Allylation Reactions of N,O-Heterocycles

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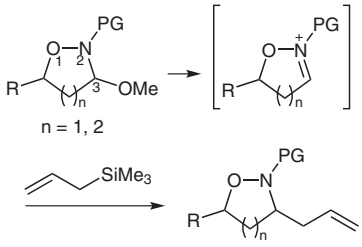
Abstract: Iminium ions generated from isoxazolidines and tetrahydro-1,2-oxazines undergo allylation under Sakurai conditions. Allylated isoxazolidines are formed predominantly as the *trans* isomer, while oxazines are formed exclusively as the *cis* isomer.

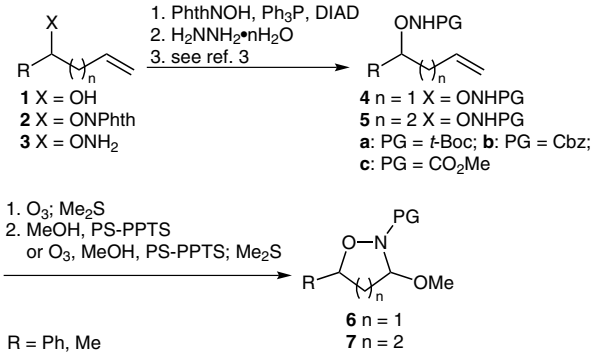
Key words: heterocycles, allylation, stereoselectivity

We have had a longstanding interest in the synthesis of heterocycles containing an N–O bond, namely cyclic hydroxylamines, by methods that do not involve the well-known cycloaddition reactions, and the use of these heterocycles for the synthesis of alkaloids through cleavage of the N–O bond to reveal an amino alcohol.[1,2] In the five-membered-ring series – isoxazolidines – we have employed both cyclocarbonylation[3] and the Claesson allene cyclisation.[4,5] Both processes favour the formation of the 3,5-*cis* isomer.[6] We have also employed the intramolecular aza-Michael addition of a hydroxylamine.[7] Again, in the five-membered-ring series, the 3,5-*cis* isomers are favoured, while in the six-membered ring series – tetrahydro-1,2-oxazines – the 3,6-*trans* products are formed exclusively. We reasoned that, if one substituent were added after ring formation, rather than before, we might be able to access the alternative stereochemical series, that is, 3,5-*trans* isoxazolidines and 3,6-*cis*-tetrahydro-1,2-oxazines. Given our interest in iminium ion chemistry,[4b,c,8] the use of a Sakurai reaction suggested itself (Scheme 1). Zhao has reported the allylation of isoxazolidines at C5 with modest stereoselectivity,[9] while Jenkins has reported the stereoselective addition of allyl zinc reagents to 4,5-dihydroisoxazoles.[10]



Scheme 1 N,O-Heterocycle allylation

The 3-methoxy-substituted heterocycles,[11] intended as iminium ion precursors, were prepared by adapting the chemistry that we had used for the preparation of earlier starting materials (Scheme 2).[3] *N*-Alkoxyphthalimides **2** were prepared by the Mitsunobu reaction between unsaturated secondary alcohols **1** and *N*-hydroxyphthalimide.[12] The phthaloyl group was then removed by hydrazinolysis, and the nitrogen was reprotected as a carbamate. Initially, using the five-membered ring series, ozonolysis in dichloromethane yielded the 3-hydroxyisoxazolidines,[13] which were converted into the 3-methoxy derivatives **6a**–**c** by treatment with methanol in the presence of polymer-supported PPTS.[14] We subsequently found that it was more efficient to carry out the ozonolysis in methanol in the presence of the acidic polymer to give the 3-methoxy derivatives after Me_2S work-up in a one-pot process. The 3-methoxyisoxazolidines **6a**–**c** were obtained as diastereoisomeric mixtures; the 3-methoxytetrahydrooxazines **7a**–**c** were obtained exclusively as the *cis* isomers, as demonstrated by X-ray crystallographic analysis of compound **7b** (Figure 1).[15,16]



Scheme 2 Synthesis of 3-methoxy heterocycles

Allylation of the 3-methoxy derivatives was achieved by treatment with allyl trimethylsilane and $BF_3{\cdot}OEt_2$ at –60 °C in anhydrous dichloromethane (Scheme 3). Good yields were obtained in all cases (Table 1) except for those compounds with a *t*-Boc protecting group, due to acid sensitivity. The isoxazolidines **8a**–**c** were formed as an inseparable mixture of isomers.[17] The stereochemistry was demonstrated by cleavage[18] of the N–O bond of isoxazolidine **8a** to give the diastereoisomeric amino alcohol derivatives which were separable. The major isomer **9** proved to be crystalline. X-ray crystallographic analysis

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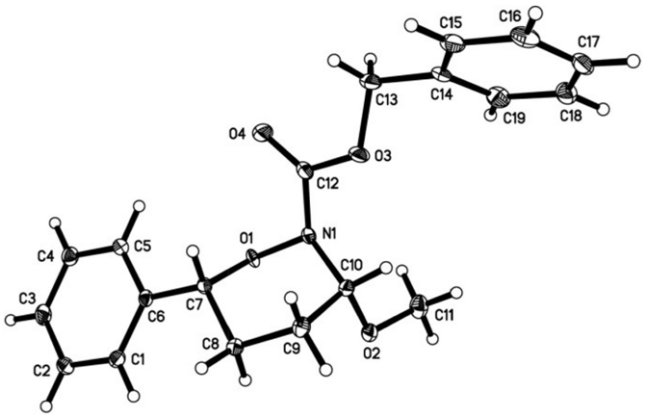


Figure 1 X-ray crystal structure of compound **7b**

(Figure 2)[15] revealed it to be the *anti* isomer, indicating that the major isoxazolidine was the *trans* isomer. In contrast, the tetrahydro-1,2-oxazines **10a**–**d** were formed as single isomers. Attempts to determine the stereochemistry by either coupling constant analysis or NOE experiments were frustrated by line broadening in the ^{1}H NMR spectra for protons at the 3- and 6-positions.[19] Corresponding broadening was also observed in the ^{13}C NMR spectra. Removal of the Boc group from compound **10a**, however, gave compound **11** with a sharply defined ^{1}H NMR spectrum. The proton at C6 showed coupling constants of 3.2 and 9.6 Hz, indicating an equatorial disposition of the phenyl group. Through homonuclear decoupling experiments, coupling constants between the proton at C3 and the protons at C4 were revealed to be 3.3 and 2.2 Hz, indicating an axial disposition of the allyl group and, therefore, *cis* stereochemistry for the heterocycle. Axial allylation is consistent with the reaction being under stereoelectronic control.[20]

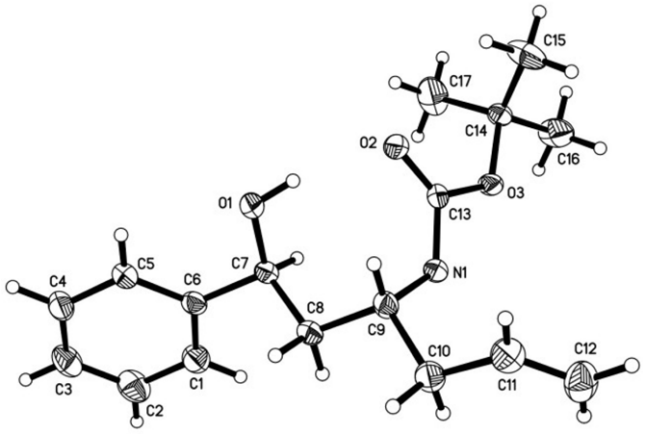
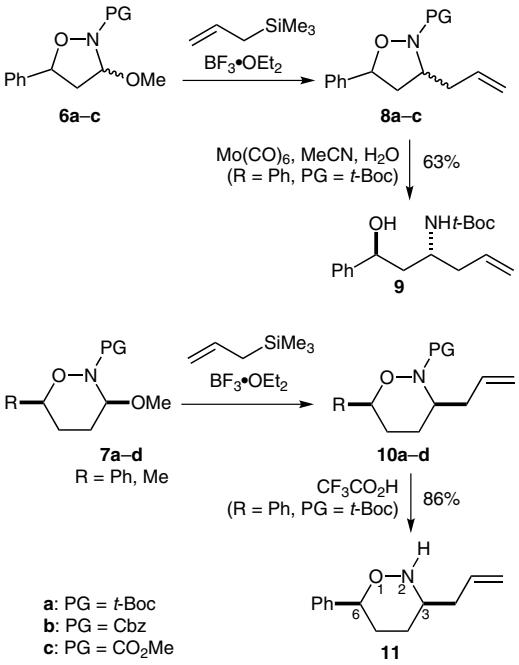


Figure 2 X-ray crystal structure of amino alcohol derivative **9**

Allylation of these N,O-heterocycles provides a useful route to derivatives of amino alcohols with useful 1,3-stereocontrol and excellent 1,4-stereocontrol which should prove to be valuable in organic synthesis.



Scheme 3 Allylation reactions

Table 1 N,O-Heterocycle Formation and Allylation

Entry	R	PG	n	Heterocycle, yield (%)	Allylation, yield (%)	Allylation dr
1	Ph	*t*-Boc	1	**6a** 54[a]	**8a** 44	3.8:1
2	Ph	Cbz	1	**6b** 41[a]	**8b** 70	3.3:1
3	Ph	CO_2Me	1	**6c** 56[a]	**8c** 73	4.8:1
4	Ph	*t*-Boc	2	**7a** 57[b]	**10a** 55	–[c]
5	Ph	Cbz	2	**7b** 85[b]	**10b** 74	–[c]
6	Ph	CO_2Me	2	**7c** 73[b]	**10c** 68	–[c]
7	Me	CO_2Me	2	**7d** 63[b]	**10d** 65	–[c]

[a] Two-step procedure.
[b] One-pot procedure.
[c] Single isomer observed in the ^{1}H NMR (300 MHz) spectrum of the crude product.

General Procedure for Allyation[21]

Boron trifluoride etherate (1.2 equiv) was added dropwise to a solution of the 3-methoxyheterocycle and allyltrimethylsilane (2 equiv) in CH_2Cl_2 under nitrogen at –60 °C. The mixture was stirred overnight at –60 °C, then quenched by addition of Et_3N (0.5 equiv) at that temperature. The mixture was allowed to warm to r.t., then diluted with H_2O. The mixture was extracted with CH_2Cl_2 (3×). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The product was purified by chromatography on silica gel.

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(15) Details have been deposited with the Cambridge Crystallographic Data Centre and may be obtained at http://www.ccdc.cam.ac.uk. CCDC deposition numbers: **7b**: 878055 and **9**: 877996.

(16) **Characterisation Data for Compound 7b**
Mp 69–71 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.50 (10 H, m), 5.35 (1 H, br), 5.33 (br d *J* = 12.0 Hz), 5.19 (d, *J* = 12.0 Hz), 4.72 (br s, 1 H), 3.35 (3 H, br s), 2.35 (1 H, app dq, *J* = 5.0, 12.0 Hz), 2.05–2.10 (1 H, m), 1.88–2.00 (1 H, m), 1.79–1.84 (1 H, m), 1.80–2.40 (4 H, m).

(17) **Spectroscopic Data for Compound *trans*-8a**
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.28 (5 H, m), 5.85 (1 H, ddt, *J* = 17.3, 10.2, 7.1 Hz), 5.27 (1 H, t, *J* = 6.6 Hz), 5.21–5.14 (2 H, m), 4.39 (1 H, tt, *J* = 8.0, 5.0 Hz); 3.68 (3 H, s), 2.65–2.38 (4 H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.5, 138.5, 134.0, 128.8, 118.4, 81.7, 59.0, 53.2, 40.0, 39.1.

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(19) **Spectroscopic Data for Compound 10c**
^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.67–5.78 (m, 1 H), 5.15 (1 H, ddd, *J* = 17.0, 3.0, 1.5 Hz), 5.08 (1 H, dt, *J* = 10.0, 1.0 Hz), 4.73 (1 H, br d), 4.35 (1 H, br), 3.78 (3 H, s), 2.70 (1 H, app quin, *J* = 7.0 Hz), 2.44 (1 H, app quin, *J* = 7.0 Hz), 2.10–2.20 (1 H, m), 1.9.0–2.05 (1 H, m), 1.8.0–1.90 (2 H, m). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 25.6, 26.6, 34.3, 53.2, 83.3 (br), 117.6, 126.6, 128.5, 128.6, 134.8, 139.4, 156.1.

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