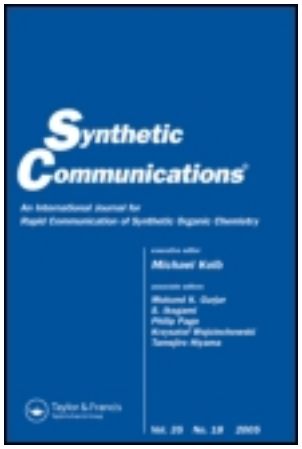

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Green Synthesis of New Boron-Containing Quinazolines: Preparation of Benzo[d][1,3,2]diazaborinin-4(1H)-one Derivatives

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GREEN SYNTHESIS OF NEW BORON-CONTAINING QUINAZOLINES: PREPARATION OF BENZO[*d*][1,3,2]DIAZABORININ-4(1*H*)-ONE DERIVATIVES

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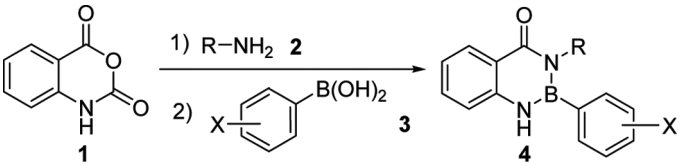
GRAPHICAL ABSTRACT



Abstract *A series of new boron-containing quinazolinones, benzo[d][1,3,2]diazaborinin-4(1H)-one derivatives, were synthesized by the sequential one-pot reaction of isatoic anhydride, amines, and arylboronic acids in the absence of a catalyst and solvent. Heating isotoic anhydride and amines led to the formation of 2-aminobenzamide intermediates, which reacted easily with boronic acids to obtain the title compounds in good yields. Solvent-free conditions provided a unique procedure because the corresponding products were not obtained using various solvents either under reflux conditions or at room temperature.*

[Supplementary materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *for the following free supplemental resource: Full experimental and spectral details.]*

Keywords 2-Aminobenzamides; boron-containing quinazolines; boronic acids; isatoic anhydride; solvent-free

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INTRODUCTION

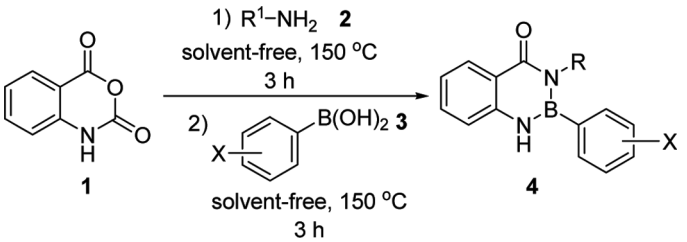
Increasing interest in organoboron compounds can be attributed to the ability of boron to create important biological properties in corresponding compounds.[1–3] For instance, boron-containing derivatives of 2-thiouracil have been introduced as good candidates for boron neutron-capture therapy of malignant melanoma.[4]

Boron-containing heterocyclic compounds have been a focus of attention because of their useful biological and medicinal effects. Baker et al. have reported synthesis of various novel boron-containing antifungal agents.[5] Their studies shows that 5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole derivative possesses significant properties for the treatment of onychomycosis. Boron heterocycles steroid mimics were provided by Grogiak as pharmaceutical agents in the treatment of estrogen-depended cancers.[6] Also, the mentioned compounds are useful in diagnostic techniques such as magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS).

N–B–N bond formation in analogs of quinazoline, one important class of heterocyclic compounds with particular biological activities,[7] is found to be very useful because these compounds have depicted high inhibitory activity against epidermal growth factor receptor protein tyrosine kinase[8] and are useful as an antitumor agent.[9]

Replacement of carbon in the quinazoline derivatives with a boron atom has been reported in the literature using different and efficient routes: (i) synthesis of boron-containing analogs of purine, pyrimidine, and perimidine derivatives by reaction of nitriles and diboranes and also reaction of amines and boron chloride;[10] (ii) synthesis of benzodiazaborinones using the reaction of boronic acids and *o*-aminobenzamide intermediates;[11] and (iii) synthesis of 1,1′-biaryl-4-boronic acid bearing anthranilamide on the boron atom which subsequently underwent Ru-catalyzed *o*-silylation.[12]

Quinazolines properties and the importance of boron-containing heterocycles directed our research interests in the synthesis of novel heterocycles[13–15] having biological activities[16] to prepare boron-containing quinazolinones, benzo[*d*][1,3,2] diazaborinin-4(1*H*)-one derivatives (Scheme 1). It seems development of rapid and selective synthetic routes to prepare a library of related compounds is of great importance to both medicinal and organic chemists and still constitutes a challenge from organic synthesis points of view.



Scheme 1. Synthesis of benzo[*d*][1,3,2]diazaborinin-4(1*H*)-one derivatives **4**.

RESULTS AND DISCUSSION

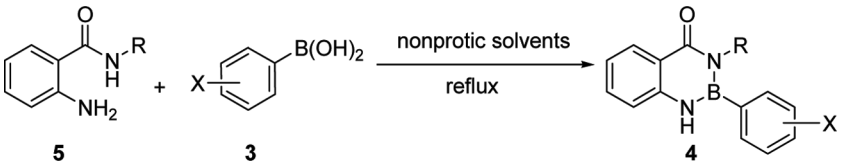
In this work, we have focused on the reaction of isatoic anhydride **1**, amines **2**, and arylboronic acids **3** to synthesize new benzo[*d*][1,3,2]diazaborinin-4(1*H*)-one derivatives **4** (Scheme 1).

Our initial investigation began by studying Yale's report (Scheme 2).[11] It indicates that reaction of 2-aminobenzamide or its substituted derivatives **5** and arylboronic acids **3** in boiling nonprotic solvents led to the formation of some benzo[*d*][1,3,2] diazaborinin-4(1*H*)-one derivatives **4**. Removing the formed water from the reaction mixture was the most problematic issue, which should be isolated mechanically using a Dean–Stark trap, slow distillation through a fractionating column, or drying apparatus with phosphorus pentoxide. It should be noted that in the case of some derivatives, the problem was more remarkable and no product was obtained.

Recently we have successfully developed a synthesis of novel 3-alkyl-2-(alkylamino)quinazolin-4(3*H*)-one derivatives via the reaction of isatoic anhydride, amines, and *N,N′*-dialkylcarbodiimes under catalyst- and solvent-free conditions.[14] We could obtain several 2-aminobenzamide intermediates **5** in situ by heating equal stoichiometric amounts of isatoic anhydride and different amines at 150 °C for 3 h in the absence of solvent and catalyst. Then, they reacted with *N,N′*-dialkylcarbodiimes under the same conditions to obtain corresponding products in good yields. We decided to apply the same procedure and replace boronic acids **3** instead of *N,N′*-dialkylcarbodiimes to solve the problem and prepare novel benzo[*d*][1,3,2] diazaborinin-4(1*H*)-ones.

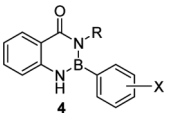
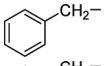
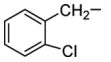
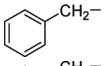
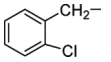
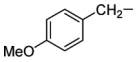
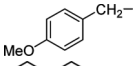
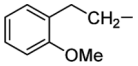
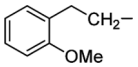
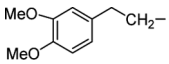
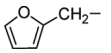
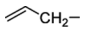
To clarify more details, the reaction of isatoic anhydride **1** (1 mmol), benzylamine **2a** (1 mmol), and phenylboronic acid **3a** (1 mmol) was investigated as a model reaction. Isatoic anhydride underwent ring opening upon heating with benzyl amine at 150 °C to produce 2-amino-*N*-benzylbenzamide after 3 h (**5a**). Then, phenylboronic acid **3a** (1 mmol) was added to the reaction mixture, stirring continued at the same temperature, and the corresponding product **4a** (Table 1, entry 1) was obtained in 50% after 3 h. It was found that using 1.2 mmol phenylboronic acid gives the product in greater yield (75%). Also the model reaction was conducted in different solvents such as toluene, methanol, ethanol, and dimethylformamide (DMF). As we expected, no product was obtained either at room temperature or under reflux condition. Therefore, using solvent-free conditions is essential for environmentally issues and has other advantages.

After confirmation of the structure of **4a** and with the optimized conditions in hand, we next set out to explore the scope of our reaction. To our delight, isatoic anhydride **1**, various amines **2**, and arylboronic acids **3** (Scheme 1) produced diverse benzo[*d*][1,3,2]diazaborinin-4(1*H*)-one derivatives **4** in good to excellent yields. The results are summarized in Table 1.



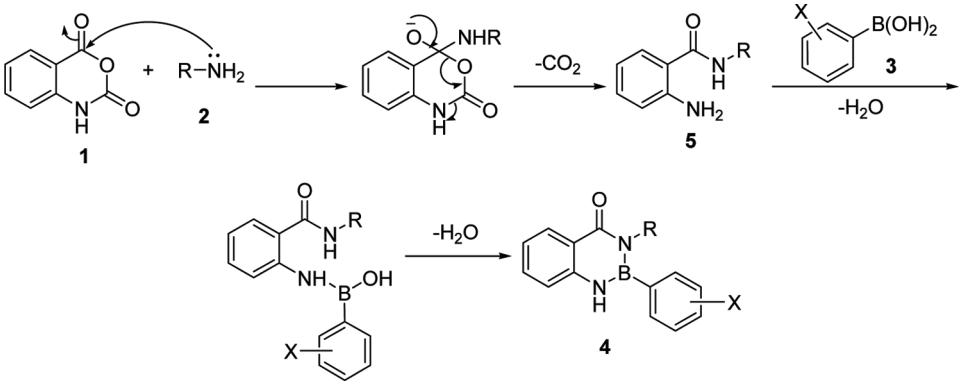
Scheme 2. Reaction of 2-aminobenzamides and boronic acids reported by Yale.[11]

Table 1. Synthesis of benzo[*d*][1,3,2]diazaborinin-4(1*H*)-ones **4**

Entry	R in amines **2**	X in boronic acids **3**	Product  **4**	Yield (%)[a]
1		H	**4a**[11]	75
2		H	**4b**	80
3		4-Cl	**4c**	80
4		4-F	**4d**	85
5		H	**4e**	70
6		4-F	**4f**	75
7		H	**4g**	80
8		4-F	**4h**	85
9		H	**4i**	80
10		4-F	**4j**	60
11		H	**4k**	80

[a]Isolated yields, and compounds **4b–4k** are new.

Sequences of the formation of benzo[*d*][1,3,2]diazaborinin-4(1*H*)-ones **4** are given in Scheme 3. It is believed that the initial event is the formation of 2-amino-*N*-alkylbenzamides **5** from the reaction of isatoic anhydride **1** and amines



Scheme 3. Mechanism of synthesis of benzo[*d*][1,3,2]diazaborinin-4(1*H*)-one derivatives **4**.

2. Then boronic acid **3** is added to **5**. Continuing cyclization of the intermediate by double elimination of H_2O gives compound **4**.

In conclusion, we have developed a practical and environmentally benign protocol to construct novel benzo[*d*][1,3,2]diazaborinin-4(1*H*)-one derivatives via reaction of isatoic anhydride, various primary amines, and arylboronic acids in the absence of a catalyst and solvent. It is noteworthy that all the reactions proceeded only under solvent-free conditions and no products were obtained using various solvents either under reflux conditions or at room temperature.

EXPERIMENTAL

Melting points was taken on a Kofler hot stage apparatus and were uncorrected. ^{1}H and ^{13}CNMR spectra were recorded on Bruker FT-500, using tetramethylsilane (TMS) as an internal standard. The infrared (IR) spectra were obtained on a Nicolet Magna FTIR 550 spectrophotometer (in KBr). Mass spectra were determined on an Agilent Technology (HP) mass spectrometer operating at an ionization potential of 70 eV. The elemental analysis was performed with an Elementar Analysensystem GmbH VarioEL CHNS mode.

Synthesis of Benzo[*d*][1,3,2]diazaoborinin-4(1*H*)-ones 4

A mixture of isotonic anhydride **1** (1 mmol) and appropriate amine **2** (1 mmol) was stirred at 150 °C for 3 h. Then, arylboronic acid derivatives **3** (1.2 mmol) were added to the reaction mixture and stirring continued at 150 °C for 3 h. After completion of the reaction, it was cooled to room temperature and the residue was purified by column chromatography (SiO_2, petrolume ether/ethyl acetate = 5/1).

3-(2-Chlorobenzyl)-2,3-dihydro-2-phenylbenzo[*d*][1,3,2]diazaborinin-4(1*H*)-one (4b)

Yield 80%, white crystals, mp 211–213 °C; IR (KBr): 3299, 2920, 2849, 1637, 1616, 1520 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta_H = 8.27$ (d, $J = 7.0$ Hz, 1H), 7.54 (dt, $J = 7.6$, 1.4 Hz, 1H), 7.42–7.40 (m, 3H), 7.36–7.31 (m, 3H), 7.20–7.16 (m, 3H), 7.11–7.08 (m, 2H), 7.04 (s, 1H, NH), 5.05 (s, 2H, NCH_2); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta_C = 166.7$, 143.5, 136.5, 134.6, 133.7, 132.4, 131.9, 129.7, 129.6, 129.4, 128.8, 128.2, 127.7, 126.9, 126.5, 121.9, 118.7, 117.3, 114.6, 46.0. Anal. calcd. for $C_{20}H_{16}BClN_2O$: C, 69.30; H, 4.65; N, 8.08. Found: C, 69.05; H, 4.88; N, 8.30.

3-Benzyl-2-(4-chlororophenyl)-2,3-dihydrobenzo[*d*][1,3,2] diazaborinin-4(1*H*)-one (4c)

Yield 80%, white crystals, mp 215–218 °C; IR (KBr): 3313, 2933, 2854, 1640, 1520 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta_H = 8.29$ (dd, $J = 7.2$, 1.5 Hz, 1H), 7.55 (ddd, $J = 8.2$, 7.2, 1.5 Hz, 1H), 7.38 (dd, $J = 6.4$, 2.0 Hz, 2H), 7.34 (dd, $J = 6.4$, 2.0 Hz, 2H), 7.26–7.20 (m, 2H), 7.22–7.18 (m, 2H), 7.12 (d, $J = 7.0$ Hz, 2H), 7.06 (d, $J = 7.2$ Hz, 1H), 6.75 (s, 1H, NH), 4.97 (s, 2H, NCH_2); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta_C = 166.6$, 143.0, 139.1, 135.8, 133.6, 133.4, 129.7, 128.4, 126.8, 126.6,

122.1, 119.1, 117.1, 47.5; MS m/z (%) = 348 $[M + 2]^+$ (33), 346 $[M]^+$ (100), 267 (31), 235 (31), 205 (10), 165 (14), 91 (82), 65 (20). Anal. calcd. for $C_{20}H_{16}BClN_2O$: C, 69.30; H, 4.65; N, 8.08. Found: C, 69.15; H, 4.77; N, 8.25.

SUPPORTING INFORMATION

Full experimental details and ^1H and ^{13}C NMR spectra are available online.

ACKNOWLEDGMENTS

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