Optically Pure 3,6-Dioxazocan-2-one Derivatives by Intramolecular Cycloaddition of Azidoformates and their Opening to Substituted α-Amino Ketones

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Azidoformates derived from chiral enol ethers, when irradiated, give 3,6-dioxazocan-2-one derivatives **7** by a highly diastereoselective intramolecular cycloaddition. The hydrolysis of **7** gives a single derivative of 2-aminocyclohexanone.

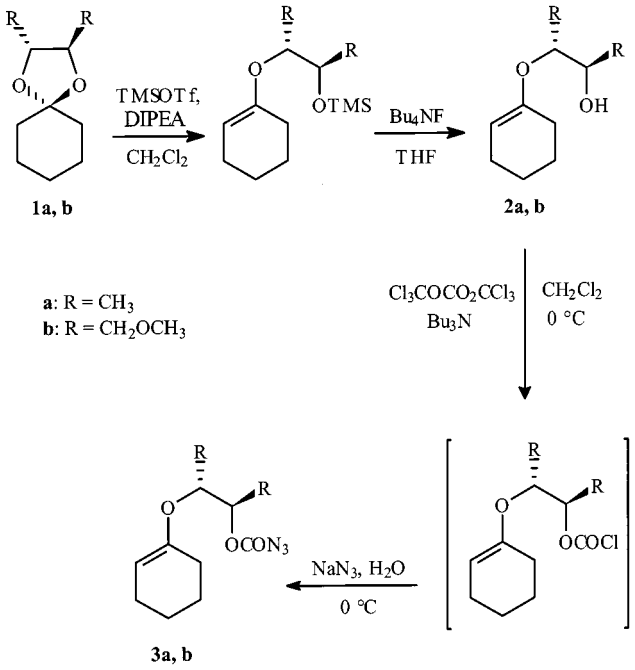
During our studies on intermolecular amination reactions[1] we have also considered chiral enol ethers and the early results seem promising.[2] The intramolecular addition of azidoformates carrying a chiral enol ether function attracted our attention in the hope that we might obtain asymmetric induction. Examples of the intramolecular cyclization of azidoformates with generic olefins are very rare in the literature,[3] while several intramolecular C−H insertion reactions, starting from azidoformates are known.[4]

The desired azides **3** were prepared, in 40−52% overall yield, from the ring-opening reaction of spirane ketals **1** with TMSOTf, followed by a desilylation step, to give **2**, which is then reacted sequentially with triphosgene and sodium azide to give **3** (Scheme 1).

The azides **3** are stable at room temperature for several weeks and for a few hours in boiling carbon tetrachloride. When stored in CH_2Cl_2 for a longer time the enol ether function of **3** undergoes complete hydrolysis to give the hydroxy azides **4**, which give **6** by treatment with silica gel. At higher temperatures (120°C, in a sealed tube for 2 h) the decomposition of **3** gave **6** directly.

A solution of **3** in dichloromethane was photolyzed for 4−12 h at room temperature under an argon atmosphere giving compounds **7** and **4**, as shown by NMR spectroscopy and, after flash-chromatography, compounds **7** (20−21%) and **6** (21−40%) could be isolated (Scheme 2).

The isolation of **7**, albeit in moderate yield, is interesting as the azocan-2-one, and its derivatives, possess important pharmacological properties.[5] The unusual 3,6-dioxazocan-2-one skeleton of **7** probably derives from the isomerization of an unstable tricyclic aziridine, as has previously been reported.[6] From a stereochemical point of view, the new C−N bond is formed with high asymmetric induction − only one diastereomer is formed as seen from spectroscopic and chromatographic evidence.



Scheme 1. Synthesis of azidoformates

The stereochemistry was tentatively assigned assuming least hindered attack, as observed in the cyclopropanation[7] and epoxidation[8] of related substrates. The heats of formation, obtained by semiempirical MO calculations, indicated that the aziridine **5a**, resulting from attack at the *si-re* face of the olefin, is more stable than the other aziridine [$\Delta\Delta H$ = −1.05 kcal/mol (PM3) or $\Delta\Delta H$ = −1.6 kcal/mol (AM1)].

The enol ether moiety of **7a** was finally hydrolyzed with $BF_3{\cdot}Et_2O$ in aqueous methanol to give the *N*-substituted 2-aminocyclohexanone **8** in 95% yield as a single stereoisomer (Scheme 3). Stereochemically pure derivatives of α-amino ketones are important as they can be employed in a variety of organic syntheses,[9] and they are also precursors of β-amino alcohols.[10]

In conclusion, by using enol ethers tethered with a chiral chain ending with an azido function it is possible to obtain optically active derivatives of α-amino ketones through useful medium ring intermediates. Further studies to test the

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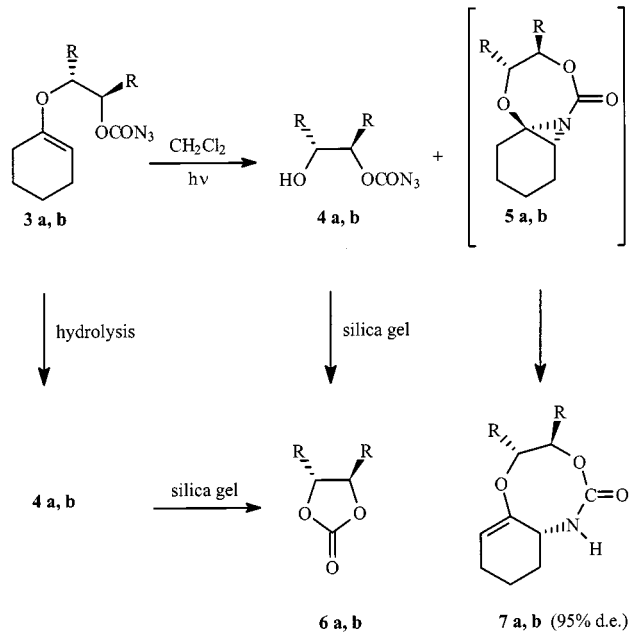
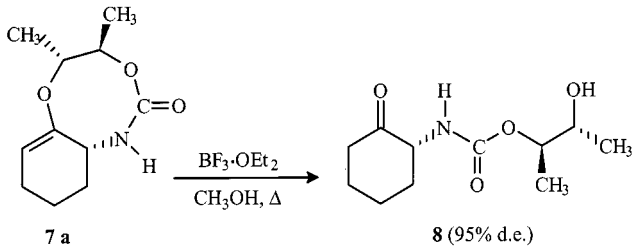


Scheme 2. Photolysis of azidoformates



Scheme 3. Hydrolysis of **7a**

versatility and to optimize the yields of the cyclization reaction are in progress.

Experimental Section

General Methods: GC analyses were performed on an HP 5890 Series II gas chromatograph with a capillary column (methyl silicone, 12.5 m × 0.2 mm). GC-MS measurements were carried out on an HP G1800A GCD System with a capillary column (phenyl methyl silicone, 30 m × 0.25 mm). The separations by HPLC were performed with a Varian 9001 instrument equipped with a Varian RI-4 differential refractometer. Solvents were HPLC-grade. The ketals **1** and the chiral enol ethers were prepared as previously reported.[2] − Optical rotations: Perkin−Elmer 241 polarimeter (10 mm, 1 mL) at room temp. − IR: Perkin−Elmer 1600 Series FTIR spectrophotometer. − NMR: Varian XL-300 and Varian Gemini 200 solvent $CDCl_3$ and $CHCl_3$ as internal standard.

Alcohols 2: To a stirred solution of the ketal **1** (5 mmol) and *N*,*N*-diisopropylethylamine (6.5 mmol for **1a** and 11.0 mmol for **1b**) in 10 mL of anhydrous CH_2Cl_2 under an atmosphere of argon was added TMSOTf (6.5 mmol for **1a** and 10.0 mmol for **1b**) dropwise at 0°C. After 4−22 h at room temperature, Bu_4NF (7.5 mL of 1 M solution in THF) was added, the mixture was stirred for 1 h, and then petroleum ether was added to precipitate the inorganic salts. After filtration, the product was purified by flash chromatography on silica gel (hexane/acetone/triethylamine, 85:14:1).

(2*R*,3*R*)-3-[(Cyclohex-1-enyl)oxy]butan-2-ol (2a): Yield: 79%. − $[\alpha]_D^{RT}$ = − 54.6 (*c* = 1.30, CH_2Cl_2). − IR (CCl_4): $\tilde{\nu}$ = 3592 cm^{-1}, 3408, 1666. − ^1H NMR ($CDCl_3$): δ = 1.14 (d, 3 H, CH_3), 1.17 (d, 3 H, CH_3), 1.50−1.75 (m, 4 H, CH_2), 1.99−2.10 (m, 4 H, CH_2), 2.52 (d, 1 H, OH), 3.59−3.72 (m, 1 H, CH), 3.75−3.88 (m, 1 H, CH), 4.68 (t, 1 H, HC=C). − ^{13}C NMR ($CDCl_3$): δ = 15.43, 18.38 (CH_3), 22.59, 22.87, 23.49, 27.96 (CH_2), 70.92, 76.36 (CH), 96.29 (H*C*=C), 152.54 (HC=*C*). − GC-MS; *m*/*z* (%): 170 (11) [M^+], 127 (22), 98 (100), 97 (51), 83 (64), 81 (27), 79 (22), 70 (87), 55 (58), 43 (29), 41 (31).

(2*R*,3*R*)-3-[(Cyclohex-1-enyl)oxy]-1,4-dimethoxybutan-2-ol (2b): Yield: 77%. − $[\alpha]_D^{RT}$ = − 22.1 (*c* = 2.44, CH_2Cl_2). − IR (CCl_4): $\tilde{\nu}$ = 3587 cm^{-1}, 3466, 1665. − ^1H NMR ($CDCl_3$): δ = 1.42−1.70 (m, 4 H, CH_2), 1.95−2.08 (m, 4 H, CH_2), 2.68 (d, 1 H, OH), 3.33 (s, 3 H, OCH_3), 3.36 (s, 3 H, OCH_3), 3.41−3.65 (m, 4 H, OCH_2), 3.91−4.01 (m, 1 H, CH), 4.10−4.19 (m, 1 H, CH), 4.77 (t, 1 H, HC=C). − ^{13}C NMR ($CDCl_3$): δ = 22.40, 22.74, 23.36, 27.67 (CH_2), 58.99, 59.19 (OCH_3), 69.97, 70.71 (OCH_2), 73.19, 73.58 (OCH), 96.56 (H*C*=C), 153.05 (HC=*C*). − GC-MS; *m*/*z* (%): 230 (<1) [M^+], 195 (11), 187 (19), 135 (14), 115 (66), 98 (20), 97 (22), 95 (14), 93 (16), 85 (30), 84 (100), 81 (43), 79 (37), 71 (35), 69 (18), 67 (14), 55 (38), 53 (20), 45 (63), 43 (11), 41 (43).

Azides 3: To a stirred solution of **2** (3 mmol) and anhydrous tributylamine (3 mmol) in 8 mL of anhydrous CH_2Cl_2 under an atmosphere of argon was added dropwise triphosgene (1 mmol) in 0.7 mL of anhydrous CH_2Cl_2 at 0°C. After 1 h of stirring, a solution of NaN_3 (6 mmol) in 10 mL of H_2O was added and the reaction was stirred for 1 h. The mixture was then extracted with CH_2Cl_2 and the solvent was evaporated. The azides **3** were purified by flash chromatography on silica gel (hexane/ethyl acetate, 98:2).

(1*R*,2*R*)-2-[(Cyclohex-1-enyl)oxy]-1-methylpropyl Azidoformate (3a): Yield: 50%. − $[\alpha]_D^{RT}$ = +20.5 (*c* = 1.32, CH_2Cl_2). − IR (CCl_4): $\tilde{\nu}$ = 2188 cm^{-1}, 2135, 1729, 1666. − ^1H NMR ($CDCl_3$): δ = 1.18 (d, 3 H, CH_3), 1.27 (d, 3 H, CH_3), 1.45−1.75 (m, 4 H, CH_2), 1.95−2.10 (m, 4 H, CH_2), 4.15 (m, 1 H, CH), 4.70 (t, 1 H, HC=C), 4.71 (m, 1 H, CH). − ^{13}C NMR ($CDCl_3$): δ = 14.79, 14.93 (CH_3), 22.57, 22.84, 23.47, 27.82 (CH_2), 71.53, 76.51 (OCH), 95.86 (H*C*=C), 152.74 (HC=*C*) 157.08 (C=O). − GC-MS; *m*/*z* (%): 211 (7) [M^+ − 28], 140 (40), 128 (11), 127 (100), 98 (21), 56 (16), 55 (38), 43 (12), 41 (16).

(1*R*,2*R*)-2-[(Cyclohex-1-enyl)oxy]-3-methoxy-1-(methoxymethyl)-propyl Azidoformate (3b): Yield: 70%. − $[\alpha]_D^{RT}$ = +7.3 (*c* = 2.62, CH_2Cl_2). − IR (CCl_4) $\tilde{\nu}$ = 2189 cm^{-1}, 2134, 1732, 1667. − ^1H NMR ($CDCl_3$): δ = 1.42−1.67 (m, 4 H, CH_2), 1.96−2.06 (m, 4 H, CH_2), 3.31 (s, 3 H, OCH_3), 3.32 (s, 3 H, OCH_3), 3.47 (d, 2 H, OCH_2), 3.55 (d, 2 H, OCH_2), 4.20−4.30 (q, 1 H, CH), 4.76 (t, 1 H, HC=C), 5.16−5.23 (q, 1 H, CH). − ^{13}C NMR ($CDCl_3$): δ = 22.33, 22.66, 23.30, 27.53 (CH_2), 58.99, 59.20 (OCH_3), 70.07, 70.34 (OCH_2), 72.47 (OCH), 76.16 (*C*HOCO), 96.55 (H*C*=C), 153.10 (HC=*C*), 157.12 (C=O). − GC-MS; *m*/*z* (%): 271 (<1) [M^+ − 28], 201 (10), 200 (77), 188 (11), 187 (100), 115 (59), 85 (17), 55 (18), 45 (25), 41 (12).

Hydrolysis of Azides 3: When stored in dichloromethane for three months the azides **3** undergo complete hydrolysis to the hydroxy azides **4**.

(1*R*,2*R*)-2-Hydroxy-1-methylpropyl Azidoformate (4a): Yield: 95%. − IR (CCl_4): $\tilde{\nu}$ = 3479 cm^{-1}, 3613, 2188, 2136, 1733. − ^1H NMR ($CDCl_3$): δ = 1.16 (d, 3 H, CH_3), 1.25 (d, 3 H, CH_3), 2.95 (br, 1 H, OH), 3.73 (m, 1 H, CH), 4.69 (m, 1 H, CH). − ^{13}C NMR ($CDCl_3$): δ = 15.55, 18.32 (CH_3), 69.98, 79.48 (CH), 157.06 (C=O). − GC-MS, *m*/*z* (%): 113 (50) [M^+ − 46], 43 (20), 42 (100), 41 (12).

(1*R*,2*R*)-2-Hydroxy-3-methoxy-1-(methoxymethyl)propyl Azidoformate (4b): Yield: 95%. − IR (CCl_4): $\tilde{\nu}$ = 3588 cm^{-1}, 2190, 2135, 1728. − ^1H NMR ($CDCl_3$): δ = 2.64 (br, 1 H, OH), 3.38 (s, 6 H, OCH_3), 3.46 (d, 2 H, CH_2), 3.65 (d, 2 H, CH_2), 3.98 (q, 1 H, CH), 5.05 (q, 1 H, CH). − ^{13}C NMR ($CDCl_3$): δ = 59.26, 59.36 (OCH_3), 69.56, 71.32 (CH_2), 72.93, 77.05 (CH), 157.14 (C=O).

Photolysis of Azides 3: A solution of the azide (1 mmol) in 20 mL of anhydrous CH_2Cl_2 was photolyzed in a quartz vessel under an argon atmosphere at room temperature, using a medium pressure Hanovia PCR lamp (100 W). When the azide band had disappeared from the IR spectrum (4 h for **3a** and 12 h for **3b**) the solvent was evaporated in vacuo. The products were separated by flash chromatography on silica gel (hexane/ethyl acetate, 70:30 for **6a** and **7a**; 45:55 for **6b** and **7b**).

(4*R*,5*R*)-4,5-Dimethyl-1,3-dioxolan-2-one (6a): Yield: 21%. − $[\alpha]_D^{RT}$ = +5.3 (*c* = 1.20, CH_2Cl_2). − IR (CCl_4): $\tilde{\nu}$ = 1824 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 1.40−1.45 (m, 6 H, CH_3), 4.25−4.35 (m, 2 H, CH). − ^{13}C NMR ($CDCl_3$): δ = 18.38 (CH_3), 79.85 (CH), 154.45 (C=O). − GC-MS; *m*/*z* (%): 116 (1) [M^+], 45 (24), 44 (27), 43 (100), 41 (10).

(4*R*,5*R*)-4,5-Bis(methoxymethyl)-1,3-dioxolan-2-one (6b): Yield: 40%. − $[\alpha]_D^{RT}$ = +38.9 (*c* = 3.16, CH_2Cl_2). − IR (CCl_4): $\tilde{\nu}$ = 1823 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 3.40 (s, 6 H, CH_3), 3.55−3.61 (m, 4 H, CH_2), 4.61−4.64 (m, 2 H, CH). − ^{13}C NMR ($CDCl_3$): δ = 59.56 (OCH_3), 71.34 (OCH_2), 76.70 (CH), 155.50 (C=O). − GC-MS; *m*/*z* (%): 176 (<1) [M^+], 45 (100).

(5*R*,6*R*)-5,6-Dimethyl-4,7-dioxa-2-azabicyclo[6.4.0]dodec-8-en-3-one (7a): Yield: 21%. − $[\alpha]_D^{RT}$ = +17.2 (*c* = 2.00, CH_2Cl_2). − IR (CCl_4): $\tilde{\nu}$ = 3417 cm^{-1}, 1738, 1666. − ^1H NMR ($CDCl_3$): δ = 1.19 (d, 3 H, CH_3), 1.36 (d, 3 H, CH_3), 1.50−2.30 (m, 6 H, CH_2), 3.35−3.50 (m, 1 H, CH_3CHO), 4.20−4.60 (m, 3 H, CH_3CHOCO, NH, HC−N), 5.35 (t, 1 H, HC=C). − ^{13}C NMR ($CDCl_3$): δ = 17.26, 17.96 (CH_3), 21.17, 23.96, 28.82 (CH_2), 50.50 (HC−N), 81.78, 85.61 (OCH), 113.07 (H*C*=C), 155.02 (HC=*C*), 161.12 (C=O). − GC-MS; *m*/*z* (%): 211 (18) [M^+], 168 (12), 142 (10), 141 (23), 140 (26), 139 (63), 116 (18), 113 (13), 112 (20), 111 (56), 98 (59), 97 (38), 96 (54), 95 (34), 91 (12), 84 (12), 83 (33), 82 (12), 81 (14), 80 (13), 79 (53), 77 (13), 73 (42), 72 (14), 70 (28), 69 (26), 68 (30), 67 (43), 57 (22), 56 (65), 55 (100), 54 (16), 53 (11), 45 (31).

(5*R*,6*R*)-5,6-Bis(methoxymethyl)-4,7-dioxa-2-azabicyclo[6.4.0]-dodec-8-en-3-one (7b): Yield: 20%. − $[\alpha]_D^{RT}$ = +23.6 (*c* = 3.10, CH_2Cl_2). − IR (CCl_4): $\tilde{\nu}$ = 3418 cm^{-1}, 3268, 1736, 1670. − ^1H NMR ($CDCl_3$): δ = 1.20−2.20 (m, 6 H, CH_2), 3.36 (s, 6 H, OCH_3), 3.50−3.60 (m, 4 H, OCH_2), 3.70−3.75 (m, 1 H, CHN), 4.27 (br, 1 H, NH), 4.53−4.56 (m, 1 H, CH_2CHO), 4.64−4.67 (m, 1 H, CH_2CHOCO), 5.42 (t, 1 H, HC=C). − ^{13}C NMR ($CDCl_3$): δ = 21.06, 23.87, 28.70 (CH_2), 50.32 (CHN), 59.46, 59.76 (OCH_3), 71.65, 72.48 (OCH_2), 80.70, 83.47 (OCH), 113.62 (H*C*=C), 154.90 (HC=*C*), 160.42 (C=O). − GC-MS; *m*/*z* (%): 271 (<1) [M^+], 139 (24), 133 (10), 115 (100), 111 (18), 101 (17), 96 (12), 95 (14), 87 (31), 85 (30), 83 (12), 79 (13), 75 (10), 71 (16), 69 (11), 68 (15), 67 (14), 59 (13), 55 (36), 45 (63), 41 (21).

2-{[(1*R*,2*R*)-2-Hydroxy-1-methyl(propoxycarbonyl)]amino}-cyclohexanone (8): To a solution of $BF_3{\cdot}OEt_2$ (1.3 mL, 10 mmol) and 1 mL of H_2O was added **7a** (0.5 mmol) in 10 mL of MeOH at room temperature. After 2 h at reflux, 50 mL of a saturated NaCl solution was added and the mixture was extracted with ethyl acetate. The recombined organic layers were washed with saturated $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered and concentrated. Compound **8** was obtained as a single product. Yield: 95%. − IR (CCl_4): $\tilde{\nu}$ = 3620 cm^{-1}, 3416, 1733, 1715. − ^1H NMR ($CDCl_3$): δ = 1.20−1.26 (m, 6 H, CH_3), 1.30−2.60 (m, 8 H, CH_2) 3.73 (br, 1 H, OH), 4.29−4.35 (m, 2 H, C*H*CH_3, CHN), 4.60−4.64 (m, 1 H, C*H*CH_3), 5.71 (br, 1 H, NH). − ^{13}C NMR ($CDCl_3$): δ = 14.11, 16.67 (CH_3), 24.03, 27.92, 35.72, 41.05 (CH_2), 59.42 (CHNH), 70.47, 76.12 (*C*HCH_3), 156.26 (CO_2), 207.27 (CO). − GC-MS; *m*/*z* (%): 239 (9) [M^+], 185 (83), 157 (26), 140 (47), 130 (13), 128 (64), 113 (15), 112 (63), 100 (19), 98 (18), 84 (11), 83 (13), 82 (11), 79 (32), 73 (40), 72 (22), 70 (12), 69 (74), 68 (18), 67 (25), 62 (21), 57 (21), 56 (79), 55 (100), 54 (12), 45 (87), 44 (24), 43 (71), 42 (28), 41 (59).

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