ORGANIC LETTERS

2009
Vol. 11, No. 1
221−224

Application of Ynamides in the Synthesis of 2-Amidoindoles

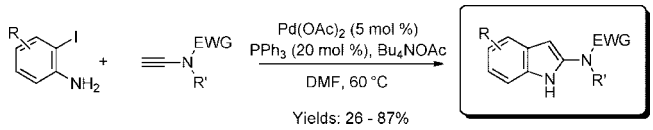
Karin Dooleweerdt,[†] Thomas Ruhland,[*,‡] and Troels Skrydstrup[*,†]

Center for Insoluble Protein Structures (inSPIN), Department of Chemistry and the Interdisciplinary Nanoscience Center, Aarhus University, Langelandsgade 140, 8000 Aarhus C, Denmark, and H. Lundbeck A/S, Ottiliavej 9, 2400 Valby, Denmark

ts@chem.au.dk

Received October 27, 2008

ABSTRACT



A Pd-catalyzed, one-pot, two-step synthesis of 2-amidoindoles from ynamides and *o*-iodoanilines is reported. A key highlight of this sequence is that after the Sonogashira reaction, intramolecular cyclization to the indole occurs spontaneously without activation of the alkyne.

The indole ring is a priviledged structural motif in many biologically active compounds, like naturally occurring alkaloids or synthetic drugs.[1,2] In comparison to classical indole synthesis methods,[3] transition-metal-catalyzed reactions have the advantage of increased functional group tolerance, as well as providing indoles with greater structural diversity and often higher overall yields.[4,5] A two-step protocol involving a Sonogashira coupling[6] with an *o*-halo-substituted aniline followed by addition of a nucleophilic amine to the triple bond represents a viable approach to these ring systems. However, the cyclization step does not in general proceed on its own and usually requires assistance via the formation of a more nucleophilic heteroatom by deprotonation[7] or either metal or Lewis acid activation of the alkyne.[8,9]

In this paper, we disclose a novel and direct access to 2-amidoindoles via a one-pot, two-step coupling of *o*-haloanilines with ynamides under palladium-catalyzed cou-

[†] Aarhus University.
[‡] H. Lundbeck A/S.

(1) For a recent review of indole-containing natural products, see: Lounasmaa, M.; Tolvanen, A. *Nat. Prod. Rep.* **2000**, *17*, 175.

(2) (a) Landwehr, J.; George, S.; Karg, E.-M.; Poeckel, D.; Steinhilber, D.; Troschuetz, R.; Werz, O. *J. Med. Chem.* **2006**, *49*, 4327. (b) Sechi, M.; Derudas, M.; Dallochio, R.; Dessi, A.; Bacchi, A.; Sannia, L.; Carta, F.; Palomba, M.; Ragab, O.; Chan, C.; Shoemaker, R.; Sei, S.; Dayam, R.; Neamati, N. *J. Med. Chem.* **2004**, *47*, 5298. (c) Flynn, B. L.; Hamel, E.; Jung, M. K. *J. Med. Chem.* **2002**, *45*, 2670.

(3) For reviews on indole syntheses, see: (a) *Indoles*; Sundberg, R. J., Ed.; Academic: London, 1996. (b) Sundberg, R. J. Pyrroles and Their Benzo Derivatives: Synthesis and Applications. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 4, pp 313−376. For a recent review on Fischer indole synthesis, see: (c) Hughes, D. L. *Org. Prep. Proced. Int.* **1993**, *25*, 607.

(4) For a review on Pd-catalyzed indole formation, see: Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873, and references therein.

(5) (a) Fang, Y.-Q.; Lautens, M. *J. Org. Chem.* **2008**, *73*, 538. (b) Jensen, T.; Pedersen, H.; Bang-Andersen, B.; Madsen, R.; Jørgensen, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 888. (c) Terrasson, V.; Michaux, J.; Gaucher, A.; Wehbe, J.; Marque, S.; Prim, D.; Campagne, J.-M. *Eur. J. Org. Chem.* **2007**, 5332. (d) Jia, Y.; Zhu, J. *J. Org. Chem.* **2006**, *71*, 7826. (e) Liu, J.; Shen, M.; Zhang, Y.; Li, G.; Khodabocus, A.; Rodriguez, S.; Qu, B.; Farina, V.; Senanayake, C.; Lu, B. *Org. Lett.* **2006**, *8*, 3573. (f) Djakovitch, L.; Dufaud, V.; Zaidi, R. *Adv. Synth. Catal.* **2006**, *348*, 715. (g) Zhao, J.; Larock, R. *J. Org. Chem.* **2006**, *71*, 5340. (h) Barluenga, J.; Fernandez, M. A.; Aznar, F.; Valds, C. *Eur. J. Org. Chem.* **2005**, *11*, 2276.

(6) (a) Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-WCH: Weinheim, 1998; p 203. (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) Tsuji, J. *Palladium Reagents and Catalysts*; John Wiley & Sons Ltd.: Chichester, 2004; *201*.

(7) (a) Dai, W.-M.; Sun, L.-P.; Guo, D.-S. *Tetrahedron Lett.* **2002**, *43*, 7699. (b) Rodriguez, A. L.; Koradin, C.; Dohle, W.; Knochel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 2488.

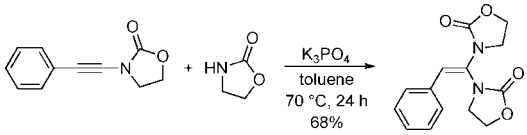
(8) For recent reviews, see: (a) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079. (b) Battistuzzi, G.; Cacchi, S.; Fabrizi, G. *Eur. J. Org. Chem.* **2002**, 2671.

(9) (a) Chemler, S. R.; Fuller, P. H. *Chem. Soc. Rev.* **2007**, *36*, 1153. (b) Yien, Y.; Ma, W.; Chai, Z.; Zhao, G. *J. Org. Chem.* **2006**, *72*, 5731. (c) Lu, B. Z.; Zhao, W.; Wei, H. X.; Dufour, M.; Farina, V.; Senanayake, C. H. *Org. Lett.* **2006**, *8*, 3271. (d) Nakamura, M.; Ilies, L.; Otsubo, S.; Nakamura, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 944. (e) Shimada, T.; Nakamura, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 10546. (f) Hiroya, K.; Itoh, S.; Ozawa, M.; Kanamori, Y.; Sakamoto, T. *Tetrahedron Lett.* **2002**, *43*, 1277.

10.1021/ol802477d CCC: $40.75
Published on Web 11/26/2008

pling conditions. First, a Sonogashira reaction takes place (C−C bond formation) followed by a spontaneous intramolecular hydroamination of the triple bond (C−N) bond formation).

Scheme 1

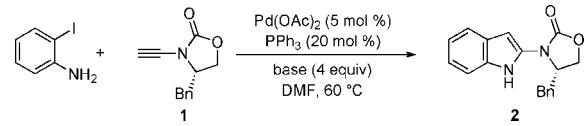


Ynamides have recently been demonstrated to be a versatile synthon for a number of synthetic transformations providing access to a variety of important functional groups and cyclic systems.[10−12] Their success as a building block stems mainly from the development of new and more efficient methods for accessing such starting materials.[11b,13] Major contributions in this respect comes from the group of Hsung[14] and Danheiser.[15]

In recent work, we observed that certain nitrogen-containing heterocycles can add to ynamides in a highly regioselective manner providing ketenaminals in the presence of potassium phosphate, as examplified in Scheme 1.[16] With this in mind, we speculated whether this addition reaction could be performed intramolecularly with anilines possessing an *o*-ynamide substituent and thereby providing the corresponding indole ring under mild basic conditions.

To examine this possibility, several ynamides were constructed according to the Hsung protocol[14b,16] involving the coupling of alkynyl bromides with amides using $CuSO_4{\cdot}5H_2O$ and 1,10-phenanthroline as the catalyst system. Initial attempts for the two-step cyclization to indoles were made with the ynamide **1** and 2-iodoaniline, using $Pd(OAc)_2$ and

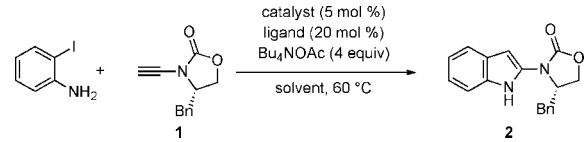
Table 1. Base screening for 2-Amidoindole Synthesis



entry	base	time (h)	yield[a] (%)
1	KOAc	22	55
2	*t*-$BuNH_2$	22	32
3	Et_3N	22	0
4	morpholine	22	0
5	diisopropylamine	22	0
6	Cs_2CO_3	3	30
7	Cs_2CO_3	24	48
8	DIPEA	22	0
9	Na_2CO_3	22	24
10	K_2CO_3	22	41
11	Bu_4NOAc	17	81
12	K_3PO_4	22	32

[a] Isolated yields after column chromatography.

Table 2. Catalyst, Ligand, And Solvent Optimization



entry	catalyst	ligand	solvent	time (h)	yield[a] (%)
1	$Pd(OAc)_2$	PPh_3	DMF	17	81
2	$Pd(OAc)_2$	PPh_3	CH_3CN	23	64
3	$Pd(OAc)_2$	PPh_3	toluene	22	65
4	$Pd(OAc)_2$	PPh_3	THF	23	75
5	$Pd(OAc)_2$	PPh_3	dioxane	23	77
6	$Pd(OAc)_2$	PPh_3	DMF	24	81[b]
7	$Pd(OAc)_2$	PPh_3	DMF	24	74[c]
8	$Pd(dba)_2$	PPh_3	DMF	22	80
9	$Pd(OAc)_2$	HBF4-*t*-Bu_3P	DMF	22	0
10	$Pd(OAc)_2$	(*o*-tol)$_3$P	DMF	22	0
11	$Pd(OAc)_2$	X-Phos	DMF	22	0

[a] Isolated yields after column chromatography. [b] Bu_4NOAc (3 equiv) [c] Bu_4NOAc (2 equiv).

(10) For a special issue dedicated ynamides, see: (a) Tetrahedron-Symposium-In-Print: "Chemistry of Electron-Deficient Ynamines and Ynamides." *Tetrahedron* **2006**, *62*,Issue No. 16. For reviews on ynamides, see: (b) Zificsak, C. A.; Mulder, J. A.; Hsung, R. P.; Rameshkumar, C.; Wei, L. L. *Tetrahedron* **2001**, *57*, 7575. (c) Zhang, Y.; Hsung, R. P. *ChemTracts* **2004**, *17*, 442. (d) Katritzky, A. R.; Jiang, R.; Singh, S. K. *Heterocycles* **2004**, *63*, 1455.

(11) For some recent examples, see: (a) Saito, N.; Katayama, T.; Sato, Y. *Org. Lett.* **2008**, *10*, 3829. (b) Istrate, F. M.; Buzas, A. K.; Jurberg, I. D.; Odabachian, Y.; Gagosz, F. *Org. Lett.* **2008**, *10*, 925. (c) Hashmi, S. K.; Rudolph, M.; Bats, J. W.; Frey, W.; Rominger, F.; Oeser, T. *Chem.—Eur. J.* **2008**, *14*, 6672. (d) Couty, S.; Meyer, C.; Cossy, J. *Synlett* **2007**, 2819. (e) Tanaka, K.; Takeishi, K. *Synlett* **2007**, 2920. (f) Kohnen, A. L.; Mak, X. Y.; Lam, T. Y.; Dunetz, J. R.; Danheiser, R. L. *Tetrahedron* **2006**, *62*, 3815. (g) Couty, S.; Meyer, C.; Cossy, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6726. (h) Tanaka, K.; Takeishi, K.; Noguchi, K. *J. Am. Chem. Soc.* **2006**, *128*, 4586.

(12) Recent applications of ynamides from the group of Hsung: (a) Zhang, X.; Hsung, R. P.; Li, H.; Zhang, Y.; Johnson, W. L.; Figueroa, R. *Org. Lett.* **2008**, *10*, 3477. (b) Al-Rashid, Z. F.; Hsung, R. P. *Org. Lett.* **2008**, *10*, 661. (c) Li, H.; You, L.; Zhang, X.; Johnson, W. L.; Figueroa, R.; Hsung, R. P. *Heterocycles* **2007**, *74*, 553. (d) You, L.; Al-Rashid, Z. F.; Figueroa, R.; Ghosh, S. K.; Li, G.; Lu, T.; Hsung, R. P. *Synlett* **2007**, 1656. (e) Oppenheimer, J.; Johnson, W. L.; Tracey, M. R.; Hsung, R. P.; Yao, P.-Y.; Liu, R.; Zhao, K. *Org. Lett.* **2007**, *9*, 2361. (f) Song, Z.; Lu, T.; Hsung, R. P.; Al-Rashid, Z. F.; Ko, C.; Tang, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 4069. (g) Zhang, X.; Hsung, R. P.; Li, H. *Chem. Commun.* **2007**, *23*, 2420. (h) Tracey, M. R.; Oppenheimer, J.; Hsung, R. P. *J. Org. Chem.* **2006**, *71*, 8629. (i) Zhang, X.; Li, H.; You, L.; Tang, Y.; Hsung, R. P. *Adv. Synth. Catal.* **2006**, *348*, 2437. Zhang, X.; Hsung, R. P.; You, L. *Org. Biomol. Chem.* **2006**, *8*, 2679. Kurtz, K. C. M.; Frederick, M. O.; Lambeth, R. H.; Mulder, J. A.; Tracey, M. R.; Hsung, R. P. *Tetrahedron* **2006**, *62*, 3928. Kurtz, K. C. M.; Hsung, R. P.; Zhang, Y. *Org. Lett.* **2006**, *8*, 231.

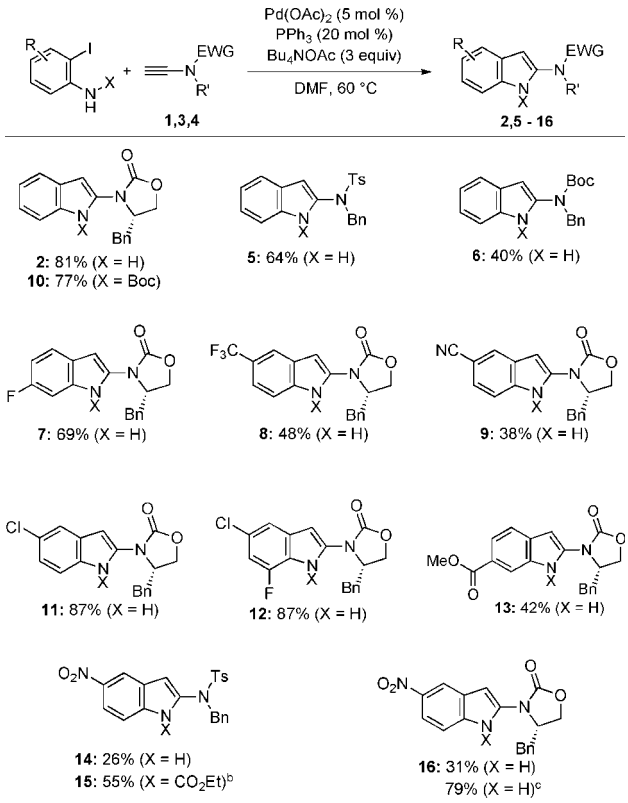
(13) (a) Hamada, T.; Ye, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 833. (b) Riddell, N.; Villeneuve, K.; Tam, W. *Org. Lett.* **2005**, *7*, 3681. For reviews on the synthesis of ynamides, see: (c) Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P. *Synlett* **2003**, 1379. (d) Zificsak, C. A.; Mulder, J. A.; Hsung, R. P.; Rameshkumar, C.; Wei, L.-L. *Tetrahedron* **2001**, *57*, 7575.

(14) Sagamanova, I. K.; Kurtz, K. C. M.; Hsung, R. P. *Org. Synth.* **2007**, *84*, 359. (b) Zhang, X.; Zhang, Y.; Huang, J.; Hsung, R. P.; Kurtz, K. C. M.; Oppenheimer, J.; Petersen, M. E.; Sagamanova, I. K.; Shen, L.; Tracey, M. R. *J. Org. Chem.* **2006**, *71*, 4170. (c) Zhang, Y.; Hsung, R. P.; Tracey, M. R.; Kurtz, K. C. M.; Vera, E. L. *Org. Lett.* **2004**, *6*, 1151.

(15) (a) Kohnen, A. L.; Dunetz, J. R.; Danheiser, R. L. *Org. Synth.* **2007**, *84*, 88. (b) Dunetz, J. R.; Danheiser, R. L. *Org. Lett.* **2003**, *5*, 4011.

(16) Dooleweerdt, K.; Birkedal, H.; Ruhland, T.; Skrydstrup, T. *J. Org. Chem.* **2008**, *73*, 9447.

Scheme 2. Synthesis of 2-Substituted Indoles from Ynamides and 2-Iodoanilinesa



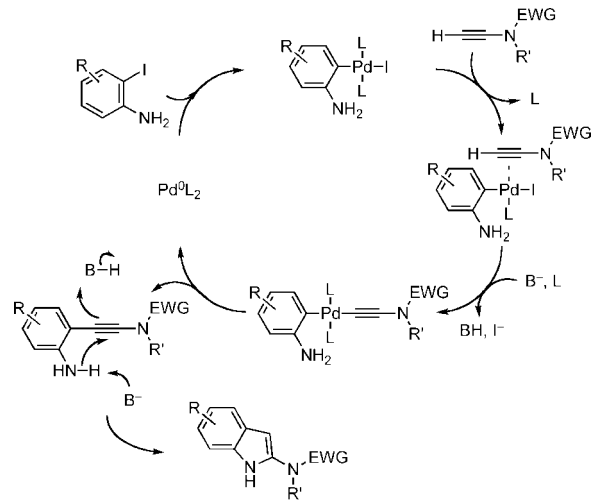
[a] Isolated yields after column chromatography. [b] In addition 22% of **14** was isolated. [c] Starting from the ethyl carbamate of *o*-iodoaniline.

triphenylphosphine, as depicted in Table 1. Running the reaction in DMF at 60 °C with potassium acetate as the base gratifyingly led to the functionalized 2-amidoindole **2** in a 55% yield via sequential Sonogashira coupling and intramolecular hydroamination (entry 1). The intermediate aryl alkyne (Sonogashira product) was not detected in the crude reaction mixture. In order to optimize this transformation, different reaction parameters (nature of the base, solvent, and catalytic system) were examined. In particular, the type of the base has a high impact on the reaction yield. After examination of various inorganic and organic bases, tetrabutylammonium acetate proved to be the most effective, furnishing **2** in 81% yield (entry 11).

The best yield for **2** was obtained with DMF as the solvent, although other solvents are acceptable alternatives (Table 2, entries 1−7). Palladium acetate can be replaced by $Pd(dba)_2$ without influencing the indole product yield (entry 8). On the other hand, examination of three other phosphine ligands were not effective in this annulation event and generally led to undefined multiple product formation (entries 9−11).

With these reaction conditions in hand, we explored this new 2-amidoindole synthesis with a variety of 2-iodoanilines and ynamides, as illustrated in Scheme 2. Coupling of *o*-iodoaniline with alkynamides **1**, **3**, and **4** led to the indoles **2**, **5**, and **6** in 40−81% yield. Other substituents proved also possible leading to the heterocyclic systems **7**−**16** in reasonable to good yields. In some cases with *o*-iodoanilines possessing electron-withdrawing substituents, the yields of the indole products were quite poor as with **14** and **16**. This can be explained by the reduced nucleophilicity of the anilinic NH_2 in the hydroamination step. To overcome this problem, we converted the anilines to the corresponding carbamates to facilitate deprotonation and thereby formation of a more nuclophilic amide anion. Pleasingly, the ethyl carbamate derivatives led to the effective formation of the indole ring. In addition, the carbamate protected indoles are either partially or fully deprotected to the free indoles under the chosen reaction conditions. This is explained by the decreased stability of carbamate protected indoles in comparison to carbamate-protected anilines.

Scheme 3. Proposed Mechanism



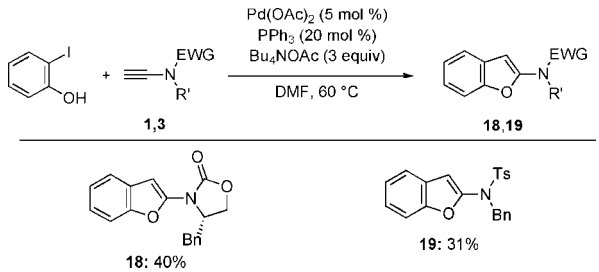
During the completion of this work, Hsung, Zhao, and co-workers published a synthetic route for the synthesis of *N*-protected 2-amidoindoles starting from *o*-haloaryl-substituted ynamides.[17] However, this work deviates significantly from our approach. Scheme 3 illustrates a possible mechanism for the observed results. Initial formation of the aryl alkyne proceeds through traditional Sonogashira coupling cycle though in the absence of a copper salt. A subsequent base-promoted hydroamination step onto the activated alkyne finally leads to the formation of the indole ring.[4,18]

Finally, two attempts were made to synthesize the analogous 2-amidobenzofurans from *o*-iodophenol and ynamides (Scheme 4). The coupling of 2-iodophenol with the ynamide **1** and **3** provided a 31% and 40% yield of **18** and **19**, respectively. Although further optimization studies are required, these results demonstrate clearly that the described methodology is extendable to other pharmaceutically relevant benzannulated heterocycles.

(17) Yao, P.-Y.; Zhang, Y.; Hsung, R. P.; Zhao, K. *Org. Lett.* **2008**, *10*, 4275.

(18) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874, and references therein.

Scheme 4. Synthesis of 2-Substituted Benzofuranes from Ynamides and 2-Iodophenola



[a] Isolated yields after column chromatography.

In conclusion, we have illustrated another useful application of ynamides for the direct synthesis of 2-amidoindoles from 2-iodoanilines and terminal ynamides. Further work is now in progress to find conditions for carrying out these transformations with other 2-haloanilines, as well as expanding the synthesis of 2-amidoindoles to include products with substitution at the C3-position. This work will be reported in due course.

Acknowledgment. We are deeply appreciative of generous financial support from the Danish National Research Foundation, The Lundbeck Foundation, the Carlsberg Foundation, H. Lundbeck A/S, the iNANO and OChem graduate schools, and Aarhus University.

Supporting Information Available: Experimental details and copies of ^{1}H NMR and ^{13}C NMR spectra for terminal ynamides and all the coupling products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL802477D