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Original article

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

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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

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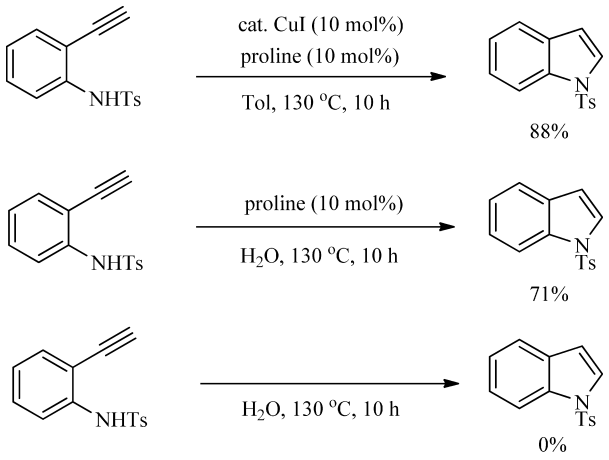


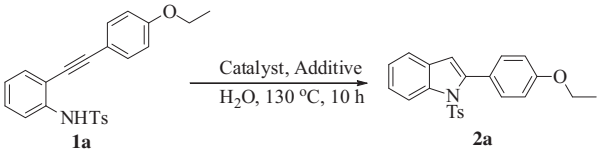
Scheme 1. Cyclization reaction promoted by proline.

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 1
Optimization of reaction conditions.[a]

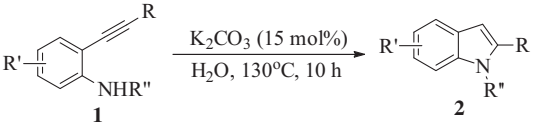


1a **2a**

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.

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



1 **2**

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.

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