The Preparation and Intramolecular Radical Cyclisation Reactions of Chiral Oxime Ethers

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Introduction

The first example of the intramolecular addition of a radical to an oxime ether was published in 1983 by Corey and Pyne. In this work a silyloxyalkyl radical was produced by the reaction of zinc and trimethyl silyl chloride on a carbonyl group which then attacks the oxime ether. The alkoxyaminyl radical which results from the cyclisation seems to have special stability which may be due to stabilisation of the nitrogen radical centre by the adjacent oxygen lone pair. Since this early work extensive studies have taken place in which alkyl radicals have been produced by reaction of a halide with tributyl tin hydride, or a related reductive method, which then undergo addition to the oxime ether usually, but not always in an intramolecular reaction. In 1990 Enholm et al., reported the intramolecular additon of an alkenyl radical to an oxime ether, the sp2 radical was generated by addition of Bu3SnH to an alkyne. Prompted by these studies we have recently reported a series of examples of intramolecular radical cyclisation reactions of oxime ethers. An unusual rearrangement was also observed when the alkoxyamine products of the cyclisation were reduced with LiAlH4. The next stage in this project was to modify the reaction to produce chiral products, we now wish to report our studies on this topic. The idea was to use a chiral hydroxylamine to produce a chiral oxime ether RCH=NOR*, nucleophilic attack on these compounds has received some attention in the literature, and has been the subject of a recent publication. However, we know of no previous work on the addition of radicals to chiral oxime ethers of this type.

Keywords: racemic hydroxylamines, oxime ester, intramolecular reactions, radical cyclisations, chiral oxime ether

Results and Discussion

We have previously reported the use of chloromethyl menthyl ether as a chiral OH protecting group useful in the measurement of the enantiomeric excess of intermediates in a synthetic sequence. In seeking new applications for this reagent we deprotonated the oxime I (Scheme 1) with sodium hydride and alkylated the resulting alkoxide with chloromethyl menthyl ether in THF with DMPU to produce
the chiral oxime ether 2 in 82% yield. Treatment of 2 with Bu₃SnH and AIBN gave alkoxyamine 3 in 78% yield as a 1:1 mixture of diastereoisomers as measured from the ¹³C- and ¹H-NMR of the product. The lack of diastereoselectivity is not surprising in view of the fact that the oxime carbon is five bonds away from the chiral centre on the menthyl group. Four of these connecting bonds are single and so we would expect a wide variety of conformations to be present hence making effective chirality transfer more difficult.

It is well known that esters have a preferred conformation in which the acyl and alkoxy substituents are trans. We therefore attempted to restrict the conformational mobility of the system by preparing oxime ester by reaction of the oxime 1 with camphanic chloride and pyridine to produce the oxime ester 4 in 93% yield. Oxime esters have previously been used in Beckmann type rearrangements¹⁰, radical cyclisation reactions have not been reported previously for the compounds. When the oxime ester 4 was treated with Bu₃SnH the starting material was consumed but no identifiable product was obtained. Clearly the chirality in oxime ethers 2 and 4 is too far away from the oxime carbon atom and the two formally diastereotopic faces of the oxime are not sufficiently different for selectivity to occur in the addition reaction. The closest we can get the stereogenic carbon to the oxime is to have it directly attached to the nitrogen of the oxime, in order to achieve this objective we need to use a chiral oxime ether.

Oxime ethers are most conveniently prepared from alcohols and N-hydroxy succinimide following the method of Grochowski and Jurczac¹¹. We therefore need to apply this method to chiral alcohols to produce chiral hydroxylamines. The first example in Scheme 2 is the reaction of racemic 1-phenyl ethanol with N-hydroxy succinimide to give the adduct 5 in 62% yield. The succinimide group is then removed by reaction with hydrazine to furnish the racemic 1-phenyl ethyl hydroxylamine 6 which was converted directly into the oxime ether 7. Successful intramolecular radical cyclisation of oxime 7 was achieved with Bu₃SnH and AIBN to produce the alkoxy amine 8 in 62% yield as a 1:1 mixture of diastereoisomers.

The other example in Scheme 2 is the reaction of (S)-naphthyl ethanol with N-hydroxy succinimide and diethyl azodicarboxylate to furnish the (R) adduct 9 in 57% yield where inversion of configuration has occurred in the substitution reaction. The succinimide group was again removed with hydrazine to yield the chiral hydroxylamine 10 which was converted directly into the chiral oxime ether 11 in 93% yield. Treatment of this oxime with Bu₃SnH and AIBN gave radical cyclisation in 68% yield to give the alkoxy amine 12 as a 1:1 mixture of diastereoisomers.

In conclusion chiral and racemic oxime ether derivatives have been prepared and subjected to intramolecular radical cyclisation reactions. This is the first study of this topic to the best of our knowledge. The lack of diastereoselectivity in the process was disappointing, however it is hoped that in the future asymmetric induction will be possible in this reaction.

**Scheme 1.** Reagents: i, NaH, DMPU, THF; ii, chloromethyl-(1R)-menthyl ether; iii, Bu₃SnH, AIBN, Benzene; iv, camphoric chloride, pyridine.
Experimental

General

$^1$H-NMR (300 MHz) and $^{13}$C-NMR (75.5 MHz) spectra were recorded on a Bruker AM-300 spectrometer at the University of Leicester. $^1$H-NMR (360 MHz and 250 MHz) and $^{13}$C-NMR (90.5 MHz and 63.5 MHz) spectra were recorded on Bruker AM-360 and AM-250 spectrometers at Merck, Sharp and Dohme, Harlow. Standard mass spectra and accurate mass measurements were made at the SERC mass spectrometry centre, University College of Swansea. Elemental analysis was carried out by Butterworth Laboratories, Teddington, Middlesex. Infra-red spectra were recorded on a Perkin-Elmer 298 spectrophotometer. Melting points were determined on a Kofler hotstage and are uncorrected.

Flash chromatography was carried out using Merck Kieselgel 60 (230-400 mesh). T.l.c. was performed on Merck aluminium sheets coated with silica gel 60 F$_{254}$ (Art 5735).

Light petroleum (b.p. 40-60 °C) and ethyl acetate were distilled prior to use. THF was distilled from sodium metal in the presence of benzophenone.

(R) menthol and its derivatives are obtained from 1R, 2S, 5R-menthol.

2-(3-Bromoallyloxy)benzaldehyde-O-((R)-menthoxymethoxy)oxime 2

2-(3-Bromoallyloxy)benzaldehyde-O-((R)-menthoxymethoxy)oxime 2

Scheme 2. Reagents: i, PPh$_3$, racemic $\alpha$-methylbenzylalcohol; ii, N$_2$H$_4$; iii, 2-(2-bromoallyloxy)-benzaldehyde, pyridine; iv, Bu$_3$SnH, AIBN, benzene; v, PPh$_3$, (S)-naphthyl ethanol.

\[ \text{Ar} = 2\text{-naphthyl} \]
(100), 69 (40), 55 (58); (Found: MH⁺, 424.1487. C₂₃H₄₃BrNO₃ requires MH⁺, 424.1487).

4-(2-(R)-Menthoxymethyloamo)chroman-3-ylidene 3

2-(2-Bromoallyl)benzaldehyde-O-(2-(R)-mentholxymethoxy) oxime 2 (250 mg, 0.59 mmol) and tributyltin hydride (206 mg, 0.71 mmol) were dissolved in benzene (30 cm³, 0.02 M dilution of 2) and the solution degassed by bubbling a steady stream of nitrogen through it for 1 h. The solution was heated to reflux temperature under a nitrogen atmosphere and azobisisobutyronitrile (AIBN) (20 mg, 0.12 mmol) in benzene (10 cm³) added over 10 h. Heating at reflux temperature was continued for a further 12 h. Benzene was evaporated in vacuo and the residue purified by chromatography on silica gel with diethyl ether-light petroleum (b.p. 40-60 °C) (1:1, v/v) as eluent. A 1:1 mixture of diastereoisomers of hydroxylamine 3 (159 mg, 78%) as a pale yellow oil. Rᵋ (diethyl ether-light petroleum [b.p. 40-60 °C], 1:4, v/v) 0.47; νmax (film)/cm⁻¹ 3200 br, w, 3010 w, 2960 m, 2920 w, 2860 w, 1650 (C=N), 1600 w, 1590 m, 1580 w, 1480 m; δH (300 MHz, CDCl₃, MeSi) 0.68-1.04 (24 H, complex m, H-2', H-7', H-8', H-9' and H-10' in both diastereoisomers), 1.18-1.43 (4 H, m, H-5' and H-2' in both diastereoisomers), 1.62 (4 H, m, H-3' in both diastereoisomers), 1.98-2.31 (4 H, m, H-6' in both diastereoisomers), 3.29 (1 H, td, J=12.6, 6.1-H-1' in diastereoisomer A), 3.35 (1 H, td, J=4.3, 10.6-H-1' in diastereoisomer B), 4.44 (1 H, s, H-4 in diastereoisomer A), 4.49 (1 H, s, H=4 in diastereoisomer B), 4.70 and 4.84 (2 H, AB q, J7.6, OCH₂O in diastereoisomer A), 4.75 and 4.86 (2 H, AB q, J7.5, OCH₂O in diastereoisomer A), 4.85 (2 H, d, H-2' in both diastereoisomers), 5.28 (2 H, s, H-E in both diastereoisomers), 5.33 (2 H, s, H-Z in both diastereoisomers), 6.84 (2 H, d, J=8.2, H-8 in both diastereoisomers), 6.90 (2 H, t, J₅,₆=J₆,₇=7.5, H-6 in both diastereoisomers), 7.15-7.27 (4 H, m, H-5 and H-7 in both diastereoisomers) ppm; δC (75.5 MHz, CDCl₃, MeSi) 15.9 (C-7'), 21.1 (C-10'), 22.3 (C-9'), 22.96 and 23.02 (C-4'), 25.3 (C-8'), 31.49 and 31.55 (C-5'), 34.31 and 34.35 (C-3'), 41.2 and 42.3 (C-6'), 48.1 and 48.2 (C-2'), 60.1 (C-4), 67.3 (C-2), 76.9 (C-1'), 96.5 and 98.0 (OCH₂O), 115.8 and 115.9 (C=CH₂), 116.9 and 117.0 (C-8), 119.70 and 119.93 (C=4a), 120.6 (C-6), 129.42 and 129.45 (C-7), 129.9 and 130.1 (C-5), 139.3 and 139.4 (C-3), 155.19 and 155.25 (C-8a); m/z (CI) 346 (MH⁺, 7), 160 (6), 145 (100), 122 (4); (Found: MH⁺, 346.2382. C₂₃H₄₃NO₃ requires MH⁺, 346.2382).

2-(2-Bromoallyl)benzaldehyde-O-camphanic oxime 4

2-(3-Bromo-3-en-1-oxo)benzaldehyde O-camphanic oxime 4 (300 mg, 0.68 mmol) and tributyltin hydride (240 mg, 0.83 mmol) in dry deoxygenated benzene (34.4 cm³), 0.02 M dilution of 4) heated at reflux temperature. Heating was continued for a further 5 h. Benzene was evaporated under reduced pressure but analysis of the crude product mixture revealed in excess of ten components that could not be isolated. All starting material was consumed.

N-(α-Methylbenzylxlo)phthalimide 5

To a stirred solution of N-hydroxypthalimide (1.00 g, 6.13 mmol), triphenylphosphine (1.61 g, 6.13 mmol) and α-methylbenzylalcohol (0.75 g, 6.13 mmol) in THF (30 cm³) under a nitrogen atmosphere was slowly added diethylzodicarboxylate (1.17 g, 6.74 mmol). The reaction mixture was stirred at room temperature for 24 h. THF was evaporated in vacuo. Chromatography on silica gel with dichloromethane-light petroleum (b.p. 40-60 °C) (1:1, v/v) as eluent afforded the phthalimide 5 (1.01 g, 62%) as plates, m.p. 89-91 °C (from light petroleum [b.p. 60-80 °C]); (Found: C, 71.86; H, 4.92; N, 5.27. C₁₆H₁₃NO₃ requires C, 71.90; H, 4.92; N, 5.24); Rᵋ (dichloromethane-
light petroleum [b.p. 40-60 °C] 1:1, v/v) 0.43; \( \nu_{\text{max}} \) (CH\(_2\)Cl\(_2\))/cm\(^{-1}\) 3080-2820 w, 1785 s, 1725 s, 1460 m, 1370 s, 1185 s; \( \delta_H \) (300 MHz, CDCl\(_3\), Me\(_2\)Si) 1.70 (3 H, d, J\(_{3H,2H}\)), 5.49 (1 H, q, PhCH(Me)), 7.26-7.36 (3 H, m, H-0 and H-2 in PhCH(Me)O-), 7.50 (2 H, m, H-2ax in PhCH(Me)O-), 7.69 (4 H, m, phthalimide protons) ppm; \( \delta_C \) (75.5 MHz, CDCl\(_3\), Me\(_2\)Si) 20.4 (CH\(_3\)), 85.0 (PhCH(Me)-), 123.3 (phthalimide), 127.5 (C-4 in PhCH(Me)O-), 128.3 (C-m in PhCH(Me)O-), 128.7 (phthalimide), 128.9 (C-p in PhCH(Me)O-), 134.2 (phthalimide), 138.8 (C in PhCH(Me)O-), 163.7 (C-1 and C-3) ppm; m/z (EI) 268 (MH\(^{+}\), 13), 164 (13), 105 (100), 90 (31). (Found: [C\(_{16}\)H\(_{13}\)BrNO\(_2\) requires MH\(^{+}\), 360.0599].

4-(\(\alpha\)-Methylbenzoxamino)chroman-3-ylidene 8

2-(2-Bromoallyloxy)benzaldehyde-O-(\(\alpha\)-methyl)benzoxime 7 (125 mg, 0.35 mmol) and tributyltin hydride (122 mg, 0.42 mmol) were dissolved in dry benzene (18 cm\(^3\), 0.02 M dilution of 7) and the solution degassed for 1 h. The reaction mixture was heated to reflux temperature and a solution of AIBN (12 mg, 0.07 mmol) in dry benzene (10 cm\(^3\)) added over 8 h. Heating was continued for 18 h. Benzene was removed under reduced pressure. Chromatography on silica gel with diethyl ether-light petroleum (b.p. 40-60 °C)(1:9, v/v) as eluent afforded a 1:1 mixture of diastereoisomers of the hydroxylamine 8 as a pale yellow oil (59 mg, 61%); \( R_f \) (diethyl ether-light petroleum [b.p. 40-60 °C], 1:4, v/v) 0.36; \( \nu_{\text{max}} \) (CH\(_2\)Cl\(_2\))/cm\(^{-1}\) 3080 w, 3010 w, 2990 m, 2860 w, 1630 m, 1610 m, 1570 w, 1485 s, 1240 s; \( \delta_H \) (300 MHz, CDCl\(_3\), Me\(_2\)Si) 1.44 (3 H, d, J 6.6, Me in isomer A), 1.52 (3 H, d, J 6.6, Me in isomer B), 4.30 (1 H, d, J\(_{2ax,2eq}\) 11.5, H-2ax in isomer B), 4.40 (1 H, s, H-4 in isomer B), 4.48 (1 H, s, H-4 in isomer A), 4.50-4.55 (2 H, m, H-2eq in isomer B and H-2ax in isomer A), 4.76-4.84 (2 H, m, CHMe in isomers A and B), 4.88 (1 H, dd, J\(_{2eq,Z}\) 1.1, J\(_{2eq,2ax}\) 11.7, H-2eq in isomer A), 5.23 (1 H, s, H-E in isomer B), 5.34 (2 H, m, H-E in isomer A and H-Z in isomer B), 5.41 (1 H, d, H-Z in isomer A), 6.77-6.90 (2 H, m, H-8 in isomers A and B), 7.07-7.29 (2 H, m, H-6 in isomers A and B), 7.40-7.48 (4 H, m, H-5 and H-7 in isomers A and B), 7.70-7.83 (10 H, m, H-0, H-m and H-p in PhCH\(_2\) in isomers A and B) ppm; \( \delta_C \) (75.5 MHz, CDCl\(_3\), Me\(_2\)Si) 23.9 and 24.9 (Me), 58.6 and 58.7 (C-4), 69.3 and 69.9 (C-2), 81.5 and 81.6 (CH(Me)Ph), 116.9 and 117.1 (C=CH\(_2\)), 120.7 and 120.8 (C-8), 120.8 and 121.1 (C-4a), 126.0 and 126.2 (C-6), 127.1 and 127.2 (C-p in PhCH\(_2\)), 127.8 and 127.9 (C-m in PhCH\(_2\)), 128.1 and 128.2 (C-o in PhCH\(_2\)), 128.5 and 128.6 (C-7), 129.7 and 129.8 (C-5), 143.5 and 143.8 (C in PhCH\(_2\)), 145.0 and 145.1 (C-3), 155.1 and 155.4 (C-8a) ppm.

(R)-N-(2-(2-naphthyl)ethoxy)phthalimide 9

Diethylazodicarboxylate (2.22 g, 12.75 mmol) was added dropwise to a stirred solution of (S)-\(\alpha\)-methyl-2-naphthalenemethanol (2.00 g, 11.61 mmol), N-hydroxyphthalimide (1.89 g, 11.61 mmol) and triphenylphosphine (3.05 g, 11.61 mmol) in THF (50 cm\(^3\)) under a nitrogen atmosphere. The reaction was left stirring at room temperature for 72 h. THF was evaporated under reduced pressure. Chromatography on silica gel with dichloromethane-light petroleum (b.p. 40-60 °C)(2:1, v/v) as eluent afforded the phthalimide 9 (2.10 g, 57%) as needles, m.p. 105-106 °C (from diethyl ether); (Found: C, 75.84; H, 4.49; N, 4.45. C\(_{20}\)H\(_{15}\)NO\(_3\) requires C, 75.69; H, 4.76; N, 4.41); \( R_f \) (dichloromethane-light petroleum [b.p. 40-60 °C], 1:1, v/v) 0.38; \( \nu_{\text{max}} \) (CH\(_2\)Cl\(_2\))/cm\(^{-1}\) 3080-2820 w, 1780 s,
1720 s, 1460 m, 1370 s, 1180 s; δH (300 MHz, CDCl3, MeSi) 1.77 (3 H, d, J 6.6, Me), 5.67 (1 H, q, ArCHMe-), 7.41 (2 H, m, H-7” and H-6”), 7.60 (4 H, m, phthalimide protons), 7.80 (5 H, m, H-1”, H-3”, H-4”, H-5” and H-8”) ppm; δC (75.5 MHz, CDCl3, MeSi) 20.6 (Me), 85.1 (ArCHMe-), 123.1 (C-4 and C-7), 124.7 (C-3”), 126.0 (C-6”), 126.2 (C-7”), 127.9 (C-4”), 127.5 (C-1”), 127.9 (C-5”), 128.1 (C-8”), 128.6 (phthalimide), 132.7 (C-8a”), 133.4 (C-4a”), 134.1 (phthalimide), 136.4 (C-2”), 163.6 (phthalimide) ppm; m/z (EI) 317 (M+, 1), 155 (100), 127 (12), 115 (8), 104 (10), 76 (13); (Found: M+, 317.1050. C20H21NO2 requires M+, 317.1050.

(R)-O-2-(2-naphthyl)ethylhydroxylamine 10

(R)-N-(2-(2-naphthyl)ethoxy)phthalimide 9 (670 mg, 2.11 mmol) and hydrazine monohydrate (106 mg, 2.11 mmol) were heated at reflux temperature in ethanol (5 cm³) for 2 h. The reaction mixture was poured into 3% sodium carbonate solution and the product extracted with diethyl ether. RF (dichloromethane-light petroleum (b.p. 40-60 °C)/(1:1, v/v)) 0.38. The hydroxylamine 10 was used without purification.

(R)-2-(2-Bromoallyloxy)benzaldehyde O-(2)-(2-naphthyl)ethoxyline 11

(R)-2-(2-Bromoallyloxy)benzaldehyde O-(2)-(2-naphthyl)ethoxyline 11 (400 mg, 2.14 mmol) and 2-(2-bromoallyloxy)benzaldehyde (430 mg, 1.78 mmol) were stirred in pyridine (5 cm³) at room temperature overnight. Pyridine was removed under reduced pressure. Chromatography on silica gel with dichloromethane-light petroleum (b.p. 40-60 °C) (1:1, v/v) as eluent afforded the oxime ether 11 as a clear, colourless oil (677 mg, 93%); RF (dichloromethane-light petroleum (b.p. 40-60 °C)) 1:1, v/v) 0.51; [α]D 7+4.2° (c 4.5, CHCl3); νmax (film/cm⁻¹) 3045 w, 2970 s, 2910 m, 2860 w, 1635 m, 1600 s, 1540 w, 1480 s, 750 s; δH (300 MHz, CDCl3, MeSi) 1.68 (3 H, d, J 6.6, Me), 4.55 (2 H, t, J1,2=3 J2,3=1.2, H-1”), 5.51 (1 H, q, OCH(Me)naphth), 5.64 (1 H, dt, J1,2=3.1 J2,3=1.3, H-3”Z), 5.90 (1 H, dt, H-3”E), 6.69 (1 H, d, J3,4=8.2 H-3), 6.87 (1 H, dd, J5,6=7.5, J5,7=7.6, H-5), 7.19 (1 H, ddd, J6,7=1.7, H-4”), 7.41 (2 H, m, H-6” and H-7”), 7.51 (1 H, dd, J6,7=1.4, H-6”), 7.71 (5 H, m, H-1”, H-3”, H-4”, H-5” and H-8”), 8.60 (1 H, s, H=NC=O) ppm; δC (75.5 MHz, CDCl3, MeSi) 21.9 (Me), 71.8 (C-1”), 81.3 (OCH(Me)naphth), 112.4 (C-3”), 118.0 (C-3”), 121.4 (C-1”), 121.4 (C-5”), 124.6 (C-3”), 125.1 (C-6”), 125.3 (C-7”), 125.9 (C-4”), 126.2 (C-5”), 126.7 (C-4”), 127.4 (C-1”), 127.9 (C-5”), 128.0 (C-8”), 130.8 (C-6”), 132.8 (C-8a”), 133.2 (C-4a”), 140.6 (C-2”), 144.4 (C=O=), 155.2 (C-4’) ppm; m/z (EI) 410/412 (MH+”, 2), 256/258 (2), 155 (100), 141 (2), 127 (15); (Found: MH+”, 410.0756. C23H20BrNO2 requires MH+”, 410.0756).

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References


