Contents lists available at ScienceDirect

Chinese Chemical Letters

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

Original article

Facile synthesis of indoles by K_2CO_3 catalyzed cyclization reaction of 2-ethynylanilines in water

Q1 Zhi Chen, Xiao-Xiao Shi, Dong-Qin Ge, Zhen-Zhen Jiang, Qi-Qi Jin, Hua-Jiang Jiang, Jia-Shou Wu *

School of Pharmaceutical and Chemical Engineering, Taizhou University, Taizhou 318000, China

ARTICLE INFO

Article history:
Received 12 June 2016
Received in revised form 8 July 2016
Accepted 12 July 2016
Available online xxx

Keywords:
2-Ethynylanilines
Cyclization reaction
Indoles
Water
Potassium carbonate

ABSTRACT

The cyclization reaction of 2-ethynyl-*N*-sulfonylanilides proceeded efficiently in water with the presence of a catalytic amount of K_2CO_3 under transition metal-free condition to give indoles in high yields. The recovery and reusability of the present catalytic system were investigated.

1. Introduction

Indoles are particular interesting building units owing to their frequent appearance in a vast number of biologically active compounds [1]. After Fischer and Jourdan discovered the well-known “Fischer indole synthesis” in 1883 [2], numerous synthetic routes to indoles have been reported [3]. Among them, intramolecular cyclization with 2-ethynylaniline derivatives is one of the efficient strategies to assemble indole rings [3,4]. The presence of transition metals greatly promoted the cyclization reaction of 2-ethynylaniline derivatives [4]. On the other hand, water is the cheapest and environmentally benign solvent. The use of water as solvent in organic synthesis is of great interest [5]. In 2005, Hiroya et al. reported the first example of synthesis of indoles from 2-ethynylanilines *via* intramolecular cyclization reaction in water catalyzed by a copper salt [4d]. Recently, Song et al. developed a recyclable polystyrene-supported copper catalyst for the cyclization reaction of 2-ethynyl-*N*-sulfonylanilides in water [4e]. In view of green chemistry, a transition metal-free version of this reaction is more attractive and environment friendly. With the aid of microwave irradiation, Carpita and Ribecai found that the intramolecular cyclization reaction of 2-ethynylanilines could be conducted in water in the absence of any catalysts to give indoles in moderate to good yields [6]. However, the use of microwave irradiation is unfavorable, especially in large-scale synthesis. Therefore, developing more efficient and metal-free approach to indoles is still desirable.

2. Experimental

2.1. General procedure for K_2CO_3 catalyzed cyclization reaction of 2-ethynylanilines in water

To a solution of K_2CO_3 (0.15 equiv., 0.045 mmol) in water (1.5 mL) was added substrate **1** (1 equiv., 0.3 mmol). The resulting mixture was stirred vigorously at 130 °C in a sealed tube under an argon atmosphere for 10 h. The reaction solution was cooled to room temperature and extracted by CH_2Cl_2 (3×5 mL), and the organic phase was collected, dried over anhydrous Na_2SO_4. Pure product **2** was obtained by direct evaporation under reduced pressure (**2a**, **2b**, **2d**, **2e**, **2g**–**2j**, **2m**, **2n**, **2p**–**2u**, **2w** or **2x**) or by flash chromatography on silica gel (**2c**, **2f**, **2k**, **2l**, **2o** or **2v**).

2.2. General procedure for recycling experiment

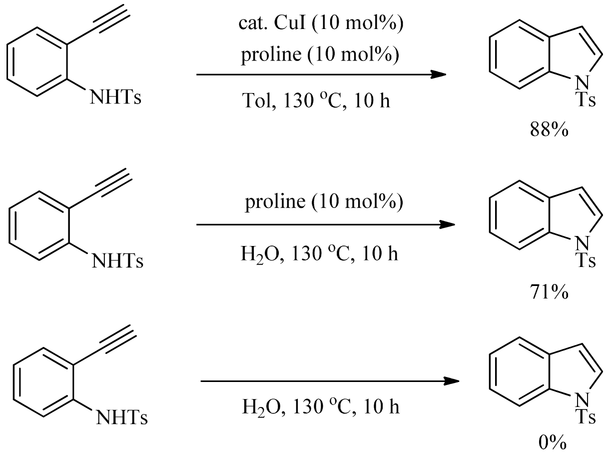
To a solution of K_2CO_3 (0.15 equiv., 0.045 mmol) in water (1.5 mL) was added **1j** (1 equiv., 0.3 mmol). The resulting mixture was stirred vigorously at 130 °C in a sealed tube under an argon

---

* Corresponding author.
E-mail address: jsw79@sina.com (J.-S. Wu).

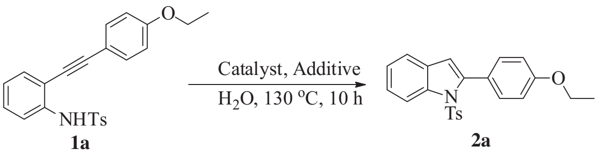
http://dx.doi.org/10.1016/j.cclet.2016.07.022

Please cite this article in press as: Z. Chen, et al., Facile synthesis of indoles by K_2CO_3 catalyzed cyclization reaction of 2-ethynylanilines in water, Chin. Chem. Lett. (2016), http://dx.doi.org/10.1016/j.cclet.2016.07.022



Scheme 1. Cyclization reaction promoted by proline.

Table 1
Optimization of reaction conditions.[a]



Entry	Catalyst (mol %)	Additive (mol %)	Yield[b] (%)
1	Proline (10)	–	15
2[c]	Proline (30)	–	19
3	Proline (30)	SDS (10)	8
4	Proline (30)	CTAB (10)	35
5	Proline (30)	CTAB (20)	37
6	$NaHCO_3$ (30)	CTAB (10)	65
7	Na_2CO_3 (30)	CTAB (10)	93
8	K_2CO_3 (30)	CTAB (10)	99
9	K_2CO_3 (30)	–	99
10	K_2CO_3 (15)	–	99
11	K_2CO_3 (10)	–	95
12	–	–	0[d]

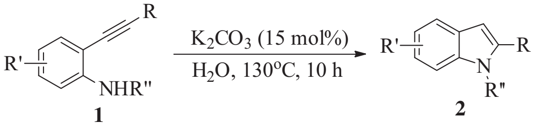
[a] Reaction conditions: **1a** (0.3 mmol), additive and catalyst in water (1.5 mL) at 130 °C (oil bath) for 10 h. [b]Isolated yield. SDS: sodium dodecyl sulphate, CTAB: cetyltrimethylammonium bromide. [c]Reaction time 18 h. [d]**1a** was recovered.

atmosphere for 10 h. The reaction solution was cooled to room temperature and extracted by CH_2Cl_2 (3 × 5 mL), and the organic phase was collected, dried over anhydrous Na_2SO_4. Pure product **2j** was obtained by flash chromatography on silica gel. The aqueous phase containing the catalyst was reused in the next cycle.

3. Results and discussion

During our study on domino coupling reaction of 2-ethynylanilines [7], we found that *N*-tosylated 2-ethynylaniline was cyclized to 1-tosyl-1H-indole in 88% yield in water in the presence of a catalytic amount of CuI and proline (Scheme 1). Interestingly, the intramolecular cyclization reaction occurred even without copper salt by adding 10 mol% proline in water at 130 °C giving 1-tosyl-1*H*-indole in 71% yield (Scheme 1). Unfortunately, when *N*-tosylated 2-(4-ethoxyphenylethynyl)aniline **1a** was used as the substrate, the reaction was rather sluggish and the cyclization product **2a** was isolated in poor yield (15%; Table 1, entry 1) even with prolonged reaction time and elevated catalyst loading (19% yield; Table 1, entry 2). It is reported that reaction yield can be enhanced by the addition of surfactants in water [8]. The addition of sodium dodecyl sulphate (SDS) afforded declined yield (entry 3). When cationic surfactant cetyltrimethylammonium bromide (CTAB) was used, the yield was improved to 35% (Table 1, entry 4). Attempt to further enhance the yield of **2a** by increasing

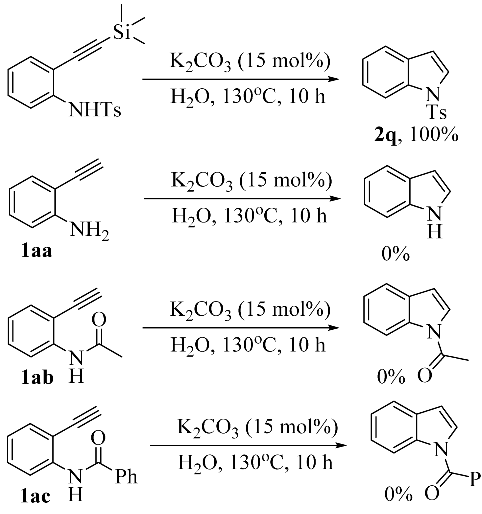
Table 2
Cyclization reaction of 2-alkynylanilines in water catalyzed by K_2CO_3.[a,b]



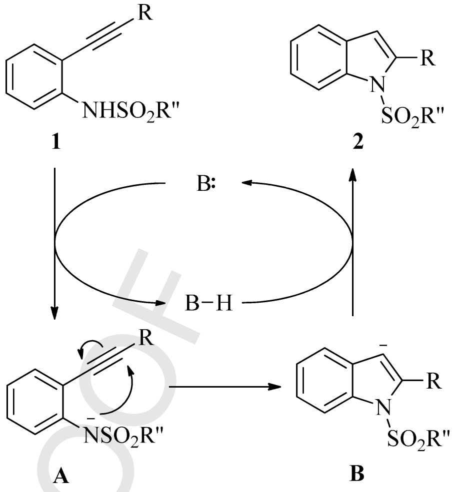
1	R	R′	R″	2	Yield (%)
1a	4-OEt-Ph	H	Ts	**2a**	99
1b	4-OMe-Ph	H	Ts	**2b**	99
1c	4-Et-Ph	H	Ts	**2c**	98
1d	4-Me-Ph	H	Ts	**2d**	99
1e	Ph	H	Ts	**2e**	98
1f	4-Cl-Ph	H	Ts	**2f**	97
1g	4-Br-Ph	H	Ts	**2g**	99
1h	4-CN-Ph	H	Ts	**2h**	100
1i	*n*-Bu	H	Ts	**2i**	100
1j	Cyclopropyl	H	Ts	**2j**	98
1k	*t*-Bu	H	Ts	**2k**	95
1l	Ph	4-Me	Ts	**2l**	92
1m	Ph	4-F	Ts	**2m**	99
1n	Ph	4-Cl	Ts	**2n**	100
1o	Ph	4-CF_3	Ts	**2o**	96
1p	Ph	5-CF_3	Ts	**2p**	99
1q	H	H	Ts	**2q**	100
1r	H	4-Me	Ts	**2r**	99
1s	H	4-F	Ts	**2s**	98
1t	H	4-Cl	Ts	**2t**	100
1u	H	5-CF_3	Ts	**2u**	98
1v	H	4-CF_3	Ts	**2v**	97
1w	H	H	Benzenesulfonyl	**2w**	97
1x	H	H	Nos	**2x**	98

[a] Reaction conditions: **1** (0.3 mmol) and K_2CO_3 (15 mol%) in water (1.5 mL) at 130 °C (oil bath) for 10 h. [b]Isolated yield.

Please cite this article in press as: Z. Chen, et al., Facile synthesis of indoles by K_2CO_3 catalyzed cyclization reaction of 2-ethynylanilines in water, Chin. Chem. Lett. (2016), http://dx.doi.org/10.1016/j.cclet.2016.07.022



Scheme 2. Cyclization reactions with different *N*-substituted 2-alkynylanilines.



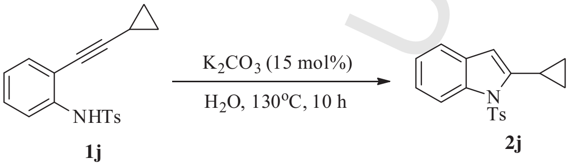
Scheme 3. Possible reaction mechanism.

the amount of CTAB to 20 mol% failed (entry 5). It has been demonstrated that the cyclization reaction of 2-ethynylanilines can be achieved in organic solvents with excesses of strong bases [9], such as EtONa [9a], *t*-BuOK or KH [9b-e]. More recently, Li et al. found that a catalytic amount of *t*-BuOK was sufficient to affect the cyclization reaction of 2-ethynylanilines in dry DMSO [10]. Inspired by these reports and the fact that proline can act as a base [11], we envisioned that simple inorganic base might be efficient catalyst for the cyclization reaction of 2-ethynylanilines in water. Indeed, with 30 mol% $NaHCO_3$ as the catalyst, the cyclization product **2a** was isolated in 65% yield after 10 h in water (Table 1, entry 6). As expected, the cyclization reaction was further improved when a stronger base Na_2CO_3 was used as catalyst, and **2a** was isolated in excellent yield, 93% (entry 7). With the presence of 30 mol% K_2CO_3, **1a** was cyclised to **2a** in almost quantitative yield, 99% (Table 1, entry 8). Notably, the addition of CTAB is not essential (entry 9), and the cyclization reaction is still highly efficient with 15 mol% K_2CO_3 (Table 1, entry 10). Further lower catalyst loading resulted in inferior yield, 95% (entry 11). No desired product was isolated in the absence of K_2CO_3 (entry 12).

The generality of this method was then tested with various substituted 2-(arylethynyl)anilines, and the results were summarized in Table 2. *N*-Tosylated 2-(arylethynyl)anilines with electron-donating (**1a**–**1d**) or electron-withdrawing (**1f**–**1h**) substituents in the aryl ring cyclised to the corresponding 2-arylindoles in high yields. Notably, the nitrile group was found to be well tolerated under the present reaction condition to afford **2h** in quantitative yield. Substrates bearing an alkyl substituent on the alkyne moiety were also applicable (**1i**–**1k**). Unlike copper catalyzed cyclization reaction of 2-ethynylanilines in organic solvent [4f], the cyclization reaction still worked highly efficient with a sterically crowded substrate, and **2k** was formed in 95% yield under the optimal reaction conditions. 2-Ethynylanilines with different substituent groups on the aniline moiety were also investigated. 2-Phenylethynyl-*N*-tosylanilines possessing F, Cl and CF_3 substituents at 4 or 5-position reacted smoothly to afford **2m**–**2p** in 96–100% yields, while relatively lower yield was obtained with substrate bearing electron-donating methyl group (**2l**, 92%). The intramolecular cyclization proceeded smoothly to give the corresponding indoles (**2q**–**2v**) in high yields irrespective of electronic variation on the aniline part of 2-ethynyl-*N*-tosylanilides. Ethynylanilines having phenylsulfonyl or 4-nitrophenylsulfonyl group on nitrogen were also good substrates furnishing the corresponding cyclization products in high yields (**2w** and **2x**). When 2-(trimethylsilylethynyl)aniline **1y** was employed, only the desilylated cyclization product **2q** was obtained in quantitative yield (Scheme 2). It is reported that the cyclization reaction is rather sensitive to the acidity of the nitrogen-attached proton [12]. Indeed, no desired product was isolated when 2-ethynylaniline **1aa**, *N*-acetyl aniline **1ab** or *N*-benzoyl derivative **1ac** was used as the substrate (Scheme 2). In light of these results and based on the cyclization reaction of 2-ethynylanilines in literature [9,10], a plausible reaction pathway is shown in Scheme 3. The reaction started with the deprotonation of **1** leading to anion intermediate **A**. Subsequent intramolecular nucleophilic addition gives alkene anion **B**. Protonolysis delivers the final product **2**.

The possibilities of recovery and reusability of the catalytic system were also investigated using **1j** by carrying out consecutive cycles. **2j** was extracted with CH_2Cl_2 after each catalytic reaction, and the results are recorded in Table 3. The catalytic system can be recycled at least six times with little loss in yield on the 6th run.

Table 3
Cyclization reaction of 2-alkynylanilines in water catalyzed by K_2CO_3.[a]



Cycle	1	2	3	4	5	6
Yield[b] (%)	99	99	99	99	97	95

[a] Reaction conditions: **1j** (0.3 mmol) and K_2CO_3 (15 mol%) in water (1.5 mL) at 130 °C (oil bath) for 10 h. [b]Isolated yield.

Please cite this article in press as: Z. Chen, et al., Facile synthesis of indoles by K_2CO_3 catalyzed cyclization reaction of 2-ethynylanilines in water, Chin. Chem. Lett. (2016), http://dx.doi.org/10.1016/j.cclet.2016.07.022

4. Conclusion

In conclusion, we have developed a highly efficient method for the synthesis of indoles *via* K_2CO_3 catalyzed cyclization reaction of 2-ethynyl-*N*-sulfonylanilides in water. It is noted that the present procedure offers several advantages, including the absence of transition metal, without the use of excess of strong base, green solvent, the ease of product isolation and cleaner reactions. Moreover, the recovery and reusability of the catalytic system were also investigated, and it could be reused at least six times.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (No. 21402137) and Xinmiao Talents Program of Zhejiang Province (No. 2016R430021).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cclet.2016.07.022.

References

[1] (a) M. Lounasmaa, A. Tolvanen, Simple indole alkaloids and those with a nonrearranged monoterpenoid unit, Nat. Prod. Rep. 17 (2000) 175–191;
(b) S. Hibino, T. Choshi, Simple indole alkaloids and those with a nonrearranged monoterpenoid unit, Nat. Prod. Rep. 19 (2002) 148–180;
(c) M. Somei, F. Yamada, Simple indole alkaloids and those with a nonrearranged monoterpenoid unit, Nat. Prod. Rep. 21 (2004) 278–311;
(d) N.E. Golantsov, A.A. Festa, A.V. Karchava, M.A. Yurovskaya, Marine indole alkaloids containing an 1-(indol-3-yl)ethane-1,2-diamine fragment (review), Chem. Heterocycl. Compd. 49 (2013) 203–225.

[2] (a) E. Fischer, F. Jourdan, Ueber die hydrazine der brenztraubensäure, Ber. Deutsch. Chem. Gesell. 16 (1883) 2241–2245;
(b) E. Fischer, O. Hess, Synthese von indolderivaten, Ber. Deutsch. Chem. Gesell. 17 (1884) 559–568.

[3] (a) G.R. Humphrey, J.T. Kuethe, Practical methodologies for the synthesis of indoles, Chem. Rev. 106 (2006) 2875–2911;
(b) R. Vicente, Recent advances in indole syntheses: new routes for a classic target, Org. Biomol. Chem. 9 (2011) 6469–6480;
(c) S. Cacchi, G. Fabrizi, Update 1 of: synthesis and functionalization of indoles through palladium-catalyzed reactions, Chem. Rev. 111 (2011) PR215–PR283;
(d) Y. Oda, N. Matsuyama, K. Hirano, T. Satoh, M. Miura, Dehydrogenative synthesis of C3-azolylindoles via copper-promoted annulative direct coupling of o-alkynylanilines, Synthesis 44 (2012) 1515–1520.

[4] (a) L.B. Huang, M. Arndt, K. Gooßen, H. Heydt, L.J. Gooßen, Late transition metal-catalyzed hydroamination and hydroamidation, Chem. Rev. 115 (2015) 2596–2697;
(b) M. Platon, R. Amardeil, L. Djakovitch, J.C. Hierso, Progress in palladium-based catalytic systems for the sustainable synthesis of annulated heterocycles: a focus on indole backbones, Chem. Soc. Rev. 41 (2012) 3929–3968;
(c) S. Cacchi, G. Fabrizia, A. Goggiamani, Copper catalysis in the construction of indole and benzo[b]furan rings, Org. Biomol. Chem. 9 (2011) 641–652;
(d) K. Hiroya, S. Itoh, T. Sakamoto, Mild and efficient cyclization reaction of 2-ethynylaniline derivatives to indoles in aqueous medium, Tetrahedron 61 (2005) 10958–10964;
(e) S.C. Song, M.N. Huang, W.J. Li, X.H. Zhu, Y.Q. Wan, Efficient synthesis of indoles from 2-alkynylaniline derivatives in water using a recyclable copper catalyst system, Tetrahedron 71 (2015) 451–456;
(f) K. Hiroya, S. Itoh, T. Sakamoto, Development of an efficient procedure for indole ring synthesis from 2-ethynylaniline derivatives catalyzed by Cu(II) salts and its application to natural product synthesis, J. Org. Chem. 69 (2004) 1126–1136.

[5] (a) A. Chanda, V.V. Fokin, Organic synthesis “On Water”, Chem. Rev. 109 (2009) 725–748;
(b) R.N. Butler, A.G. Coyne, Water: nature’s reaction enforcer – comparative effects for organic synthesis “In-Water” and “On-Water”, Chem. Rev. 110 (2010) 6302–6337;
(c) M.O. Simon, C.J. Li, Green chemistry oriented organic synthesis in water, Chem. Soc. Rev. 41 (2012) 1415–1427.

[6] (a) A. Carpita, A. Ribecai, Microwave-assisted synthesis of indole-derivatives via cycloisomerization of 2-alkynylanilines in water without added catalysts, acids, or bases, Tetrahedron Lett. 50 (2009) 6877–6881;
(b) A. Carpita, A. Ribecai, P. Stabile, Microwave-assisted synthesis of indole- and azaindole-derivatives in water via cycloisomerization of 2-alkynylanilines and alkynylpyridinamines promoted by amines or catalytic amounts of neutral or basic salts, Tetrahedron 66 (2010) 7169–7178.

[7] Z.N. Jin, H.J. Jiang, J.S. Wu, et al., Synthesis of 2-heterocyclic substituted pyrrolidines by copper-catalyzed domino three-component decarboxylative coupling and cyclization reactions, Tetrahedron Lett. 56 (2015) 2720–2723.

[8] F. Wang, H. Liu, L.F. Cun, et al., Asymmetric transfer hydrogenation of ketones catalyzed by hydrophobic metal-amido complexes in aqueous micelles and vesicles, J. Org. Chem. 70 (2005) 9424–9429.

[9] (a) J.J. Wang, N. Soundarajan, N. Liu, K. Zimmermann, B.N. Naidu, Highly convergent synthesis of a rebeccamycin analog with benzothioeno(2,3-a)pyrrolo(3, 4-c)carbazole as the aglycone, Tetrahedron Lett. 46 (2005) 907–910;
(b) A.L. Rodriguez, C. Koradin, W. Dohle, P. Knochel, Versatile indole synthesis by a 5-endo-dig cyclization mediated by potassium or cesium bases, Angew. Chem. Int. Ed. 39 (2000) 2488–2490;
(c) C. Koradin, W. Dohle, A.L. Rodriguez, B. Schmid, P. Knochel, Synthesis of polyfunctional indoles and related heterocycles mediated by cesium and potassium bases, Tetrahedron 59 (2003) 1571–1587;
(d) A.H. Stoll, P. Knochel, Preparation of fully substituted anilines for the synthesis of functionalized indoles, Org. Lett. 10 (2008) 113–116;
(e) Y. Kondo, S. Kojima, T. Sakamoto, General and facile synthesis of indoles with oxygen-bearing substituents at the benzene moiety, J. Org. Chem. 62 (1997) 6507–6511.

[10] D.Y. Li, K.J. Shi, X.F. Mao, et al., Selective cyclization of alkynols and alkynylamines catalyzed by potassium *tert*-butoxide, Tetrahedron 70 (2014) 7022–7031.

[11] B. List, Proline-catalyzed asymmetric reactions, Tetrahedron 58 (2002) 5573–5590.

[12] (a) K. Hiroya, S. Itoh, M. Ozawa, Y. Kanamori, T. Sakamoto, Efficient construction of indole rings from 2-ethynylaniline derivatives catalyzed by copper(II) salts and its application to the tandem cyclization reactions, Tetrahedron Lett. 43 (2002) 1277–1280;
(b) K.C. Majumdar, S. Samanta, B. Chattopadhyay, A convenient synthesis of pyrrolopyridines and 2-substituted indoles by gold-catalyzed cycloisomerization, Tetrahedron Lett. 49 (2008) 7213–7216;
(c) A. Yasuhara, Y. Kanamori, M. Kaneko, et al., Convenient synthesis of 2-substituted indoles from 2-ethynylanilines with tetrabutylammonium fluoride, J. Chem. Soc. Perkin Trans. 1 (1999) 529–534.

Please cite this article in press as: Z. Chen, et al., Facile synthesis of indoles by K_2CO_3 catalyzed cyclization reaction of 2-ethynylanilines in water, Chin. Chem. Lett. (2016), http://dx.doi.org/10.1016/j.cclet.2016.07.022