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Synthesis and Stability of Boratriazaroles

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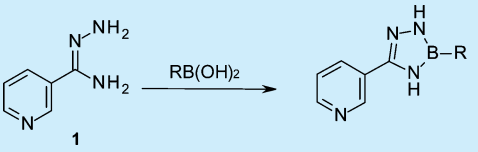
Supporting Information

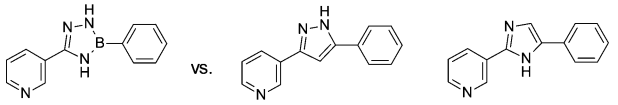
ABSTRACT: We describe the synthesis and stability analysis of novel boratriazaroles that can be viewed as bioisosteres of imidazoles or pyrazoles. These heterocycles could conveniently be obtained by condensing a boronic acid and amidrazone **1** in various solvents. A detailed stability analysis of selected compounds at different pH values as a function of time led to the identification of steric hindrance around the boron atom as a key element for stabilization.



In recent years, interest in the synthesis and properties of boron-containing heterocycles has seen a renaissance, notably by the work of Liu[1] and most recently by Molander.[2] In such heterocycles, a B−N bond serves as an isosteric and isoelectronic replacement of a C=C unit. Thus, a degree of aromaticity is retained.[3] Examples of both 5-membered and 6-membered heterocycles are known. Pioneering work by Dewar dates back to 1960.[4] While research in the field was limited for some decades thereafter, it has become an area of growing interest since the beginning of this century. An excellent review is available by Liu.[5]

Bioisosteric replacement is a frequently used tool to mimic biological activity by using different chemical scaffolds.[6] Imidazoles and pyrazoles are important motifs present in various pharmaceutical and agrochemical compounds.[7] Boratriazaroles, as bioisosteres to the aforementioned heterocycles, could be useful not only to mimic biological activity but also to modify physicochemical properties and to optimize bioavailability (Scheme 1).

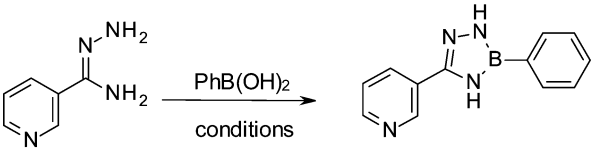
Scheme 1. Boratriazaroles as Bioisosteres of Pyrazoles and Imidazoles



Being interested in this field, we became aware of Dewar's[8] work describing the synthesis of compounds such as **2**. Starting from Dewar's work, the condensation reaction between amidrazone **1**[9] and phenylboronic acid was evaluated in different solvents and temperatures. Under the initially tested conditions (MeOH or water, reflux), we could not identify the formation of product **2** by routinely applying LCMS analysis. However, careful analysis of the mass spectral data led to the conclusion that **2** must have been formed. In addition, monitoring by TLC indicated the formation of a product. We speculated whether even low amounts of formic acid present in the eluent (0.05% v/v) could have led to the nearly complete hydrolysis back to the starting materials, namely the amidrazone **1** and the boronic acid. Although the instability of compounds such as **2** toward acid is mentioned in the seminal publication by Dewar, no data are provided, which would describe the extent of the instability.[10] The pronounced effect of even traces of acid on the stability of **2** was unexpected. Because of the lack of thorough experimental data also with respect to the stability of the boratriazaroles, we devoted ourself to a program aiming at understanding the stability profile and identifiying key parameters for the stabilization of such structures.

When we repeated the reaction of **1** and phenylboronic acid in MeOH and resorted to an LCMS analysis omitting acid, the formation of a new product was observed, which after evaporative workup and purification could be identified indeed as compound **2** in 59% yield. TLC analysis also proved to be useful for routinely checking the reaction outcome. The condensation reaction between **1** and phenylboronic acid works in a diverse range of commonly used solvents such as 1,4-dioxane, THF, DMF, and pyridine in yields varying between 59 and 86% at elevated temperature (see Table 1). Notably, product **2** precipitated in MeOH during the reaction, and thus, the product might be isolated conveniently by filtration. The physical properties of **2** could potentially have led to a simple

Table 1. Study of Condensation Conditions for 1 to 2



entry	solvent	temp (°C)	yield (%)
1	1,4-dioxane	95	73
2	THF	95	66
3	DMF	95	86
4	pyridine	95	73
5	MeOH	95	59
6	water	80	21

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isolation procedure by means of filtration; however, routinely applied purification of the reaction mixture by flash chromatography after evaporative workup led to higher yields in general. Interestingly, the condensation reaction also works in water, where **2** precipitates and could be isolated in 21% yield. With **2** in hand, we proceeded in studying a qualitative stability profile in DMSO (as the preferred solvent for storage and biological screening) as well as at different pH values (pH 5, 7, 9 and water). Although **2** was completely stable over 4 months in DMSO, the compound decomposed within hours at pH 5 but showed increased stability at higher pH values, being the most stable at pH 9 (see the Supporting Information). This rather pronounced susceptibility toward lower pH values was surprising, and in retrospect, it might explain why compounds such as **2** did not appear in the literature over the last few decades.

We confirmed the structure of **2** by single-crystal X-ray analysis (Figure 1). The molecule is mostly flat, with torsion angles of

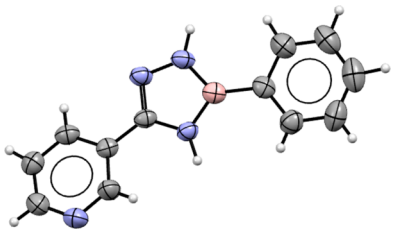

Figure 1. X-ray structure of boratriazarole **2** with thermal ellipsoids shown at 50% probability level.

2.0° and 15.6° between the central borotriazarole and the phenyl and pyridine rings, respectively. A comparison of ring geometry reveals the borotriazarole moiety to be an excellent isostere for pyrazole and imidazole (Figure 2). A superposition with both

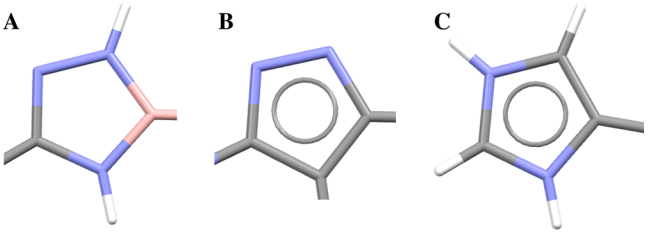

Figure 2. Comparison of ring geometry: (A) central borotriazarole ring from compound **2**; (B) pyrazole (taken from CCDC code ESOYIU); (C) imidazole (CCDC code REPLIH). Non-hydrogen substituents omitted for clarity.

yields root-mean-square deviations of just 0.057 and 0.056 Å, respectively, and the three ring systems have virtually identical bond distances and angles.

We speculated whether it might be possible to overcome the observed susceptibility of **2** toward acid by increasing steric bulk and varying electronic density around the boron center. At first, we put substituents in both ortho positions of the phenyl ring, which is linked to boron. The stability profiles of these compounds were then qualitatively determined at different pH values (5, 7, water, and 9) to get a basic understanding of the structure–stability relationship. While the 2,6-bisfluoro compound **4** showed a similar pH-dependent stability as **2**, the 2,6-bischloro compound **5** showed a much higher stability, with the 2,6-bismethyl compound **6** being the most stable under acidic conditions (pH 5) (see the Supporting Information). The stability of these compounds toward neutral and slightly basic conditions (pH 7, water, and 9) appeared to be increased. Notably, **5** and **6** were stable under the routinely applied LCMS conditions. These results clearly showed that it is in principle possible to increase stability of the boratriazaroles in a wider pH range.

It was interesting to notice that the condensation reaction (as given in Table 2) between **1** and 2- or 4-pyridylboronic acid did

Table 2. Scope and Limitations

1 3-14

entry	R	solvent	product	yield (%)
1	Me	THF[a]	**3**	47
2	2,6-$F_2C_6H_3$	MeOH[b]	**4**	56
3	2,6-$Cl_2C_6H_3$	MeOH[c]	**5**	47
4	2,6-$Me_2C_6H_3$	MeOH[d]	**6**	26
5	1-naphthyl	DMF[e]	**7**	52
6	2,5-Me_2-3-thienyl	DMF	**8**	56
7	2,4-$Me_2C_6H_3$	DMF	**9**	62
8	(E)-CH=CH-*p*-toluyl	DMF	**10**	50
9	2-$(CF_3)C_6H_4$	DMF	**11**	58
10	2,6-$(MeO)_2$-3-pyridyl	DMF	**12**	55
11	2-pyridyl	MeOH[f]	**13**	0
12	4-pyridyl	MeOH[g]	**14**	0

[a]7 d at 95 °C. No reaction in MeOH at 95 °C. [b]95 °C for 2 h. [c]90 °C for 17 h. [d]95 °C for 1 d. [e]Entries 5–10: the reaction was stirred for 3 h at 100 °C. [f]No product formation in MeOH (95 °C) or in pyridine (90 °C). [g]In MeOH at 95 °C, only the formation of bismethoxy ester of the boronic acid was observed.

not proceed at all (see entries 11 and 12, respectively) under the tested conditions. In the case of 4-pyridylboronic acid, the only product isolated was the bismethoxy ester of 4-pyridylboronic acid, which could potentially serve as a coupling partner itself for the formation of **14**. Unfortunately, we could not see any product formation under the same conditions as described in Table 1 or 2 if the latter compound was used as a boronic ester source. Changing reaction conditions such as temperature and time were unsuccessful in delivering **14**. Interestingly, more electron-rich pyridine systems such as 2,6-$(MeO)_2$pyridine boronic acid (see entry 10 in Table 2) afforded the condensation product **12**. This example indicated that subtle electronic and steric effects might be a key for the successful outcome of the condensation reaction.

To have a broader view about the structure–stability profile of boratriazaroles, we resorted to the help of our in-house chemistry automation laboratory, where a set of 47 different boronic acids (aromatic, vinylic, and aliphatic) were screened (Scheme 2). Amidrazone **1** was reacted with a specific boronic acid in DMF at 95 °C for 1 h, and the reaction was followed by LCMS analysis (method omitting formic acid). Aliquots of the crude reaction

Scheme 2. Procedure for the Automation Lab Study

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mixtures of the resulting boratriazaroles were diluted in a mixture of DMSO and an equivalent amount of aqueous phosphate buffer pH 7. For each of these boratriazarole solutions, the stability as a function of time was determined once a day over a period of 1 week. The evalution of these data led to a stability rating of the compounds, of which the seven most stable candidates (**6**–**12**, see entries 4–10, Table 2) were selected for a detailed stability analysis. It should be emphasized that this first series of 47 boratriazaroles can give only a rough idea of the order of hydrolytic stability because the products have not been isolated in pure form.

Compounds **6**–**12** (see entries 4–10, Table 2) were then prepared in pure form, according to the conditions in Table 1 (DMF as solvent, see the Supporting Information), and the stability of each compound as a function of time was determined over a period of 3 weeks, where in the first day, a measurement was acquired every 3 h. Furthermore, in the first week, every day one measurement was acquired and for the remaining 2 weeks, one measurement per week was performed. 3-Methylbiphenyl was taken as the internal standard for the determination of the stability analysis including the half-life times.[11]

Figure 3 represents the stability profile for compounds **6**–**12** for the first 24 h at pH 5.

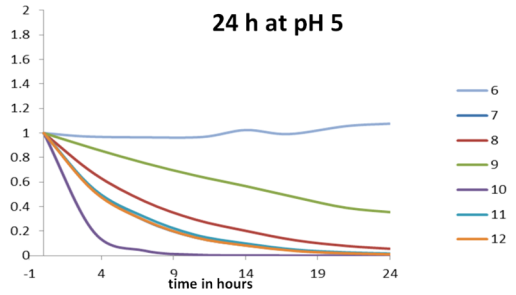

Figure 3. Overview of the stability profiles of compounds **6**–**12** in aqueous buffer pH 5 over 24 h.

The graph clearly shows that all except one compound exhibit pronounced decomposition within the first few hours. Compound **6** appeared to be the most stable compound followed by the slightly less stable product **9**, which is the ortho/para-disubstituted phenyl isomer of **6**. The rather good correlation with a linear decomposition kinetics over 24 h for **9** allowed the determination of the half-life time $t_{1/2}$ as given in Table 3.

Table 3. Determination of Half-Life Time $t_{1/2}$ for Compound 9[a]

conditions	DMSO	pH 5	pH 7	H_2O
$t_{1/2}$ (h)	stable after 3 months	17.2	24.3	86.2

[a]See the Supporting Information for decomposition kinetics and linear regression.

Figure 4 shows the stability profile of compounds **6**–**12** over 3 weeks. Whereas all other compounds readily decomposed after 1 week at ambient temperature, compound **6** was stable over 3 weeks.

A similar stability profile was seen for compounds **6**–**12** at neutral pH value and in water, where all except compound **6** were decomposed after 1 week (Figure 5). Interestingly, in water (pH 7), compound **9** was a bit more stable than in aqueous buffer at

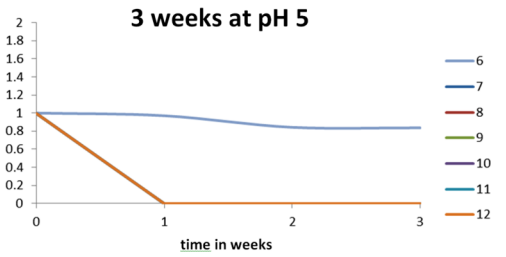

Figure 4. Stability of compounds **6**–**12** over a 3-week period in aqueous buffer pH 5.

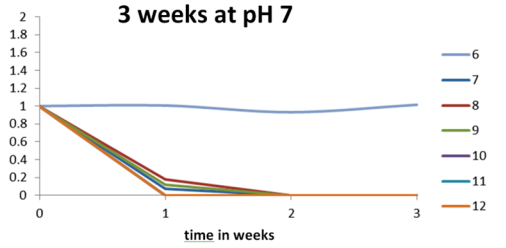

Figure 5. Stability of compounds **6**–**12** over 3 weeks in aqueous buffer pH 7.

pH 7. This indicates that the stability might also be related to ionic effects (a figure for stability in H_2O is shown in the Supporting Information).

The stability of the tested compounds appears to be slightly better at basic pH values (see Figure 6) compared to neutral or

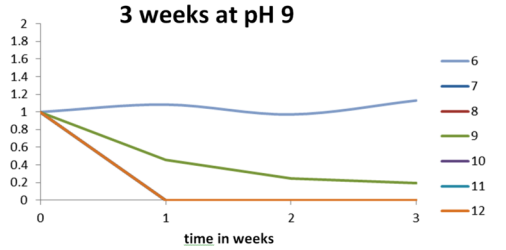

Figure 6. Stability of compounds **6**–**12** over 3 weeks in aqueous buffer pH 9.

acidic conditions. This was along the lines with the results we obtained from our preceding HSS screening cascade. Again, **6** was completely stable over the time range of 3 weeks, and in addition, compound **9** showed better stability than at lower pH values (pH 5 and 7).

Interestingly, all compounds were perfectly stable over 3 weeks in DMSO, which is good news for use of such compounds for biological testing (a figure for stability in DMSO is shown in the Supporting Information). In addition, ^{1}H NMR analysis identified compounds **2**–**4** to be perfectly stable over 4 months of measurement, and most probably this is valid for the whole class of boratriazaroles as discussed in this work.

We have studied the condensation reaction of amidrazone **1** and different arylboronic acids to gain access to boratriazaroles, which are bioisosteres of pyrazoles and imidazoles. For the first time, we provide stability data of such compounds (such as **6**–**12**) at different pH values in water and in DMSO solution. In general, we found that the stability appears to be better at higher pH values as compared to lower pH. From the screening of differently substituted boratriazaroles (**2** compared to **4**–**12**), a significant increase of stability within the tested pH range was

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found. Stability correlated with ortho substitution on the aryl residue at the boron atom, compared to phenyl derivative **2**. Introduction of two ortho substituents on the phenyl residue provided compound **6** showing the highest stability, where no hydrolysis was observed even at pH 5 over the time period of the experiment (3 weeks). Interestingly, the isomer of **6**, compound **9** (ortho/para substituted), showed a reduced stabilty profile at all pH values tested, indicating that steric effects count more for the stabilization of the boratriazaroles than electronic effects.

Further studies will be necessary for a more detailed understanding of how this rather unexplored class of heterocycles can be stabilized in other ways and, thus, might find application in the agrochemical or pharmaceutical industry as potential replacement of imidazoles or pyrazoles.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, results of the initial stability study of 47 boratriazaroles, spectral data of the products, and copies of the ^{1}H, ^{13}C, and ^{11}B NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(11) Note: An internal standard was used to avoid an overlap of LCMS UV signals of the products and decomposition products **1** and the corresponding boronic acid.