Pergamon

Tetrahedron Letters 43 (2002) 7267–7270

TETRAHEDRON
LETTERS

The successive substitution of halogens in 4-chloro-6-iodoquinoline by aryl groups in cross-coupling reactions with arylboronic acids

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Received 22 May 2002; revised 12 July 2002; accepted 19 July 2002

Abstract—The conditions for selective stepwise substitution of iodine and chlorine atoms in 4-chloro-6-iodoquinoline which allow the synthesis of the corresponding diarylquinolines with different aryl groups in the 4- and 6-positions, in a one-pot procedure, in high yields are reported. A significant effect of the addition of water or Bu_4NBr on the rate and yield of both stages was discovered. © 2002 Elsevier Science Ltd. All rights reserved.

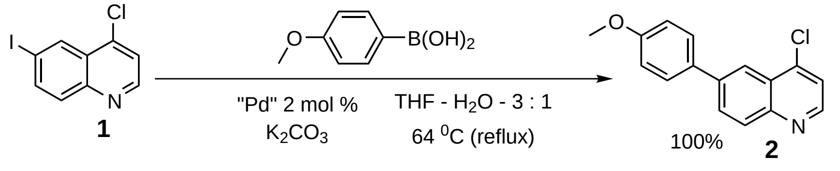
Over the past 5 years the elaboration of strategies for regioselective Pd-catalyzed C–C bond forming reactions in dihaloheteroarenes has attracted considerable attention.[1] We used 4-chloro-6-iodoquinoline **1**[2] as a model compound for the study of selective cross-coupling reactions as polysubstituted quinolines are known to possess versatile biological activity.[3] A priori it was difficult to predict how different the reactivity of the two C_{sp^2}–Hal bonds in **1** would be during Suzuki-coupling, taking into consideration that the C–Cl bond in the pyridine ring is activated. The search for a catalyst was performed in the reaction of **1** with 4-anisylboronic acid in the ratio 1:1 in THF–H_2O (3:1) using K_2CO_3 as a base. In all cases we observed only iodine replacement.

The best results were obtained either with phosphine-free catalyst precursor $Pd(OAc)_2$ or $PdCl_2(dppf)$ (Scheme 1). The structure and purity of the isolated product **2** was proved by ^1H NMR spectroscopy and elemental analysis.

On the contrary for the second step, substitution of chlorine (Scheme 2), the best result was achieved with $Pd(PPh_3)_4$ as the catalyst. After 48 h, the yield of diaryl substituted product was 82%. Other Pd catalysts showed unsatisfactory results.

We have found that the two-step reaction can be performed in a one-pot manner with $Pd(PPh_3)_4$ (Scheme 3). The second arylboronic acid was added to the reaction mixture after the first reaction was complete.

Using $Pd(PPh_3)_4$ (2 mol%) as catalyst in the reaction (Scheme 3), we studied the influence of solvent, temperature, bases, addition of water and Bu_4NBr (Table 1).



$Pd(PPh_3)_4$	15 h	$PdCl_2(dppf)$	4 h
$PdCl_2(PPh_3)_2$	5 h	$Pd(OAc)_2$	4 h

Scheme 1.

Keywords: palladium; Suzuki reaction; successive cross-coupling; diarylquinolines.

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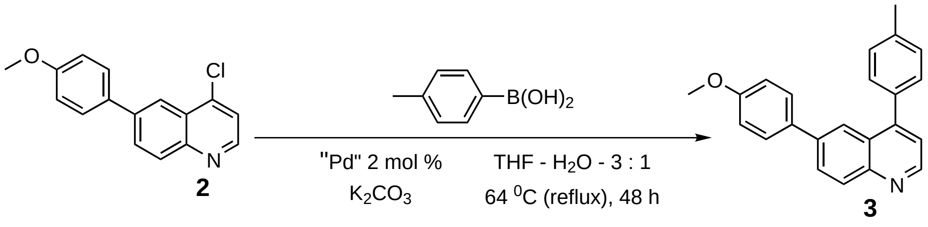
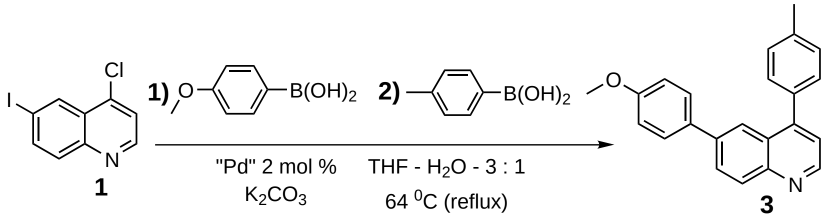
PII: S0040-4039(02)01516-2



$Pd(PPh_3)_4$	82 %	$PdCl_2(dppf)$	11 %
$PdCl_2(PPh_3)_2$	21 %	$Pd(OAc)_2$	4 %

Scheme 2.



	first step time*	second step time	yield of **3**
$Pd(PPh_3)_4$	15 h	48 h	69 %
$PdCl_2(PPh_3)_2$	5 h	48 h	19 %
$PdCl_2(dppf)$	4 h	48 h	2.5 %
$Pd(OAc)_2$	4 h	48 h	<1 %

*The yield of the reaction after the first step is quantitative.

Scheme 3.

In a benzene–H_2O mixture the result was practically the same as in aqueous THF but in aqueous MeCN and particularly in aqueous dioxane the reaction proceeds much faster (100% in 0.5 h for the first step and 97% in 4 h for the second step) (entries 1–4). However, this difference is mainly accounted for by the difference in the reflux temperature, because in aqueous dioxane at 64°C the first step is faster than in aqueous THF while the second step does not proceed at all. At room temperature even the first step of the reaction is very slow (entries 9 and 10).

The nature of base is also an important factor. The best result was obtained with K_3PO_4. The activity of the bases decreases in the order $K_3PO_4 > K_2CO_3 > Ba(OH)_2 >$ CsF, but the general yield is high in all cases (entries 5–8). The presence of water significantly accelerates the reaction. In anhydrous dioxane, the reaction requires 4 h for completion of the first step and after the second step only 7% of product was obtained after 48 h (entry 11). The addition of the phase-transfer agent Bu_4NBr (0.5 equiv.) to the reaction in anhydrous dioxane resulted in an increase in yield of the second reaction to 37% after 48 h, while the effect of this agent on the first reaction was negative, essentially leading to retardation (entry 12). The deleterious effect of Bu_4NBr on the cross-coupling at iodine is unexpected. In a separate experiment this effect was confirmed to take place in a simple cross-coupling reaction of 4-iodotoluene with 4-anisylboronic acid. The addition of Bu_4NBr into dioxane–H_2O (3:1) does not influence the rate or yields of the products of the first and second steps (entry 13).

Under the optimal conditions chosen above we have synthesized several diarylquinolines with the same or different aryl substituents in very high yields (Scheme 4).[4]

The substituent on the phenyl ring in the product forming at the first stage influences the rate of the second step. Thus the substitution of chlorine in 4-chloro-6-(4-chlorophenyl)quinoline proceeds faster then in 4-chloro-6-(4-tolyl)quinoline or 4-chloro-6-(4-anisyl)quinoline.

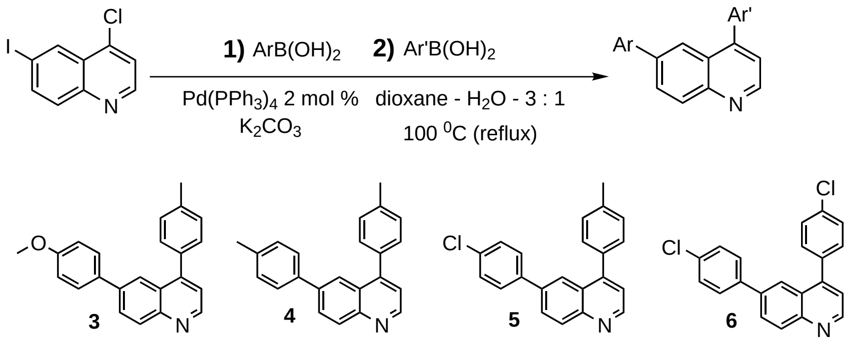
All compounds obtained were characterized by ^1H NMR spectroscopy[5] and elemental analyses.

Acknowledgements

We are grateful to Russian Foundation for Basic Research (Grant No. 00-15-97406 and 01-03-33144) and the foundation 'Integration of High School and Academy of Sciences' (Grant AO-115) for financial support.

Table 1.

No.	Solvent, additives	Base	T (°C)	Time of first stage (h)	Yield of first stage (%)	Time of second stage (h)	Yield of second stage (%)
1	THF/H_2O–3/1	K_2CO_3	64	15	100	48	69
2	Dioxane/H_2O–3/1	K_2CO_3	100	0.5	100	4	97
3	Benzene/H_2O–3/1	K_2CO_3	69	15	100	48	50
4	MeCN/H_2O–3/1	K_2CO_3	76	2	100	14	83
5	Dioxane/H_2O–3/1	K_2CO_3	100	0.5	100	4	97
6	Dioxane/H_2O–3/1	K_3PO_4	100	0.25	100	4	97
7	Dioxane/H_2O–3/1	CsF	100	7	100	12	97
8	Dioxane/H_2O–3/1	$Ba(OH)_2$	100	0.25	100	4	88
9	Dioxane/H_2O–3/1	K_2CO_3	64	5	100	48	0
10	Dioxane/H_2O–3/1	K_2CO_3	20	48	44	48	0
11	Dioxane	K_2CO_3	100	4	100	48	7
12	Dioxane+0.5 equiv. Bu_4NBr	K_2CO_3	100	15	100	48	37
13	Dioxane/H_2O–3/1+0.5 equiv. Bu_4NBr	K_2CO_3	100	0.5	100	4	93



	3	4	5	6
first step time, h	0.5	0.5	0.5	3
second step time, h	4	4	2.5	
yield of product, % (isolated)	97 (96)	97 (96)	89 (87)	100 (99)

Scheme 4.

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4. Typical experiment: 4-Chloro-6-iodoquinoline (50 mg, 0.172 mmol), 0.172 mmol of first the boronic acid, 144 mg of K_2CO_3 (1.032 mmol), 1.5 ml of dioxane and 0.5 ml of water were refluxed under argon with 3.4 µmol (2 mol%) of catalyst. The reaction was monitored by TLC. After the reaction was finished, the second boronic acid (0.224 mmol, 1.3 equiv.) was added to the reaction mixture. After the second reaction was finished the reaction mixture was diluted with ether, filtered through silica gel, evaporated in vacuo, and purified by column chromatography using silica gel (ether–hexane 1:1).
5. ^1H NMR data ($CDCl_3$, 400 MHz) of coupling products. Compound **2**: δ 3.86 (s, 3H), 7.02 (m, 2H), 7.47 (d, J (H,H) = 4.7 Hz, 1H), 7.66 (m, 2H), 7.98 (dd, J (H,H) = 8.8 Hz, J (H,H) = 2.1 Hz, 1H), 8.15 (d, J (H,H) = 8.8 Hz, 1H), 8.33 (d, J (H,H) = 2.1 Hz, 1H), 8.73 (d, J (H,H) = 4.7 Hz, 1H). Compound **3**: δ 2.44 (s, 3H), 3.81 (s, 3H), 6.95 (m, 2H), 7.31 (m, 3H), 7.42 (m, 2H), 7.52 (m, 2H), 7.92 (dd, J (H,H) = 8.8 Hz, J (H,H) = 2.1 Hz, 1H), 8.06 (d, J (H,H) = 2.1 Hz, 1H), 8.20 (d, J (H,H) = 8.8 Hz, 1H), 8.87 (d, J (H,H) = 4.7 Hz, 1H). Compound **4**: δ 2.35 (s, 3H), 2.43 (s, 3H), 7.21 (m, 2H), 7.29 (m, 3H), 7.42 (m, 2H), 7.47 (m,

2H), 7.93 (dd, *J* (H,H) = 8.8 Hz, *J* (H,H) = 2.1 Hz, 1H), 8.09 (d, *J* (H,H) = 2.1 Hz, 1H), 8.19 (d, *J* (H,H) = 8.8 Hz, 1H), 8.86 (d, *J* (H,H) = 4.7 Hz, 1H). Compound **5**: δ 2.46 (s, 3H), 7.36 (m, 7H), 7.50 (m, 2H), 7.90 (dd, *J* (H,H) = 8.8 Hz, *J* (H,H) = 2.1 Hz, 1H), 8.07 (d, *J* (H,H) = 2.1 Hz, 1H), 8.21 (d, *J* (H,H) = 8.8 Hz, 1H), 8.91 (d, *J* (H,H) = 4.4 Hz, 1H). Compound **6**: δ 7.29 (d, *J* (H,H) = 4.4, 1H), 7.36 (m, 2H), 7.43 (m, 2H), 7.48 (m, 4H), 7.91 (dd, *J* (H,H) = 8.8 Hz, *J* (H,H) = 2.1 Hz, 1H), 7.96 (d, *J* (H,H) = 2.1 Hz, 1H), 8.24 (d, *J* (H,H) = 8.8 Hz, 1H), 8.92 (d, *J* (H,H) = 4.4 Hz, 1H).