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An improved synthesis of quinolines from β-bromovinyl aldehydes and primary arylamines in the presence of a palladium catalyst

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β-Bromovinyl aldehydes are effectively cyclized with primary arylamines in DMF at 110 °C in the presence of a catalytic amount of a palladium catalyst to give the corresponding quinolines in high yields.

Keywords: arylamines; β-bromovinyl aldehydes; cyclization; palladium catalyst; quinolines

Introduction

β-Bromovinyl aldehydes are readily prepared from α-methylene ketones via the bromo analog of the Vilsmeier reaction and used as a building block for the construction of versatile cyclic compounds.[1–16] In connection with this report, we recently found that 2-bromobenzaldehyde is carbonylatively cyclized with primary amines in the presence of a palladium catalyst along with a base under carbon monoxide pressure to give isoindol-1-ones.[17] This was discovered during the course of the extension of this carbonylative cyclization protocol to the reaction with β-bromovinyl aldehydes. Namely, when β-bromovinyl aldehydes were treated with primary arylamines under similar conditions, in addition to the expected carbonylatively cyclized hydroisoindol-1-ones, quinolines were produced as minor product.[18] Regarding the formation of quinolines, it is known that β-chlorovinyl aldehydes react with anilines in acetic acid to afford quinolines, **D,** via *N*-arylenaminoimine hydrochloride intermediate, **A**, in low to moderate yields (Scheme 1, route a) and thermolysis of intermediate **A** always shows such a cyclization mode.[19–21] On the other hand, Kirsch *et al*. have reported that β-chlorovinyl aldehydes can undergo a selective amination on their chloro position with anilines without imine formation in the presence of a palladium catalyst along with a base.[22] Based on this result, several groups developed a two-step procedure for the synthesis of quinolines by such a selective palladium-catalyzed arylamination of β-halovinyl aldehydes by arylamines followed by CF_3COOH- and *p*-toluenesulfonic acid-catalyzed cyclization (Scheme 1, route b).[21,23] Imines, **C**, formed from β-halovinyl aldehydes and anilines by tuning the reaction conditions were found to be cyclized to **D** as well as **E** (Scheme 1, route c).[21,22,24,25] Herein this report describes an improved palladium-catalyzed synthesis of quinolines from β-bromovinyl aldehydes and arylamines.

Results and Discussion

The results of several attempted cyclizations of 2-bromocyclohex-1-enecarbaldehyde (**1a**) with aniline (**2a**) under various conditions are listed in Table 1. Treatment of equimolar amount of **1a** and **2a** in DMF in the presence of a catalytic amount of $PdCl_2$ at 110 °C for 10 h afforded 1,2,3,4-tetrahydroacridine (**3a**) in 77% yield as a sole cyclization product (entry 1). The yield of **3a** increased with prolonging the reaction time up to 20 h (entry 2). From the activity of several palladium precursors examined under the employed conditions, all exhibited nearly the same catalytic activity as $PdCl_2$ (entries 3–6). However, performing the reaction in the absence of a palladium catalyst resulted in lower yield of **3a** (entry 7). This result indicates that palladium plays an ancillary role in cyclization. Lower reaction temperature also resulted in lower yield of **3a** (entry 8). When the reaction was carried out with further addition of K_2CO_3, unidentifiable complex mixture was formed without the formation of **3a** (entry 9). Among the solvents examined, DMF was crucial for the formation of **3a**. Performing the reaction in toluene or dioxane scarcely afforded **3a** with incomplete conversion of **1a** (entries 10 and 11).

After the reaction conditions had been established, various β-bromovinyl aldehydes, **1**, were subjected to reaction with anilines, **2**, in order to investigate the reaction scope and several representative results are summarized in Table 2. Cyclic β-bromovinyl aldehyde, **1a**, was readily cyclized with an array of anilines having electron-donating and -withdrawing substituents to give the corresponding quinolines (**3a–j**) in the range of 59–76% yields. The product yield was not significantly affected by the position and electronic nature of the substituent on the aromatic ring of **2a–j**. 2-Bromo-5-methylcyclohex-1-enecarbaldehyde (**1b**) reacts similarly with **2a** to afford 2-methyl-1,2,3,4-tetrahydroacridine (**3k**). To test the effect of the position of formyl group and bromide

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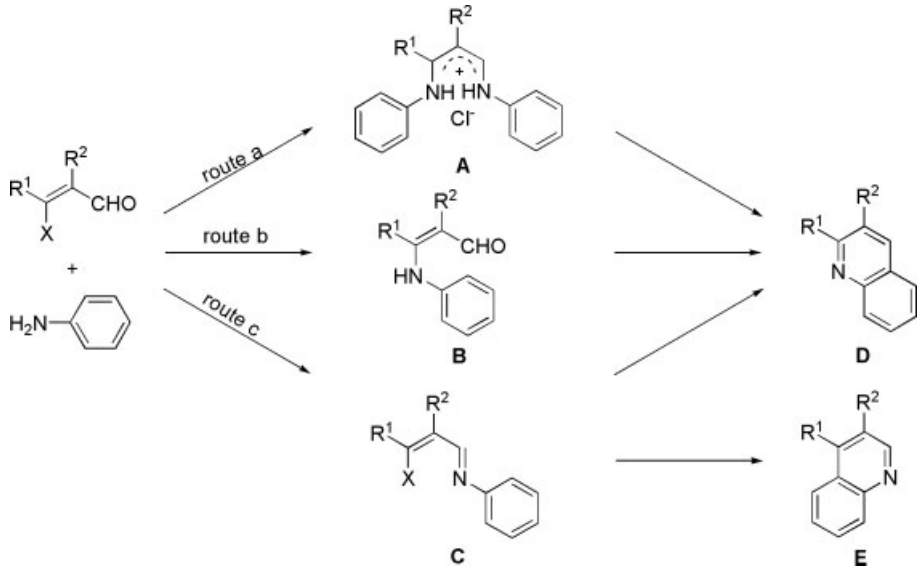
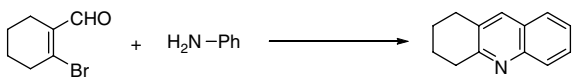


Scheme 1. Synthetic routes for quinolines from β-bromovinyl aldehydes and anilines.

Table 1. Optimization of conditions for the reaction of **1a** with **2a**[a]



1a **2a** **3a**

Entry	Palladium catalyst	Solvent	Temperature (°C)	Time (h)	Yield[b] (%)
1	$PdCl_2$	DMF	110	10	77
2	$PdCl_2$	DMF	110	20	86
3	$PdCl_2(PhCN)_2$	DMF	110	20	81
4	$PdCl_2(PPh_3)_2$	DMF	110	20	81
5	$Pd(OAc)_2$	DMF	110	20	74
6	$PdCl_2/2PPh_3$	DMF	110	20	79
7	–	DMF	110	20	63–66[c]
8	$PdCl_2(PhCN)_2$	DMF	80	20	47
9[d]	$PdCl_2$	DMF	110	20	0
10	$PdCl_2$	Toluene	110	20	0
11	$PdCl_2$	Dioxane	110	20	5

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), palladium catalyst (0.02 mmol), solvent (10 ml), under argon.
[b] GLC yield.
[c] Several runs.
[d] In the presence of K_2CO_3 (1 mmol).

on cyclic β-bromovinyl aldehydes, **1d** and **1e** were employed. Even though the cyclization took place irrespective of the position, higher product yield was observed with **1d**. From the reactions with several cyclic β-bromovinyl aldehydes (**1f**–**h**), the corresponding quinolines were also produced and the product yield was not significantly affected by the ring size of **1f**–**h**. Lower reaction rate and yield were observed with acyclic β-bromovinyl aldehyde **1i**, the product being obtained in only 34% yield. On the other hand, similar treatment of 2-bromobenzaldehyde with **2a** under the employed conditions did not produce acridine at all.

Conclusion

In summary, it has been shown that the cyclization of β-bromovinyl aldehydes with a variety of primary arylamines was accelerated by the addition of a catalytic amount of a palladium catalyst. Although the role of a palladium catalyst is still obscure, it seems to work as a Lewis acid.

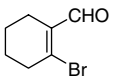
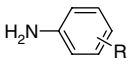
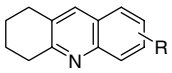
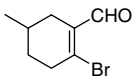
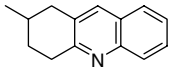
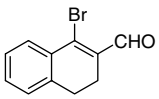
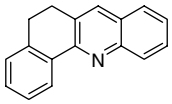
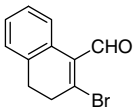
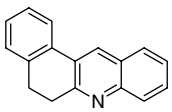
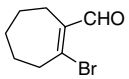
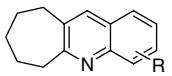
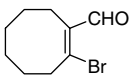
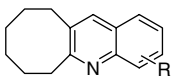
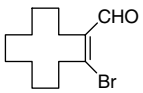
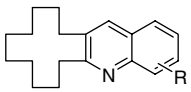
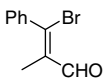
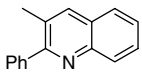
Experimental

^1H and ^{13}C NMR (400 and 100 MHz) spectra were recorded on a Bruker Avance Digital 400 spectrometer using Me_4Si as an internal standard. Melting points were determined on a Standford Research Inc. MPA100 automated melting point apparatus. GLC analyses were carried out with Shimadzu GC-17A equipped with a CBP10-S25-050 column (Shimadzu, a silica fused capillary column, 0.33 mm × 25 m, 0.25 µm film thickness) using N_2 as carrier gas. The isolation of pure products was carried out via thin-layer (silica gel 60 GF_{254}, Merck) chromatography. Commercially available organic and inorganic compounds were used without further purification. β-Bromovinyl aldehydes **1** were synthesized from the corresponding ketones by treatment of PBr_3–DMF–$CHCl_3$.[1]

Typical Experimental Procedure for the Formation of Quinolines 3 from β-Bromovinyl Aldehydes 1 and Anilines 2 in the Presence of a Palladium Catalyst

To an organic reactor were added 2-bromocyclohex-1-enecarbaldehyde (**1a**) (0.095 g, 0.5 mmol), aniline (**2a**) (0.047 g, 0.5 mmol) and $PdCl_2$ (0.0035 g, 0.02 mmol) in DMF (10 ml). After the system was flushed with argon, the reaction mixture was stirred at 110 °C for 20 h. The reaction mixture was filtered through a short silica gel column (ethyl acetate–chloroform mixture) to eliminate black precipitate. To the extract was added an appropriate amount of undecane as internal standard and it was analyzed by GLC. Removal of the solvent left a crude mixture, which was separated by thin-layer chromatography (silica gel, ethyl acetate–hexane mixture) to give 1,2,3,4-tetrahydroacridine (**3a**; 0.070 g, 76%). Except for new compounds (**3e, 3g, 3r**), which were characterized

Table 2. Palladium-catalyzed synthesis of quinolines **3** from **1** and **2**[a]

β-Bromovinyl aldehyde **1**	Aniline **2**	Quinoline **3**	Isolated yield (%)
			
1a	**2a** R = H	**3a**	76
	2b R = 2-Me	**3b**	69
	2c R = 3-Me	**3c**	62
	2d R = 4-Me	**3d**	68
	2e R = 2, 3-$(Me)_2$	**3e**	72
	2f R = 2, 5-$(Me)_2$	**3f**	66
	2g R = 3, 5-$(Me)_2$	**3g**	68
	2h R = 4-OMe	**3h**	59
	2i R = 2, 5-$(OMe)_2$	**3i**	64
	2j R = 4-Cl	**3j**	72
			
1b	**2a**	**3k**	70
			
1d	**2a**	**3l**	86
			
1e	**2a**	**3m**	64
			
1f	**2a**	**3n**	74
	2d	**3o**	75
			
1g	**2a**	**3p**	76
			
1h	**2a**	**3q**	69
	2f	**3r**	70
			
1i	**2a**	**3s**	34

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), $PdCl_2$ (0.02 mmol), DMF (10 ml), 110 °C, for 20 h under Ar.

spectroscopically as shown below, all quinolines were identified by spectroscopic comparision with those in the literature.[26–33]

*5,6-Dimethyl-1,2,3,4-tetrahydroacridine (**3e**)*

Solid; m.p. 117–118 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.84–1.91 (m, 2H, CH_2), 1.94–2.00 (m, 2H, CH_2), 2.46 (s, 3H, CH_3), 2.73 (s, 3H, CH_3), 2.92 (t, J_{HH} = 6.3 Hz, 2H, CH_2), 3.11 (t, J_{HH} = 6.4 Hz, 2H, CH_2), 7.22 (d, J_{HH} = 8.3 Hz, 1H, *CH*), 7.42 (d, J_{HH} = 8.3 Hz, 1H, *CH*), 7.68 (s, 1H, *CH*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.36 (CH_3), 20.81 (CH_3), 23.32 (CH_2), 23.64 (CH_2), 29.22 (CH_2), 34.15 (CH_2), 124.02 (aromatic *C*), 125.65 (aromatic *C*), 128.51 (aromatic *C*), 129.52 (aromatic *C*), 133.51 (aromatic *C*), 135.10 (aromatic *C*), 135.94 (aromatic *C*), 145.94 (aromatic *C*), 158.15 (aromatic *C*). Anal. Calcd for $C_{15}H_{17}N$: C, 85.26; H, 8.11; N, 6.63. Found: C, 85.21; H, 8.06; N, 6.49.

*6,8-Dimethyl-1,2,3,4-tetrahydroacridine (**3g**)*

Solid; m.p. 85–86 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.85–1.92 (m, 2H, CH_2), 1.94–2.01 (m, 2H, CH_2), 2.47 (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 2.96 (t, J_{HH} = 6.2 Hz, 2H, CH_2), 3.09 (t, J_{HH} = 6.6 Hz, 2H, CH_2), 7.09 (s, 1H, *CH*), 7.60 (s, 1H, *CH*), 7.88 (s, 1H, *CH*). ^{13}C NMR (100 MHz, $CDCl_3$) δ

18.67 (CH_3), 21.95 (CH_3), 23.24 (CH_2), 23.51 (CH_2), 29.62 (CH_2), 33.59 (CH_2), 124.71 (aromatic *C*), 125.77 (aromatic *C*), 128.50 (aromatic *C*), 129.63 (aromatic *C*), 131.59 (aromatic *C*), 133.38 (aromatic *C*), 138.25 (aromatic *C*), 147.35 (aromatic *C*), 158.70 (aromatic *C*). Anal. calcd for $C_{15}H_{17}N$: C, 85.26; H, 8.11; N, 6.63. Found: C, 85.38; H, 8.03; N, 6.44.

*6,7,8,9,10,11,12,13,14,15-Decahydro-1,4-dimethylcyclododeca[b]quinoline (**3r**)*

Solid; m.p. 130.9–132.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36–1.58 [m, 12H, -(CH_2)$_6$-], 1.76–1.83 (m, 2H, CH_2), 1.97–2.03 (m, 2H, CH_2), 2.59 (s, 3H, CH_3), 2.74 (s, 3H, CH_3), 2.85 (t, J_{HH} = 7.7 Hz, 2H, CH_2), 3.00 (t, J_{HH} = 7.7 Hz, 2H, CH_2), 7.12 (d, J_{HH} = 7.1 Hz, 1H, *CH*), 7.31 (d, J_{HH} = 7.1 Hz, 1H, *CH*), 8.00 (s, 1H, *CH*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.06 (CH_3), 18.68 (CH_3), 23.43 (CH_2), 23.56 (CH_2), 25.62 (CH_2), 25.78 (CH_2), 26.31 (CH_2), 26.76 (CH_2), 28.36 (CH_2), 30.00 (CH_2), 30.50 (CH_2), 32.53 (CH_2), 125.76 (aromatic *C*), 126.43 (aromatic *C*), 128.06 (aromatic *C*), 131.37 (aromatic *C*), 132.51 (aromatic *C*), 134.02 (aromatic *C*), 134.60 (aromatic *C*), 146.04 (aromatic *C*), 160.84 (aromatic *C*). Anal. Calcd for $C_{21}H_{29}N$: C, 85.37; H, 9.89; N, 4.74. Found: C, 85.39; H, 9.92; N, 4.65.

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