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An effective BINAP and microwave accelerated palladium-catalyzed amination of 1-chloroisoquinolines in the synthesis of new 1,3-disubstituted isoquinolines

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ABSTRACT

A facile and microwave accelerated reaction of 1-chloro-3-(4-chlorophenyl)isoquinoline with various heterocyclic amines, catalyzed by Pd, in the presence of BINAP additive and sodium carbonate as the base, leads to the formation of 3-(4-chlorophenyl)-1-(1*H*-1,2,3-triazol-1-yl)isoquinoline, 3-(4-chlorophenyl)-1-(1*H*-imidazol-1-yl)isoquinoline and 3-(4-chlorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)isoquinoline via Buchwald protocol in good yields. Similarly pyrazolylisoquinolines are also reported.

1. Introduction

The Pd-catalyzed cross-coupling methods have been utilised exponentially over the years for the construction of C–C, C–N, and C–O bonds.[1] As coupling protocols of mild and chemoselective conditions are very desirable for the preparation of compounds with highly functionalized and complex molecular structures, this methodology was applied for preparing new drug candidates on a small scale as well as for manufacturing on a commercial scale by pharmaceutical companies.[2] Similarly, a widely used and preferred tool for accelerating reactions namely microwave irradiation (MWI) has been applied to organic reactions,[3] in the absence of a solvent or in the presence of a solid support, such as clays, alumina and silica, resulting in shorter reaction times and higher product yields than those obtained by using conventional heating. Disubstituted isoquinolines are endowed with an extensive range of biological activities.[4] They have emerged as potent non-nucleoside inhibitors of HIV-1 reverse transcriptase,[5] and specific inhibitors of the NS5B polymerase of the hepatitis C virus (HCV).[6] Appropriately functionalized disubstituted isoquinolines are used as agonists against gamma amino butyric acid A receptor (GABAA).[7] Moreover, they display potent thrombin inhibitory activity and antibacterial activity against Gram-positive bacteria.[8]

A number of methods have been developed for the synthesis of disubstituted isoquinolines including palladium-catalyzed cross-coupling of *N*-*tert*-butyl-2-(1-alkynyl)benzaldimines and aryl, allylic, benzylic, alkynyl halides, as well as a vinylic halide,[9] Disubstituted isoquinolines were prepared under mild conditions from allylbenzenes and nitriles using silver trifluoromethanesulfonate and iodine.[10] Silver-assisted reaction of β-arylvinyl bromides and the photolysis in nitriles gave isoquinoline derivatives, indicating that the Ritter reaction involving a vinyl cation took place.[11] 3-aryl 4-(1-alkenyl)isoquinolines have been prepared by the Pd(II)-catalyzed cyclization of 2-(1-alkynyl)benzaldimines, followed by alkenylation (Heck reaction) in good to excellent yields. But one of the major limitations of these methodologies is that they gave poor yields.

These applications of Pd catalysis, microwave enhancement and disubstituted isoquinolines and continued interest of our research on Pd catalysis, microwave-assisted reactions, C–C and C–N bond formations,[12–19] prompted us to develop a simple and facile MW accelerated synthesis of 1,3-disubstituted isoquinolines using bis-(dibenzylideneacetone)palladium(0) catalyst by Buchwald coupling of 1-chloroisoquinoline and heterocyclic amines.

2. Results and discussion

In this Letter, we report the reaction of 1-chloroisoquinoline derivative, **1** with various nitrogenous heterocyclic amine, **2** in 1,4-dioxane and in the presence of bis-(dibenzylidene acetone)

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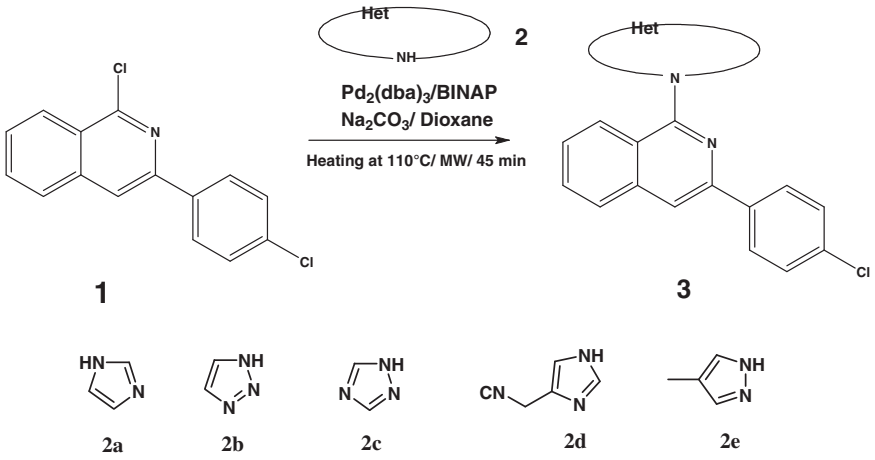
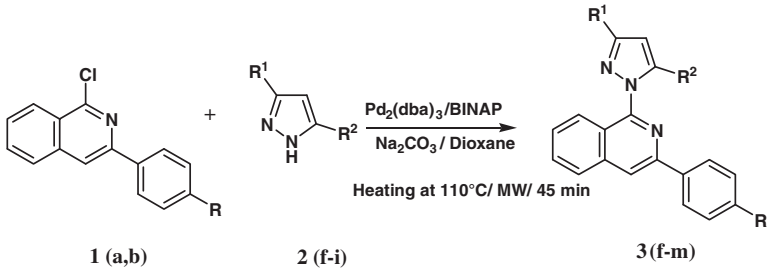


Scheme 1. Synthesis of 1,3-disubstituted isoquinolines.



Scheme 2. Synthesis of pyrazolylisoquinolines compounds.

Table 1
Amination of 1-chloro-3-(4-chlorophenyl)isoquinoline, **1** with various heterocyclic amines[a]

Entry	Amines, **2**	Time in min	Yield%
1	**2a**	45	90
2	**2b**	45	85
3	**2c**	45	83
4	**2e**	45	95
5	**2d**	65	80

[a] Reaction conditions: **1** (1 mmol), **2** (1 mmol), base (3 mmol), Pd (0.05 equiv), BINAP (0.5 equiv) at MW watts 155–160 W, 110 °C.

palladium(0) catalyst, *rac*-BINAP, and sodium carbonate at 110 °C.[20] The 1,3-disubstituted isoquinolines **3a–m** was obtained in moderate to high yields (Schemes 1 and 2, Tables 1 and 4). The reactions were carried out under argon atmosphere.

Optimization of the reaction conditions was done by choosing the reaction of 1-chloroisoquinoline, **1** with imidazole, **2a** as model reaction. Initially, several bases were screened for the reaction in the presence of a catalytic amount of bis-(dibenzylideneacetone)palladium(0) catalyst. As shown in Table 2, the reaction is significantly influenced by the nature of the base employed. The reaction works very well in most common inexpensive bases such as alkali carbonate (Table 2, entries 2–4), with best results being in the case of sodium carbonate (Table 2, entry 2). However the most common Pd/phosphine reaction bases like Cs_2CO_3, KF were found to be least effective.

The influence of the amounts of chelating ligand BINAP, and the catalyst were investigated using the reactions of compound **1** with **2a**. The results are shown in Table 3. Increasing the amount of the palladium catalyst could shorten the reaction time but does not increase the yield (entries 10 and 11). Low palladium concentration often prolonged the reaction time and decreased the yield (entry 1). The use of BINAP is also critical for the success of the reaction, without which, the yield dropped from 90% to 30% (Table 3, com-

Table 2
Effect of base on coupling of compound, **1** with imidazole, **2a**

Entry	Base	Time in min	Yield%
1	KOH	60	20
2	Na_2CO_3	60	90
3	K_2CO_3	60	62
4	CS_2CO_3	60	68
5	Et_3N	60	25
6	DIEA	60	38
7	Pyrrolidine	60	27
8	Piperidine	60	23
9	KF	60	52

Reaction conditions: **1** (1 mmol), **2** (1 mmol), base (3 mmol), Pd (0.05 equiv), BINAP (0.5 equiv) at MW watts 155–160 W, 110 °C.

Table 3
Effect of BINAP and Pd catalyst on coupling of compound, **1** with imidazole, **2a**

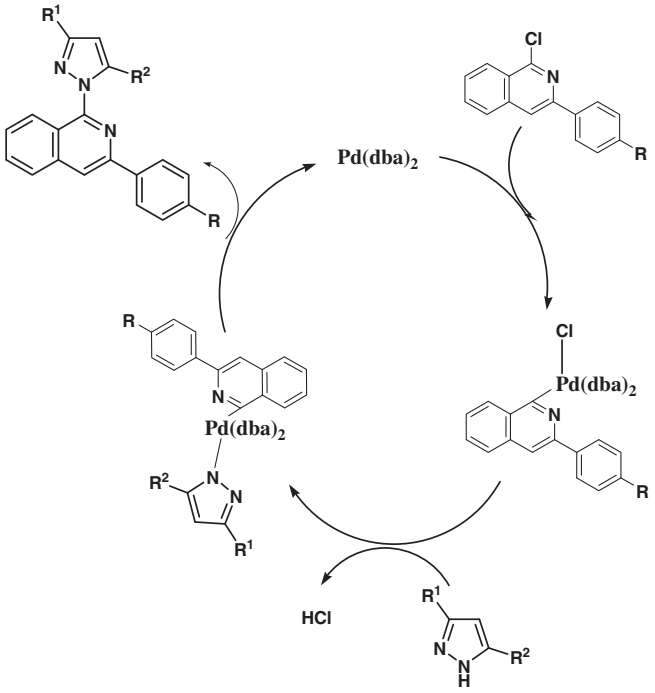
Entry	Additive/catalyst	Time in min	Yield%
1	Nil	60	NR
2	BINAP (0.5 equiv)	60	NR
3	Pd (0.05 equiv)	60	30
4	BINAP (0.1 equiv)/Pd (0.05 equiv)	60	54
5	BINAP (0.3 equiv)/Pd (0.05 equiv)	60	73
6	BINAP (0.5 equiv)/Pd (0.05 equiv)	60	90
7	BINAP (0.7 equiv)/Pd (0.05 equiv)	60	25
8	BINAP (0.5 equiv)/Pd (0.01 equiv)	60	38
9	BINAP (0.5 equiv)/Pd (0.03 equiv)	60	52
10	BINAP (0.5 equiv)/Pd (0.07 equiv)	60	65
11	BINAP (0.5 equiv)/Pd (0.07 equiv)	45	66

Reaction conditions: **1** (1 mmol), **2** (1 mmol), base (3 mmol), at MW watts 155–160 W, 110 °C.

Table 4
Pyrazolylisoquinolines, **3f–m**

Sl. No.	Substrate **1**, **2** and product **3**				Yield[a] %
	Entry	R	R^1	R^2	
1	**3f**	H	CH_3	CH_3	80
2	**3g**	H	Ph	Ph	82
3	**3h**	H	CH_3	Ph	85
4	**3i**	H	C_2H_5	C_2H_5	76
5	**3j**	Cl	CH_3	CH_3	83
6	**3k**	Cl	Ph	Ph	87
7	**3l**	Cl	CH_3	Ph	85
8	**3m**	Cl	C_2H_5	C_2H_5	83

[a] Isolated product yield, characterized by spectral techniques.



Scheme 3. Mechanism of the reaction.

pare entries 3 and 6). The addition of chelating ligand racemic-BINAP is significant in modification of yields, moreover, addition of 0.5 equiv for 0.05 equiv Pd catalyst is essential for the reaction and any excess of BINAP did not modify the yields under our experimental conditions. An investigation of the influence of solvents on coupling reaction was carried out with a range of solvent systems and it was observed that dioxane gave near quantitative yield within 1 h. It is worth to mention the Buchwald coupling reaction when carried out under conventional method under same optimized condition required 6–7 h however with a low yield 57%.

Subsequently, the reaction of a variety of heterocyclic amines, **2a–e** and 1-chloroisoquinoline derivative, **1** were studied under optimised conditions (Table 1). Similarly under optimised conditions, various pyrazoles were reacted with the 1-chloroisoquinoline derivative to give the pyrazolylisoquinolines **3f–m** (Table 4). The plausible mechanism for the reaction is depicted below (Scheme 3).

3. Conclusion

In conclusion, we have developed a successful microwave irradiated palladium-catalyzed reaction for the synthesis of various 1,3-disubstituted isoquinolines in the presence of BINAP and sodium carbonate as the base in 1,4-dioxane.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.06.045.

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20. *General procedure for the synthesis of 1,3-disubstituted isoquinolines:* A mixture of the 1-chloroisoquinoline (1 mmol), Pd catalyst (0.05 equiv), BINAP (0.5 equiv), and sodium carbonate (3 mmol) was stirred in dioxane (5 mL) at 60 °C for 2 min under argon atmosphere. Different heterocyclic amines were then added, and the mixture was microwave irradiated at 110 °C for 1 h. After completion of the reaction, the resulting solution was concentrated in vacuo, and the crude product was subjected to silica-gel column chromatography using $CHCl_3$–CH_3OH (95:5) as eluent to afford the pure product (Table 1). The compounds were conformed by FT-IR, ^1H NMR, ^{13}C NMR and MS techniques.[21]
21. The analysis data of **3a**, **3b**, **3f** and **3g** are given below and for the data of the **3c–e**, **3h–m** see Supplementary data.
3-(4-Chlorophenyl)-1-(1H-imidazol-1-yl)isoquinoline (**3a**): Yellow solid, mp 138.5–138.8 °C, ^1H NMR (400 MHz, $CDCl_3$): δ 8.49 (br s, 1H), 8.19 (br s, 1H), 8.12–8.09 (d, J = 8.6 Hz, 2H), 8.01–8.05 (m, 2H), 7.83–7.85 (t, J = 7.6 Hz, 1H), 7.51–7.48 (d, J = 8.6 Hz, 2H), 7.48 (br s, 1H), ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.0, 135.9, 135.0, 131.6, 129.1, 128.9, 128.0, 127.8, 123.7, 117.2, IR (ν cm^{-1}), 3069, 2921, 2852, 2186, 2118, 1662, 1624, 1593, 1567, 1488, 1437, 1400, 1350, 1322, 1290, 1245, 1145, 1109, 1101, 1091, 1034, 1012, 954, 905, 858, 822, 737, 677, 652, 520, 454, LC–MS: m/e 306.2, $C_{18}H_{12}ClN_3$.
3-(4-Chlorophenyl)-1-(1H-1,2,3-triazol-1-yl)isoquinoline (**3b**): Yellow solid, mp 120–121 °C, ^1H NMR (400 MHz, $CDCl_3$): δ 8.44–8.42 (d, J = 8.5 Hz, 1H), 8.20 (br s, 1H), 8.16–8.14 (d, J = 8.4 Hz, 2H), 8.075 (br s, 2H), 8.00–7.98 (d, J = 8.2 Hz, 1H), 7.80–7.76 (t, J = 7.2 Hz, 1H), 7.68–7.64 (t, J = 7.7 Hz, 1H), 7.49–7.47 (d, J = 8.4 Hz, 2H), ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.2, 139.6, 136.6, 136.2, 135.1, 131.2, 129.0, 128.5, 128.3, 127.3, 125.9, 121.4, 117.9.; IR (ν cm^{-1}), 3131, 3121, 3058, 2955, 2919, 2851, 1624, 1591, 1569, 1495, 1443, 1404, 1346, 1259, 1146, 1089, 1003, 959, 946, 881, 836, 808, 744, 716, 674, 650, 590, 516, 476, 453, LC–MS: m/e 307.2, $C_{17}H_{11}ClN_4$.
1-(3,5-Dimethyl-1H-pyrazol-1-yl)-3-phenylisoquinoline (**3f**): Colorless solid, mp 170 °C, ^1H NMR (400 MHz, DMSO-d_6) 8.52 (s, 1H), 8.19–8.17 (m, 2H), 8.11–8.06 (m, 2H), 7.83–7.79 (m, 1H), 7.66–7.62 (m, 1H), 7.52–7.49 (m, 2H), 7.44–7.40 (m, 1H), 6.21 (s, 1H), 2.35 (s, 3H, -CH_3), 2.24 (s, 3H, -CH_3), ^{13}C NMR (100 MHz, DMSO-d_6) 150.07 (–C=N, isoquinoline ring), 149.0 (C=C–C_6H_5), 148.0 (–N–N=C–CH_3), 141.9 (–C=C–CH_3), 139.6, 138.3, 131.6, 129.4, 2 × 129.4, 2 × 128.5, 127.8, 126.8, 126.8, 122.9, 117.0, 107.7 (–C=C–CH_3), 13.9 (–CH_3), 13.55 (–CH_3), IR (ν cm^{-1}) 3050, 2922, 1623, 1589, 1566, 1488, 1463, 1439, 956, 883, 764, 695, LC–MS: m/e 300.0; $C_{20}H_{17}N_3$; Mol. Wt.: 299.37; Calculated: C, 80.24; H, 5.72; N, 14.04. Found: C, 79.98; H, 5.30; N, 14.01.
3-Phenyl-1-(3,5-diphenyl-1H-pyrazol-1-yl)isoquinoline (**3g**): Colorless solid, mp 120 °C, ^1H NMR (400 MHz, DMSO-d_6): 8.57 (s, 1H), 8.18–8.16 (d, J = 8.3 Hz, 1H), 8.08–8.08 (d, J = 8.4 Hz, 1H), 7.99–7.97 (t, 2H), 7.89–7.85 (t, 1H), 7.80–7.77 (m, 2H), 7.73–7.69 (t, 1H), 7.50–7.46 (m, 2H), 7.40–7.37 (m, 5H), 7.27–7.24 (m, 5H).

^{13}C NMR (100 MHz, DMSO-d_6): 152.2 (–*C*═N, isoquinoline ring), 150.2 (C═*C*–C_6H_5), 148.3 (–N–*N*═*C*–C_6H_5), 147.2 (–C═*C*–C_6H_5), 139.6, 138.0, 132.9, 131.9, 130.7, 2 × 129.4, 2 × 129.3, 2 × 129.2, 2 × 128.9, 2 × 128.8, 2 × 128.7, 2 × 128.3, 2 × 128.1, 126.8, 126.1, 125.7, 123.3, 117.9, 105.3 (–*C*═C–CH_3), IR (ν cm^{-1}) 3057, 2922, 1624, 1572, 1492, 1405, 980, 884, 775, 692; LC–MS: *m*/*e* 424.2; $C_{30}H_{21}N_3$, Mol. Wt.: 423.51; Calculated: C, 85.08; H, 5.00; N, 9.92. Found: C, 85.02; H, 4.93; N, 9.84.