Oxidative rearrangement of 2-vinyl-1,3-thiazetidines

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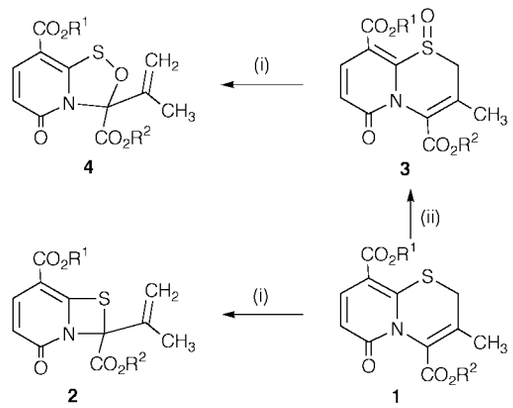
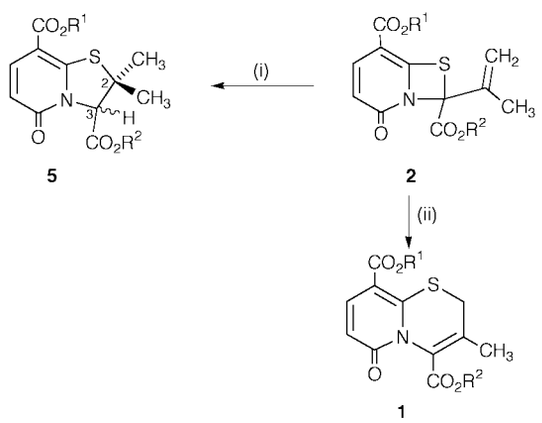
The 2-vinyl-1,3-thiazetidines **6** and **11** undergo rearrangement to the thiazine sulfones **7** and **12** respectively when treated with peracids. In one case, the sultine **9** was obtained as a by-product in low yield.

We have prepared the vinyl-1,3-thiazetidines **2** and 2,1,4-oxathiazolidines **4** by novel, high yielding photochemical rearrangements of the 1,3-thiazines **1** and their corresponding sulfoxides (**3**) respectively as shown in Scheme 1.[1] The chemistry



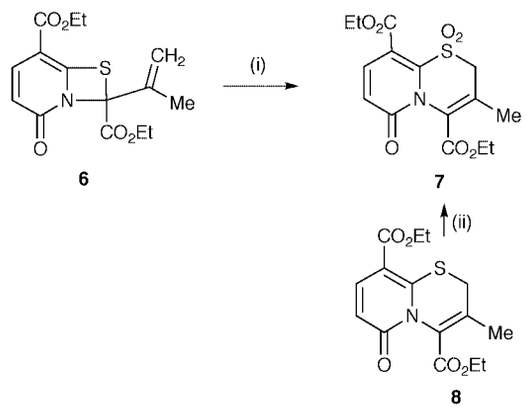
Scheme 1 *Reagents and conditions*: (i) *hν*/dioxane; (ii) MCPBA/$CHCl_3$.

of the vinyl-1,3-thiazetidines (**2**) proved to be interesting, and the compounds underwent rearrangement to thiazolidines such as **5** on catalytic hydrogenation over either Adam's catalyst or palladised charcoal[2] and underwent rearrangement to thiazines such as **1** on treatment with Wilkinson's catalyst[2] as shown in Scheme 2.



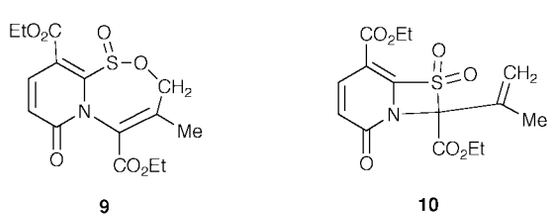
Scheme 2 *Reagents and conditions*: (i) H_2/Pt/EtOH; (ii) $(Ph_3P)_3RhCl$/benzene.

During our investigation of the photochemical rearrangement of the sulfoxide **3** to the 2,1,4-oxathiazolidine **4**, we attempted to prepare the sulfoxide of the vinylthiazetidine **6**[1] by peracid oxidation. The sulfoxide was not obtained, but when the reaction conditions were optimised, a new product, $C_{15}H_{17}NO_7S$, was obtained in 66% yield. The spectra suggested that the product was the thiazine sulfone **7**, as shown in Scheme 3, and when this compound was synthesised rationally by oxid-

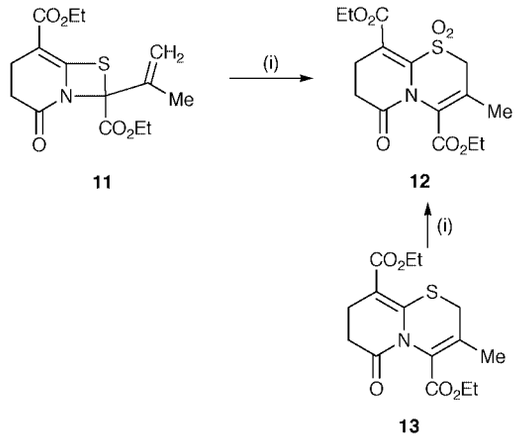


Scheme 3 *Reagents and conditions*: MCPBA/$CHCl_3$; (ii) F_3CCO_3H/CH_2Cl_2.

ation of the authentic thiazine **8**,[3] the two samples proved to be identical in all respects. A second compound, $C_{15}H_{17}NO_7S$, was also obtained as a by-product from peracid treatment of the vinylthiazetidine **6** in 6% yield. The ^1H NMR spectrum of this compound showed pyridone and vinylic methyl signals but the CH_2S protons of the thiazine **1** at δ 3.17 ppm, which had shifted to a singlet at δ 3.83 ppm for CH_2SO_2 in the sulfone **7**, now appeared as a two proton AB system at δ 4.7 and 4.5 ppm. The ^{13}C NMR spectral shift for these protons was δ 73.12 ppm. The shift to lower field suggested a CH_2OSO group and the most likely structure for the by-product was therefore that of the sultine **9** which would be the result of a [2,3]-sigmatropic rearrangement of the sulfone **10**.

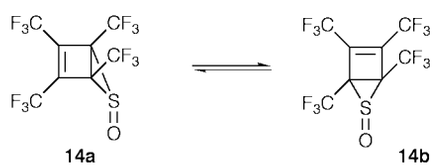


When the reduced vinylthiazetidine **11**[1] was oxidised with peracid, the product appeared to be the thiazine sulfone **12** but no product corresponding to the sultine **9** was seen. The structure of the sulfone **12** was confirmed by rational synthesis by peracid oxidation of the authentic thiazine **13**.[3]



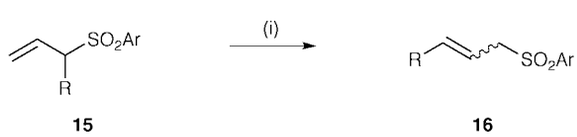
Scheme 4 *Reagents and conditions*: (i) F_3CCO_3H/CH_2Cl_2.

We have thus discovered that oxidation of the vinylthiazetidines **6** and **11** results in a high yielding apparent [1,3]-rearrangement to the sulfones **7** and **12**. This rearrangement is preferred to the allowed [2,3]-sigmatropic rearrangement which is evidenced in isolation of the low yielding by-product **9** in one of the reactions. Examples of thermal [1,3]-shifts are the sulfoxide automerisation of the Dewar thiophene sulfoxide **14** in Scheme 5 which is thought to be a pseudopericyclic process,[4] and the



Scheme 5

thermal rearrangement of the allylic sulfone **15** in Scheme 6 which is thought to proceed *via* a radical pathway.[5]



Scheme 6 *Reagents and conditions*: (i) Δ.

Experimental

Melting points were determined on a Kofler hot stage apparatus and were uncorrected. Ultra-violet spectra were recorded on a PyeUnicam SP800 spectrophotometer and infra-red spectra on Perkin-Elmer 257 and 477 spectrometers with calibration on the polystyrene 1603 cm^{-1} band. ^{1}H-NMR spectra were recorded on Perkin-Elmer R12 (60 MHz) and Bruker WH360 (360 MHz) spectrometers. *J* Values are given in Hz. ^{13}C-NMR spectra were recorded on a JEOL EC-100 (25.1 MHz) Fourier transform spectrometer. Other ^{1}H- and ^{13}C-NMR spectra were recorded by Mr B. Wright and Mr H. Beeley, Zeneca Pharmaceuticals, Alderley Park, Cheshire. Mass spectra were recorded on an AEI-MS 30 spectrometer, used in conjunction with an AW-DS 50 computer for accurate mass measurement, on Kratos MS80 or MS25 spectrometers and by Mrs M. Vickers at Zeneca Pharmaceuticals, Alderley Park, Cheshire. Combustion microanalyses were carried out at The University of Sussex by Mr and Mrs A. G. Olney. Other spectra were provided by the staff of Zeneca Pharmaceuticals, Alderley Park, Cheshire. Thin layer chromatography was carried out using Kieselgel GF 254 from E. Merck of thickness 0.25 mm (analytical) and 0.75 mm (preparative). Preparative chromatography was carried out using a chromatotron (Harrison Research) with plates of silica PF_{254} (E. Merck). Petroleum ether refers to that fraction boiling between 40 and 60 °C.

Reaction of diethyl 8-(1-methylethenyl)-2-oxo-7-thia-1-azabicyclo[4.2.0]octa-3,5-diene-5,8-dicarboxylate (6) with *m*-chloroperbenzoic acid

A solution of diethyl 8-(1-methylethenyl)-2-oxo-7-thia-1-azabicyclo[4.2.0]octa-3,5-diene-5,8-dicarboxylate **6**[1] (700 mg, 2.167 mmol) and *m*-chloroperbenzoic acid (1.05 g, 6.1 mmol) in dry chloroform (50 ml) was stirred at room temperature overnight. The mixture was washed with saturated aqueous sodium hydrogen carbonate, dried (Na_2SO_4) and allowed to evaporate slowly overnight to yield white crystals of *diethyl 1,1,6-trioxo-3-methyl-2H,6H-pyrido[2,1-b][1,3]thiazine-4,9-dicarboxylate* (**7**) (362 mg). The mother liquors were subjected to preparative TLC on silica gel using diethyl ether–dichloromethane (1 : 1) as eluant and a further portion of the crystalline sulfone **7** (149 mg) was obtained (total 511 mg, 66%); mp 175–177 °C (Found: C, 50.7; H, 4.8; N, 3.9%. $C_{15}H_{17}NO_7S$ requires C, 50.7; H, 4.8; N, 3.9%); *m*/*z* (EI) 355 ($[M]^+$); λ_{max} (MeOH)/nm 253 and 333 (ε/dm^3 mol^{-1} cm^{-1} 6580 and 4120); ν_{max} (Nujol)/cm^{-1} 1746 and 1730 (unsaturated ester); δ_H (60 MHz, C^2HCl_3) 1.23 (3H, t, *J* 7, CH_3), 1.39 (3H, t, *J* 7, CH_3), 2.35 (3H, s, CH_3C=), 3.83 (2H, s, CH_2SO_2), 4.26 (2H, q, *J* 7, CH_2O), 4.41 (2H, q, *J* 7, CH_2O) and 6.78 and 7.71 (2 × 1H, dd, *J* 10, pyridone-CH); δ_C (25.1 MHz, C^2HCl_3) 13.89 (2 × Me), 20.39 (Me-C=), 54.06 (CH_2SO_2), 62.07 (CH_2O), 63.16 (CH_2O), 113.52 (pyridone-CH), 124.80 (pyridone-CH), 126.44 (C=), 129.17 (C=), 138.88 (pyridone-CH), 143.85 (N-C=), and 159.33, 160.84 and 163.45 (3 × C=O). Two further TLC fractions were also isolated as oils. The first was assigned as *diethyl 1,7-dioxo-4-methyl-3H,7H-1λ^4-pyrido-[2,1-c][1,2,4]oxathiazepine-5,10-dicarboxylate* (**9**) (43 mg, 6%); *m*/*z* (EI) 355 ($[M]^+$); (Found 355.0742. $C_{15}H_{17}NO_7S$ requires *M* 355.0725); λ_{max} (MeOH)/nm 257 and 324 (ε/dm^3 mol^{-1} cm^{-1} 7750 and 4640); ν_{max} (film)/cm^{-1} 1765 sh, 1750–1650; δ_H (360 MHz, C^2HCl_3) 1.24 (3H, t, *J* 7, CH_3), 1.36 (3H, t, *J* 7, CH_3), 2.45 (3H, s, CH_3C=), 4.26 (2H, q, *J* 7, CH_2O), 4.50 (2H, q, *J* 7, CH_2O), 4.50 and 4.70 (2H, AB, *J* 11, CH_2OSO), 6.72 and 7.93 (2 × 1H, dd, *J* 10, pyridone-CH); δ_C (25.1 MHz, C^2HCl_3) 13.94 (CH_3), 14.18 (CH_3), 19.37 (CH_3C=), 61.80 (CH_2O), 62.57 (CH_2O), 73.12 (CH_2OSO), 111.91 (C=), 122.46 (pyridone-CH), 123.83 (C=), 130.27 (C=), 111.91 (pyridone CH), 140.52 (N-C=) and 161.08, 161.23 and 163.10 (3 × C=O).

Rational synthesis of diethyl 1,1,6-trioxo-3-methyl-2*H*,6*H*-1λ^6-pyrido[2,1-*b*][1,3]thiazine-4,9-dicarboxylate 7

A solution of freshly prepared trifluoroperacetic acid (1 ml of a 2 M solution, 2 mmol) in dichloromethane was added to a stirred solution of diethyl 6-oxo-3-methyl-2*H*,6*H*-pyrido[2,1-*b*]-[1,3]thiazine-4,9-dicarboxylate **8**[3] (200 mg, 0.62 mmol) in dry dichloromethane (10 ml) at room temperature. The solution was filtered through a silica plug and the solvent was removed *in vacuo* to yield an oil which was purified by chromatography using a chromatotron with silica gel and diethyl ether–petroleum ether (3 : 1) as eluant. The crude material was recrystallised from ethyl acetate to give white needles of *diethyl 1,1,6-trioxo-3-methyl-2H,6H-1λ^6-pyrido[2,1-b][1,3]thiazine-4,9-dicarboxylate* **7** (160 mg, 73%); mp 174–176 °C (Found: C, 50.4; H, 4.7; N, 3.9%. $C_{15}H_{17}NO_7S$ requires C, 50.7; H, 4.5; N, 3.9%). Spectra were identical to those of the sample prepared above.

Peracid rearrangement of diethyl 8-(1-methylethenyl)-2-oxo-7-thia-1-azabicyclo[4.2.0]oct-5-ene-5,8-dicarboxylate 11

Diethyl 8-(1-methylethenyl)-2-oxo-7-thia-1-azabicyclo[4.2.0]-oct-5-ene-5,8-dicarboxylate **11**[1] (30 mg, 0.092 mmol) was dissolved in deuteriated chloroform (1.5 ml) in an NMR tube at room temperature and an excess of trifluoroperacetic acid (0.1

ml of a 3 M solution in chloroform, 0.3 mmol) was added. When the ^{1}H NMR spectrum showed the reaction to be complete, the solution was washed with saturated aqueous sodium bicarbonate solution (1 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo* and the crude material was recrystallised from chloroform–petroleum ether to yield white needles of *diethyl 7,8-dihydro-1,1,6-trioxo-3-methyl-2H,6H-1λ⁶-pyrido-[2,1-b][1,3]thiazine-4,9-dicarboxylate* **12** (18 mg, 56%); mp 166–168 °C. The IR (KBr) was identical to that of the sample prepared by the rational synthesis below. A mixed melting point of the two samples was undepressed.

Rational synthesis of diethyl 7,8-dihydro-3-methyl-1,1,6-trioxo-2*H*,6*H*-1λ⁶-pyrido[2,1-*b*][1,3]thiazine-4,9-dicarboxylate 12

Diethyl 7,8-dihydro-3-methyl-6-oxo-2*H*,6*H*-pyrido[2,1-*b*][1,3]-thiazine-4,9-dicarboxylate **13**[3] (100 mg, 0.31 mmol) was dissolved in deuteriated chloroform (2 ml) at room temperature in an NMR tube. A solution of trifluoroperacetic acid (0.3 ml of a 3.2 M solution in chloroform, 0.96 mmol) was added and when the ^{1}H NMR spectrum showed that the reaction had gone to completion, the solution was washed with saturated aqueous sodium bicarbonate solution (1 ml), dried ($MgSO_4$) and the solvent was removed *in vacuo*. The crude material was recrystallised from chloroform–petroleum ether to yield *diethyl 7,8-dihydro-3-methyl-1,1,6-trioxo-2H,6H-1λ⁶-pyrido[2,1-b][1,3]thiazine-4,9-dicarboxylate* **12** as white needles (42 mg, 38%); mp 165–167 °C (Found: C, 50.5; H, 5.3; N, 4.1%. $C_{15}H_{19}NO_7S$ requires C, 50.4; H, 5.4; N, 3.9%); *m*/*z* (EI) 357 ($[M]^+$); λ_{max} (MeOH, pH 1–7)/nm 283 (ε/dm^3 mol^{-1} cm^{-1} 4000); λ_{max} (MeOH, pH > 7)/nm 237 (ε/dm^3 mol^{-1} cm^{-1} 11 400); ν_{max} (KBr)/cm^{-1} 1725 (ester) and 1710 (ester); δ_H (360 MHz, C^2HCl_3) 1.30 and 1.38 (2 × 3H, t, *J* 7.1, 2 × CH_3), 2.31 (3H, s, CH_3C=), 2.67 (2H, dd, J_1 7.8, J_2 9.0, CH_2C=), 2.89 (2H, dd, J_1 7.8, J_2 9.0, CH_2CO), 3.72 (2H, s, CH_2S), 4.26 and 4.35 (2 × 2H, 2 × q, *J* 7.1, 2 × CH_2O).

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