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1,3-Dipolar Cycloadditions to Unsaturated Organoboranes . III - Regio- and Stereocontrolled Access to Boronic Ester Substituted Isoxazolidines.

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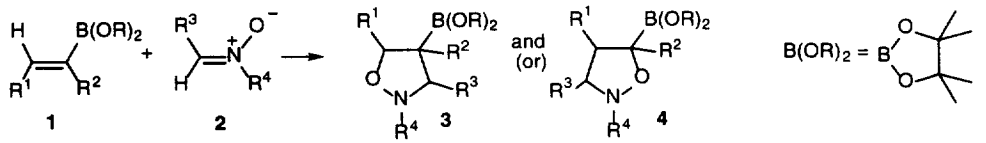
Abstract : Alkenylboronic esters undergo regio- and stereoselective 1,3-dipolar cycloadditions with nitrones. These reactions give access to boronic ester substituted isoxazolidines which can be easily converted by oxidation with hydrogen peroxide to the corresponding 4-hydroxy derivatives.

The 1,3-dipolar cycloaddition of nitrones to carbon-carbon double bonds is a well-established synthetic protocol to prepare isoxazolidines, an important class of heterocycles. Additions to a large variety of alkenes have been reported and the resulting cycloadducts have served as precursors to a diverse array of cyclic and acyclic compounds.[1] To the best of our knowledge, alkenyl boronic esters **1** have been hitherto exclusively used as substrates in diazoalkane [2] and nitrile oxide [3,4] cycloadditions. Unfortunately,these reactions often generated a carbon-nitrogen double bond α to the boron atom. Only *in situ* oxidation can then be successfully performed before a spontaneous 1,3-boratropy and, finally, the loss of the borylated moiety.[5] As a part of our ongoing interest in the exploitation of α,β-unsaturated organoboranes in pericyclic reactions, we have investigated the cycloadditions of nitrones to alkenyl boronic esters (Scheme 1). Coupling the synthetic potential of isoxazolidines with the great versatility of organoboranes [6] should allow the access to a wide variety of structures not easily available from other routes.



Scheme 1

The pinacol alkenyl boronic esters **1** were readily prepared by hydroboration of alkynes or borylation of alkenyl metals according to the literature procedures.[6] Our initial studies involved the use of the highly reactive

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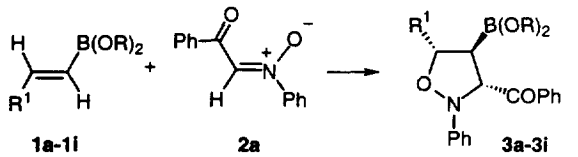
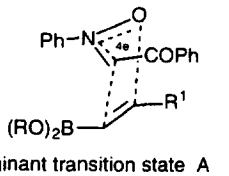
C-benzoyl-N-phenyl nitrone **2a** (R^3=PhCO, R^4=Ph).[7] The cycloadditions were carried out under mild conditions at room temperature in toluene and the resulting cycloadducts **3a-3h** were obtained in good yields in a regio- and stereochemically pure form with no evidence of any other diastereoisomers in the ^{1}H NMR spectra or TLC of the crude products (Scheme 2, Table 1).[8,9] The structures of **3a**, **3b** and **3i** were established unambiguously by X-ray crystal analysis.[10] They both present a *trans* relationship at C_3-C_4 stereocenters and, for **3b** and **3i**, also a *trans* relationship between H_4 and H_5. The same relative stereochemistry of other isoxazolidines **3c-3h** was assigned considering their closely related chemical shifts and coupling constants.



1a-1i **2a** **3a-3i**

Scheme 2



Dominant transition state A

Table 1 . 1,3-dipolar cycloaddition of nitrone **2a** to alkenyl boronic esters **1a-1i**

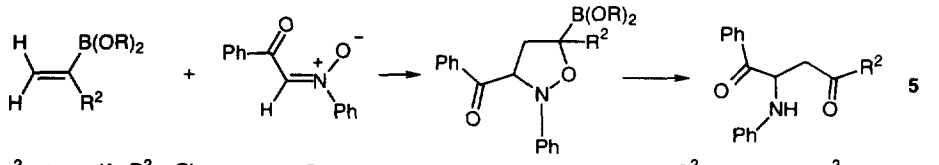
alkene	R^1	Yield [a] (%)	alkene	R^1	Yield [a] (%)	alkene	R^1	Yield [a] (%)
1a	H	65	**1d**	^{t}BuO-$(CH_2)_4$-	80	**1h**	HOCH(Me)	78 [b]
1b	nBu	83	**1e**	Cl-$(CH_2)_4$-	75	**1i**	MeO_2C	61
1c	$PhCH_2$	70	**1f**	$AcOCH_2$	81			

[a] Yields based on isolated material

[b] Mixture of two diastereoisomers (75/25)

C-Benzoyl-N-phenyl nitrone **2a** is known to exist in the stable *Z* configuration under the experimental conditions.[7] The observed stereochemistry of the cycloadducts **3a-3i** therefore suggest that these cycloadditions proceeded through a preferred transition state A that could be the result of a favorable interaction between the boronic ester and the amino group or simply directed by steric effects.

1,1-Disubstituted alkenyl boronic esters **1j-1k** also afforded single diastereoisomers **4**, but with the opposite regiochemistry as was established by analysis of the ^{1}H NMR spectrum (ABX system for the isoxazolidine protons) (Scheme 3).[11] The resulting cycloadducts were very air sensitive and were readily converted in the presence of water to the corresponding β-aminoketones **5** *via* an unclear mecanism.[12]

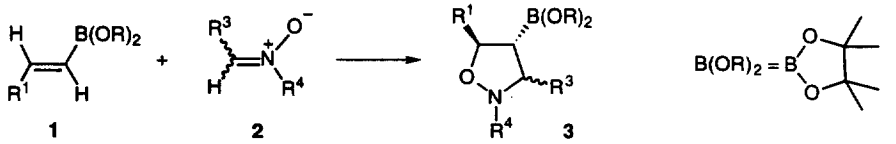


1j R^2 = Me **1k** R^2 = Ph **2a** **4** R^2 = Me 58% R^2 =Ph 65%

Scheme 3

The previous results encouraged us to test other nitrones with three representative alkenylboronic esters **1a**, **1b** and **1i** (Scheme 4, Table II). The presence of an electron withdrawing group on the double bond β to the boronic ester substantially increased the reactivity (entries 3, 6 and 8). The structure of the nitrone has also a significant effect on the rate of cycloaddition reactions since C-benzoyl-N-phenylnitrone **2a** displayed a markedly enhanced reactivity compared with the C-methoxycarbonyl-N-benzyl compound [13] **2d** (entries 2 and 7, 3 and 8). If N-benzylnitrone [14] **2b** yielded a cycloadduct at room temperature, C-phenyl-N-methylnitrone [15]

2c was found to be much less reactive (entries 4 and 6). For the latter, heating the reaction mixture at 60°C for 21h gave a complex mixture with no starting boronate **1i** and only moderate amounts of isoxazolidine.



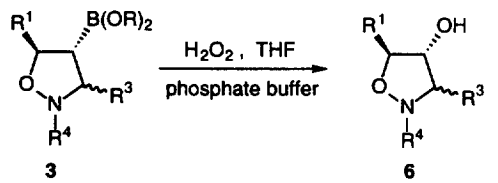
Scheme 4

Table II - Cycloadditions of nitrones **2a-2d** to boronic ester **1a**, **1b** and **1i**.[a]

Entry	Alkene	R^1	Nitrone	R^3, R^4	T(°C)	Time (h)	Conversion (%)	Yield (%)[b]
1	**1a**	H	**2a**	COPh, Ph	25	1.5	45	55
2	**1b**	Bu	**2a**	COPh, Ph	25	1.5	40	83
3	**1i**	CO_2Me	**2a**	COPh, Ph	25	1.5	100	61
4	**1i**	CO_2Me	**2b**	H, CH_2Ph	25	24	100	80
5	**1b**	Bu	**2a**	Ph, Me	25	48	0	-
6	**1i**	CO_2Me	**2c**	Ph,Me	60	21	100	45 [c]
7	**1b**	Bu	**2d**	CO_2Me,CH_2Ph [d]	60	12	50	74 [e]
8	**1i**	CO_2Me	**2d**	CO_2Me,CH_2Ph [d]	25	4	70	83 [f]

[a] 0.5M solution in toluene. [b] Yield based on isolated material after having conducted the reaction to completion. [c] Estimated yield by ^1H NMR on the crude reaction mixture (two diastereoisomers (1/4). [d] Mixture of geometric isomers (E/Z=3/2). [e] Mixture of diastereoisomers (1/6). [f] Mixture of diastereoisomers (1/2).

Treatment of boronic ester substituted isoxazolidines with hydrogen peroxide in THF in the presence of a phosphate buffer results in the stereospecific replacement of boron by oxygen, thus giving access to 4-hydroxy derivatives **6** (Scheme V). [16]



6	R^1	R^3	R^4	Yield (%) [a]
a	Bu	COPh	Ph	78
b	Bu	CO_2Me	CH_2Ph	61 [b]
c	CO_2Me	CO_2Me	CH_2Ph	58 [c]

[a] Yield based on isolated material .[b] Two diastereoisomers (1/6).[c] Two diastereoisomers (1/2).

Scheme 5

In summary, we have reported a simple and efficient procedure for the regio- and streoselective synthesis of 4-borylated isoxazolidines. The presence of the versatile boronic ester functionality should result in a broad range of synthetic utility and other transformations of these heterocycles are currently underway.

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8 In a typical procedure, 2 mmol of the boronic ester **1** was added to a solution of 2 mmol of nitrone **2a** in 5 ml of toluene. The reaction was stirred overnight or until the starting material disappeared as followed by TLC. The solvent was removed under reduced pressure and the residue crystallized from diisopropylether. All products gave satisfactory spectroscopic and analytical data. For example : **3b** yield=83%. mp=122°C. ^{1}H NMR (200 MHz, $CDCl_3$) : 0.89 (t, 3H, J = 6.8) ; 1.07 (s, 6H) ; 1.10 (s, 6H) ; 1.32-1.78 (m, 6H) ; 2.39 (dd, 1H, J=6.0 and 8.9) ; 4.19 (dt, 1H, J = 6.3 and 8.9) ; 5.18 (dd, 1H, J = 6.0) ; 6.94-7.53 (m, 8H) ; 8.15-8.20 (m, 2H). ^{13}C NMR (50.3 MHz, $CDCl_3$) : 13.9 (CH_3) ; 22.7 (CH_2) ; 24.4 (CH_3) ; 24.6 (CH_3) ; 28.7 (CH_2) ; 32.9 (CH_2) ; 37.1 (CH α to B) ; 74.2 (CH) ; 81.1 (CH) ; 84.0 (C) ; 114.4 (CH) ; 121.6 (CH) ; 128.4 (CH) ; 129.0 (CH) ; 129.4 (CH) ; 133.1 (CH) ; 135.0 (C) ; 150.9 (C) ; 197.5.(CO). Anal. Calc. for $C_{22}H_{34}BNO_4$ (435.4) : C, 71.73 ; H, 7.87 ; N, 3.22. Found : C, 71.7 ; H, 7.9 ; N, 2.9.

9 It is interesting to compare the regiochemical course of the cycloaddition of **3i** with the tendency of crotonates to afford the corresponding isoxazolidines bearing the carboxyl group at the 4-position (ref 1).

10 **3a**. $BC_{22}H_{26}NO_4$; MW 379.3 ; monoclinic, $P2_1/n$, a = 12.375(6), b = 12.525(5), c = 13.226(6) Å, β=100.80, V = 2013.9(8) Å^3, Z = 4, D_X = 1.25 g.cm^{-3}, λ(MoKα)= 0.71069 Å, T=296K, F(000) = 808, R = 0.075 for 1725 reflections. **3b**. $BC_{26}H_{34}NO_4$; MW 435.4 ; monoclinic, P-1, a = 8.316(4), b = 9.974(2), c = 15.521(2) Å, β=74.77(2), V = 1234(1) Å^{-3}, Z = 2, D_{calc} = 1.172 g.cm^{-3}, μ(MoKα)= 0.72 Å, T=294K, F(000);= 468, R = 0.060 for 2721 observations. **3i**. $BC_{22}H_{26}NO_4$; MW 379.3 ; monoclinic, $P2_1/n$,a = 12.375(6), b = 12.525(5), c = 13.226(6) Å, β=100.80, V = 2013.9(8) Å^3, Z = 4, D_X = 1.25 g .cm^{-3}, λ(MoKα)= 0.71069Å, T=296K, F(000) = 808, R = 0.075 for 1725 reflections. **3i**. $BC_{24}H_{28}NO_6$; MW 437.3 ; monoclinic, $P2_1/c$, a = 20.193(4), b = 6.654(3), c = 18.901(3) Å, β=114.45(1), V = 2312(1) Å^3, Z = 4, D_{calc} = 1.256 g.cm^{-3}, μ(MoKα)= 0.83 Å, T=294K, F(000):= 928, R = 0.059 for 2342 reflections. X-ray crystallographic data have been deposited at the Cambridge Crystallographic Data Centre.

11 **4k**. ^{1}H NMR (200 MHz, C_6D_6) : 0.72 (s, 6H) ; 0.83 (s, 6H) ; 2.99 (dd, 1H, J = 7.2 and 11.9) ; 3.34 (dd, 1H, J = 8.6 and 11.9) ; 4.94 (dd, 1H, J = 7.2 and 8.6) ; 6.80-7.25 (m, 9H) ; 7.32-7.40 (m, 2H) ; 7.55-7.68 (m, 2H) ; 8.15-8.25 (m, 2H).^{13}C NMR (50.3 MHz, C_6D_6) : 24.6 (CH_3) ; 24.8 (CH_3) ; 44.5 (CH_2) ; 74.0 (CH) ; 79.0 (Cα to B) ; 84.9 (C) ; 115.8 (CH) ; 122.2 (CH) ; 128.9 (CH) ; 129.0 (CH) ; 129.3 (CH) ; 129.5 (CH) ; 130.2 (CH) ; 130.3 (CH) ; 133.5 (CH) ; 137.5 (C) ; 143.3 (C) ; 152.0 (C) ; 198.1 (CO).

12 **5k**. mp =138-139°C (lit : 138°C, Paal, C. ; Schulze, H. *Chem. Ber.* , **1900**, *33*, 3795-3800). ^{1}H NMR (200 MHz, $CDCl_3$) : 3.46 (dd, 1H, J = 5.3 and 17.5) ; 3.62 (dd, 1H, J = 6.3 and 17.5) ; 4.45 (br s, 1H); 4.94 (dd, 1H, J = 5.3 and 6.3) ; 6.70-6.85 (m, 3H) ; 7.10-7.28 (m, 3H) ; 7.35-7.65 (m, 5H) ; 7.85-7.95 (m, 2H) ; 8.02-8.12 (m, 2H).^{13}C NMR (50.3 MHz, $CDCl_3$) : 40.9 (CH_2) ; 54.4 (CH) ; 114.0 (CH) ; 118.8 (CH) ; 128.3 (CH) ; 128.7 (CH) ; 128.8 (CH) ; 129.5 (CH) ; 133.5 (CH) ;133.6 (CH) ; 135.1 (C) ;136.6 (C) ; 146.3 (C) ; 197.9 (CO) ; 199.1 (CO).

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16 **6a** yield=78%. mp=96-98°C. ^{1}H NMR (200 MHz, $CDCl_3$) : 0.94 (t, 3H, J = 6.2) ; 1.28-1.82 (m, 6H) ; 2.90 (br s, 1H) ; 3.95-4.05 (m, 1H) ; 4.72 (dd, 1H, J = 3.6 and 5.7) ; 5.02 (dd, 1H, J = 3.6) ; 7.00-7.11 (m, 3H) ; 7.23-7.34 (m, 2H) ; 7.42-7.54 (m, 2H) ; 7.54-7.62 (m, 1H) ; 8.11-8.19 (m, 2H). ^{13}C NMR (50.3 MHz, $CDCl_3$) : 13.9 (CH_3) ; 22.6 (CH_2) ; 28.4 (CH_2) ; 30.3 (CH_2) ; 78.9 (CH) ; 83.5 (CH) ; 84.9 (CH) ; 114.1 (CH) ; 121.9 (CH) ; 128.7 (CH) ; 129.2 (CH) ; 129.4 (CH) ; 133.6 (CH) ; 135.0 (C) ; 150.7 (C) ; 196.7 (CO).

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