium-Catalyzed Synthesis of 7-Azaindoles **4** from 2-Phenylethynyl-3-trifluoroacetamidopyridine **1**[a]



entry	R^2X **3**	t (h)	yield % of **4**[b]	
1	*p*-EtOOC-C_6H_4-I	3.5	83	**4a**
2	*p*-MeO-C_6H_4-I	1.5	89	**4b**
3	*p*-F-C_6H_4-I	6	80	**4c**
4	3,5-$(CF_3)_2$-C_6H_4-I	20	93	**4d**
5	2-Me-5-NO_2-C_6H_3-I	6	73	**4e**
6	*p*-Ph-C_6H_4-Br	20	55	**4f**
7		16	66	**4g**

[a] Reactions were carried out at 100 °C on a 0.345-mmol scale, in 3 mL of MeCN, under an argon atmosphere, using 1 equiv of **1**, 1.5 equiv of **3**, 0.05 equiv of $Pd(PPh)_4$, and 3 equiv of Cs_2CO_3. [b] Yields refer to isolated products.

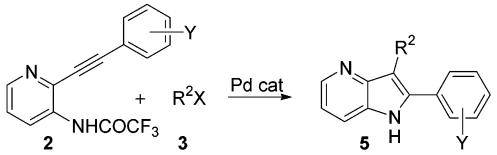
We next turned our attention to the preparation of 2,3-disubstituted 4-azaindole and 7-azaindole libraries. Our preparative results are summarized in Tables 1 and 2. With alkynes **1** and **2** containing neutral and electron-poor substituents, the reaction proceeded smoothly in good to excellent yield with a variety of electron-rich, electron-poor, and almost neutral aryl iodides, bromides, and triflates. Substituents close to the oxidative addition site are tolerated (Table 1, entry 5; Table 2, entries 2 and 8). Good results were also obtained with heteroaryl bromides (Table 2, entry 12) and vinyl triflates (Table 1, entry 7; Table 2 entries 13 and 14). Only moderate yields were, instead, obtained with 2-alkynyl-3-trifluoroacetamidopyridines containing electron-rich substituents, at least with the two aryl halides that we have investigated (Table 2, entries 15 and 16).

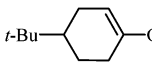
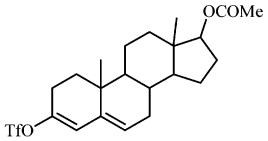
In summary, we have developed exploratory 2,3-disubstituted azaindole libraries based on natural products as templates. The procedure involves the aminopalladation−reductive elimination of readily available acyclic precursors and allows for the introduction of diversities at the C-2 or the C-3 positions of the free N−H azaindole system, usually in good to excellent yields. The experimental procedure is simple, and the reaction tolerates many important functional groups both in the alkyne component and in the aryl/heteroaryl halide or vinyl triflate.

Acknowledgment. Work carried out in the framework of the National Project Stereoselezione in Sintesi Organica. Metodologie ed Applicazioni supported by Ministero dell'Istruzione, dell'Università e della Ricerca (MIUR). The authors are also greatly indebted to the University La Sapienza for financial support of this research.

Supporting Information Available. Experimental procedures and complete description of product characterization.

Table 2. Palladium-Catalyzed Synthesis of 4-Azaindoles **5** from 2-Alkynyl-3-trifluoroacetamidopyridines **2**[a]



entry	**2** Y	R^2X **3**	t (h)	yield % of **5**[b]	
1	H	*p*-MeO-C_6H_4-I	0.5	96	**5a**
2	H	*o*-MeO-C_6H_4-I	5	84	**5b**
3	H	*p*-EtOOC-C_6H_4-I	3	93	**5c**
4	H	*m*-CH_2OH-C_6H_4-I	2	79	**5d**
5	H	3,5-$(CF_3)_2$-C_6H_4-I	5	73	**5e**
6	H	*m*-NO_2-*p*-Me-C_6H_4-I	3	85	**5f**
7	H	*p*-Ph-C_6H_4-Br	2	70	**5g**
8	H	*o*-F-C_6H_4-Br	3	69	**5h**
9	H	*m*-CN-C_6H_4-Br	3	65	**5i**
10	H	*m*-CHO-C_6H_4-Br	2	55	**5j**
11	H	*p*-CN-C_6H_4-OTf	1	55	**5k**
12	H		1	70	**5l**
13	H		3	90	**5m**
14	H		1	77	**5n**
15	*p*-OMe-	*p*-Cl-C_6H_4-I	2	50	**5o**
16	*p*-OMe-	*p*-Bu^t-C_6H_4-Br	2	38	**5p**
17	*p*-CO_2Et-	Ph-I	4	63	**5q**
18	*p*-CO_2Et-	*p*-OMe-C_6H_4-I	2	65	**5r**
19	*p*-CO_2Et-	*p*-COMe-C_6H_4-I	2	69	**5s**

[a] Reactions were carried out at 100 °C on a 0.345-mmol scale, in 3 mL of MeCN, under an argon atmosphere, using 1 equiv of **2**, 1.5 equiv of **3**, 0.05 equiv of $Pd(PPh)_4$, and 3 equiv of Cs_2CO_3. [b] Yields refer to isolated products.

This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) For some recent reviews, see: (a) Hall, D. G.; Manku, S.; Wang, F. *J. Comb. Chem.* **2001**, *3*, 125. (b) Watson, C. *Angew. Chem., Int. Ed.* **1999**, *38*, 1903. (c) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555.

(2) Katritzky, A. R.; Boulton, A. J. *Advances in Heterocyclic Chemistry*; Academic Press: New York, 1969; Vol. 19, Chapter 2.

(3) For some recent references, see: (a) Trejo, A.; Arzeno, H.; Browner, M.; Chanda, S.; Cheng, S.; Comer, D. D.; Dalrymple, S. A.; Dunten, P.; Lafargue, J.; Lovejoy, B.; Freire-Moar, J.; Lim, J.; Maintosh, J.; Miller, J.; Papp, E.;

Reuter, D.; Roberts, R.; Sanpablo, F.; Saunders: J.; Song, K.; Villasenor, A.; Warren, S. D.; Welch, M.; Weller, P.; Whiteley, P. E.; Zeng, L.; Goldstein, D. M. *J. Med. Chem.* **2003**, *46*, 4702. (b) Hodge, C. N.; Aldrich, P. E.; Wasserman, Z. R.; Fernandez, C. H.; Nemeth, G. A.; Arvanitis, A.; Cheeseman, R, S.; Chorvat, R. J.; Ciganek, E.; Christos, T. E.; Gilligan, P. J.; Krenitsky, P.; Scholfield, E.; Strucely, P. *J. Med. Chem.* **1999**, *42*, 819. (c) Marot, C.; Chavatte, P.; Morin-Allory, L.; Viaud, M. C.; Guillaumet, G.; Renard, P.; Lesieur, D.; Michel, A. *J. Med. Chem.* **1998**, *41*, 4453. (d) Henry, J. R.; Rupert, K. C.; Dodd, J. H.; Turchi, I. J.; Wadsworth, S. A.; Cavender, D. E.; Fahmy, B.; Olini, G. C.; Davis, J. E.; Pellegrino-Gensey, J. L.; Schafer, P. H.; Siekierka, J. J. *J. Med. Chem.* **1998**, *41*, 4196. (e) Henry, J. R.; Dodd, J. H. *Tetrahednm Lett.* **1998**, *39*, 8763. (f) Kulagowski, J. J.; Broughton, H. B.; Curtis, N. R.; Mawer, I. M.; Ridgill, M. P.; Baker, R.; Emms, F.; Freedman, S. B.; Marwood, R.; Patel, S.; Patel, S.; Ragan, C. I.; Leeson, P. D. *J. Med. Chem.* **1996**, *39*,1941.

(4) For a recent review, see: Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

(5) (a) Xu, L.; Lewis, I. R.; Davidsen, S. K.; Summers, J. B. *Tetrahedron Lett.* **1998**, *39*, 5159. (b) Kumar, V.; Dority, J. A.; Bacon, E. R.; Singh, B.; Lesher, G. Y. *J. Org. Chem.* **1992**, *57*, 6995.

(6) (a) Chi, S. M.; Choi, J.-K.; Yum, E. K.; Chi, D. Y. *Tetrahedron Lett.* **2000**, *41*, 919. (b) Ujjainwalla, F.; Warner, D. *Tetrahedron Lett.* **1998**, *39*, 5355. (c) Park, S. S.; Choi, J.-K.; Yum, E. K. *Tetrahedron Lett.* **1998**, *39*, 627. (d) Wensbo, D.; Eriksoon, A.; Jeshke, T.; Annby, U.; Gronowitz, S. *Tetrahedron Lett.* **1993**, *34*, 2823.

(7) (a) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652. (b) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689.

(8) For a review, see: (a) Battistuzzi, G.; Cacchi, S.; Fabrizi, G. *Eur. J. Org. Chem.* **2002**, 2671. See also: (b) Cacchi, S.; Fabrizi, G.; Parisi, L. M. *Synthesis* **2004**, 1889. (c) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Parisi, L. M. *Tetrahedron Lett.* **2004**, *45*, 2431. (d) Cacchi, S.; Fabrizi, G.; Lamba, D.; Marinelli, F.; Parisi, L. M. *Synthesis* **2003**, 728.

(9) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467. For reviews, see: (b) Sonogashira, K. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley & Sons: New York, 2002; Vol. 1, p 493. (c) Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-WCH: Weinheim, 1998; p 203.

(10) Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron Lett.* **1992**, *33*, 3915.

(11) The use of $Pd(OAc)_2$ and PPh_3 (1:4 molar ratio) in MeCN at 100 °C was also attempted. Indeed, the mixture of PPh_3 and $Pd(OAc)_2$ is known to generate spontaneously a zerovalent palladium complex that gives rise to oxidative addition reactions (Amatore, C.; Jutand, A.; M'Barki, M. A. *Organometallics* **1992**, *11*, 3009). However, under these conditions, the desired **4a** was isolated only in 47% yield after 24 h along with 4% of the 2-phenylazaindole product. 2-Amino-3-(phenylethynyl)pyridine, derived from the hydrolysis of **1**, was also isolated in 40% yield.

CC049821G