

Note

Palladium-catalyzed Sonogashira coupling reaction followed by isomerization and cyclization

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Abstract

2-Iodoaniline reacts with terminal acetylenic carbinols in THF at 80 °C in the presence of a catalytic amount of PdCl₂(PPh₃)₂ and CuI along with aqueous tetrabutylammonium hydroxide to afford the corresponding 2-arylquinolines in good yields. The catalytic pathway seems to be proceeded via a sequence involving initial Sonogashira coupling between 2-iodoaniline and terminal acetylenic carbinols to form coupled acetylenic carbinols, isomerization of coupled acetylenic carbinols to α,β -unsaturated ketones, and cyclodehydration.

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1. Introduction

Pd/Cu-catalyzed sp-carbon-sp²-carbon bond forming reaction by the cross-coupling of terminal alkynes with aryl and vinyl halides (or triflates) is known as Sonogashira coupling reaction [1]. This protocol has been widely used as a powerful synthetic tool for the formation of conjugated acetylenic compounds, which frequently plays an important role as an intermediate for the design of pharmaceuticals and organic materials [1]. Thus, many elegant systems which facilitate Sonogashira coupling under a milder conditions have been developed by the tuning of phosphine ligand combined with palladium [2] or the addition of promoter [3]. As an exceptional case, it was reported by several groups that limited aromatic halides are coupled with terminal acetylenic carbinols to give coupled enones via isomerization of initially coupled acetylenic carbinols under usual Sonogashira coupling conditions [4]. In connec-

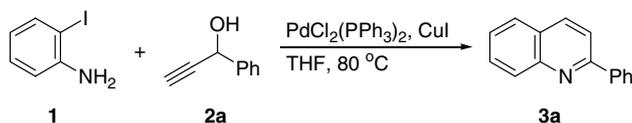
tion with this report, Kundu et al. have also reported on the step-by-step synthesis of quinolines by an initial Sonogashira coupling reaction of *o*-iodoanilide or *o*-iodoaniline with terminal acetylenic carbinols and subsequent treatment of the coupled acetylenic carbinols with a base or Pd(OAc)₂-LiCl [5]. Under these circumstances, herein this report describes a one-pot convenient palladium-catalyzed synthesis of 2-arylquinolines from 2-iodoaniline and terminal acetylenic carbinols [6–8].

2. Results and discussion

The results of several attempted reactions of 2-iodoaniline (**1**) with 1-phenylprop-2-yn-1-ol (**2a**) are listed in Table 1. Typically, **1** was subjected to react with **2a** in the presence of PdCl₂(PPh₃)₂ (2 mol%) and CuI (4 mol%) along with an additive to afford 2-phenylquinoline (**3a**). Among the activity of several additives examined, tetrabutylammonium hydroxide (TBAOH, 1 M aqueous solution) is the choice of preference for the

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Table 1
Palladium-catalyzed reaction of **1** with **2a** under several conditions^a



Run	Additives	Time (h)	Isolated yield (%)
1	Bu ₄ NOH (1 M aqueous)	20	84
2	Pr ₄ NOH (1 M aqueous)	20	67–74 ^b
3	Bu ₄ NF (1 M THF)	40	11 ^c
4	Bu ₄ NCl	40	0
5	KOH	20	3

^a Reaction conditions: **1** (1 mmol), **2a** (1.2 mmol), PdCl₂(PPh₃)₂ (2 mol%), CuI (4 mol%), additive (2 mmol), THF (5 ml), 80 °C.

^b Several runs.

^c 3-(2-Aminophenyl)-1-phenylprop-2-yn-1-ol was formed in 65% yield.

effective formation of **3a** (run 1). The activity toward the formation of **3a** using tetrapropylammonium hydroxide (TBAOH, 1 M aqueous solution) was revealed to be as similarly effective as that using TBAOH (run 2). It is known that TBAOH and tetrabutylammonium fluoride (TBAF) are used as an activator in Pd/Cu-catalyzed coupling reaction of terminal alkynes with aryl halides (Sonogashira coupling) [3c]. However, in contrast to TBAOH, TBAF was not effective for the formation of **3a** (11% yield), whereas conventional Sonogashira coupling product was rather produced as a major identifiable product (65%) (run 3). On the other hand, neither coupling nor cyclization took place at all with the introduction of tetrabutylammonium chloride (run 4). Performing the reaction under the addition of KOH produced **3a** in only 3% yield without the production of coupled acetylenic carbinols and both startings were recovered almost completely (run 5).

Having controlled reaction conditions, various terminal acetylenic carbinols **2** were subjected to react with **1** in order to investigate the reaction scope and several representative results are summarized in Table 2. With terminal acetylenic carbinols (**2a–2j**) the coupling and cyclized products (**3a–3j**) were formed in the range of 59–92% yields without any identifiable side product. The product yield was not significantly affected by the electronic nature of the substituent on the aromatic ring of **2a–2j**, whereas the position of that had some relevance to the product yield. The reaction proceeds likewise with 1-(2-thienyl)prop-2-yn-1-ol (**2k**) to give the corresponding quinoline **3k** in similar yield. 1-(2-Naphthyl)prop-2-yn-1-ol (**2l**) was also readily coupled and cyclized with **1** to afford 2-(2-naphthyl)quinoline (**3l**) in 68% yield. In the case of dec-1-yn-3-ol (**2m**), the reaction did not proceed at all toward cyclization, coupling product, 1-(2-aminophenyl)dec-1-yn-3-ol being produced in 68% yield as an only identifiable product. The uneasy isomerization of a coupled acetylenic carbinol produced from **1** and **2m** seems to be due to deficient resonance

stabilization as compared with that produced from **1** and **2a–2l**. Similar treatment of **1** with bispropargyl alcohol **2n** under the employed conditions afforded bisquinoline **3n** [9] in 64% yield.

As to the reaction pathway, this seems to proceed via initial coupling between **1** and **2** to produce coupled acetylenic carbinol **4**, which in turn triggers isomerization to form α,β -unsaturated carbonyl compound **5** via an allenol **5** and subsequent cyclodehydration to give quinoline **3** (Scheme 1). It is known that several bases [10] and transition metals [5b,11] catalyze the isomerization of propargyl alcohols to enones or enals. Thus, it appears that TBAOH in the present reaction works as a promoter for both coupling [3c] and isomerization.

3. Conclusion

In summary, it has been shown that 2-iodoaniline undergoes tandem coupling, isomerization and cyclodehydration with an array of terminal acetylenic carbinols in the presence of a catalytic amount of PdCl₂(PPh₃)₂ and CuI along with aqueous tetrabutylammonium hydroxide to give 2-arylquinolines in high yields. The present reaction is a convenient one-pot synthetic route for 2-arylquinolines from 2-iodoaniline and terminal acetylenic carbinols. Further study on the synthetic applications for heterocycles using present catalytic system is currently under investigation.

4. Experimental

¹H- and ¹³C NMR (400 and 100 MHz) spectra were recorded on a Bruker Avance Digital 400 spectrometer using Me₄Si as an internal standard. Melting points (m.p.) were determined on a Thomas–Hoover capillary melting point apparatus and were uncorrected. The

Table 2
Palladium-catalyzed synthesis of **3** from **1** and **2**^a

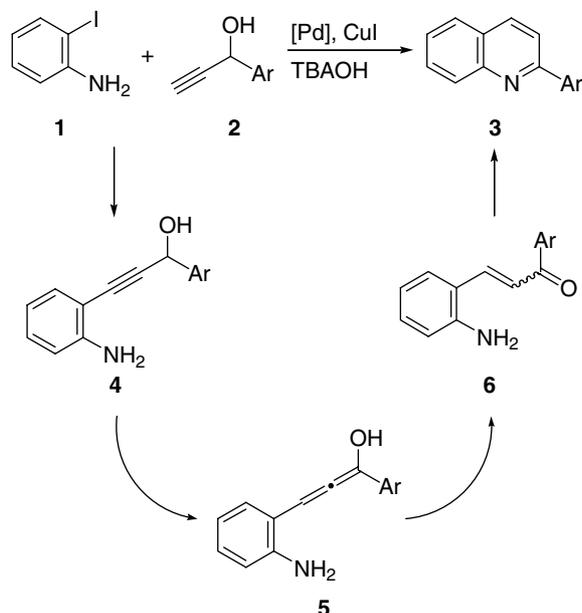
2	3	Yield (%)
		84
2a R = H	3a R = H	84
2b R = 2-Me	3b R = 2-Me	59
2c R = 3-Me	3c R = 3-Me	92
2d R = 4-Me	3d R = 4-Me	90
2e R = 2-OMe	3e R = 2-OMe	74
2f R = 3-OMe	3f R = 3-OMe	84
2g R = 4-OMe	3g R = 4-OMe	68
2h R = 4-Cl	3h R = 4-Cl	71
2i R = 4-F	3i R = 4-F	74
2j R = 2,3-(OMe) ₂	3j R = 2,3-(OMe) ₂	70
		80
2k	3k	
		68
2l	3l	
		0 ^b
2m	3m	
		64 ^c
2n	3n	

^a All reactions were carried out with **1** (1 mmol), **2** (1.2 mmol), PdCl₂(PPh₃)₂ (0.02 mmol), CuI (0.04 mmol), and TBAOH (2 mmol) in THF (5 ml) at 80 °C for 24 h unless otherwise stated.

^b 1-(2-Aminophenyl)dec-1-yn-3-ol was isolated in 58% yield.

^c Reaction conditions: **1** (2 mmol), **2n** (1.2 mmol), PdCl₂(PPh₃)₂ (0.04 mmol), CuI (0.08 mmol), and TBAOH (4 mmol) in THF (5 ml) at 80 °C for 24 h.

GLC analyses were carried out with Shimadzu GC-17A (FID) equipped with CBP10-S25-050 column (Shimadzu, a silica fused capillary column, 0.33 mm × 25 m, 0.25 μm film thickness) using N₂ as carrier gas. The isolation of pure products was carried via column chromatography (silica gel 60, 70–230 mesh, Merck). Commercially available organic and inorganic compounds were used without further purification. Terminal acetylenic carbinols (**2a–2n**) were prepared from aldehydes and ethynylmagnesium bromide by the reported method [12].



Scheme 1.

4.1. Typical experimental procedure

A mixture of **1** (0.219 g, 1 mmol), **2a** (0.159 g, 1.2 mmol), PdCl₂(PPh₃)₂ (0.014 g, 0.02 mmol), CuI (0.008 g, 0.04 mmol) and tetrabutylammonium hydroxide (2 ml of 1 M aqueous solution) in THF (5 ml) was placed in a 20 ml flask and allowed to react at 80 °C (oil bath temperature). The reaction mixture was filtered through a short silica gel column (ethyl acetate) to eliminate inorganic salts. Removal of the solvent left a crude mixture, which was separated by column chromatography (silica gel, EtOAc-hexane = 1/5) to give **3a** (0.172 g, 84%).

Except for **3n**, all quinolines prepared by the above procedure were characterized by GLC and spectroscopic comparison with authentic samples synthesized by our recent reports [7g,10c].

4.1.1. 1,3-Di-(2'-quinolinyl)benzene (**3n**)

Yellow orange solid, m.p. 138–139 °C (from ether-CH₂Cl₂) (lit. [9] 139–140 °C); ¹H NMR (CDCl₃): δ 7.51 (td, *J* = 7.5 and 1.0 Hz, 2H), 7.66 (t, *J* = 7.8 Hz, 1H), 7.70–7.74 (m, 2H), 7.80 (d, *J* = 8.0 Hz, 2H), 7.97 (d, *J* = 9.0 Hz, 2H), 8.19–8.28 (m, 6H), 8.95 (s, 1H); ¹³C NMR (CDCl₃): δ 119.09, 126.33, 126.75, 127.26, 127.48, 128.49, 129.37, 129.67, 136.81, 140.18, 148.25, 157.04.

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