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A new route for isoquinolines catalyzed by palladium

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Abstract

3-Bromopyridine-4-carbaldehyde is tethered with suitably electron withdrawing group substituted alkenes via Heck coupling followed by aldol reaction in dioxane at 150 °C under a catalytic system of $Pd(OAc)_2/PPh_3$/NaOAc to afford the corresponding isoquinolines in good yields.

Keywords: Alkenes; 3-Bromopyridine-4-carbaldehyde; Heck and aldol reactions; Isoquinolines; Palladium catalyst

1. Introduction

It is known that many isoquinoline containing compounds are found in naturally occurring alkaloids. Thus, besides conventional named routes such as Bischler-Napieralski, Pictet-Spengler [1] and Pomeranz-Fritsch syntheses [2], homogeneous palladium-catalyzed synthetic methods have also been developed as alternative methods for the construction of isoquinoline framework because of efficiency of reaction and wide availability of substrates [3–9]. As part of our continuing studies directed towards transition metal-catalyzed cyclization reactions, we recently reported on palladium-catalyzed synthesis of various carbo- and heterocycles [10–16]. Among them, in connection with this report, 2-bromobenzaldehydes [17] and β-bromovinyl aldehydes [18] were found to be aromatized with suitably functionalized alkenes in the presence of a palladium catalyst to afford naphthalenes and benzenes, respectively. This protocol led us to extend to the reaction with 3-bromopyridine-4-carbaldehyde, which is easily prepared from commercial 3-bromopyridine by the known method (Scheme 1) [19]. Herein, we describe a palladium-catalyzed annulation of 3-bromopyridine-4-carbaldehyde with functionalized alkenes leading to isoquinolines via an intrinsic Heck reaction followed by aldol reaction.

2. Experimental

2.1. General

^1H and ^{13}C NMR (400 and 100 MHz) spectra were recorded on a Bruker Avance Digital 400 spectrometer using TMS as an internal standard. Melting points (mp) were determined on a Thomas-Hoover capillary melting point apparatus and were uncorrected. The isolation of pure products was carried out via thin layer chromatography (silica gel 60 GF_{254}, Merck). 3-Bromopyridine-4-carbaldehyde was synthesized by the treatment of 3-bromopyridine with LDA and DMF [19]. Commercially available organic and inorganic compounds were used without further purification. Alkenes **2c**–**2e** [20,21], **2f** [22], **2g** [22], **2h** [23], **2i** [23], **2j** [24] were prepared by the reported methods.

2.2. Typical experimental procedure for palladium-catalyzed synthesis of isoquinolines from 3-bromopyridine-4-carbaldehyde and alkenes

A mixture of 3-bromopyridine-4-carbaldehyde (0.093 g, 0.5 mmol), dimethyl itaconate (0.079 g, 0.5 mmol), $Pd(OAc)_2$ (0.0056 g, 0.025 mmol), PPh_3 (0.013 g, 0.05 mmol) and NaOAc (0.123 g, 1.5 mmol) in dioxane (10 mL) was placed in a 50 mL pressure vessel. After the system was flushed with argon, the reaction mixture was allowed to react at 150 °C for 24 h. The reaction mixture was filtered through a short silica gel column (ethyl acetate–hexane mixture) to eliminate

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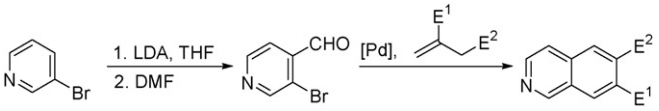


Scheme 1.

inorganic salts. Removal of the solvent left a crude mixture, which was separated by thin layer chromatography (silica gel, ethyl acetate–hexane = 1/1) to give dimethyl isoquinoline-6,7-dicarboxylate (0.082 g, 67%). All products prepared by the above procedure were characterized spectroscopically as shown below.

Dimethyl isoquinoline-6,7-dicarboxylate (**3a**): solid; mp 87–88 °C (hexane–chloroform); ^{1}H NMR ($CDCl_3$) δ 3.98 (s, 6H), 7.74 (d, J = 6.0 Hz, 1H), 8.17 (s, 1H), 8.46 (s, 1H), 8.69 (d, J = 6.0 Hz, 1H), 9.37 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 53.30, 53.40, 121.09, 128.40, 128.53, 129.77, 130.59, 133.79, 136.55, 146.11, 153.57, 167.22, 168.13. Anal. Calcd for $C_{13}H_{11}NO_4$: C 63.67; H 4.52; N 5.71. Found: C 63.69; H 4.48; N 5.82.

Diethyl isoquinoline-6,7-dicarboxylate (**3b**): solid; mp 64–65 °C (hexane–chloroform); ^{1}H NMR ($CDCl_3$) δ 1.42 (t, J = 7.0 Hz, 3H), 1.43 (t, J = 7.0 Hz, 3H), 4.44 (q, J = 7.0 Hz, 2H), 4.45 (q, J = 7.0 Hz, 2H), 7.74 (d, J = 5.5 Hz, 1H), 8.16 (s, 1H), 8.46 (s, 1H), 8.69 (d, J = 5.5 Hz, 1H), 9.37 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.51, 14.56, 62.40, 62.51, 121.09, 128.37, 128.41, 130.17, 130.44, 134.15, 136.49, 145.99, 153.55, 166.83, 167.72. Anal. Calcd for $C_{15}H_{15}NO_4$: C 65.92; H 5.53; N 5.13. Found: C 65.72; H 5.56; N 5.01.

7-Ethyl 6-methyl isoquinoline-6,7-dicarboxylate (**3c**): solid; mp 93–94 °C (hexane–chloroform); ^{1}H NMR ($CDCl_3$) δ 1.35 (t, J = 7.0 Hz, 3H), 3.90 (s, 3H), 4.36 (q, J = 7.0 Hz, 2H), 7.70 (d, J = 5.5 Hz, 1H), 8.09 (s, 1H), 8.42 (s, 1H), 8.62 (d, J = 5.5 Hz, 1H), 9.33 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.57, 53.40, 62.52, 121.39, 128.33, 128.45, 130.21, 130.68, 134.18, 136.67, 145.33, 153.19, 166.64, 168.15. Anal. Calcd for $C_{14}H_{13}NO_4$: C 64.86; H 5.05; N 5.40. Found: C 64.76; H 4.95; N 5.21.

7-Cyclohexyl 6-methyl isoquinoline-6,7-dicarboxylate (**3d**): oil; ^{1}H NMR ($CDCl_3$) δ 1.29–1.35 (m, 1H), 1.41–1.49 (m, 2H), 1.54–1.63 (m, 3H), 1.80–1.83 (m, 2H), 2.02–2.05 (m, 2H), 3.98 (s, 3H), 5.04–5.10 (m, 1H), 7.74 (d, J = 5.5 Hz, 1H), 8.15 (s, 1H), 8.46 (s, 1H), 8.69 (d, J = 5.5 Hz, 1H), 9.38 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 24.22, 25.70, 31.95, 53.37, 75.12, 121.07, 123.44, 128.36, 130.45, 133.90, 136.43, 145.93, 145.96, 153.56, 166.20, 168.29.

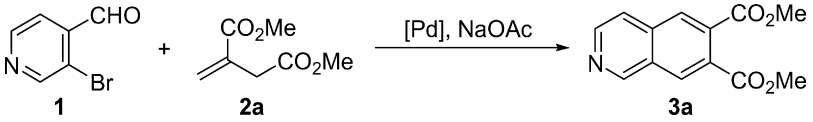
6-Methyl 7-phenyl isoquinoline-6,7-dicarboxylate (**3e**): solid; mp 96–97 °C (hexane–chloroform); ^{1}H NMR ($CDCl_3$) δ 3.99 (s, 3H), 7.29–7.33 (m, 3H), 7.45–7.49 (m, 2H), 7.79 (d, J = 5.5 Hz, 1H), 8.26 (s, 1H), 8.64 (s, 1H), 8.74 (d, J = 5.5 Hz, 1H), 9.44 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 53.64, 121.22, 121.79, 126.72, 128.40, 128.97, 129.40, 130.07, 131.22, 133.61, 136.74, 146.39, 151.12, 153.69, 165.52, 167.86. Anal. Calcd for $C_{18}H_{13}NO_4$: C 70.35; H 4.26; N 4.56. Found: C 70.05; H 4.25; N 4.50.

Ethyl 7-acetylisoquinoline-6-carboxylate (**3f**): solid; mp 100–101 °C (hexane–chloroform); ^{1}H NMR ($CDCl_3$) δ 1.43 (t, J = 7.0 Hz, 3H), 2.69 (s, 3H), 4.44 (q, J = 7.0 Hz, 2H), 7.76 (d, J = 5.5 Hz, 1H), 8.16 (s, 1H), 8.27 (s, 1H), 8.69 (d, J = 5.5 Hz, 1H), 9.37 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.44, 29.71, 62.61, 121.25, 127.79, 128.66, 129.45, 132.33, 136.16, 139.53, 145.88, 153.36, 167.42, 200.89. Anal. Calcd for $C_{14}H_{13}NO_3$: C 69.12; H 5.39; N 5.76. Found: C 69.06; H 5.61; N 5.41.

Ethyl 7-benzoylisoquinoline-6-carboxylate (**3g**): solid; mp 98–99 °C (hexane–chloroform); ^{1}H NMR ($CDCl_3$) δ 1.14 (t, J = 7.0 Hz, 3H), 4.17 (q, J = 7.0 Hz, 2H), 7.47 (t, J = 7.5 Hz, 2H), 7.60 (t, J = 7.5 Hz, 1H), 7.81–7.84 (m, 3H), 8.06 (s, 1H), 8.56 (s, 1H), 8.72 (d, J = 5.5 Hz, 1H), 9.36 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.07, 62.49, 121.43, 128.32, 129.03, 129.98, 130.42, 132.10, 133.77, 135.70, 137.43, 139.29, 145.52, 153.28, 166.02, 196.11. Anal. Calcd for $C_{19}H_{15}NO_3$: C 74.74; H 4.95; N 4.59. Found: C 74.50; H 4.96; N 4.45.

Phenyl isoquinoline-6-carboxylate (**3h**): solid; mp 135–136 °C (hexane–chloroform); ^{1}H NMR ($CDCl_3$) δ 7.26–7.33 (m, 3H), 7.45–7.49 (m, 2H), 7.81 (d, J = 5.5 Hz, 1H), 8.10 (d, J = 8.5 Hz, 1H), 8.33 (d, J = 8.5 Hz, 1H), 8.65 (d, J = 5.5 Hz, 1H), 8.76 (s, 1H), 9.38 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 121.81, 122.00, 126.61, 127.36, 128.58, 130.04, 130.60, 131.35, 135.40, 144.48, 151.17, 153.01, 164.97.

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



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

Run	Pd catalysts	Solvents (mL)	Temperature (°C)	Time (h)	Yield[a] (%)
1	$Pd(OAc)_2/2PPh_3$	THF (5)	100	20	9
2	$Pd(dba)_2/2PPh_3$	THF (5)	100	20	4
3	$Pd(OAc)_2$/dppf	THF (5)	100	20	8
4	$Pd(OAc)_2/2PPh_3$	THF (5)	125	20	16
5	$Pd(OAc)_2/2PPh_3$	THF (10)	150	24	59
6[b]	$Pd(OAc)_2/2PPh_3$	THF (10)	150	24	65
7	$Pd(OAc)_2/2PPh_3$	Dioxane (10)	150	24	67

Reaction conditions: **1** (0.5 mmol), **2a** (0.5 mmol), $Pd(OAc)_2$ (0.025 mmol), NaOAc (1.5 mmol).
[a] Isolated yield.
[b] [**2a**]/[**1**] = 2.0.

Cyclohexyl isoquinoline-6-carboxylate (**3i**): solid; mp 71–72 °C (hexane–chloroform); ^{1}H NMR ($CDCl_3$) δ 1.33–1.42 (m, 1H), 1.44–1.53 (m, 2H), 1.59–1.70 (m, 3H), 1.82–1.85 (m, 2H), 1.99–2.04 (m, 2H), 5.08–5.14 (m, 1H), 7.77 (d, J = 5.5 Hz, 1H), 8.03 (d, J = 8.5 Hz, 1H), 8.21 (dd, J = 1.5 and 8.5 Hz, 1H), 8.59 (s, 1H), 8.62 (d, J = 5.5 Hz, 1H), 9.34 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 24.11, 25.80, 32.03, 74.30, 121.78, 127.24, 128.21, 129.55, 130.34, 132.77, 135.41, 144.14, 152.90, 165.71. Anal. Calcd for $C_{16}H_{17}NO_2$: C 75.27; H 6.71; N 5.49. Found: C 74.96; H 6.95; N 5.43.

6-(Phenylsulfonyl)isoquinoline (**3j**): solid; mp 179–180 °C (hexane–chloroform); ^{1}H NMR ($CDCl_3$) δ 7.52–7.56 (m, 2H), 7.59–7.63 (m, 1H), 7.80 (d, J = 5.5 Hz, 1H), 7.99–8.03 (m, 3H), 8.09 (d, J = 8.5 Hz, 1H), 8.57 (s, 1H), 8.68 (d, J = 5.5 Hz, 1H), 9.34 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 121.74, 124.66, 127.84, 128.36, 129.77, 129.92, 129.95, 134.13, 135.28, 141.03, 143.39, 145.17, 153.00. Anal. Calcd for $C_{15}H_{11}NO_2S$: C 66.89; H 4.12; N 5.20. Found: C 66.53; H 4.33; N 5.05.

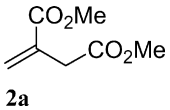
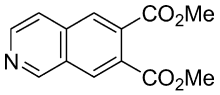
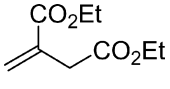
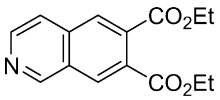
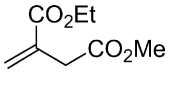
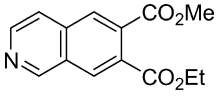
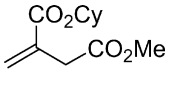
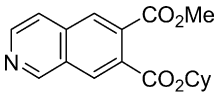
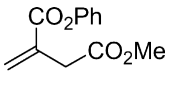
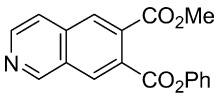
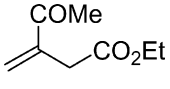
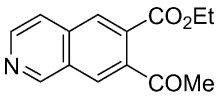
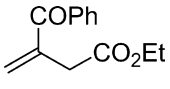
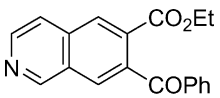
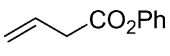
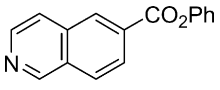
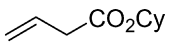
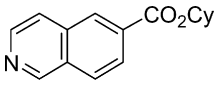
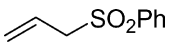
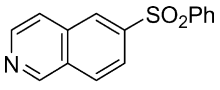
3. Results and discussion

Based on a similar catalytic system for the synthesis of benzenes and naphthalenes from β-bromovinyl aldehydes and 2-bromobenzaldehydes [17,18], respectively, with functionalized alkenes, the results of several attempted annulation of **1** with dimethyl itaconate (**2a**) are listed in Table 1. Treatment of equimolar amounts of **1** and **2a** in THF in the presence of a catalytic amount of $Pd(OAc)_2$ (5 mol%) and PPh_3 (10 mol%) along with NaOAc at 100 °C for 20 h afforded dimethyl isoquinoline-6,7-dicarboxylate (**3a**) in only 9% yield (run 1). The catalytic systems using $Pd(dba)_2$ combined with PPh_3 and $Pd(OAc)_2$ combined with 1,1′-bis(diphenylphosphino)ferrocene (dppf) were also revealed to be as ineffective as that using $Pd(OAc)_2$ combined with PPh_3 (runs 2 and 3). The reaction temperature was critical for the effective formation of **3a**. When the reaction was carried out at 150 °C along with dilution, the reaction rate was remarkably enhanced toward **3a** (run 5). However, performing the reaction under the molar ratio of [**2a**]/[**1a**] = 2.0 did not show any significant change of the yield of **3a** under the employed conditions (run 6). As a result, the best result in terms of both yield and complete conversion of **1a** is accomplished by the standard set of reaction conditions shown in run 7 of Table 1.

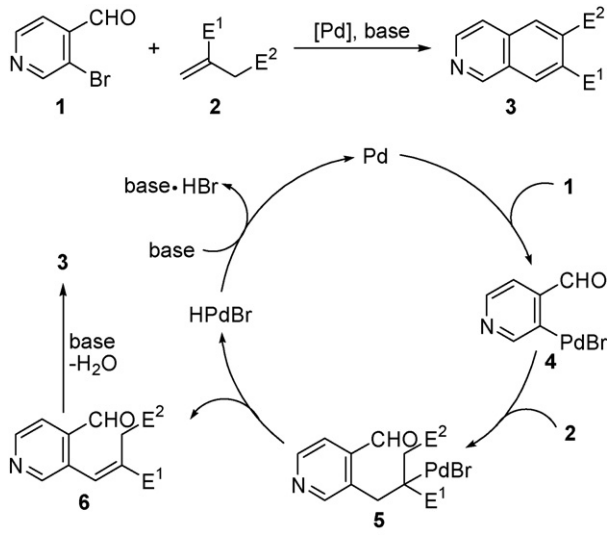
Having optimized reaction conditions, various suitably electron withdrawing group substituted alkenes (**2**) were subjected to react with **1** in order to investigate the reaction scope and several representative results are summarized in Table 2. With dialkyl itaconates (**2a**–**2c**), alkyl 3-butenoates, which have carboalkoxy substituents at position 3, the tethered aromatized products (**3a**–**3c**) were formed in the range of 67–78% yields without any identifiable side product. The reaction proceeds likewise with methyl 3-butenoate (**2d**) having bulky carbocyclohexyloxy group at position 3 to give the corresponding isoquinoline (**3d**) in a similar yield. Methyl 3-butenoate (**2e**) having carbophenoxy group at position 3 was also readily aromatized with **1** to give 6-methyl 7-phenyl isoquinoline-6,7-dicarboxylate (**3e**) in 52% yield. The reaction of ethyl 3-butenoates (**2f** and **2g**), which have acyl group at position 3, with **1** also proceed to give the corresponding isoquinolines and the product yield was not significantly changed when compared to the reaction with dialkyl itaconates. From the reactions between **1** and butenoates (**2h** and **2i**) having no substituent at position 3, the corresponding isoquinolines (**3h** and **3i**) were also produced in good yields. Allyl phenyl sulfone (**2j**) was similarly coupled and cyclized with **1** to afford 6-(phenylsulfonyl)isoquinoline (**3j**) in 70% yield.

The present reaction, consistent with the product formed, seems to proceed via a pathway shown in Scheme 2. Oxida-

Table 2
Palladium-catalyzed synthesis of isoquinolines (**3**)

Alkenes (**2**)	Isoquinolines (**3**)	Yield (%)
 **2a**	 **3a**	67
 **2b**	 **3b**	78
 **2c**	 **3c**	77
 **2d**	 **3d**	60
 **2e**	 **3e**	52
 **2f**	 **3f**	62
 **2g**	 **3g**	50
 **2h**	 **3h**	57
 **2i**	 **3i**	52
 **2j**	 **3j**	70

Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), $Pd(OAc)_2$ (0.025 mmol), PPh_3 (0.05 mmol), NaOAc (1.5 mmol), dioxane (10 mL), 150 °C, 24 h.



Scheme 2.

tive addition of a carbon-bromide bond of **1** to palladium(0) produces an arylpalladium(II) intermediate **4**, which is followed by the insertion of an olefinic double bond of alkene (**2**) into a carbon-palladium bond of **4** to give an alkylpalladium species **5**. Subsequent β-hydrogen elimination of **5** produces a Heck product **6**, which triggers an intramolecular aldol reaction to give isoquinoline (**3**).

4. Conclusion

In summary, it has been shown that 3-bromopyridine-4-carbaldehyde undergoes tethering with suitably electron withdrawing group substituted alkenes via Heck coupling followed by aldol reaction in the presence of a catalytic amount of a palladium catalyst to afford isoquinolines in good yields. The present reaction provides a new route for isoquinolines and further elaborated synthetic application using this protocol is currently under investigation.

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