Tetrahedron Letters 50 (2009) 2943–2945

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Palladium-free zinc-mediated hydroamination of alkynes: efficient synthesis of indoles from 2-akynylaniline derivatives

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ARTICLE INFO

Article history:
Received 17 March 2009
Accepted 30 March 2009
Available online 5 April 2009

ABSTRACT

Reaction of 2-phenylethynyl *N*-tosylanilide prepared by Pd-free procedure with $ZnBr_2$ (3 equiv) in refluxing toluene gave *N*-tosyl-2-phenylindole in 93% yield. Treatment of 2-phenylethynylaniline with $ZnBr_2$ (1 equiv) in refluxing toluene resulted in the formation of 2-phenylindole in 91% yield. Catalytic $ZnBr_2$ (0.05 equiv) effectively reacted with 2-alkynylanilines to afford 2-substituted indoles in high yields. Thus, complete Pd-free zinc catalyzed hydroamination of 2-alkynylanilines was achieved.

Nitrogen-containing heterocycles, especially indole derivatives, have attracted much attention because they widely occur in nature as partial structures of alkaloids and having unique biological activities.[1] Until now, many kinds of catalysts have been reported for the synthesis of indole derivatives from 2-ethynylaniline derivatives (**1**).[2] As the synthetic procedure for the functionalized 2-ethynylanilines **1** by using Pd(II) or Cu(II) catalysts has been established,[3] the methods for indoles syntheses with these compounds as the starting materials are some of the most efficient procedures.[4]

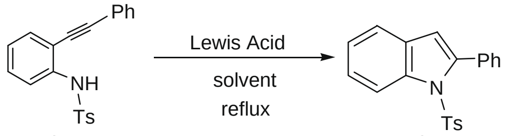
However, not only the palladium-mediated reactions, but also other reagents (Et_2Zn, $ZnCl_2$–$PdCl_2$, Zn–Cu, etc.) are known to have some disadvantages depending on the nature of the reagents, namely, metal alkoxide mediated reactions cannot be applied to the alkaline-sensitive substrates and the carbonyl or sulfonyl groups have to be on the nitrogen atom for most procedures (e.g., sulfonamides, amides, and carbamates are usually used).[2,4,5]

From the background described above, we decided to develop an efficient and cost-effective procedure for the palladium-free zinc catalyzed synthesis of indoles from **1**. Herein, we now report a mild, applicable, and versatile method for indole cyclization catalyzed by zinc halides and its application to the sequential cyclization reaction.

As a starting point for the development of our transition metal-free methodology, we chose to study the reaction of 2-phenylethynyl *N*-tosylanilide (**2a**) with Lewis acid. To show that the reaction is indeed palladium-free, we have used new glassware, apparatus, and reagents. Starting anilide **2a** was synthesized by the following three steps: palladium-free Sonogashira coupling reaction (microwave, CuI as a catalyst) of 2-nitroiodobenzene with phenylacetylene,[6] reduction of 2-phenylethynylnitrobenzene with Sn/HCl and $NaBH_4$,[2] and protection with tosyl chloride. Optimization data are shown in Table 1. Reaction of anilide **2a** with $SnCl_2$, $AlCl_3$, or $TiCl_4$ resulted in recovery of starting material (entries 1–3). Reaction of anilide **2a** with $ZnBr_2$ in refluxing EtOH for 12 h resulted in the formation of 2-phenyl-*N*-tosylindole (**3a**) in 36% yield (entry 4). When 3 equiv of $ZnBr_2$ was treated with anilide **2a** in refluxing toluene, the reaction was completed within 16 h (entry 5). Similarly, the reaction of 3 equiv of ZnI_2 with **2a** gave **3a** in 92% yield (entry 9). Catalytic amount of $ZnBr_2$ gave indole **3a** in low yields (10–21%) (entries 7 and 8). When the reaction was carried out in the absence of Lewis acid, starting **2a** was recovered unchanged (entry 10).

Under these optimum conditions (3 equiv $ZnBr_2$, refluxing toluene), we turned our attention to compare a variety of 2-alkynyl-*N*-tosylanilides bearing different substituted groups at meta position on the aromatic ring. As shown in Table 2, *N*-tosylindoles (**3a**–**d**) were obtained in high yields.

Table 1
Reaction of **2a** with Lewis acids



2a **3a**

Entry	Lewis acid	Equiv	Solvent	Time (h)	**3a**: yield (%)
1	$SnCl_2$	3	Toluene	24	0
2	$AlCl_3$	3	Toluene	24	0
3	$TiCl_4$	3	Toluene	24	0
4	$ZnBr_2$	3	EtOH	24	36
5	$ZnBr_2$	3	Toluene	16	93
6	$ZnBr_2$	1	Toluene	16	52
7	$ZnBr_2$	0.1	Toluene	16	21
8	$ZnBr_2$	0.05	Toluene	16	10
9	ZnI_2	3	Toluene	16	92
10	None	–	Toluene	24	0

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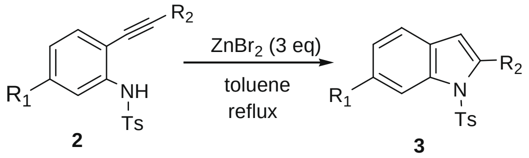
doi:10.1016/j.tetlet.2009.03.210

Table 2
Reaction of **2** with $ZnBr_2$



2	R_1	R_2	Time (h)	**3**	Yield (%)
2a	H	Ph	16	**3a**	93
2b	OMe	Ph	48	**3b**	88
2c	H	*n*-Pr	33	**3c**	90
2d	H	Pentyl	32	**3d**	91

It is well known that Ag(I) or Zn(II) salts have mild Lewis acidity and have been used as catalysts in organic synthesis.[7] 2-Alkynylarylmethylphosphate reacted with AgOTf leading to isoquinolines in good yields.[8] Recently, Yin et al. have reported the Et_2Zn catalyzed hydroamination of alkynyl sulfonamides, which produced *N*-tosyl indoles **3**, whereas synthesis of unprotected indoles failed under these conditions.[5] Nakamura et al. also reported the tandem cyclization of *N*-benzyl protected alkynylanilines by using BuLi/$ZnCl_2$/[$Pd_2(dba)_3$] or BuLi/$ZnCl_2$/CuCN leading to *N*-benzylindoles, whereas the reaction proceeded under basic conditions.[9] Gold, Indium, or Ruthenium-catalyzed hydroamination of 2-alkynylanilines to give unprotected indoles was recently reported.[10] However, to our knowledge, there is no report on the synthesis of unprotected indoles from 2-alkynylanilines and catalytic amount of ZnX_2 under neutral conditions.

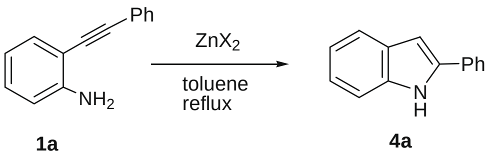
We then investigated the reaction of unprotected 2-alkynylanilines with zinc halides whether unprotected indoles would be formed in the presence of catalytic amount of zinc halides. When a solution of 2-phenylethynylaniline (**1a**) in toluene was treated with $ZnBr_2$ (1 equiv) in refluxing toluene for 2 h, 2-phenylindole (**4a**) was obtained in 91% yield (Table 3, entry 1). When ZnI_2 was used as a Lewis acid, a similar result was obtained (entry 5).

Interestingly, by using catalytic amount of $ZnBr_2$ (0.05 equiv), **4a** was formed in 90% yield (entry 3). When 0.01 equiv of $ZnBr_2$ was used, the yield decreased to 21% (entry 4), whereas 0.01 equiv of ZnI_2 gave **4a** in 90% yield (entry 8). Thus, Zn catalyzed intramolecular hydroamination of 2-alkynylanilines was achieved.

Under these optimum conditions ($ZnBr_2$ 0.05 equiv or ZnI_2 0.01 equiv, toluene reflux, 24 h), and other substituted indoles were obtained in high yields (Table 4).

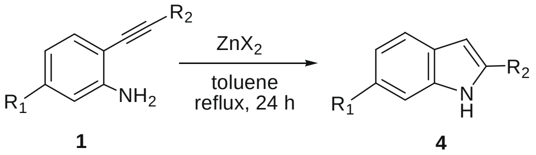
How do we account for the reaction mechanism? We have performed theoretical calculations on the reaction mechanism for the intramolecular hydroamination reaction of 2-(1-propynyl)aniline with $ZnCl_2$ giving 2-methylindole as a model system.[11] The structural optimization for the reaction gave four stable intermediates, that is, N-coordinated complex **A**, π-coordinated complex **B**, *N*- and π-coordinated complex **C**, and σ-complex **D**. The calculation suggested that the most stable structure was complex **C**.[12] Since the difference in potential energy between **B** and **C** is within 16.8 kcal/mol, the reaction might proceed as follows: catalytic ZnX_2 reacted with 2-alkynylaniline **1** to give the most stable complex **C**, which equilibrates to afford complex **B**. Structure **B** finally cyclized to give sigma complex **D**, protodemetallation of which afforded indole **4** and ZnX_2 (Scheme 1).

Table 3
Reaction of 2-Phenylethynylaniline **1a** with ZnX_2[14]



Entry	ZnX_2	Equiv	Time (h)	Yield (%)
1	$ZnBr_2$	1	3	91
2	$ZnBr_2$	0.5	3	91
3	$ZnBr_2$	0.05	6	90
4	$ZnBr_2$	0.01	24	21
5	ZnI_2	1	0.5	91
6	ZnI_2	0.05	24	90
7	ZnI_2	0.01	24	90
8	$ZnCl_2$	3	24	72
9	None	–	24	0

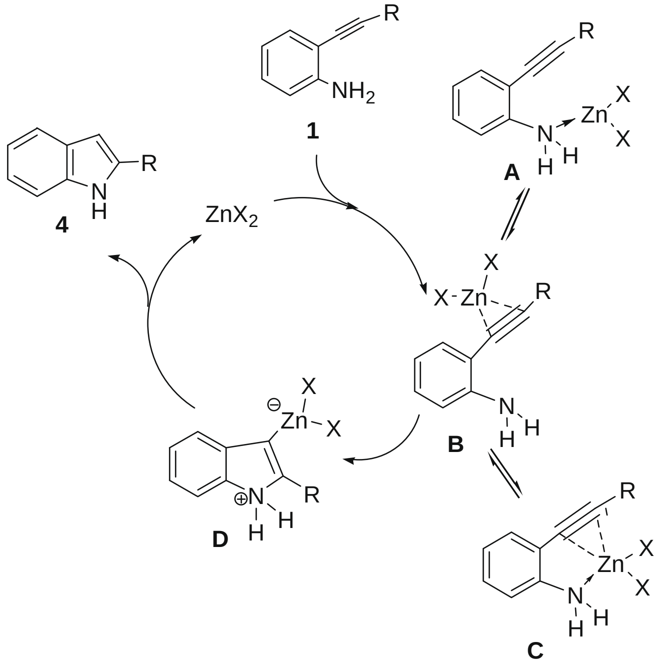
Table 4
Reaction of **1** with cat. $ZnBr_2$ and ZnI_2



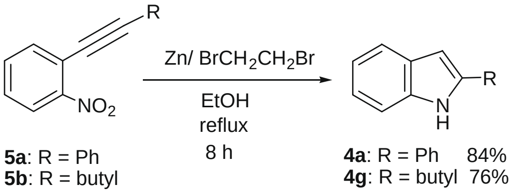
1	R_1	R_2	ZnX_2	Equiv	**4**	Yield (%)
1b	OMe	Ph	$ZnBr_2$	0.05	**4b**	92
1c	H	Pr	$ZnBr_2$	0.05	**4c**	90
1c	H	Pr	ZnI_2	0.01	**4c**	90
1d	H	Pentyl	$ZnBr_2$	0.05	**4d**	91
1d	H	Pentyl	ZnI_2	0.01	**4d**	91
1e	Br	Ph	$ZnBr_2$	0.05	**4e**	92
1f	Cl	Ph	$ZnBr_2$	0.05	**4f**	92

The reaction mechanism was also supported by the following results. The reactivity of **2a** bearing a tosyl group (Table 1, entries 6–8) is lower than that of unprotected alkynylanilines (Table 3), the nucleophilicity of *N*-Ts group is lower than that of unprotected amino group. When ethanol was used as a solvent, catalytic reaction did not proceed, suggesting that zinc halide was solvated with polar solvent.

Since zinc dust reduction of nitrobenzenes to anilines is well known,[13] we then tried the one-pot synthesis of indoles from 2-phenylethynylnitrobenzene (**5a**) prepared by palladium-free Sonogashira coupling reaction of 2-iodonitrobenzene with phenylacety-



Scheme 1.



Scheme 2.

lene.[6] When **5a** was treated with zinc (8 equiv) and dibromoethane in refluxing ethanol for 12 h, 2-phenylindole **4a** was obtained in 86% yield. Similarly, 2-heptynylnitrobenzene (**5b**) reacted with zinc/dibromoethane to give 2-butylindole **4g** in 76% yield (Scheme 2).

In conclusion, we have demonstrated that zinc halides serve as effective catalysts for the intramolecular hydroamination of 2-alkynylanilines. Thus a practical and cost effective method for the preparation of unprotected indoles has been demonstrated by using these catalysts.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.03.210.

References and notes

1. Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875; Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873; Hibino, S.; Choshi, T. *Nat. Prod. Rep.* **2002**, *19*, 148; Gupta, R.. In *Heterocyclic Chemistry*; Springer Publishing: New York, 1999; Vol. 2; Rahman, A.; Basha, A. *Indole Alkaloids*; Harwood Academic: Amsterdam, The Netherlands, 1998; Dewick, P. M. *Medicinal Natural Products*; Wiley & Sons: Chichister, UK, 1997.
2. Sakai, N.; Annnaka, K.; Konakahara, T. *Tetrahedron Lett.* **2006**, *47*, 631; Hiroya, K.; Itoh, S.; Skamaot, T. *J. Org. Chem.* **2004**, *69*, 1126; Hiroya, K.; Matsumoto, S.; Sakamoto, T. *Org. Lett.* **2004**, *6*, 2953; Kamijo, S.; Sasaki, Y.; Yamamoto, Y. *Tetrahedron Lett.* **2004**, *45*, 35; Koradin, C.; Dhohle, W.; Rodriguez, A. L.; Schmid, B.; Knochel, P. *Tetrahedron* **2003**, *59*, 1571.
3. Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *17*, 4467–4470; Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46.
4. Kondo, Y.; Kojima, S.; Sakamoto, T. *J. Org. Chem.* **1997**, *62*, 6507; Ezquerra, J.; Pedregal, C.; Lamas, C.; Barluenga, J.; Perez, M.; Garcia-Martin, M. A.; Gonzarez, J. M. *J. Org. Chem.* **1996**, *61*, 5804; Kondo, Y.; Kojima, S.; Sakamoto, T. *Heterocycles* **1996**, *43*, 2741; Rudisill, D. E.; Stille, J. K. *J. Org. Chem.* **1989**, *54*, 5856.
5. Hong, K. B.; Lee, C. W.; Yum, E. K. *Tetrahedron Lett.* **2004**, *45*, 693; Yin, Y.; Ma, W.; Chai, Z. C.; Zhao, G. *J. Org. Chem.* **2007**, *72*, 5731.
6. Chen, G.; Zhu, X.; Cai, J.; Wan, Y. *Synth. Commun.* **2007**, *37*, 1355.
7. Black, T. H.. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley & Sons: Chichister, UK, 1995; Vol. 6, p 4476.
8. Ding, Q.; Ye, Y.; Fan, R.; Wu, J. *J. Org. Chem.* **2007**, *72*, 5439.
9. Nakamura, M.; Ilies, L.; Otsubo, S.; Nakamura, E. *Org. Lett.* **2006**, *8*, 2803; Nakamura, M.; Ilies, L.; Otsubo, S.; Nakamura, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 944.
10. Ambrogio, I.; Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F. *Synlett* **2007**, 1775; Miyazaki, Y.; Kobayashi, S. *J. Comb. Chem.* **2008**, *10*, 355; Sakai, N.; Annaka, K.; Fujita, A.; Sato, A.; Konakahara, T. *J. Org. Chem.* **2008**, *73*, 4160; Kondo, T.; Okada, T.; Suzuki, T.; Mitsudo, T. *J. Organomet. Chem.* **2001**, *622*, 149.
11. The theoretical calculations for reaction of 2-(1-propynyl)aniline with $ZnCl_2$ giving 2-methylindole are shown in the Supplementary data.
12. Relative stabilization energies [kcal/mol] of intermediates **A**–**D** based on the sum of all electron energy of 2-(1-propynyl)aniline and $ZnCl_2$ were estimated to be -24.9 for **A**, -18.9 for **B**, -29.3 for **C**, and -12.5 for **D** at the B3LYP/6-31G(d) level. The molecular structures and theoretically optimized coordinates of **A**–**D** are shown in Figure S8 and Tables S1–S4, respectively, in the Supplementary data.
13. Naffziger, M. R.; Ashburn, B. O.; Perkins, J. R.; Carter, R. G. *J. Org. Chem.* **2007**, *72*, 9857; Maya, A. B. S.; Melero, C. P.; Mateo, C.; Alonso, D.; Fernandez, J. L.; Gajate, C.; Mollinedo, F.; Pelaez, R.; Caballero, E.; Madarde, M. *J. Med. Chem.* **2005**, 556; Aerssens, M. H. P. J.; Brandsma, L. *J. Chem. Soc., Chem. Commun.* **1984**, 735.
14. Typical reaction is as follows: To a refluxing solution of 2-phenylethynylaniline **1a** (1.0 mmol) in toluene was added zinc bromide (0.05 mmol) in one portion. After refluxing for 6 h, the reaction mixture was washed with water and extracted with dichloromethane. The combined extracts were dried over sodium sulfate, filtered, and evaporated to give a pale brown solid, which was chromatographed over silica gel by elution with hexane/ethyl acetate (5:1) to afford 2-phenylindole **4a** (0.90 mmol).