Asymmetric 1,3-Dipolar Cycloaddition Reactions of Nitrones with (S)-(−)-4-Benzyl-N-methacryloyl-2-oxazolidinone

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Received 11 March 2005

SYNTHESIS 2005, No. 14, pp 2393–2399
Advanced online publication: 13.07.2005
DOI: 10.1055/s-2005-869992; Art ID: P03805SS
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Abstract: The [3+2]-nitrone-mediated cycloaddition reaction of (S)-(−)-4-benzyl-N-methacryloyl-2-oxazolidinone has been applied to the synthesis of highly substituted isoxazolidines with controlled stereochemistry. The absolute configuration of the major diastereoisomer derived from the reaction between N-(p-nitrobenzylidene)methylamine N-oxide and (S)-(−)-4-benzyl-N-methacryloyl-2-oxazolidinone has been deduced from the corresponding X-ray structure.

Key words: chiral auxiliary, nitrones, dipolar cycloaddition reaction, isoxazolidine, isoxazolidinone

Asymmetric 1,3-dipolar cycloaddition reactions between nitrones and chiral acrylamide derived dipolarophiles have attracted considerable interest in recent times.1 This is part due to the enhanced π-diastereoselectivity associated with chiral auxiliary based dipolarophiles2 coupled with the ease with which the chemistry may then be transferred onto a solid support media3 by immobilising either the dipole or the dipolarophile onto a polymer-derived support. Some recent examples of immobilisation have been revealed using a chiral sultam,4 a sugar5 or a chiral oxazolidinone.6

In conjunction with clinical collaborators we were keen to establish methods for accessing γ-lactams for biological evaluation, in particular, a range of examples containing a C-3 tertiary hydroxyl group.

Previous studies7 from our laboratories revealed that lactams such as 2 may be readily accessed via a TiCl3-mediated cleavage of the comparatively weak N–O of an isoxazolidine such as 1 (Scheme 1).

That being the case we reasoned that suitable candidates for screening would be readily available from a nitrone-mediated cycloaddition reaction using a methacryloyl-based amide dipolarophile such as 3.

The corresponding lactam 5 might then be produced directly in one step from isoxazolidine 4 using TiCl3 or by a two-step process involving an initial hydrolysis of the auxiliary followed by an N–O bond cleavage reaction (Scheme 2).

From our survey of the chemical literature we found relatively few examples8 of methacryloyl-based amides as partners in nitrone cycloaddition reactions. However 3-hydroxy-β-lactams and related compounds have been synthesised via nitrone cycloaddition reactions with 3-methylene β-lactams.9

As a general observation the regioselectivity of reactions involving nitrones and 1,1-disubstituted dipolarophiles, such as 3, are completely unambiguous in affording the corresponding 5,5-disubstituted isoxazolidinone. It is an outcome which is largely influenced by the substituent effects of the dipolarophile rather than electronic influences.10

Our preliminary investigation focussed upon a comparatively simple model that involved the cyclisation reaction between the dipolarophile 7 and the dipoles 6a,b (Scheme 3).
In both cycloaddition reactions the 5-disubstituted isoxazolidines \( 8a,b \) prevailed using the procedure described by Fornefeld.\(^{11}\) This involved the in situ formation of the nitrone in the presence of the dipolarophile \( 7 \) and provided the isoxazolidines \( 8a,b \) as clear oils. Inspection of the corresponding \(^1\)H NMR spectra however revealed that the methylene protons appeared as broadened signals thus providing us with limited information. A similar result emerged when the cyclisation reaction were conducted with \( N \)-methylnitrone \( 6a \) and the dipolarophile \( 3 \) to afford the corresponding isoxazolidine \( 9 \) (Scheme 4).

![Scheme 4](image)

**Scheme 4**

Signal broadening in isoxazolidines has been reported previously and the cause attributed to pyramidal inversion of the ring nitrogen. We observed a significant reduction in this effect when we ran the \(^1\)H NMR spectra at an elevated temperature. However the resolution of the resulting spectra were still poor.

Attempts to suppress nitrogen inversion in cyclisations such as these have been attempted by targeting the \( N \)-substituent. For instance the use of both an \( N \)-benzotriazole moiety\(^{12}\) and an \( N \)-methoxy group\(^{13}\) have been reported to successfully prevent signal broadening. In light of our result using nitrone \( 6b \), however, the precise mechanism by which this may be achieved in terms of steric/electronic factors appears unclear. As well as the effect of the \( N \)-substituent on nitrogen inversion the substitution patterns of the isoxazolidine ring are thought to be significant. Thus when the cyclisation reaction was conducted between \( N \)-(benzylidene)methylamine \( \text{N-oxide} \) \( 10 \) and the oxazolidinone \( 3 \) the corresponding isoxazolidine \( 11 \) was formed in a very high yield. \(^1\)H NMR analysis of the crude reaction mixture showed the presence of two new compounds that were related as diastereoisomers in a ratio of 4:1. Importantly a complete absence of signal broadening was observed in the corresponding NMR spectra (Scheme 5).

![Scheme 5](image)

**Scheme 5**

Although we anticipated that information with regard to the newly formed asymmetric centres in isoxazolidine \( 11 \) may not be obtained directly via extensive NMR studies we did envisage that the absolute configuration may be obtained from single X-ray crystallography or by the transformation of \( 11 \) into a known compound. Chromatographic separation of the major diastereoisomer provided a semi-solid, which despite careful recrystallisation proved unsuitable for X-ray purposes. In order to achieve a satisfactory sample for this purpose we synthesised a range of derivatives \( 14a-c \) (Scheme 6).

![Scheme 6](image)

**Scheme 6**

The synthesis of the dipoles \( 13a-c \) were efficiently accomplished by a condensation reaction between the relevant aldehyde and \( N \)-alkylhydroxylamine.\(^{14}\) The nitrones were then heated, with the dipolarophile \( 3 \), in boiling toluene to afford the cycloadducts in excellent yields. The distribution of diastereoisomers was similar in all cases consisting of a major and two minor diastereoisomers. Isolation of the major isomer obtained from the reaction between nitrone \( 12c \) and \( 3 \) was obtained as a crystalline solid suitable for X-ray analysis. These data were thus able to provide us with confirmation of the stereochemistry of the asymmetric centres formed in the cycloaddition reaction (Figure 1). This series of cycloaddition reactions appear to proceed with good regioselectivity in affording the C-5 disubstituted isoxazolidine with the nitrene approaching the dipolarophile from the face opposite to the benzyl group of \( 3 \). This observation was based not only upon the \(^1\)H NMR chemical shift for the quaternary methylene protons \( 11 \) which fluctuated within the narrow range of \( \delta = 1.67-1.69 \) ppm\(^{15}\) but also upon the observed stereodifferentiation between the major and minor isomers. In general the major diastereoisomer appearing to be deshielded compared to the minor. This non-equivalence in chemical shifts between functional groups in diastereoisomers have been described\(^{16}\) and conformational models provided in order to rationalise this phenomena.\(^{17}\)

The formation of the major diastereoisomer during these cycloaddition reactions may be rationalised in terms of an aryl-endo and aryl-exo approach of the dipole to the dipolarophile \( 3 \) (Scheme 7).

Having accomplished our aim of establishing a reproducible procedure for the efficient and controlled synthesis of C-5 disubstituted isoxazolidines\(^{18}\) we looked at the cleav-
Reactions of Nitrones with Benzyl-N-methacryloyl-2-oxazolidinone

Evans described a general method for the selective exo-cyclic hydrolysis of sterically hindered carboximides using LiOH–H₂O₂ (Scheme 8). Thus removal of the chiral auxiliary using lithium hydroperoxide provided isoxazolidine 15 in very high yield. However our attempts to purify this compound by chromatography on silica led to the formation of the amino-ketone 16 in variable yields depending upon the duration of exposure to silica. We speculate that this compound arises from an initial decarboxylation reaction accompanied by the subsequent cleavage of the comparatively weak N–O bond of the isoxazolidine. The synthesis of 16 was an unexpected outcome and at the present time our investigations are continuing and remain focussed not only on the cleavage reaction itself but also on the generality and synthetic applications of the silica promoted decarboxylation step.

In summary this paper describes a series of [3+2]-nitrene-mediated cycloaddition reactions using a methacryloyl-based amide dipolarophile. Although the low reactivity of N-methylnitrones in these cycloaddition reactions led to long reaction times the yields were excellent. In all cases the cyclisation was regioselective in favour of the C-5 di-substituted isoxazolidine. The major diastereoisomer has been isolated and characterised and for one example, the synthesis of 14c the absolute stereochemistry has been obtained from X-ray analysis. Cleavage of the chiral auxiliary was accomplished in high yield. However the isoxazolidine was found to undergo spontaneous decarboxylation and ring opening upon exposure to silica. This may provide a general method for the asymmetric synthesis of amino-ketones based upon 16 with a high enantiomeric excess.

Melting points were recorded on a Buchi 512 capillary tube apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1600 series FTIR spectrophotometer and were calibrated using a standard polystyrene film. The spectra were recorded either as thin films or between NaCl discs for liquids or as a Nujol mull for solids. All IR data are quoted in cm⁻¹. ¹H NMR spectra were recorded at 400 MHz using a Bruker AMX400 FT NMR spectrometer, or at 300 MHz on a Bruker AC-300 FTNMR spectrometer. Peak positions are quoted using the δ scale relative to TMS (δ = 0) as an internal standard. ¹³C NMR spectra were recorded at 75.45 MHz on a Bruker AC-300 FTNMR spectrometer using CDCl₃ as an internal standard. Low resolution mass spectra were recorded on a VG TRIO-2 mass spectrometer under EI conditions at an ionising potential of 70 eV and/or with a Hewlett Packard GC–MS HP5890 (GC) with capillary column and HP 5971 (MS). Accurate mass analyses were performed and reported on a VG-ZAB-E under EI conditions by the EPSRC National Mass Spectrometry Service Centre (Swansea) using the EI Peak Match on M⁺ method.

(S)-(−)-4-Benzyl-N-methacryloyl-2-oxazolidinone (3)²²

n-BuLi (4.52 mL, 11.29 mmol, 2.5 M) was added to (S)-(−)-4-benzyl-2-oxazolidinone (2.00 g, 11.29 mmol) dissolved in THF (20 mL) at −78 °C. The mixture was stirred for 15 min whereupon freshly distilled methacryloyl chloride (1.21 mL, 12.42 mmol) was added dropwise over 10 min. The mixture was stirred for a further 30 min and then allowed to reach an ambient temperature whereupon a sat. solution of NH₄Cl (30 mL) was added and the organic solvent was removed in vacuo. The aqueous solution was extracted with Et₂O (2 × 30 mL) and the organic layer then extracted sequentially with sat. NaHCO₃ (3 × 30 mL) followed by a sat. NaCl solution (30 mL). The organic layer was dried over anhyd MgSO₄, filtered and the solvent removed in vacuo to afford a white amorphous powder. Recrystallisation from hexane gave the title compound as a white crystalline solid (2.66 g, 96%); mp 81–82 °C; [α]D₂⁰ +70.10 (c = 0.97, CHCl₃).

IR: 3026.4, 1787.4, 1681.9, 1639.6, 1352.2, 1217.0 cm⁻¹.

Figure 1 X-ray crystal analysis of 14c

Scheme 7

Figure 1 X-ray crystal analysis of 14c

Scheme 8
**MgSO₄**, filtered and the solvent removed in vacuo to afford the title compound as a clear oil (0.96 g, 67%).

**UV–Vis (MeOH):** \(\lambda_{\text{max}} = 239.6\) nm.

**MS (EI):** \([M + H]^+\) calcd for \(\text{C}_7\text{H}_{14}\text{NO}_3\): 160.0966; found: 160.0974.

**13C NMR (75.5 MHz, CDCl₃):** \(\delta = 23.9, 39.2, 45.3, 52.4, 57.1, 81.9, 175.1\).

**N,5-Dimethyl-5-(methylformyl)isoxazolidine (8a)**

This compound was prepared according to the following procedure for the in situ synthesis of nitrones.\(^\text{11}\) \(\text{NaOAc} (0.75\, \text{g, 9.08 mmol})\) was added to a stirred solution of \(\text{N}-\text{methylhydroxylamine hydrochloride (0.76 g, 9.08 mmol) in EtOH–water (10:1, 10 mL) at an ambient temperature.}\) After 30 min the solution was filtered and added dropwise, via syringe pump (over 2.5 h), to a solution of formaldehyde (37% solution in water, 0.98 mL, 12.12 mmol). The mixture was stirred for 1 h whereupon methyl methacrylate (1.07 mL, 0.99 mmol) was added and left to stir for about 3 h. After this period water (10 mL) was added and the organics were removed in vacuo. The resulting aqueous solution was extracted with \(\text{Et}_2\text{O} (3 \times 10 \text{ mL})\). The organic layers were recombined, dried over anhyd \(\text{MgSO}_4\), filtered and the solvent removed in vacuo to afford the title compound as a clear oil (0.96 g, 67%).

**IR:** 2998.1, 2957.4, 1735.6 cm⁻¹.

**UV–Vis (MeOH):** \(\lambda_{\text{max}} = 239.6\) nm.

**[M + H]^+** calcd for \(\text{C}_7\text{H}_{14}\text{NO}_3\): 160.0966; found: 160.0974.

**UV–Vis (MeOH):** \(\lambda_{\text{max}} = 206\) nm.

**N-Benzyl-5-methyl-5-(methylformyl)isoxazolidine (8b)**

This compound was prepared according to the following procedure for the in situ synthesis of nitrones.\(^\text{11}\) \(\text{NaOAc} (0.75\, \text{g, 9.08 mmol})\) was added to a stirred solution of \(\text{N}-\text{methylhydroxylamine hydrochloride (0.76 g, 9.08 mmol) in EtOH–water (10:1, 10 mL) at an ambient temperature.}\) After 30 min the solution was filtered and added dropwise, via syringe pump (over 2.5 h), to a solution of formaldehyde (37% solution in water, 0.98 mL, 12.12 mmol). The mixture was stirred for 1 h whereupon methyl methacrylate (1.07 mL, 0.99 mmol) was added and left to stir for about 3 h. After this period water (10 mL) was added and the organics were removed in vacuo. The resulting aqueous solution was extracted with \(\text{Et}_2\text{O} (3 \times 10 \text{ mL})\). The organic layers were recombined, dried over anhyd \(\text{MgSO}_4\), filtered and the solvent removed in vacuo to afford the title compound as a clear oil (1.70 g, 80%).

**MS (EI):** \([M + H]^+\) calcd for \(\text{C}_{14}\text{H}_{15}\text{NO}_3\): 236.1287; found: 236.1287.

**UV–Vis (MeOH):** \(\lambda_{\text{max}} = 237\) nm.

**[S(-)-4-Benzyl-N-(5-carbonyl-N,5-dimethylisoxazolidine)-2-oxazolidinone (9)**

This compound was prepared according to the following procedure for the in situ synthesis of nitrones.\(^\text{11}\) \(\text{NaOAc} (0.13\, \text{g, 1.63 mmol})\) was added to a stirred solution of \(\text{N}-\text{methylhydroxylamine hydrochloride (0.16 g, 1.63 mmol) in EtOH–water (10:1, 1.5 mL) at an ambient temperature.}\) After 30 min the mixture was filtered and added dropwise, via syringe pump (over 2.5 h), to a solution of formaldehyde (37% solution in water, 0.17 mL, 2.12 mmol). The mixture was stirred for 1 h whereupon \(\text{S}(-)-4\)- benzyl-N-methacryloyl-2-oxazolidinone (3) (0.20 g, 0.82 mmol) was added and left to stir for about 40 h. After this period water (10 mL) was added and the organics were removed in vacuo. The resulting aqueous solution was extracted with \(\text{Et}_2\text{O} (3 \times 10 \text{ mL})\). The organic layers were recombined, dried over anhyd \(\text{MgSO}_4\), filtered and the solvent was removed in vacuo to afford a mixture of two diastereoisomers in a ratio of 3:1 (0.11 g, 42%).

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The title compound was obtained as a white crystalline solid (yield: 82%); mp 127.2–129 °C.

**1H NMR (300 MHz, CDCl3):** δ = 1.67 (s, 3 H, CH3), 2.56 (s, 3 H, NCH3), 2.61 (dd, J = 9.5, 3.5 Hz, 1 H, CH), 2.71–2.84 (m, 2 H, CH2), 3.23 (dd, J = 13.5, 3.5 Hz, 1 H, CH), 3.48 (t, J = 8.5 Hz, 1 H, CH), 4.07–4.19 (m, 2 H, OCH2), 4.69–4.77 (m, 1 H, NCH), 7.15–7.27 (m, 10 H, ArH).

**13C NMR (75.5 MHz, CDCl3):** δ = 22.6, 37.7, 42.8, 50.5, 56.5, 66.6, 73.4, 83.2, 127.4, 127.7, 128.1, 128.9, 129.0, 129.5, 135.3, 137.9, 152.2, 174.2.

MS: m/z [M + H]+ calcd for C23H25N2O4: 381.1814; found: 381.1814.

UV–Vis (MeOH): λmax = 296 nm.

**N-(p-Bromobenzylidene)methylamine N-Oxide (13a)**

The title compound was obtained as white crystalline plates (yield: 90%); mp 123.9–124.4 °C.

**1H NMR (300 MHz, CDCl3):** δ = 3.76 (s, 3 H, NCH3), 7.26 (s, 1 H, CH), 7.44 (dd, J = 8.5 Hz and others, 2 H, ArH), 8.01 (dd, J = 8.5 Hz and others, 2 H, ArH).

**13C NMR (75.5 MHz, CDCl3):** δ = 54.4, 124.2, 129.3, 129.7, 131.7, 134.2.

MS (EI): m/z (rel. intensity, %) = 212 [M]+ (99), 214 (100).

UV–Vis (MeOH): λmax = 297 nm.

**N-(p-Chlorobenzylidene)methylamine N-Oxide (13b)**

The title compound was obtained as a white crystalline solid (yield: 82%); mp 127.2–129 °C.

**1H NMR (300 MHz, CDCl3):** δ = 3.78 (s, 3 H, NCH3), 7.27 (s, 1 H, CH), 7.28 (d, J = 8.5 Hz, 2 H, ArH), 8.08 (d, J = 8.5 Hz, 2 H, ArH).

**13C NMR (75.5 MHz, CDCl3):** δ = 54.4, 128.7, 128.9, 129.6, 134.2, 135.8.

MS (EI): m/z (rel. intensity, %) = 168 (100).

UV–Vis (MeOH): λmax = 296 nm.

**N-(p-Nitrobenzylidene)methylamine N-Oxide (13c)**

The title compound was obtained as a white crystalline solid (yield: 98%); mp 215–217 °C (lit. 217–218.2 °C).25

**1H NMR (300 MHz, CDCl3):** δ = 3.94 (s, 3 H, NCH3), 7.51 (s, 1 H, CH), 8.257–8.262 (d, J = 9.0 Hz, 2 H, ArH), 8.357–8.379 (d, J = 9.0 Hz, 2 H, ArH).

**13C NMR (75.5 MHz, CDCl3):** δ = 55.13, 123.79, 128.62, 130.42, 133.07, 147.80.

MS (EI): m/z (rel. intensity, %) = 180 [M]+, (70), 179 (100), 163 (98), 133, 117, 105, 77, 63.

UV–Vis (MeOH): λmax = 296 nm.

**N-(p-Methoxybenzylidene)methylamine N-Oxide (13d)**

The title compound was obtained as a white crystalline solid (79%); mp 82.4 °C.

**1H NMR (300 MHz, CDCl3):** δ = 3.94 (s, 3 H, CH3), 5.14 (s, 1 H, CH), 7.48 (d, J = 8.5 Hz, 2 H, ArH), 7.52 (d, J = 8.5 Hz, 2 H, ArH).

**13C NMR (75.5 MHz, CDCl3):** δ = 47.91, 64.73, 123.97, 129.95, 133.70, 135.57, 136.76, 139.92, 152.92.

MS (EI): m/z (rel. intensity, %) = 180 [M]+, (70), 179 (100), 163 (98), 133, 117, 105, 77, 63.

UV–Vis (MeOH): λmax = 290 nm.

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2397

Reactions of Nitrones with Benzyl-N-methacryloyl-2-oxazolidinone

2397
Amino Ketone 17

compound (0.12 g, 97%). This was purified by chromatography on UV–Vis (CHCl3):

448.1494.

IR: 3643.6, 3583.9, 1706.8, 1527.8, 1348.2, 1215.8 cm–1.

NCH3), 2.63 (m, 2 H, CH 2), 2.82 (br, 1 H, NH disappears on D 2O –4.79 (m, 1 H, CH2), 3.60 (t, $J$ = 8.5 Hz, 2 H, ArH), 7.6 (br s, 1 H, OH disappears on D 2O –4.15 (d, $J$ = 9.0, 3.5 Hz, 1 H, OCH3), 4.18–4.24 (m, 1 H, OCH3), 4.71–4.79 (m, 1 H, CH), 7.16–7.29 (m, 5 H, ArH), 7.41 (dd, $J$ = 9.0, 2.0 Hz, 2 H, ArH), 8.07 (dd, $J$ = 9.0, 2.0 Hz, 2 H, ArH).


Acknowledgment

The authors wish to thank the EPSRC National Mass Spectrometry Centre, University of Swansea for High Resolution Mass Spectra and Dr John Fawcett at the University of Leicester for generously conducting the single crystal X-ray analysis. Special thanks to the Department of Chemistry at the University of Poitiers and Mr Jean-Rene DeFaye for providing me with an excellent Maitrise student (RB).

References


(18) All compounds provided satisfactory spectral data that were consistent with the assigned structures.
(20) Only one isomer was detectable by 1H NMR studies on the crude isolate.
(21) The enantiomeric excess (92%) was determined by chiral GC using a Supercot α-dex 225 column.