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Microwave Promoted Suzuki Cross-coupling Reactions of Quinazoline Halides with Aryl boronic Acids

KALYAN CHAKRAVARTHY AKULA*, RAMESH CHAKKA, USHA RANI PURI† and
DEEPA KRANTHI KUNAMALLA‡
Dr. Reddy's Laboratories Limited, 7-1-27, Ameerpet, Hyderabad-500 016, India
Tel: (91)9849128069; E-mail: kalyanca@drreddys.com; drkalyanakula@gmail.com

The microwave promoted Suzuki coupling reaction of quinazoline halides with boronic acids performed was studied using stable catalyst tetrakis triphenyl phosphine palladium (0). This catalyst under microwave conditions (175ºC, 6 m) provided coupled products with yields ranging from 76 to 90 %. This method tolerated a variety of boronic acids in the absence of ligand.

Key Words: Microwave synthesis, Suzuki Cross-coupling Reactions, Quinazoline halides, Aryl boronic acids.

INTRODUCTION

The palladium catalyzed cross-coupling reactions of aryl halides and triflates has been shown to be a powerful and frequently employed method for the formation of carbon-carbon bonds[1-8]. The broad availability of organo-boron compounds and a high functional group tolerance make the Suzuki coupling particularly attractive. The key to the success of the reaction in addition of a base, *e.g.*, NaOH, NaOEt, KOH or CsOH, which presumably activates the weakly nucleophilic boranes, borinates, or boronates for the transmetalation step. Nonetheless, high temperatures (90-120ºC) are often required, with palladium chloride as the catalyst and DMF/H_2O, acetone/H_2O, toluene/ H_2O, or benzene/H_2O as typical solvent systems[9,10]. The option for an aqueous biphasic solvent system is the ability to dissolve cesium carbonate, the base of choice for this chemistry. In fact this solvent system gave better results than other neat solvents such as DMF, THF or dioxane. It is also reported that use of *t*-butylammonium iodide (TBAI) as an additive was beneficial in this mixed solvent system.

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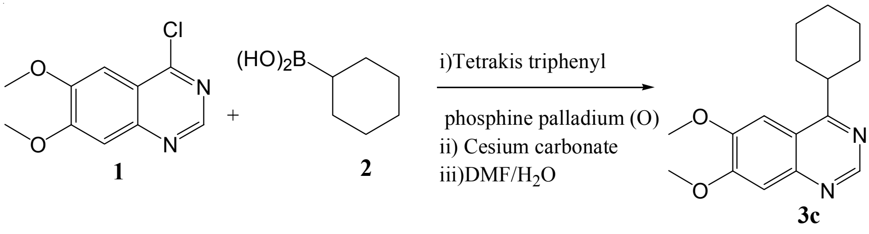
†Department of Chemistry, University Arts and Science College, Kakatiya University, Warangal-506 009, India.

‡International School of Chemical Biology; Plot # 2, IDA Uppal, Hyderabad-500 039, India.

The use of biologically active quinazoline halides particularly in this reaction has limited reports. Hence it is thought worthy enough to synthesize quinazoline chlorides due to their broad spectrum of activity. The discovery of 4-substituted quinazolines as a lead series for the inhibition of epidermal growth factor receptor tyrosine kinase (EGFR-TK) activity[11,12] and the rationale behind the inhibition of this enzyme as a potential method for treating human cancer[13,14] are well documented. Conventional structure-activity relationship studies have established the substitution patterns within 4-substituted quinazolines which provide the most potent compounds against EGFR-TK *in vitro*[15,16].

EXPERIMENTAL

General procedure (3c): 4-Chloro-6,7-dimethoxy quinazoline (1, mmol), cyclohexyl boronic acid (1.2 mmol), tetrakis triphenyl phosphine palladium (0) (0.02 mmol), cesium carbonate (2 mmol) and tetra butyl ammonium bromide (0.12 mmol) were taken in a mixture of DMF/ water (50:10 mL) and heated under microwave conditions for 6 min at 175 °C. The reaction mixture was then cooled to room temperature, filtered off and concentrated (**Scheme-I**). The product was purified by column chromatography (10 % ethyl acetate and hexane). Similarly, the coupling reaction of quinazoline halides with different boronic acids were carried out. The yield and product are given in Table-1. The spectral data of all the synthesized product are given in Table-2.



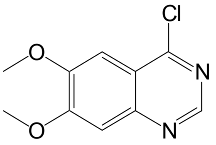
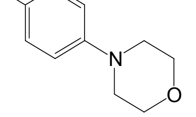
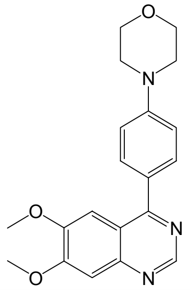
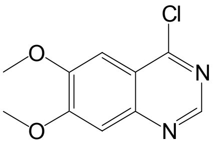
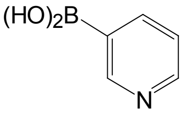
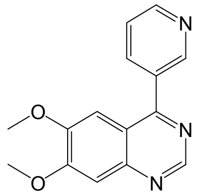
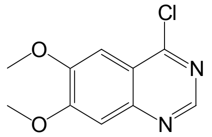
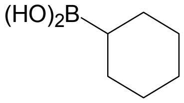
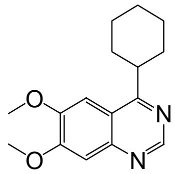
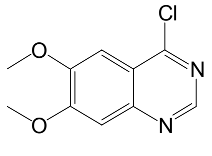
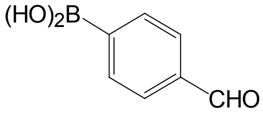
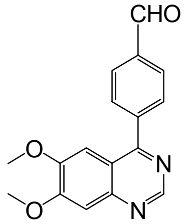
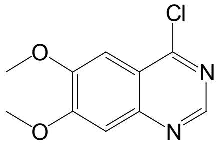
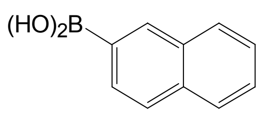
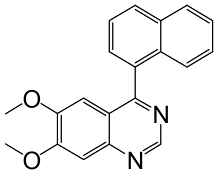
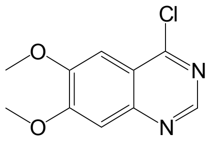
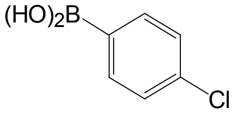
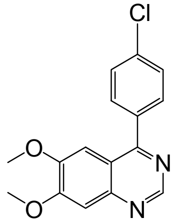
Scheme-I

Reaction conditions: 1 equiv of quinazoline chloride, 1.2 equiv of arylboronic acid, 2 mol % of Pd catalyst, 2 equiv of Cs_2CO_3, 12 mol % of TBAI, in DMF/H_2O (5/1), Under microwave conditions (175 °C, 6 m)

RESULTS AND DISCUSSION

In our approach we have identified 4-chloro-6,7-dimethoxy quinazoline, a readily accessible and commercially available compound, as an starting material. Suzuki coupling reactions with different aryl boronic acids in organic media under conventional heating conditions yielded low-quality

TABLE-1
SUZUKI CROSS-COUPLING OF QUINAZOLINE CHLORIDES WITH ARYL BORONIC ACIDS

Entry	Quinazoline halide	Boronic acid	Product	Yield (%)
3a				64
3b				77
3c				69
3d				81
3e				94
3f				72

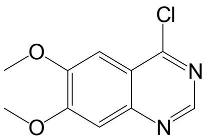
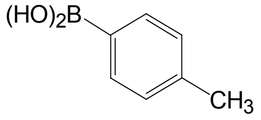
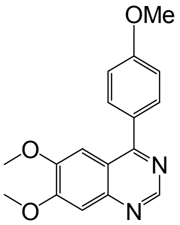
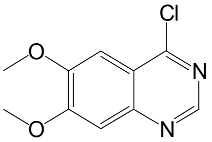
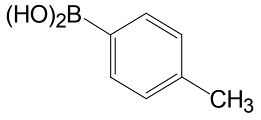
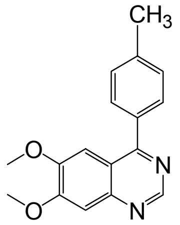
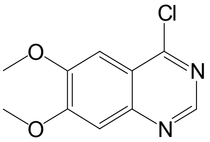
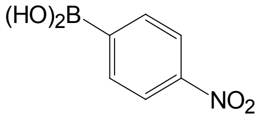
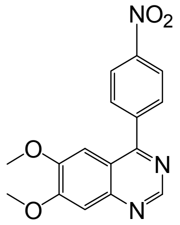
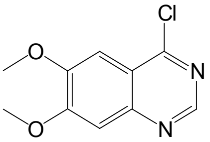
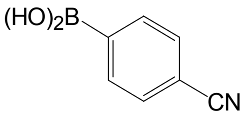
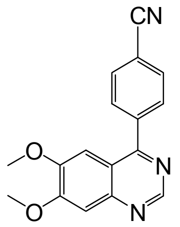
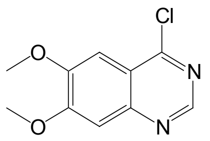
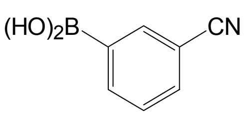
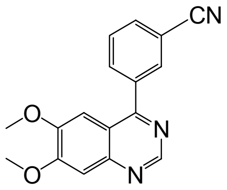
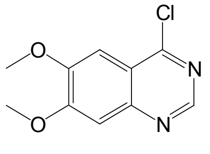
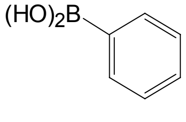
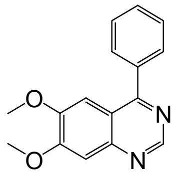
Entry	Quinazoline halide	Boronic acid	Product	Yield (%)
3g				81
3h				76
3i				69
3j				86
3k				82
3l				95

TABLE-2
SPECTRAL AND ANALYTICAL DATA OF COUPLED PRODUCTS

Entry	^{1}H NMR (δ ppm DMSO-d_6)	^{13}CMR (δ ppm)	MASS (m/e)	Elemental analysis: Found (Calcd.) %		
				C	H	N
3a	3.03 (m, 4H, 2x OCH_2), 3.76 (m, 4H, 2x NCH_2), 3.93 (s, 6H 2x CH_3), 6.81-7.69 (m, 6H, Ar-H), 9.19 (s, 1H azomethane)	160.1, 158.0, 154.7, 151.6, 149.3, 136.2, 130.6, 117.3, 111.8, 99.0, 67.3, 57.8, 56.0, 46.3.	351.16	68.36 (68.12)	6.02 (5.98)	11.96 (11.99)
3b	3.91 (s, 6H 2x CH_3), 7.14-7.91 (m, 7H, Ar-H), 9.19 (s, 1H azomethane)		267.28	67.40 (67.51)	4.90 (4.81)	15.72 (15.79)
3c	1.49-172 (m, 10H, cyclohexyl), 3.93 (s, 6H 2x CH3), 6.81-7.69 (m, 6H, Ar-H), 9.21 (s, 1H azomethane)	164.2, 161.7, 154.3, 153.2,147.9, 118.6, 113.4, 102.6, 57.7, 56.1, 39.5, 28.8, 27.5, 26.0	272.34	70.49 (70.56)	7.39 (7.40)	10.37 (10.29)
3d	3.93 (s, 6H 2x CH_3), 7.14-7.93 (m, 6H, Ar-H), 9.19 (s, 1H azomethane), 9.95 (s, 1H, CHO)	190.1, 162.4, 158.3, 156.0,154.6, 150.1, 142.7, 138.9, 130.2,127.0, 126.3, 109.1, 98.7, 57.2, 56.0	294.30	69.44 (69.38)	4.87 (4.79)	9.61 (9.52)
3e	3.96 (s, 6H 2x CH_3), 7.14-8.22 (m, 9H, Ar-H), 9.11 (s, 1H azomethane)		316.35	75.84 (75.93)	5.21 (5.10)	8.94 (8.86)
3f	3.91 (s, 6H 2x CH_3), 7.17-7.95 (m, 6H, Ar-H), 9.22 (s, 1H azomethane)		300.74	63.81 (63.90)	4.47 (4.36)	9.24 (9.31)
3g	3.96 (s, 6H 2x CH_3), 7.14-8.22 (m, 9H, Ar-H), 9.11 (s, 1H azomethane)		296.32	68.87 (68.91)	5.32 (5.44)	9.51 (9.45)
3h	2.36 (s, 3H, CH_3), 3.93 (s, 6H 2x CH3), 7.14-7.89 (m, 6H, Ar-H), 9.19 (s, 1H azomethane)	160.3, 158.9, 155.6, 154.4,151.3, 138.6, 136.2, 133.1, 127.9,118.0, 109.7, 98.1, 56.6, 55.3, 21.2	280.32	72.79 (72.84)	5.69 (5.75)	10.06 (9.99)
3i	3.93 (s, 6H 2x CH_3), 7.14-8.26 (m, 6H, Ar-H), 9.19 (s, 1H azomethane)		311.29	61.84 (61.73)	4.30 (4.21)	13.42 (13.50)
3j	3.93 (s, 6H 2x CH_3), 7.14-7.93 (m, 6H, Ar-H), 9.19 (s, 1H azomethane)		291.30	70.21 (70.09)	4.61 (4.50)	14.53 (14.42)
3k	3.93 (s, 6H 2x CH_3), 7.14-7.99 (m, 6H, Ar-H), 9.19 (s, 1H azomethane)		291.30	70.19 (70.09)	4.59 (4.50)	14.51 (14.42)
3l	3.91 (s, 6H 2x CH_3), 7.14-7.91 (m, 7H, Ar-H), 9.19 (s, 1H azomethane)		266.29	72.23 (72.16)	5.43 (5.30)	10.65 (10.52)

and poor yields and several times the reaction did not proceed to completion. When we employed the microwave conditions in biphasic medium in the presence of cesium carbonate and tetra butylammonium bromide (catalytic) the reaction afforded coupled products in high yields.

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