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# 1,3-Dipolar cycloadditions of azomethine ylides to alkenylboronic esters. Access to substituted boron analogues of β-proline and 3-hydroxypyrrolidines

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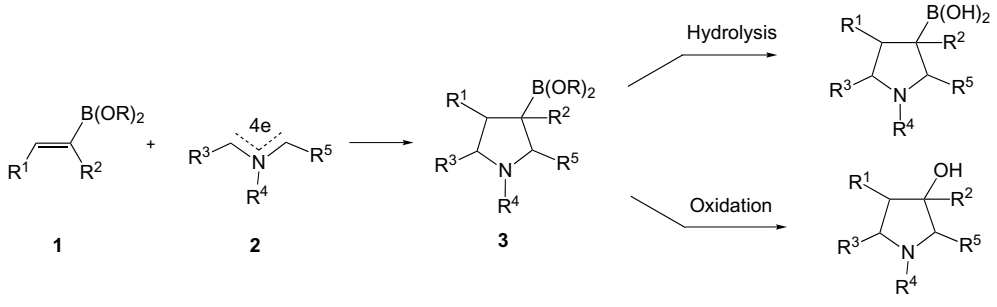
**Abstract**—3-Boronic esters-substituted pyrrolidines were prepared via 1,3-dipolar cycloadditions of azomethine ylides to alkenyl boronates. Hydrolysis gave boron analogues of substituted β-prolines, while treatment with trimethylamine oxide afforded the corresponding pyrrolidin-3-ols.


Boronic acid-based enzyme inhibition has emerged three decades ago with the discovery of good inhibitors of chymotrypsin.[1] Since these pioneering works, significant advances have been obtained in this field, mainly as regards inhibition of thrombin,[2] proteasome[3] and dipeptidyl-peptidase IV.[4] Because boronic acids easily interconvert between the neutral $sp^2$ (trigonal planar substituted) and the anionic $sp^3$ (tetrahedral substituted) hybridization states, inhibition of proteases and other hydrolytic enzymes has been based on a close structural similarity between a tetrahedral boronate fragment and the tetrahedral intermediate in the enzymatic sequence.[5] Boron-containing amino acid derivatives have been also examined as potential agents for treatment of cancer in boron neutron capture therapy (BNCT) strategy.[6] If most of these compounds possess an α-aminoboronic acid moiety, other boron derivatives have also recently attracted attention due to their β-lactamase, arginase or γ-glutamyltranspeptidase activities.[7] In the course of our ongoing programme related to the synthesis of bioactive organoboranes,[8] we here report an efficient route to substituted boron analogues of β-proline[9,10] via 1,3-dipolar cycloadditions of azomethine ylides **2** to alkenyl boronates **1**. Heterocyclic cycloadducts **3** are also good precursors of the corresponding pyrrolidin-3-ols by treatment with triethylamine oxide (Scheme 1).




**Scheme 1.**

*Keywords*: Boronic esters; Dipolar cycloaddition; Azomethine ylide; Aminoacids analogues; Pyrrolidines.
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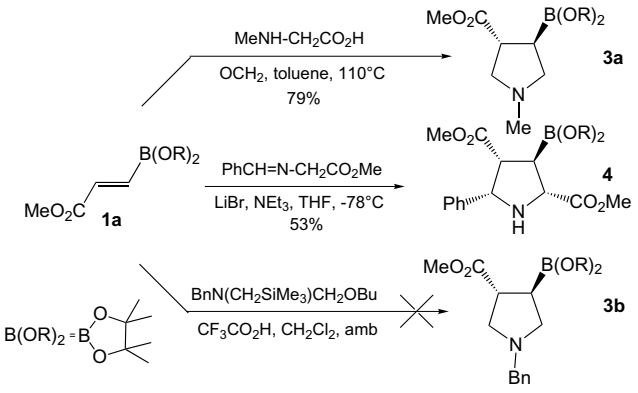
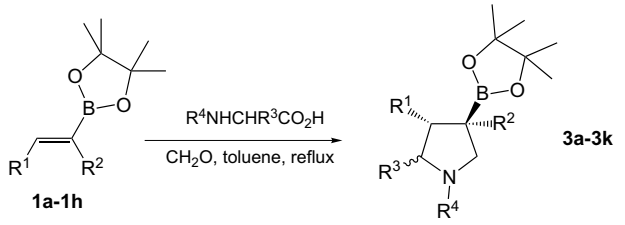
Recently, several groups have examined the reactivity of various 1,3-dipoles, as diazoalcanes,[11] nitrones[12] and nitrile oxides,[13] towards alkenyl boronic esters. In continuation of our efforts in this area, we have investigated the hitherto unreported [3+2] cycloadditions of azomethines ylides **2** to this class of dipolarophiles. We first selected activated boronate **1a** ($R^1 = CO_2Me$, $R^2 = H$), prepared by hydroboration of methyl propiolate,[14] and explored various methods of azomethine ylide generation. Treatment of benzylideneimine of methylglycinate with $Et_3N$ in the presence of LiBr[15] or heating a mixture of formaldehyde and sarcosine[16] afforded the expected cycloadducts as single diastereoisomers and good yields. In our hands, despite several attempts, the use of *N*-trimethylsilylmethyl *N*-butyloxymethyl benzylamine in the presence of trifluoroacetic acid as dipole precursor[17] was unsuccessful (Scheme 2). The structures of **3a** and **4** were assigned on the basis of their $^1H$ and $^{13}C$ NMR spectra by comparison with similar reported pyrrolidines.[18,19] The regiochemistry (2,4-dicarboxylate structure) and the 4,5-*cis* configuration of **4** were confirmed by the shielding of the 4-$CO_2CH_3$ by the adjacent 5-phenyl group. Furthermore, the values of coupling constants $J_{H_2-H_3} = 9.5$ Hz, $J_{H_3-H_4} = 8.3$ Hz and $J_{H_4-H_5} = 8.3$ Hz are also very close to those measured when methyl crotonate or cinnamate were used as dipolarophile instead **1a**, that is in agreement with an *endo* cycloadduct of the *syn* form of N-lithiated azomethine ylide.[20]

Following this initial study, we then turned our attention to other alkenylboronic esters **1b**–**1h** with different electronic properties. These organoboranes were prepared by borylation of vinylmagnesium bromide ($R^1$, $R^2 = H$, **1b**),[21] hydroboration of an alkyne ($R^1 = Ph$, $R^2 = H$, **1c** and $R^1 = PhS$, $R^2 = H$, **1f**),[14] halosulfonylation–dehydrohalogenation reactions ($R^1 = TolSO_2$, $R^2 = H$, **1d** and $R^1 = TolSO_2$, $R^2 = Me$, **1e**)[22] or functional modification of **1f** and **1a** ($R^1 = PhSO$, $R^2 = H$, **1g** and $R^1 = CONHCH(CH_3)Ph$, $R^2 = H$, **1h**).[14] We selected the decarboxylative route to generate nonstabilized azomethine ylides **2** from formaldehyde and *N*-methyl-, *N*-benzylglycine or proline (Scheme 3).[23]

As outlined in Table 1, the reaction proceeded readily with satisfactory yields with alkenyl boronic esters possessing an electron-withdrawing group as ester, sulfone or amide (entries 1–3, 6–8 and 11). The presence of this activating group is essential since no adduct was detected with the monosubstituted olefin **1b** ($R^1 = H$) and styrylboronate **1c** ($R^1 = Ph$) (entries 4 and 5). The boronate **1f**, with an electron-donating substituent ($R^1 = SPh$), failed to react (entry 9), while the sulfoxide **1g** ($R^1 = SOPh$) was completely consumed. However, the expected cycloadduct underwent an elimination reaction of phenylsulfinic acid to afford a pyrroline derivative. As previously observed in Diels–Alder reaction[24] and radical addition,[25] the boronate group provides little if any of the activation of the double bond towards azomethine cycloaddition. In the case of alk-




**Scheme 2.**




**Scheme 3.**

**Table 1.** Synthesis of 3-boronate pyrrolidines **3**

| Entry | Boronate | $R^1$ | $R^2$ | $R_3$, $R_4$ | Yield (%)[a] |
|---|---|---|---|---|---|
| 1 | **3a** | $CO_2Me$ | H | H, Me | 79 |
| 2 | **3b** | $CO_2Me$ | H | H, $PhCH_2$ | 85 |
| 3 | **3c** | $CO_2Me$ | H | $(CH_2)_3$ | 66[b] |
| 4 | **3d** | H | H | H, Me | — |
| 5 | **3e** | Ph | H | H, Me | — |
| 6 | **3f** | $TolSO_2$ | H | H, Me | 57 |
| 7 | **3g** | $TolSO_2$ | Me | H, $PhCH_2$ | 64 |
| 8 | **3h** | $TolSO_2$ | Me | H, Me | 59 |
| 9 | **3i** | PhS | H | H, Me | — |
| 10 | **3j** | PhSO | H | H, Me | [c] |
| 11 | **3k** | PhCH(Me)NHCO | H | H, Me | 53[d] |

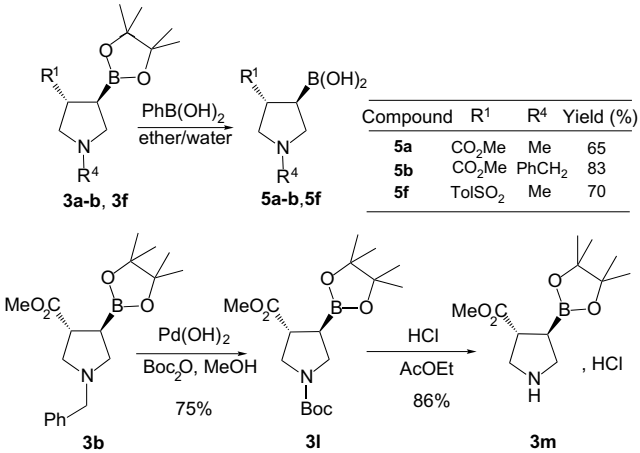
[a] Yield of isolated product after purification.
[b] Mixture of regio- and stereoisomers.
[c] Formation of a pyrroline derivative by loss of phenylsulfinic acid.
[d] Mixture of diastereoisomers (1/1).

enes **1a** and **1d**, the reactivity is similar to the methylacrylate or phenylvinyl sulfone. It is also worthy to note that the cycloadditions of azomethine ylide **2** ($R^3 = R^5 = H$, $R^4 = Me$) with optically active alkenyl boronic esters **1a′** and **1d′**, respectively, prepared by transesterification of **1a** and **1d** with (+)-pinanediol, afforded the corresponding cycloadducts with no diastereoselectivity (1/1).

Pyrrolidines boronates were easily converted to the corresponding boronic acids **5** in a mild way by transesterification with phenylboronic acid according to the method of Coutts and co-workers (Scheme 4).[26–28] Alternately, since the NH derivative of aminoboronate are required to synthesize boropeptides by coupling reactions with protected amino acids,[29] we first attempted the direct hydrogenolysis of **3b**, selected as an example, in the presence of Pd/C.[30] Unfortunately, only mixtures of inseparable compounds were then obtained. By contrast, when the cleavage of the C–N bond was carried out in the presence of $Boc_2O$ and $Pd(OH)_2$ as catalyst, the corresponding carbamate **3l** was obtained in a 75% yield.[31] Treatment with HCl in EtOAc afforded the hydrochloride **3m** in a 86% yield.[32]

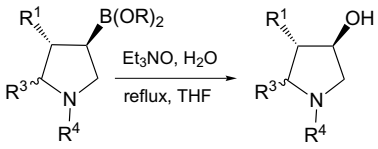
Moreover, the versatility of the organoboranes creates the potential to prepare functionalized pyrrolidines from cycloadducts **3**.[33] In this preliminary study, we only examined the oxidative replacement of the carbon–boron bond by a carbon–oxygen bond. In our hands, all attempts to achieve this transformation with hydrogen peroxide in the presence of sodium hydroxide or a phosphate buffer were unsuccessful. We were delighted to find that treatment with triethylamine oxide[34] in refluxing THF afforded the pyrrolidin-3-ol in good yields after purification by column chromatography (Scheme 5).[35]

In conclusion, we have developed a novel and practical method for the preparation of 3-boronic esters-substituted pyrrolidines, which are convenient precursors of the corresponding pyrrolidin-3-ols or β-proline analogues. Further studies including the development of an asymmetric variation using chiral azomethine ylide and the incorporation of the corresponding β-aminoboronic acids in peptidic chains are currently under investigation.




| Compound | $R^1$ | $R^4$ | Yield (%) |
|---|---|---|---|
| **5a** | $CO_2Me$ | Me | 65 |
| **5b** | $CO_2Me$ | $PhCH_2$ | 83 |
| **5f** | $TolSO_2$ | Me | 70 |

**Scheme 4.**




| Compound | $R^1$ | $R^3$, $R^4$ | Yield (%) |
|---|---|---|---|
| **6a** | $CO_2Me$ | $PhCH_2$ | 59 |
| **6c** | $TolSO_2$ | $-(CH_2)_3-$ | 47[a,b] |
| **6g** | $TolSO_2$ | $PhCH_2$ | 61 |

[a] Mixture of regio- and diastereoisomers.
[b] Cumulated yield from **1d** and proline

**Scheme 5.**

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18. **3a**. $Eb_{0.05}$ = 80–85 °C, 79%. $^1$H NMR (200 MHz, $CDCl_3$, $\delta$ ppm, $J$ Hz): 3.67 ($OCH_3$, s, 3H), 3.16–3.04 (m, 1H), 2.97–2.89 (m, 1H), 2.86 (t, $J$ = 8.5, 1H), 2.57 (t, $J$ = 8.5, 1H), 2.36 (t, $J$ = 8.5, 1H), 2.32 ($NCH_3$, s, 3H), 1.96 (q, $J$ = 8.5, 1H), 1.17 (s, 12H). $^{13}$C NMR (50 MHz, $CDCl_3$): 175.7 (C), 83.9 (C), 59.3 ($CH_2$), 58.6 ($CH_2$), 52.2 ($CH_3$), 45.4 (CH), 42.2 ($CH_3$), 25.0 ($CH_3$) (the resonance of the carbon α to boron was not detected). Anal. calcd for $C_{13}H_{24}BNO_4$ (269.15): C, 58.01; H, 8.99; N, 5.20. Found: C, 57.6; H, 8.9; N, 4.8.
19. **4**. Mp = 156–158 °C, 53%. $^1$H NMR (200 MHz, $CDCl_3$, $\delta$ ppm, $J$ Hz): 7.30–7.18 (m, 5H), 4.51 (d, $J$ = 8.3, 1H), 3.93 (d, $J$ = 9.5, 1H), 3.78 (s, 3H), 3.34 (t, $J$ = 8.3, 1H), 3.18 (s, 3H), 2.40 (br s, 1H), 2.10 (dd, $J$ = 8.3 and 9.5, 1H), 1.22 (s, 12H). $^{13}$C NMR ($\delta$ ppm): 174.0 (C), 172.8 (C), 140.1 (C), 128.5 (CH), 127.9 (CH), 127.4 (CH), 84.3 (C), 66.0 (CH), 63.1 (CH), 53.8 (CH), 52.6 ($CH_3$), 51.6 ($CH_3$), 25.0 ($CH_3$), 24.9 ($CH_3$) (the resonance of the carbon α to boron was not detected). HRMS $m/z$ calcd for $C_{19}H_{27}BNO_4$ $(M-CO_2CH_3)^+$ 344.20331, found 344.2056.
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23. To 10 mmol of vinylboronate **1** dissolved in dry toluene (40 mL) was added, under magnetic stirring, 2 equiv (20 mmol) of sarcosine and 2 equiv of $CH_2O$ (50 mmol). The reaction mixture was refluxed for 12 h with removing of the formed water by means of a Dean Stark trap. A second addition of the same amount of formaldehyde was done after 2 h of reflux. The oil bath was removed and the mixture was then allowed to cool to room temperature. After filtration of the solid material, the filtrate was concentrated under reduced pressure. The residue was purified by distillation with Kügelrhor apparatus or by recrystallization.
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32. **3m**. 86%. $^1$H NMR (200 MHz, $D_2O$, $\delta$ ppm, $J$ Hz): 3.69–3.40 (m, 3H), 3.68 (s, 3H), 3.20–3.32 (m, 1H), 3.11 (t, $J$ = 11.8, 1H), 1.93–1.84 (m, 1H). 1.12 (s, 12H). $^{13}$C NMR ($\delta$ ppm): 174.0 (C), 75.6 (C), 52.9 ($CH_3$), 48.6 (CH), 46.7 ($CH_2$), 45.2 ($CH_2$), 23.7 ($CH_3$) (the resonance of the carbon α to boron was not detected).
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35. Selected NMR data for **6g**: 61%. $^1$H NMR (200 MHz, $CDCl_3$, $\delta$ ppm, $J$ Hz): 7.69 (d, $J$ = 8.2, 2H), 7.27 (d, $J$ = 8.2, 2H), 7.20–7.12 (m, 5H), 4.61 (q, $J$ = 4.1, 1H), 3.64 (d, $J$ = 12.9, 1H), 3.62–3.40 (m, 1H), 3.48 (d, $J$ = 12.9, 1H), 3.16 (br s, 1H), 2.95 (dd, $J$ = 8.5 and 10.2, 1H), 2.74–2.63 (m, 3H), 2.37 (s, 3H). $^{13}$C NMR ($\delta$ ppm): 144.0 (C), 136.3 (C), 134.2 (C), 129.0 (CH), 127.7 (CH), 127.4 (CH), 127.2 (CH), 126.3 (CH), 70.5 (CH), 70.4 (CH), 60.4 ($CH_2$), 58.3 ($CH_2$), 51.7 ($CH_2$), 20.6 ($CH_3$). HRMS $m/z$ calcd for $C_{18}H_{21}NO_3S(M)^+$ 331.12422, found 331.1218.