Beckmann Rearrangement of Oximes Derived from Ring and Side Chain Substituted 3-Phosphonomethylcyclohexenones†

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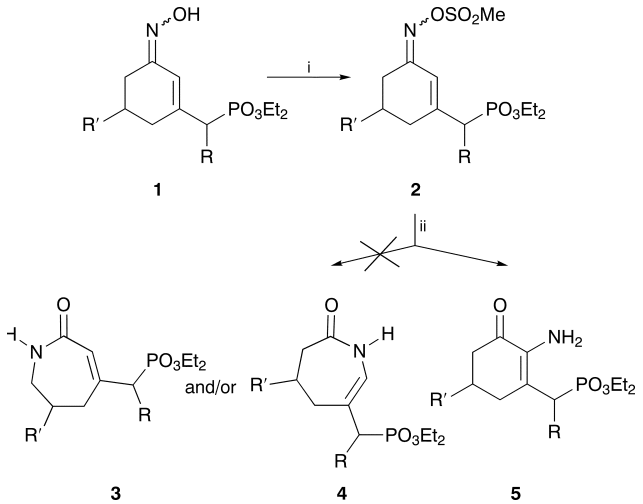
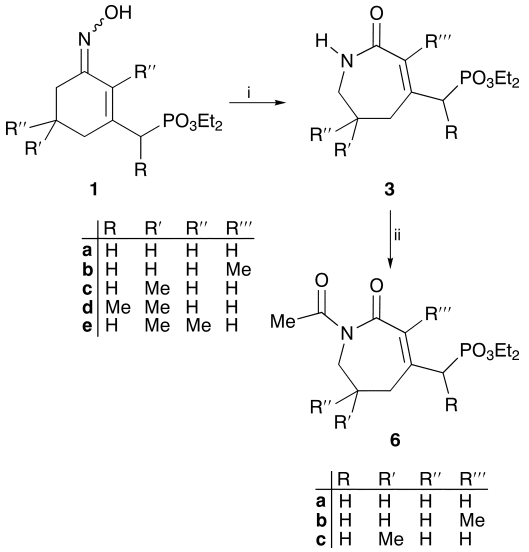
Beckmann rearrangement of the oximes of 3-phosphonoalkylcyclohexenones affords lactams resulting from the regioselective migration of the 6-CH_2 ring carbon atom.

The pharmacological activity of aminophosphonic acids and their derivatives is well documented, and a number of these compounds are in clinical and agricultural use as antibacterial, antiviral, pesticidal, insecticidal, or herbicidal agents.[1] In our research on the synthetic applications of 3-phosphonoalkylcycloalkenones,[2] their conversion into seven-membered, N-containing heterocyclic systems was investigated.[3] We are currently interested in the analogues of the known aminoalkylphosphonic acids that include such structural modifications as different relative location of the heteroatoms, the degree of unsaturation in the phosphonic skeleton, and (in some cases) the presence of the tetrazole ring. The preparation of the latter systems from 3-phosphonomethylcyclohexenones has been described before,[3] and the attempts to synthesize the ring-enlarged lactams derived from the same substrates *via* the Me_3SiN_3–TFA mediated Schmidt rearrangement resulted only in the recovery of the subtrates.[3] An alternative approach using basic Al_2O_3 induced Beckmann rearrangement of the *O*-mesylated oximes of the cyclohexenonephosphonate systems **2** was then investigated. However, instead of the expected α,β-unsaturated lactams **3** (or their enamine-isomers **4**), we isolated the 2-amino-3-phosphonoalkylcyclohexenones **5** formed *via* the Neber rearrangement (Scheme 1).[4] Here we report the results of further investigation of the Beckmann rearrangement of the previously described oximes.[4]



Scheme 1 *Reagents and conditions*: i, $MeSO_2Cl$, Et_3N, THF; ii, Al_2O_3, C_6H_6, then MeOH

The typical reagents used for the Beckmann rearrangement of oximes of cyclic ketones include H_2SO_4[5,6] polyphosphoric acid,[6] PCl_5[7] and $SOCl_2$.[8,9] The sensitivity of some oximes to strongly acidic media and their isolation problems often complicate the application of some of these reagents. In this work, oximes **1** were treated with $SOCl_2$ in 1,4-dioxane; the conditions applied before to the non-phosphorus cyclohexenone derivatives.[8,9] ^{31}P NMR spectroscopic analysis of the crude reaction mixture after the aqueous work-up revealed the presence of only one major phosphorus containing product. The isolation of the pure product presented some problems (*e.g.* chromatography on SiO_2 drastically reduced the yields) and the products were isolated only in moderate yields when Al_2O_3 was used for column chromatography. In all cases, only lactams **3** resulting from the migration of the 6-CH_2 group were obtained and no products of the vinylic carbon (2-CH) shift were detected (Scheme 2). The selectivity of the migration was clear from the significant down-field shift (*ca.* 0.6 ppm) of the ^1H NMR signal of the 6-CH_2 methylene group in **1** upon its migration to the position adjacent to the nitrogen atom in the corresponding **3**. The structure of the ring-enlarged products **3** was determined by NMR (^1H, ^{13}C, ^{31}P) and IR spectroscopy, mass spectrometry and elemental analysis. In some cases isolated lactams **3** still contained some impurities and further purification led to extensive decomposition. Those products were converted into their *N*-acetyl derivatives **6** (Scheme 2) which could be purified and characterized. The acetylation resulted in the further down-



	R	R′	R″	R‴
a	H	H	H	H
b	H	H	H	Me
c	H	Me	H	H
d	Me	Me	H	H
e	H	Me	Me	H

	R	R′	R″	R‴
a	H	H	H	H
b	H	H	H	Me
c	H	Me	H	H

Scheme 2 *Reagents and conditions*: i, $SOCl_2$, 1,4-dioxane; ii, MeCOCl, Et_3N–THF

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field shift of the ^{1}H NMR signal of the 6-CH_2 protons (*ca.* 0.6 ppm relative to **3**). Products **3** and their *N*-acetyl derivatives still contain the allylic phosphonate moiety (or can be considered as vinylogues of a phosphonoacetic system) and thus constitute potential substrates for further transformations. Their application in synthesis is currently studied in our laboratories.

Experimental

Solvents and commercially available substrates were purified by conventional methods. Merck Kieselgel 60 (0.063–0.200) was used for column chromatography. Mass spectra were recorded on a Varian MAT-212 double-focusing direct-inlet spectrometer at an ionisation potential of 70 eV. NMR spectra were recorded on a Bruker AC 300 spectrometer in $CDCl_3$, and the chemical shift values (δ) are given in ppm relative to the solvent (^{1}H, δ 7.24; ^{13}C, δ 77.0). ^{31}P NMR chemical shifts are given relative to 85% H_3PO_4 as external standard. For structural assignments both ^{1}H-decoupled and ^{1}H-coupled ^{13}C NMR spectra were recorded. *J* values are given in Hz. For the sake of clarity, the ^{1}H and ^{13}C NMR signals of the POEt ester groups, present in each compound, are not listed. In all cases those groups gave rise to the following signals: δ_H 1.16–1.31 (6 h, t, $^3J_{HH}$ 7.0–7.1), 3.96–4.10 (4 H, dq, $^3J_{HP}$ *ca.* 11, $^3J_{HH}$ *ca.* 7.2); δ_C *ca.* 16 (d, $^3J_{CP}$ *ca.* 6), *ca.* 62 (d, $^2J_{CP}$ *ca.* 7.5). Elemental analyses were performed at the Department of Chemistry, University of Cape Town.

Diethyl (3-Oxo-5,5-dimethylcyclohex-1-enyl)methylphosphonate was prepared according to the procedure published previously[10] and purified by column chromatography (EtOAc). Oil (60%); δ_H 1.10 (6 H, s), 1.83 (2 H, m), 2.64 (2 H, d, $^2J_{HP}$ 23.6), 3.16 (2 H, m), 5.95 (1 H, dd, $^4J_{HH}$ 5.0, 1.6); δ_C 27.6, 28.6, 31.5 (d, $^1J_{CP}$ 139.5), 37.6, 44.5, 124.7 (d, $^3J_{CP}$ 8.7), 150.1 (d, $^2J_{CP}$ 9.7), 169.5; δ_P 26.7; ν_{max}/cm^{-1} 1675 (CO); *m/z* 274 (M^+, 83%), 246 (60), 219 (22), 152 (66), 138 (99) (Found: C, 56.58; H, 8.50%. $C_{13}H_{23}O_4P$ requires C, 56.93; H, 8.45%).

General Procedure for the Preparation of Oximes **1**.—A solution of ketophosphonate (1 equiv.; typically 3.5 mmol), $HONH_2$·HCl (2 equiv.) and $AcONa·3H_2O$ in EtOH (10 mL per mmol of phosphonate) was heated under reflux for 1.5 h. The reaction mixture was filtered, the precipitate washed with cold EtOH, the combined ethanolic solution was evaporated under reduced pressure, the crude product was dissolved in ether, and the solution was washed with water. After drying ($MgSO_4$) and evaporation of the solvent, crude **1** was purified by column chromatography. Oximes **1a** and **1c** were described previously.[3] **1b** (70%), eluted with EtOAc, waxy solid; δ_H 1.60 (2 H, m), 1.76 (3 H, s), 2.19 (2 H, m), 2.48 (2 H, t, $^3J_{HH}$ 6.6), 2.67 (2 H, d, $^2J_{HP}$ 25.2), 8.05 (1 H, br s); δ_C 16.1 (s), 20.1 (s), 22.2 (s), 31.1 (s), 32.7 (d, $^1J_{CP}$ 137.4), 127.9 (d, J_{CP} 12.4), 133.5 (d, J_{CP} 12.9), 156.7 (d, J_{CP} 6.1); δ_P 27.0; ν_{max}/cm^{-1} 3272 (NOH); *m/z* 275 (M^+, 12%), 258 (51), 230 (23), 202 (84), 120 (100) (Found: C, 51.95; H, 8.20; N, 4.99%. $C_{12}H_{22}NO_4P$ requires C, 52.36; H, 8.06; N, 5.09%). **1d** (83%), eluted with $CHCl_3$–AcOEt (3:1), oil (mixture of diastereoisomers); δ_H 1.02, 1.04 (3 H, 2 s), 1.30 (3 H, m, overlapping with the signal of Me of POEt), 1.86 (3 H, m), 2.38 (1 H, m), 2.68 (1 H, m), 2.97 (1 H, m), 6.04 (1 H, m), 6.76 (1 H, br s); δ_S 12.8, 13.4 (2 s), 20.6, 21.1 (2 s), 28.0 (s), 29.2 (s), 29.8 (s), 39.5 (d, $^1J_{CP}$ 136.2), 40.1 (d, $^1J_{CP}$ 139.3), 115.1 (d, J_{CP} 17.4), 122.2 (d, J_{CP} 11.2), 144.3 (d, J_{CP} 9.7); δ_P 28.8, 29.1; *m/z* 274 ($M^+ - CH_3$, 23%), 258 (60), 233 (39), 203 (100) (Found: C, 53.06; H, 8.36; N, 5.33%. $C_{13}H_{24}NO_4P$ requires C, 53.97; H, 8.36; N, 4.84%). **1e** (65%), eluted with EtOAc, waxy solid; δ_H 1.04 (6 H, s), 1.56 (2 H, 2 d, $^4J_{HH}$ 6.8), 2.55 (2 H, s), 2.63 (2 H, $^2J_{HP}$ 23.1), 6.12 (1 H, d, $^4J_{HP}$ 4.9), 9.40 (1 H, br s); δ_C 19.1 (s), 26.4 (s), 29.1 (d, $^1J_{CP}$ 140.5), 35.0 (s), 36.4 (s), 123.5 (d, $^3J_{CP}$ 9.7), 144.5 (d, $^2J_{CP}$ 11.0), 155.9 (d, $^4J_{CP}$ 4.7); δ_P 27.3; ν_{max}/cm^{-1} 3268 (NOH); *m/z* 289 (M^+, 22%), 272 (29), 152 (43), 138 (100) (Found: C, 53.60; H, 8.45; N, 4.70%. $C_{13}H_{24}NO_4P$ requires C, 53.97; H, 8.36; N, 4.84%).

General Procedure for the Preparation of Lactams **3**.—To a solution of oxime **1** (1.0 g, 3.5–3.8 mmol) in 1,4-dioxane (2.5 mL per mmol of **1**), $SOCl_2$ (2 equiv.) was added dropwise with stirring at 10 °C. The mixture was stirred at room temperature for 12 h and added dropwise to ice-cold aq. Na_2CO_3. The mixture was extracted with ether (3 × 15 mL), the combined etheral solution was washed with water, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The crude products were purified by column chromatography (basic Al_2O_3, EtOAc). **3a** (40%), oil, isolated as *N*-acetyl derivative **6a** (60%), oil; δ_H 1.92 (2 H, m), 2.35 (2 H, t, $^3J_{HH}$ 4.7), 2.42 (3 H, s), 2.63 (2 H, d, $^2J_{HP}$ 22.8), 3.91 (2 H, t, $^3J_{HH}$ 4.4), 5.89 (1 H, d, $^4J_{HP}$ 5.1); δ_C 25.5 (s), 26.3 (s), 29.8 (s), 37.5 (d, $^1J_{CP}$ 142.1), 40.7 (s), 126.4 (d, $^3J_{CP}$ 12.7), 145.9 (d, $^3J_{CP}$ 11.2), 170.6 (s), 172.1 (s); δ_P 24.7; ν_{max}/cm^{-1} 1761 (CO) (Found: C, 51.20; H, 7.44; N, 4.60%. $C_{13}H_{22}NO_5P$ requires C, 51.48; H, 7.31; N, 4.62%). **3b** (50%), oil, isolated as *N*-acetyl derivative **6b** (75%), oil; δ_H 1.88 (2 H, m), 1.92 (3 H, s), 2.32 (2 H, m), 2.45 (3 H, s), 2.74 (2 H, d, $^2J_{HP}$ 23.9), 3.76 (2 H, t, $^3J_{HH}$ 6.3); δ_C 22.2 (s), 25.4 (s), 30.3 (s), 33.0 (s), 33.8 (d, $^1J_{CP}$ 136.0), 40.6 (s), 132.0 (d, $^3J_{CP}$ 13.0), 135.2 (d, $^2J_{CP}$ 12.5), 167.7 (s), 172.3 (s); δ_P 25.7; ν_{max}/cm^{-1} 1761 (CO) (Found: C, 52.80; H, 7.77; N, 4.15%. $C_{14}H_{24}NO_5P$ requires C, 53.00; H, 7.62; N, 4.41%). **3c** (35%), oil, isolated as *N*-acetyl derivative **6c** (52%), oil; δ_H 0.92 (3 H, d, $^3J_{HH}$ 6.8), 1.02 (1 H, m), 2.12 (2 H, m), 2.46 (3 H, s), 2.72 (2 H, dd, $^2J_{HH}$ 13.6, $^2J_{HP}$ 22.9), 3.59 (1 H, dd, $^2J_{HH}$ 14.1, $^3J_{HH}$ 5.9), 3.80 (1 H, dd, $^2J_{HH}$ 14.1, $^3J_{HH}$ 5.5), 5.92 (1 H, d, $^4J_{HP}$ 5.3); δ_C 19.2 (s), 26.4 (s), 33.1 (s), 37.8 (s), 38.0 (d, $^1J_{CP}$ 136.0), 46.6 (s), 126.5 (d, $^3J_{CP}$ 12.8), 145.9 (d, $^2J_{CP}$ 11.1), 170.6 (s), 172.7 (s); δ_P 24.4; ν_{max}/cm^{-1} 1761 (CO) (Found: C, 52.99; H, 7.60; N, 4.28%. $C_{14}H_{24}NO_5P$ requires C, 53.00; H, 7.62; N, 4.41%). **3d** (54%, two diastereomers, *ca.* 1:1), oil; δ_H 0.90 (3 H, 2 d, $^3J_{HH}$ 6.7), 1.32 (3 H, 2 d, $^3J_{HH}$ 7.3), 2.00–3.00 (6 H, m), 5.76 (1 H, d, $^4J_{HH}$ 4.5); δ_C 13.7 (s), 19.2 (d, $^2J_{CP}$ 6.6), 35.8 (s), 36.6 (s), 41.0 (d, $^1J_{CP}$ 136.6), 41.3 (d, $^1J_{CP}$ 135.2), 46.6 (s), 123.7 (d, $^3J_{CP}$ 11.3), 124.2 (d, $^3J_{CP}$ 11.8), 149.6 (d, 2 J_{CP} 7.9), 171.7 (s); δ_P 28.2, 28.6; ν_{max}/cm^{-1} 1654 (CO), 3365 (br, NH); *m/z* 289 (M^+, 4%), 136 (100) (Found: C, 53.75; H, 8.40; N, 4.52%. $C_{13}H_{24}NO_4P$ requires C, 53.97; H, 8.36; N, 4.84%). **3e** (60%), oil; δ_H 1.10 (6 H, s), 1.83 (2 H, m), 2.64 (2 H, d, $^2J_{HP}$ 23.6), 3.16 (2 H, m), 5.95 (d, $^4J_{HP}$ 4.0); δ_P 26.7; ν_{max}/cm^{-1} 1653 (CO), 3268 (br, NH); *m/z* 289 (M^+, 18%), 274 (18), 246 (100) (Found: C, 53.25; H, 8.60; N, 4.48%. $C_{13}H_{24}NO_4P$ requires C, 53.97; H, 8.36; N, 4.84%).

Acetylation of Lactams **3**.—To a solution of **3** (1 equiv.) and Et_3N (1.2 equiv.) in THF (5 mL per mmol of **3**), acetyl chloride (1.1 equiv.) was added dropwise at room temperature. The mixture was stirred for 3 h and filtered. Water was added to the filtrate and the solution was extrated with diethyl ether. The combined etheral solution was washed with 10% aq. Na_2CO_3, dried ($MgSO_4$) and evaporated under reduced pressure. Crude products **6** were purified by column chromatography (SiO_2, EtOAc).

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