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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 5013–5016

Chemoselective arylamination of β-bromovinylaldehydes followed by acid catalyzed cyclization: a general method for polycyclic quinolines

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Received 11 April 2007; revised 11 May 2007; accepted 18 May 2007
Available online 24 May 2007

Abstract—A synthesis of polycyclic quinolines is described via palladium-catalyzed chemoselective arylamination of β-bromovinylaldehydes with aromatic amines followed by acid catalyzed cyclization.

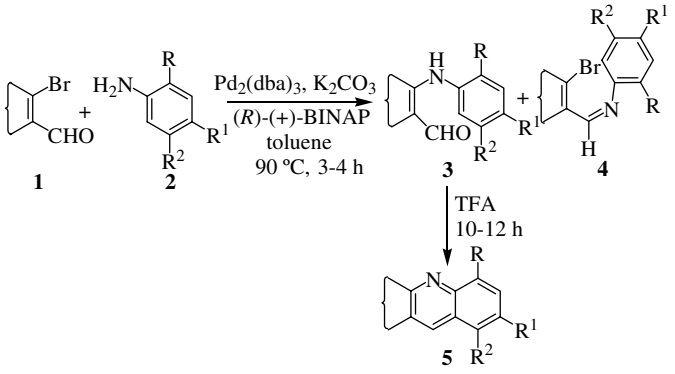
1. Introduction

Polycyclic azaarenes (PAA)[1,2] have attracted the attention of organic chemists due to the interesting properties exhibited by these classes of compounds, in the form of cavity shaped molecules,[3] bay region diol epoxides,[2,4] molecular tweezers,[5] heterohelicenes,[6] polycyclic aromatic alkaloids,[7] quinoline-5,8-quinone,[8] prototype inhibitors of Hsp-90, geldamycin[9] and substituted quinolines.[10] Several methods have already been reported for the synthesis of PAAs including the Combes method.[11] Previously, we reported the synthesis of PAAs by thermal cyclization of arylenaminoimine hydrochlorides.[12]

Herein we report a simple, two-step procedure for the facile synthesis of the polycyclic quinolines, which involves selective Pd-catalyzed arylamination of β-bromovinylaldehydes by substituted aromatic amines followed by acid catalyzed cyclization[13] with trifluoroacetic acid (Scheme 1).

On the basis of our results and evidence in the literature,[14] it was interesting and worthwhile to study the amination of β-bromovinylaldehydes.

We found that β-bromovinylaldehyde **1a** (1 mmol) (Fig. 1) reacted with substituted aromatic amine **2a**



Scheme 1.

Keywords: Polycyclic azaarenes; Acid cyclization; Selective amination.
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doi:10.1016/j.tetlet.2007.05.111

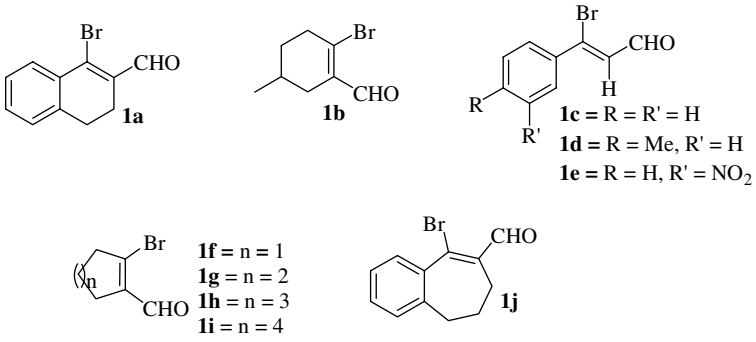

Figure 1. Structures of β-bromovinylaldehydes.

Table 1. Optimization of the reaction conditions for selective arylamination[a]

Entry	Catalyst	Base	Yield (% of **3**)	Yield (% of **4**)
1	$Pd(OAc)_2$	Cs_2CO_3	75	20
2	$Pd(OAc)_2$	Cs_2CO_3	0	60[b]
3	$Pd(PPh_3)_4$	Cs_2CO_3	55	22
4	$PdCl_2$	Cs_2CO_3	10	5
5	$PdCl_2(PPh_3)_4$	Cs_2CO_3	66	25
6	$PdCl_2(PhCN)_2$	Cs_2CO_3	64	23
7	$PdCl_2(MeCN)_2$	Cs_2CO_3	68	25
8	$Pd(dba)_2$	Cs_2CO_3	60	18
9	$Pd_2(dba)_3$	Cs_2CO_3	40	22[b]
10	$Pd_2(dba)_3$	Cs_2CO_3	75	20
11	$Pd_2(dba)_3$	K_2CO_3	80	18
12	$Pd_2(dba)_3$	Na_2CO_3	20	5
13	$Pd_2(dba)_3$	$NaHCO_3$	0	4
14	$Pd_2(dba)_3$	NaH	0	5
15	$Pd_2(dba)_3$	NaOAc	20	5

[a] β-Bromovinylaldehyde **1a** (1 mmol), amine **2a** (1 mmol), Pd catalyst (3 mol %), base (1.4 mmol) and BINAP (4 mol %) at 90 °C for 3–4 h under an argon atmosphere.
[b] (*R*)-(+)-BINAP not added.

(1 mmol) at 90 °C in the presence of a Pd catalyst (3 mol %), base (1.4 mmol) and BINAP (4 mol %) for 3–4 h under an argon atmosphere in toluene to afford **3a** and **4a**. We studied the reaction with various Pd sources as well as the base (Table 1).

Thus, the optimized conditions for reaction between **1a** and **2a** required $Pd_2(dba)_3$ (3 mol %), K_2CO_3 (1.4 mmol), (*R*)-(+)-BINAP (4 mol %) at 90 °C for 3–4 h under an argon atmosphere. Next we used our optimized reaction conditions to investigate the reaction between 1-bromo-3,4-dihydronaphthalene-2-carbaldehyde **1a** and various substituted anilines to extend the scope of this method for polycyclic quinoline synthesis (Table 2).

According to the above observations electron-donating substituents present on aniline increase the reactivity. Thus, 2,5-dimethoxyaniline was found to have greater regioselectivity for **3e**, which was obtained in high yield (Table 2, entry 5).

Thus, when β-bromovinylaldehydes **1a–j** were treated with 2,5-dimethoxyaniline in toluene, in the presence of K_2CO_3 and catalytic amounts of $Pd_2(dba)_3$ and (*R*)-(+)-BINAP at 90 °C for 3–4 h, the aminated products

Table 2. Reaction of **1a** with various substituted anilines **2a–h**[a]

Entry	R	R^1	R^2	Yield (% of **3**)	Yield (% of **4**)
1	H	OMe	H (**2a**)	80	18
2	Me	H	Me (**2b**)	50	30
3	OMe	H	H (**2c**)	70	18
4	Me	H	H (**2d**)	45	24
5	OMe	H	OMe (**2e**)	95	0
6	OH	H	H (**2f**)	14	5
7	H	OH	H (**2g**)	20	8
8	NO_2	H	H (**2h**)	10	2

[a] β-Bromovinylaldehyde **1a** (1 mmol), amine (1 mmol), $Pd_2(dba)_3$ (3 mol %), K_2CO_3 (1.4 mmol) and (*R*)-(+)-BINAP (4 mol %) at 90 °C for 3–4 h under an argon atmosphere.

3a–j were obtained in excellent yields (Table 3, Fig. 2). The aminated products on treatment with trifluoroacetic acid for 10–12 h at room temperature gave the corresponding polycyclic quinolines **5a–j** (Fig. 3) in moderate to good yields. The experimental results are summarized in Tables 3 and 4.

In conclusion we have developed a two-step methodology for the synthesis of various polycyclic quinolines. We found that our method required short reaction times and gave improved yields of products.

2. Typical experimental procedure for palladium-catalyzed amination

A round bottom flask was charged with bromovinylaldehyde (1 mmol), 2,5-dimethoxyaniline (1 mmol),

Table 3. Selective Pd-catalyzed amination of bromovinylaldehydes **1a–j** with 2,5-dimethoxyaniline **2e**

Entry	β-Bromovinylaldehyde	Product[a]	Yield (%)	Time (h)
1	**1a**	**3a**	95	3
2	**1b**	**3b**	89	3
3	**1c**	**3c**	82	4
4	**1d**	**3d**	85	3.5
5	**1e**	**3e**	86	3.5
6	**1f**	**3f**	82	4
7	**1g**	**3g**	88	3
8	**1h**	**3h**	86	3.5
9	**1i**	**3i**	80	3.5
10	**1j**	**3j**	80	4

[a] See Figure 1 for the structures of the aminated products.

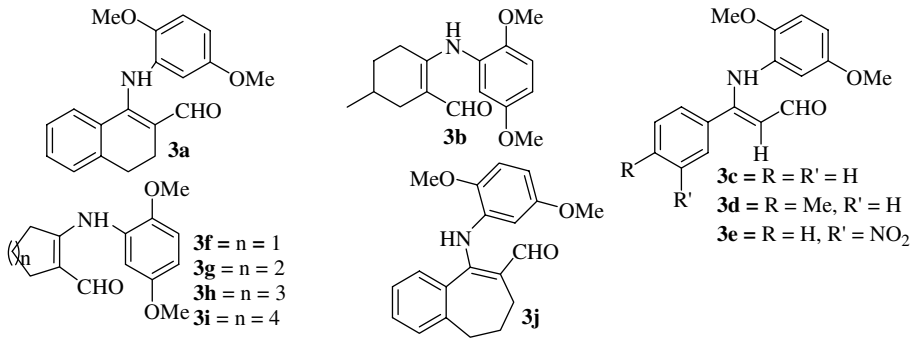

Figure 2. Aminated products **3a**–**j**, produced by selective Pd-catalyzed reactions between bromovinylaldehydes **1a**–**j** and 2,5-dimethoxyaniline **2e**.

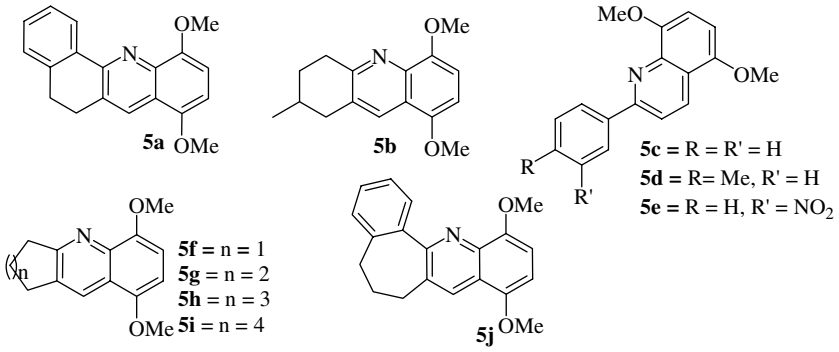

Figure 3. Polycyclic quinolines produced by acid cyclization of **3a**–**j**.

Table 4. Polycyclic quinolines prepared by acid catalyzed cyclization of **3a**–**j** with trifluoroacetic acid

Entry	Product[a]	Yield (%)	Time (h)
1	**5a**[8]	88	10
2	**5b**	85	10
3	**5c**[9]	80	12
4	**5d**	82	10.5
5	**5e**	80	12
6	**5f**[15]	45	12
7	**5g**[7]	85	10
8	**5h**	65	11.5
9	**5i**	60	11.5
10	**5j**	45	12

[a] See Figure 3 for the structures of the acid cyclized products.

K_2CO_3 (1.4 mmol), $Pd_2(dba)_3$ (3 mol %) and (*R*)-(+)-BINAP (4 mol %) in dry toluene (6 mL) under an argon atmosphere. The reaction mixture was heated at 90 °C for 3–4 h and then allowed to cool to room temperature. The reaction mixture was diluted with diethyl ether, washed thoroughly with water, dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure. The crude product was purified by preparative thin layer chromatography.

3. Typical experimental procedure for acid cyclization with trifluoroacetic acid

The aminated product (1 mmol) was placed in a flask, flushed with N_2, then TFA (8–10 mL) was added and the resultant solution was stirred for 10–12 h at room temperature. The solvent was removed under reduced pressure, the residue diluted with water and quenched with solid $NaHCO_3$ and extracted with dichloromethane. The organic layer was dried over Na_2SO_4 and the crude product was purified by preparative thin layer chromatography.

4. Selected spectroscopic data

4.1. Compound 3g

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.55–1.67 (m, 4H), 2.39–2.47 (m, 4H), 3.75 (s, 3H), 3.80 (s, 3H), 6.62–6.71 (m, 2H), 6.79–6.84 (d, 1H, $J = 8.7$ Hz), 9.14 (s, 1H), 12.18 (br s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 21.59, 22.67, 24.34, 27.29, 55.59, 56.19, 103.55, 109.82, 111.94, 112.25, 128.36, 147.16, 153.17, 159.63, 190.18. HRMS: M^++H, found, 262.1435; $C_{15}H_{20}NO_3$ requires M^++H, 262.1443.

4.2. Compound 5g

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.85–2.02 (m, 4H), 2.94–3.00 (t, 2H, $J = 6.2$ Hz), 3.16–3.22 (t, 2H, $J = 6.2$ Hz), 3.93 (s, 3H), 4.00 (s, 3H), 6.62–6.66 (d, 1H, $J = 8.4$ Hz), 6.79–6.83 (d, 1H, $J = 8.4$ Hz), 8.19 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 22.87, 23.15, 29.25, 33.68, 55.77, 55.88, 102.52, 105.53, 120.51, 130.05, 130.73, 138.66, 148.27, 148.82, 158.75. HRMS:

M^++H, found, 244.1347; $C_{15}H_{18}NO_2$ requires M^++H, 244.1338.

Acknowledgements

Financial support from the CSIR (New Delhi) is greatly acknowledged. S.S. is thankful to the UGC (New Delhi) for his fellowship.

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