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Borylated Oximes: Versatile Building Blocks for Organic Synthesis

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Abstract

Herein, we demonstrate the synthesis and functionalization of α -boryl aldoximes from α -boryl aldehydes, with no sign of c-to-n boryl migration. selective modification of the oxime functionality enables access to a wide range of borylated compounds, such as borylated heterocycles and *N*-acetoxyamides. by reducing the α -boryl aldoximes, mild deprotection yields the corresponding β -boryl hydroxylamines. as part of this study, we also demonstrate the utility of the boryl aldoxime motif in peptide conjugation.

Oximes represent a class of highly diverse compounds that have found utility in numerous synthetic applications. The oxime functionality can be introduced into a molecule through the condensation between carbonyls and hydroxylamines, nitrosation of hydrocarbons, and reduction of nitro compounds.¹ The resulting oximes can be subsequently applied towards the synthesis of more complex structures. Oximes have been utilized in the synthesis of nitrile oxides^{2,3} to afford a variety of cycloadducts such as isoxazolines,⁴ isoxazoles⁵ and oxadiazoles.⁶ Metal-catalyzed rearrangements of oxime-containing molecules have also yielded biologically relevant structures, such as oxazepines,⁷ pyridols,⁸ pyridines,⁹ and pyrroles.¹⁰

Compared to imines and hydrazones, oximes exhibit much greater hydrolytic stability.¹¹ The relative stability of oximes compared to their imine analogues can be attributed to the electron donating ability of the oxygen lone pair, which causes a decrease in the electrophilicity of the carbon center and makes the oxime adduct less prone to hydrolysis.¹² In addition, oximes are less prone to protonation at the imine nitrogen position due to the inductive effects of the hydroxyl group.¹¹ As a result of their intrinsic hydrolytic stability, oximes are also desired functional moieties in bioconjugation chemistry.¹³

Among the numerous strategies,¹⁴ oxime ligation is an attractive approach because it is chemoselective and compatible with most biomolecule functionalities.¹² Another method to conjugate biomolecules is through the use of aryl boronic acids, which can either act as the conjugate unit,¹⁵ enhance the properties of a particular ligand,¹⁶ form stable adducts with the

linkage,¹⁷ or catalyze its formation.¹⁸ Recently, it has been demonstrated that proximal boronic acids are able to increase the rate of oxime condensation at neutral pH.¹⁹

Beyond applications in bionconjugation, molecules containing both oxime and boronic acid functional moieties have been applied towards the synthesis of boron-containing heterocycles, such as borylated pyridines²⁰ and benzoxaborines.²¹ Additionally, studies on the asymmetric reduction of β -boronate oxime ethers to their corresponding amine have been conducted.²² Despite the prevalence of borylated oximes in the literature, compounds containing an oxime alpha to an aliphatic boronate have not been previously reported (Figure 1). This connectivity and the use of an aliphatic boronate is expected to influence the properties of the corresponding borylated oximes providing access to novel borylated compounds. Inspired by the utility of oximes in both chemical biology and synthetic chemistry, we became interested in utilizing the amphoteric α -*N*-methyliminodiacetyl (MIDA) boryl aldehyde²³ to access α -MIDA boryl aldoximes and study their corresponding reactivity profile and application.

Previous attempts to condense α -boryl aldehydes and primary amines has been met with some difficulty. For instance, the major product of condensation with aniline is the *N*-boryl enamine, which is the result of a 1,3-migration of the boryl group from carbon-to-nitrogen.^{24,25} This is in contrast to condensation with *tert*-butylsulfonamide, where the *C*-boryl imine is the major product with *N*-boryl enamine as the byproduct. Boron migration from carbon-to-nitrogen leads to a decrease in hydrolytic stability and product decomposition. We have since reported a number of methods to circumvent the boryl migration through *in situ* trapping of the condensation intermediates. These include trapping the enamine intermediate *via* the addition of an acyl halide to produce *C*-boryl enamides,²⁶ or alternatively, trapping the imine species *via* reductive amination.²⁵ Herein, we present a new strategy to overcome 1,3-boryl migration. The condensation between α -boryl aldehyde and hydroxylamine exclusively furnishes α -boryl aldoximes with no signs of boryl migration. By preserving the C–B bond, we were able to modify the oxime group in the vicinity of boron.

The condensation between α -boryl aldehyde (**1**) with hydroxylamine (**2**) in the presence of catalytic aniline²⁷ and under pH buffered conditions in acetonitrile successfully afforded α -MIDA boryl aldoximes **3a** – **3e**. Full conversion of the aldehyde into the desired α -boryl aldoxime was achieved with excess hydroxylamine hydrochloride in less than 30 minutes. In most cases, the product readily decomposed when reacted for longer than 30 minutes. Fortunately, performing a work-up immediately after reaction completion led to the isolation of various α -boryl aldoximes in high yields (Table 1). The substituted boryl aldehydes yielded the *E*-aldoxime, while unsubstituted aldoxime **3c**, existed as a 1.5:1 *E*:*Z* mixture as determined by ¹H NMR spectroscopy. Aldoxime **3b** was crystallized from deuterated acetonitrile to obtain X-ray quality crystals. In the crystal, two molecules of the *E*-aldoxime participate in intermolecular hydrogen bonding in a dimeric fashion (Figure 2). In addition to the unsubstituted aldoximes, *O*-benzyl aldoximes were accessed under a different set of conditions (Table 1). Aldoximes **4a** – **4c** were obtained in good yields *via* the condensation of α -boryl aldehyde and *O*-benzylhydroxylamine hydrochloride with triethylamine in acetonitrile at 50 °C.

We investigated the synthesis of MIDA boryl oxadiazoles and isoxazoles through the use of our α -boryl aldoxime. The aldoximes were treated with *N*-chlorosuccinimide (NCS) in DMF to afford the aldoximoyl chlorides (**5**), which were unstable to purification. The crude product was immediately subjected to triethylamine and superstoichiometric equivalents of nitriles to furnish the corresponding benzylic MIDA boryl oxadiazoles in moderate to excellent yields. A number of substrates were synthesized from acetonitrile (**7a**), trichloroacetonitrile (**7b** – **7c**), benzonitrile (**7d** – **7f**) and 2-fluorobenzonitrile (**7g**, Scheme 1). In addition to cycloaddition with nitriles, electrophilic alkynylesters, such as dimethyl acetylenedicarboxylate (DMAD) and ethyl-2-butyrate were also competent dipolarophiles to furnish substituted isoxazoles **7h** – **7j**.

Aldoximes have been used towards the synthesis of *N*-acetoxyamides, which are present in a variety of biologically active molecules with anti-inflammatory, anti-asthmatic, and anti-cancer properties.²⁸ In the presence of diacetoxyiodobenzene and acetic acid, aldoximes are converted to the nitrile oxide (**6**) *in situ* and trapped by acetic acid (**8**) to give the desired *N*-acetoxyamide after an intramolecular acyl transfer from C-to-O. We found the transformation to be compatible with the MIDA protecting group and produced the boron containing *N*-acetoxyamide products **9a** – **9d** in good yields (Scheme 2).

MIDA boronates have been successfully deprotected to the free boronic acid using mild aqueous acid and base in various solvents.^{25,29} With a number of α -boryl aldoximes and their downstream derivatives in hand, we sought to investigate their compatibility under MIDA deprotection conditions. A series of variations were attempted, such as stirring the compounds in aqueous NaOH or HCl, however, exclusive formation of the protodeboronated products was observed. Empirically, we came to the conclusion that sp^3 MIDA boronates with a β - sp^2 center to boron were unstable as their free boronic acids (Figure 2a). Recently, our group demonstrated that the reductive conjugation of α -boryl aldehydes with a variety of amines followed by MIDA deprotection is an efficient route to hydrolytically stable β -aminoboronic acid derivatives.^{25,30} In contrast, these products contain a β - sp^3 center relative to boron, which are more stable compared to the β -imino boronic acids (Figure 2b). Using this knowledge to our advantage, we attempted the synthesis of β -boryl hydroxylamine derivatives by employing our α -boryl aldoximes. A number of conditions were screened for the reduction of *O*-benzylaldoxime **4a**, wherein sodium cyanoborohydride in a 2:1 acetonitrile:water mixture with 6 equivalents of HCl led to full conversion in 15 minutes (Scheme 3). The hydroxylamines were unstable to normal phase silica gel chromatography, but were isolable using reverse phase flash chromatography in good yields (**10a** – **10b**). These reduction conditions were not compatible with the unprotected aldoxime **3a** and the major product observed by LC/MS analysis was the protodeboronated hydroxylamine.

The synthesized β -MIDA boryl hydroxylamines were then subjected to MIDA deprotection conditions. Compounds **10a** and **10b** were stirred in 10 equivalents of sodium bicarbonate in a 20:1 MeOH:H₂O mixture. The desired boronic acids were detected by LCMS and confirmed by ¹¹B NMR spectroscopy, wherein a diagnostic change in chemical shift from 12 ppm to 30 ppm was observed. The products were purified by reverse phase flash chromatography and isolated in good yields (**11a** and **11b**, Scheme 3). In agreement with our hypothesis, reduction of the oxime to the corresponding hydroxylamine enabled

successful MIDA deprotection, since sp^3 MIDA boronates are stable as their corresponding free boronic acid when they are beta to a sp^3 carbon center.

Based on their high stability and straightforward preparation, oxime ligation has become a commonly employed strategy for conjugating biologically relevant molecules. Guided by boron's versatility in chemical biology,^{15–19} we sought to demonstrate the facile conjugation of our MIDA boronates onto a biomolecule. Aminoxyacetyl-functionalized peptide **12** was dissolved in pH 4.5 sodium acetate buffer and combined with two equivalents of MIDA-boryl aldehyde **1c** (Figure 3a). Clean conversion into the desired borylated peptide **13** was achieved in one hour at room temperature. Liquid chromatography-mass spectrometry (LC-MS) was utilized to confirm the presence of product (Figure 3b). Recently, it has been reported that alkyl boronic acids associate strongly with carbohydrate derivatives.³⁰ This conjugation approach has the potential to equip biologically relevant architectures with saccharide-binding abilities.^{16,30} Additionally, this methodology represents an attractive route to produce isotopically labelled peptides.³¹

In summary, we have demonstrated the mild synthesis of a novel class of amphoteric building blocks – α -boryl aldoximes. We successfully applied these molecules towards the synthesis of previously inaccessible MIDA boryl oxadiazoles, isoxazoles, and borylated *N*-acetoxyamides. The reduction and subsequent MIDA deprotection of α -boryl aldoximes led to the isolation of β -boryl hydroxylamines. We demonstrated the value of our approach by applying it towards the conjugation to an aminoxyacetyl-functionalized peptide. Through a simple and efficient oxime linkage we can incorporate an alkyl boronate onto a biological target of interest and modify its properties.

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Figure 1.
The α -boryl aldoxime motif.

Figure 2.
Molecular structure of α -MIDA boryl aldoxime **3b**.

Figure 2.
Hypothesized trends of boronic acid stability.

Figure 3.

a. Oxime ligation of aminoxyacetyl-functionalized peptide **12** with MIDA-boronic aldehyde **1c**. A 250 μM solution of **1c** in MeCN was combined with a 500 μM solution of **12** in 50 mM pH 4.5 sodium acetate buffer. The final volume was brought to 1 mL using the buffered solution and the reaction was carried out for one hour at 25 $^{\circ}\text{C}$. Following filtration, the sample was run on LC-MS to confirm and detect product. **b.** LC-MS trace of the starting material (top) and crude conjugation reaction (bottom).

Scheme 1. Selective oxidation and cycloaddition of α -MIDA boryl aldoximes.

Scheme 2.
Synthesis and scope of borylated *N*-acetoxyamides.

Scheme 3.
Preparation of boron-containing hydroxylamines.

Table 1Preparation of α -MIDA boryl aldoximes.

Entry	R ¹	R ²	Product	Yield (%) ^a
1	phenyl	H	3a	80 ^b
2	cyclohexyl	H	3b	75 ^b
3	H	H	3c	75 ^b (1.5:1 <i>E:Z</i>)
4	benzyl	H	3d	94 ^b
5	isobutyl	H	3e	95 ^b
6	phenyl	benzyl	4a	80 ^c (11:1 <i>E:Z</i>)
7	benzyl	benzyl	4b	88 ^c
8	isobutyl	benzyl	4c	93 ^c

^a Isolated yields after flash column chromatography.^b Reaction conditions: **1** (1 equiv.) and **2** (3 equiv.) dissolved in 1:1 MeCN: 0.1 M pH 4.5 sodium acetate buffer (0.1 M). Aniline (1 equiv.) added and stirred for 10-30 mins.^c **1** (1 equiv.) and **2** (1.5 equiv.) dissolved in MeCN (0.2 M). Et₃N (1.5 equiv.) added and stirred at 50 °C for 48 h.