



Original article

A novel and efficient strategy involving a CuI catalyzed cascade reaction to synthesize acenaphtho[1,2-b]quinoline derivatives



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ABSTRACT

A novel and efficient approach for the straightforward synthesis of biologically significant acenaphtho[1,2-b]quinoline derivatives in good yields utilizing CuI as a catalyst with a broad array of substrates has been developed. The strategy features as a CuI-catalyzed cascade reaction involving the formation of two new C–C bonds and one new C–N bond with high atom economy. A proposed mechanism for the reaction is described.

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1. Introduction

Quinolines [1,2], a versatile class of heterocyclic compounds, are found extensively in natural products [3] and frequently investigated for their broad biological properties [4–13], such as antitumor activities [10,11] and HIV inhibitory potencies [12,13]. Thus, many synthetic approaches have been reported and a large number of quinolines are synthesized [14–18]. However, the synthesis of acenaphtho[1,2-b]quinolines has rarely been reported in the literature. Therefore, the development of a novel and efficient approach to construct this fused heterocyclic scaffold is highly desirable.

Compared to other strategies, a cascade strategy [19–22] could conveniently and quickly assemble the chemical skeletons of quinolines with metal catalysts [23,24] playing important roles in the chemical reactions. The synthesis of dihydrobenzo-[4,5][1,3]oxazino[2,3-a]isoquinolines from 2-aminobenzyl alcohol and 2-phenylethynyl-benzaldehyde was reported recently [25–28], in which the metal-catalyzed cascade reaction performed fundamental roles. As a continuation of our previous work [29],

we hypothesize that the coupling reactions of 8-substituted phenylethynyl-1-naphthaldehydes **1** with substituted anilines **2** through an intermolecular condensation could provide the corresponding imines, which could subsequently proceed to acenaphtho[1,2-b]quinoline derivatives in the presence of appropriate catalysts in an apparently simple process (Scheme 1). Herein, we report the successful realization of this concept by utilizing CuI as a catalyst. The cascade transformation proceeds with broad array of substrates providing diverse analogs of 8-substituted phenylethynyl-1-naphthaldehydes **1** and substituted anilines **2**.

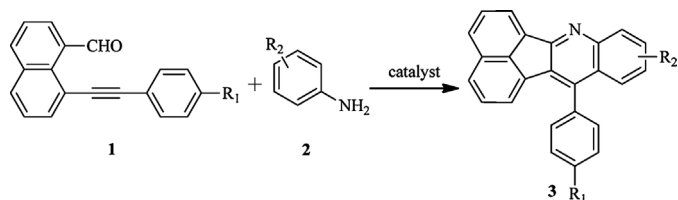
2. Experimental

General procedure for synthesis of **3a–m**: To a stirred solution of 8-substituted phenylethynyl-1-naphthaldehydes **1** (0.1 mmol) and CuI (0.02 mmol) in 1,2-dichloroethane (DCE, 10 mL), substituted anilines **2** were added. The resulting mixture was heated to reflux for 12 h. After the reaction was completed, the mixture was concentrated under reduced pressure, and the obtained residue was purified by column chromatography (PE/EA = 10:1–3:1) to give the corresponding compounds **3a–m** in yields of 46%–76%. All compounds were confirmed by ¹H NMR, ¹³C NMR and HRMS. Additionally, **3b** was further characterized by X-ray crystallography (Fig. 1). Single crystal data (CCDC 1416928) has been deposited

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Scheme 1. Concept of metal-catalyzed cascade reactions.

in the Cambridge Crystallographic Data Centre. Details of spectral data are provided in Supporting information.

(12-Phenyl-acenaphtho[1,2-b]quinolin-8-yl)-methanol **3a**: Yield (27 mg, 75%), mp 183–184 °C. ¹H NMR (500 MHz, CDCl₃): δ 8.46 (d, 1H, *J* = 6.5 Hz), 8.04 (d, 1H, *J* = 8.0 Hz), 7.88 (d, 1H, *J* = 8.0 Hz), 7.83 (t, 1H, *J* = 7.2 Hz), 7.68–7.71 (m, 3H), 7.60–7.64 (m, 2H), 7.57–7.55 (m, 2H), 7.41–7.46 (m, 2H), 6.92 (d, 1H, *J* = 7.0 Hz), 5.61 (brs, 1H), 5.39 (s, 2H). ¹³C NMR (125 MHz, CDCl₃): δ 158.4, 142.9, 138.3, 136.2, 135.5, 134.7, 133.6, 130.1, 129.3, 129.2, 129.1, 129.05, 128.7, 128.4, 128.2, 127.7, 127.6, 127.3, 126.98, 126.3, 125.9, 122.7, 121.4, 65.46. HRMS (TOF-ESI): [M + H]⁺, calcd. for C₂₆H₁₈NO: 360.1383. found: 360.1379.

3. Results and discussion

Initially, our efforts focused on discovering the optimal reaction conditions to perform the proposed reaction. All results are summarized in Table 1. Preliminary experiments to optimize the reaction conditions were performed with 8-phenylethynyl-1-naphthaldehyde **1a** and 2-aminobenzyl alcohol **2a** as model substrates. When the reaction was initially performed using DCE as the solvent at the reflux temperature for 3 h in the absence of the catalyst, a new fluorescent spot emerged upon TLC analysis. The product was subsequently isolated and confirmed to be the desirable cascade product **3a** by ¹H NMR and ¹³C NMR in a low yield (25%, Table 1, entry 1). Furthermore, the yield improved slightly to 30% with the increase of the reaction time from 3 h to 12 h (Table 1, entry 2). According to the report of Patil *et al.* [25], AgNO₃ and PdCl₂ were efficient catalysts for cascade reactions involving the synthesis of dihydrobenzo [4,5][1,3]oxazino[2,3-a]isoquinolines, and thus we searched for the most suitable metallic catalyst. Copper ion [30,31] was identified as effective in the screening of metallic catalysts (Table 1, entries 3–10). Among them, CuI [32,33] was proved to be one of the most optimal

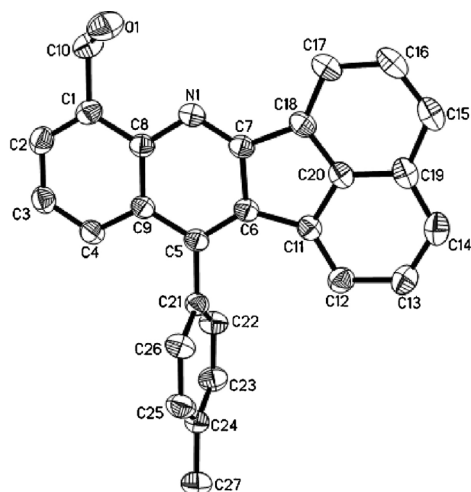


Fig. 1. ORTEP drawing of X-ray structure of **3b**.

Table 1
Optimization of the reaction conditions^a.

Entry	Catalyst (mmol%)	Solvent	Ratio (2a/1a)	Temp (°C)	Yield (%) ^b
1 ^c	–	DCE	1	Reflux	25
2	–	DCE	1	Reflux	30
3	PdCl ₂ (20)	DCE	1	Reflux	35
4	AuCl (20)	DCE	1	Reflux	37
5	NiCl ₂ (20)	DCE	1	Reflux	42
6	CuSO ₄ (20)	DCE	1	Reflux	49
7	CuBr ₂ (20)	DCE	1	Reflux	71
8	CuI (20)	DCE	1	Reflux	75
9	CuBr (20)	DCE	1	Reflux	73
10	CuCl (20)	DCE	1	Reflux	72
11	CuI (20)	DCE	1	80	59
12	CuI (20)	DCE	1	50	15
13	CuI (20)	DCE	1	25	– ^d
14	CuI (20)	DCM	1	Reflux	– ^d
15	CuI (20)	CH ₃ OH	1	Reflux	– ^d
16	CuI (20)	THF	1	Reflux	– ^d
17	CuI (20)	CH ₃ CN	1	Reflux	50
18	CuI (20)	TCE	1	Reflux	23
19 ^e	CuI (20)	DCE	1	Reflux	73
20	CuI (10)	DCE	1	Reflux	70
21	CuI (30)	DCE	1	Reflux	74
22	CuI (20)	DCE	1.2	Reflux	74
23	CuI (20)	DCE	1.5	Reflux	75

^a Reactions performed on 0.1 mmol scale, 10 mL of the solvent, 12 h.

^b All yields after isolation by column chromatography.

^c Reaction time is 3 h.

^d No product obtained.

^e Pyridine used as ligand.

catalysts for this cascade reaction, increasing the yield up to 75% (Table 1, entry 8). Apparently, the solvent exerted a significant influence on the yield of the reactions (Table 1, entries 14–18). DCE was found to be most suitable in the preliminary screening.

Table 2
Scopes and limitations of the cascade reaction^a.

Entry	1	2	R ₂	Product	Yield (%) ^b
1	1a (R ₁ = H)	2a	2-CH ₂ OH	3a	75
2	1b (R ₁ = CH ₃)	2a	2-CH ₂ OH	3b	64
3	1c (R ₁ = OCH ₃)	2a	2-CH ₂ OH	3c	52
4	1a	2b	H	3d	46
5	1a	2c	4-Me	3e	58
6	1a	2d	4-CN	3f	71
7	1a	2e	4-Br	3g	69
8	1a	2f	4-CF ₃	3h	76
9	1a	2g	2-CF ₃	3i	68
10	1a	2h	4-OCF ₃	3j	61
11	1a	2i	4-CO ₂ Me	3k	62
12	1a	2j	2-CO ₂ Me	3l	57
13	1a	2k	2-OCHF ₂	3m	66

^a Reaction conditions: **1** (0.1 mmol), **2** (0.1 mmol), CuI (20 mmol%), DCE 10 mL, reflux, 12 h.

^b All yields after isolation by column chromatography.

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