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Petasis reaction of activated quinoline and isoquinoline with various boronic acids

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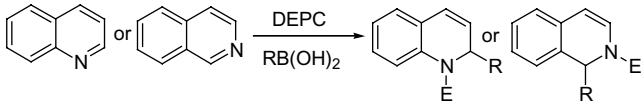
Abstract—Petasis reactions of activated forms of quinolines and isoquinolines with electron sufficient boronic acids such as 2-benzofuranboronic acid, *trans*-2-phenylvinylboronic acid etc in DCM proceeded smoothly at room temperature to provide the corresponding dihydroquinolines and dihydroisoquinolines in good to high yields.

Addition reaction of activated aza-aromatics is of great importance for the synthesis of biologically active nitrogen compound including alkaloids.[1] Generally, aza-aromatics for this transformation were activated by chloroformates, acyl chlorides, and diethyl pyrocarbonate (DEPC). The Petasis boronic acid–Mannich reaction is one of the MCC (multicomponent condensation) reactions,[2,3] which provides a convenient method for the preparation of α-amino acids via the reactions between a carbonyl compound, an amine and a boronic acid. The reaction has also been applied to the synthesis of heterocyclic system[4] and solid phase synthesis of peptide.[5] The reaction is most efficient with alkenyl and electron-rich aromatic boronic acids. Secondary amines, sterically hindered primary amines, and tertiary aromatic amines in addition to primary amine can also participate in these transformations. As an effort toward the development of synthetic methods of the quinoline and isoquinoline derivatives from quinoline and isoquinoline, a mild, practical, and novel method for the synthesis of C–C bond formation of quinoline and isoquinoline using Petasis reaction through in situ generated EEDQ (2-ethoxy-1-ethoxylcarbonyl-1,2-dihydroquinoline) and EEDI (1-ethoxy-2-ethoxycarbonyl-1,2-dihydroisoquinoline) was developed and we report the results (see Scheme 1).

The commercially available EEDQ and 2-benzofuranboronic acid chosen for a model study was reacted in various solvent systems and the results are illustrated in Table 1. While the reaction of EEDQ with 2-benzofuranboronic acid (1.2 equiv) in ethanol, DMF, and 1,4-dioxane did not proceed at all (entries 1, 2, and 3), the reaction in THF under reflux provide the expected product after 3 h in 42.3% yield due to unidentified side product formation (entry 4). EEDQ in acetonitrile or toluene at room temperature was reacted with 2-benzofuranboronic acid to give coupling product in 71.5% and 81.3% yield, respectively (entries 5 and 6). The best result has been obtained from the reaction of EEDQ with 2-benzofuranboronic acid in dichloromethane to give the expected product in 91.2% yield in 3 h (entry 7).

Under the reaction condition, the reactions of EEDQ with a variety of boronic acids in dichloromethane were



R = Aryl or vinyl, E = COOEt

Scheme 1.

Keywords: Petasis reaction; Quinoline; Isoquinoline; EEDQ; Boronic acid.
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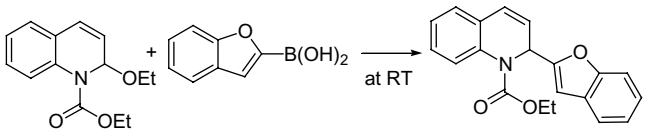
Table 1. The reaction of EEDQ with 2-benzofuranboronic acid in various solvents



Entry	Solvent	Time (h)	Yield (%)[b]
1	Ethanol	24	No rex.
2	DMF	24	No rex.
3	1,4-Dioxane	24	No rex.
4[a]	THF	3	42.3
5	Acetonitrile	8	71.5
6	Toluene	5	81.3
7	DCM	3	91.2

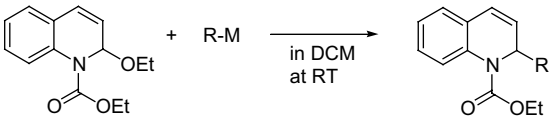
[a] At reflux; The reaction did not proceed at all at rt.
[b] Isolated yields.

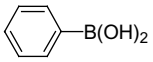
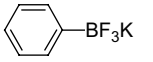
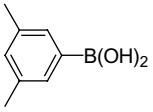
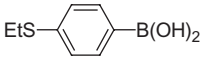
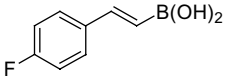
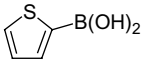
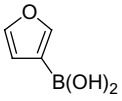
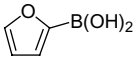
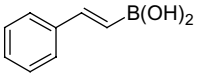
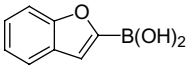
carried out and the results are shown in Table 2. In our previous research of the lithium chloride mediated alkylation of EEDQ, a mixture of α- and γ-alkylated products with α-selectivity was obtained and the ratio of the two isomers depended on the alkylating agents. However, the reaction of EEDQ with boronic acid was found to afford only one α-regioisomer. The reactions with electron sufficient aromatic boronic acids proceeded in good yields (entries 8, 9, and 10), but those of phenylboronic acid and 2,4-dimethylphenylboronic acid did not proceed at all (entries 1 and 3). On the assumption that the reaction of phenylboronic acid is not working due to its low reactivity, more reactive potassium trifluorophenylborate[6] instead of phenylboronic acid was employed and the result was turned out to be disappointing (entry 2). The reaction of EEDQ with other electron sufficient boronic acid such as *trans*-2-(4-fluorophenyl)vinylboronic acid, 3-furanboronic acid and 2-thiopheneboronic acid showed complete conversion of EEDQ into the corresponding products according to TLC, but the yields were relatively low due to unidentified side products (entries 5, 6, and 7).

Next, we tried to expand the reaction of EEDQ to quinoline and isoquinoline activated by activating group. For the activation of quinoline and isoquinoline, several activating reagents such as phenyl chloroformate, ethyl chloroformate, and diethyl pyrocarbonate (2 equiv) were tested to give the results shown in Table 3. Whereas the reactions of 2-benzofuranboronic acid (1.2 equiv) with quinoline activated with phenyl chloroformate (2 equiv) and ethyl chloroformate (2 equiv) at rt were relatively faster than that with quinoline activated diethyl pyrocarbonate at rt, the yields were lower. The reaction of quinoline using DEPC with 2-benzofuranboronic acid, even if slower, gave the expected product in 86.3% yield, which result is almost equivalent to that of the reaction of EEDQ with 2-benzofuranboronic acid.

The reaction of several quinoline derivatives activated with DEPC with 2-benzofuranboronic acid as a representative of boronic acids showed the result listed in

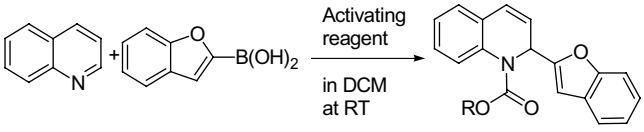
Table 2. The reaction of EEDQ with various boronic acids[7]



Entry	R–M	Time (h)	Yield (%)[a]
1		48	0
2		48	0
3		48	0
4		48	Trace
5		2	43.7
6		3	53.7
7		3	53.9
8		1	96.4
9		3	83.5
10		3	91.2

[a] Isolated yields.

Table 3. The reaction of quinoline with 2-benzofuranboronic acid using various activating reagents[a]

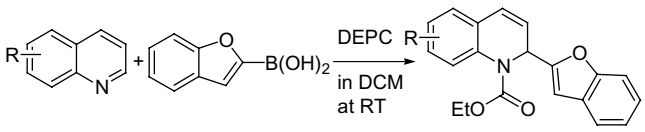


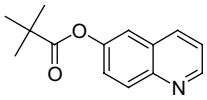
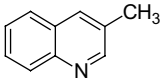
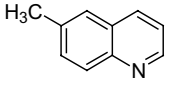
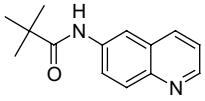
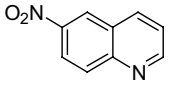
Entry	Activating reagents	Time (h)	Yield (%)[b]
1	$ClCO_2Ph$	0.5	42.9
2	$ClCO_2Et$	3	58.6
3	$(EtO_2C)_2O$	21	86.3

[a] Two equivalents of activating reagents and 1.2 equiv of 2-benzofuranboronic acid were used.
[b] Isolated yields.

Table 4. The real substrate of the reaction is EEDQ formed by the reaction of quinoline with diethyl pyrocarbonate in situ. While electron sufficient quinolines having electron donating groups under the reaction condition were converted into the corresponding

Table 4. The reaction of quinoline with 2-benzofuranboronic acid[9]



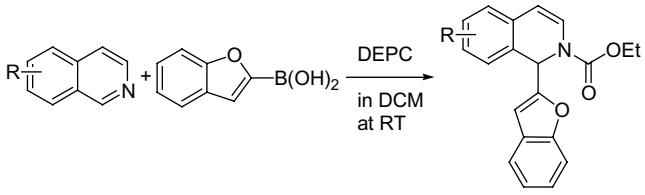
Entry	Quinolines	Time (h)	Yield (%)[a]
1		24	88.6
2		24	83.2
3		24	89.1
4		24	92.4
5		3	91.7

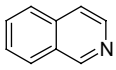
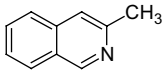
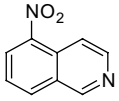
[a] Isolated yields.

dihydroquinoline in high yields (entries 1–4), 6-nitroquinoline did not react at all due to low nucleophilicity of nitrogen of 6-nitroquinoline. To evade its low reactivity problem, 6-nitro-EEDQ was prepared from the reaction of 6-nitroquinoline with ethyl chloroformate in the presence of triethylamine and ethanol via known procedure[8] and exposed to reaction with 2-benzofuranboronic acid to give the expected dihydroquinoline in 91.7% yield (entry 5).

Isoquinoline activated with diethyl pyrocarbonate in dichloromethane was reacted with 2-benzofuranboronic acid at rt to afford a dihydroisoquinoline in 97.5% yield

Table 5. The reaction of isoquinoline with 2-benzofuranboronic acid[9]



Entry	Isoquinolines	Time (h)	Yield (%)[a]
1		1	97.5
2		24	80.3
3		16	79.7

[a] Isolated yields.

(entry 1 of Table 5). The real substrate for this reaction is EEDI, the formation of which was identified by TLC and ^{1}H NMR. The reaction of isoquinolines bearing electron donating group and electron withdrawing group with 2-benzofuranboronic acid gave the corresponding dihydroisoquinoline in 80.3% and 79.7%, respectively (entries 2 and 3). The longer reaction time and the relatively lower yield of 3-methylisoquinoline and 5-nitroisoquinoline seemed to be ascribed from the steric and electronic effect, respectively (entries 2 and 3).

In conclusion, EEDQ was successfully coupled with various electron sufficient aryl boronic acids or vinyl boronic acid to give the corresponding coupling products in high yields. The methodology was expanded to the reaction of in situ generated EEDQ and EEDI, formed from the reaction of quinoline and isoquinoline with DEPC, with 2-benzofuranboronic acid to give the corresponding coupling products in respective high yields. The mild reaction conditions, experimental simplicity and high yields are the advantage of our protocol.

Acknowledgements

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7. Typical procedure for the reaction of EEDQ with 2-benzofuranboronic acid: To a solution of EEDQ (50 mg, 0.202 mmol) in dichloromethane (2 mL) was added 2-benzofuranboronic acid (39.3 mg, 1.2 equiv) at rt. After the reaction mixture was stirred for 3 h at rt, it was concentrated and chromatographed on silica gel using a solution of ethyl acetate and hexane (1:20) to give 2-(2-benzofuranyl)-1-ethoxycarbonyl-1,2-dihydroquinoline in 91.2% yield.
8. To a solution of 6-nitroquinoline (198.0 mg, 1 mmol) in ethyl chloroformate (0.5 mL) was added a solution of ethanol (1 mL) and triethylamine (1 mL). After the reaction mixture was stirred for 2 h at rt, it was quenched with water and dried with $MgSO_4$. The concentrate was chromatographed on silica gel using a solution of ethyl acetate and hexane (1:4) to give 2-ethoxy-1-ethoxycarbonyl-6-nitro-1,2-dihydroquinoline in 22.1% yield. And then, to a solution of 2-ethoxy-1-ethoxycarbonyl-6-nitro-1,2-dihydroquinoline (59.1 mg, 0.202 mmol) in dichloromethane (2 mL) was added 2-benzofuranboronic acid (39.3 mg, 1.2 equiv) at rt. After the reaction mixture was stirred for 3 h at rt, it was concentrated and chromatographed on silica gel using a solution of ethyl acetate and hexane (1:4) to give 2-(2-benzofuranyl)-1-ethoxycarbonyl-6-nitro-1,2-dihydroquinoline in 91.7% yield.
9. Typical reaction procedure of the reaction of in situ generated EEDQ with 2-benzofuranboronic acid: To a solution of quinoline (26.1 mg, 0.202 mmol) and diethyl pyrocarbonate (66.1 mg, 2 equiv) in dichloromethane (2 mL) was added 2-benzofuranboronic acid (39.3 mg, 1.2 equiv) at rt. After the reaction mixture was stirred for 21 h at rt, it was concentrated and chromatographed on silica gel using a solution of ethyl acetate and hexane (1:20) to give 2-(2-benzofuranyl)-1-ethoxycarbonyl-1,2-dihydroquinoline in 86.3% yield.