Acylation of ambident vinylogous urethanes exocyclic to thiazolidines and reduced thiazines

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The vinylogous thiazine urethanes **1** are invariably acylated on carbon and not on nitrogen, even when the carbon is "blocked" as in **18.** The analogous thiazolidine **2** is acylated either on carbon or nitrogen, depending on the electrophile used.

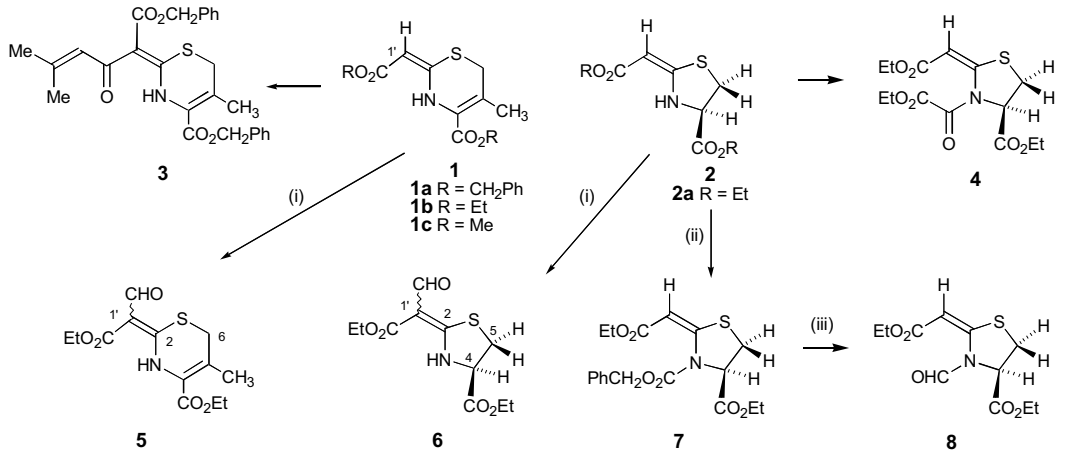
Keywords: thiazolidines, thiazolines, 1,3-thiazines, acylation

We have used the vinylogous urethanes **1** and **2** as nucleophiles in our syntheses of reactive lactams which are structurally related to penicillins and cephalosporins.[1,2] The ambident nature of these nucleophiles meant that they might react either at nitrogen or carbon. Reaction of the reduced thiazine **1a** with 3,3-dimethylacrylic acid in the presence of PCl_3 gave the carbon-acylated product **3**,[3] whereas reaction of the thiazolidine **2a** with ethyl chlorooxalate gave the *N*-acylated product **4**.[1] Since the thiazine reacted differently from the corresponding thiazolidine in these instances, it was of interest to see if this were a general phenomenon and whether the nature of the electrophile might have a bearing on the reaction.

We therefore reacted the thiazine **1b** and the thiazolidine **2a** separately with formic acetic anhydride acting as both solvent and electrophile as shown in Scheme 1. In each case the product proved to be the result of *C*-acylation, **5** and **6** being obtained in 97% and 92% yields respectively. The compound **5** was a mixture of geometric isomers in a ratio of 3: 1 at room temperature, changing to 5: 2 at 80°C and 7: 2 at –50°C. The presence of two exchangeable NH signals at δ 14.7 ppm and δ 13.1 ppm integrating as a total of one proton in the ^{1}H NMR spectrum in C^2HCl_3 confirmed that *C*-acylation had taken place. The product **6** was also a mixture of geometric isomers (2: 1) at room temperature. The broad exchangeable NH signals in the ^{1}H NMR spectrum supported C-acylation as did the coupling between the signals for H-4 and NH.

When benzyl chloroformate was used as the electrophile under Schotten Baumann conditions, no reaction was observed with the thiazine **1b** but the thiazolidine **2a** gave the *N*-acylated product **7**. The olefinic signal in the ^{1}H NMR spectrum at δ 6.87 ppm was broad at room temperature but sharpened at 40°C and became progressively broader as the temperature was lowered, eventually separating at –60°C into two sharp signals at δ 6.97 ppm and δ 6.43 ppm in a ratio of 8 : 1. There was long range coupling of 0.7 Hz between one of the signals assigned to CH_2S (δ 3.22 ppm) and the broad olefinic signal at δ 6.87 ppm. When the urethane **7** was reacted with formic acetic anhydride as solvent and electrophile at room temperature overnight, a new product was obtained which exhibited no signals associated with the benzyl urethane in the ^{1}H NMR spectrum, but showed signals for both formyl and olefinic atoms in both ^{13}C and ^{1}H NMR spectra. This was evidently the *N*-formyl compound **8** and the spectrum was free of the conformational isomerism exhibited by some formyl amides. Transamidation had evidently occurred to give the *N*-formyl product **8** which was distinct from the C-formyl product **6** obtained by direct formylation.

The thiazolidine **2a** was now treated with acetyl chloride and triethylamine in dichloromethane to form two new products in equal amounts (Scheme 2). These were separated by chromatography on silica gel, the *N*-acetyl compound **9** eluting first. The ^{1}H NMR spectrum at room temperature had some broadening of the signals assigned to the olefinic and NC*H* protons. Variable temperature ^{1}H NMR spectroscopy showed that, at 245 ± 2 K, two signals coalesced into one with $\Delta G^{\ddagger}_{A\rightarrow B}$ 48.09 ± 0.4 kJmol^{-1} and $\Delta G^{\ddagger}_{B\rightarrow A}$ 46.75 ± 0.4 kJmol^{-1} for interconversion of the two rotamers.[4] The ^{13}C NMR spectrum at room temperature was sharp. The *C*-acylated compound **10** eluted second and was a 2: 1 mixture of geometric isomers at room temperature. Acylation using acetic anhydride gave **9** and **10** in a ratio of 1: 9, *C*-acylation predominating. Heating the acetyl derivatives **9** and **10** separately in tetrahydrofuran in sealed tubes at 100°C did not result in rearrangement.



Scheme 1 *Reagents and conditions:* (i) HCO_2COCH_3, rt, overnight (97% **5**, 92% **6**); (ii) $ClCO_2CH_2Ph$, Et_2O, aq K_2CO_3, rt, 6 h (56%); (iii) HCO_2COCH_3, rt, overnight (67%).

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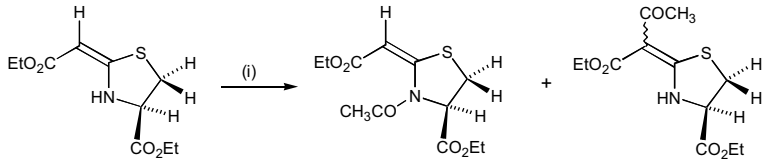
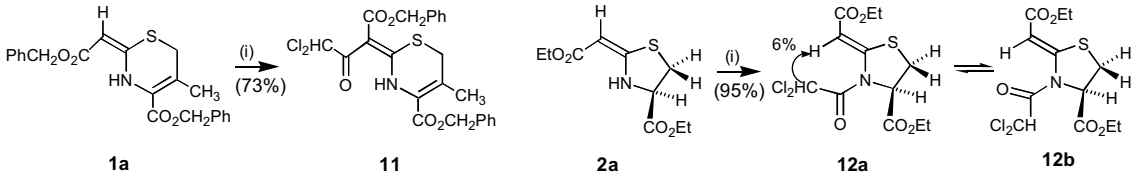


2a **9** **10**

Scheme 2 *Reagents and conditions:* (i) CH_3COCl, CH_2Cl_2, Et_3N, rt, overnight (42% **9** + 45% **10**); *or* (i) Ac_2O, rt, overnight (9% **9** + 87% **10**).



1a **11** **2a** **12a** **12b**

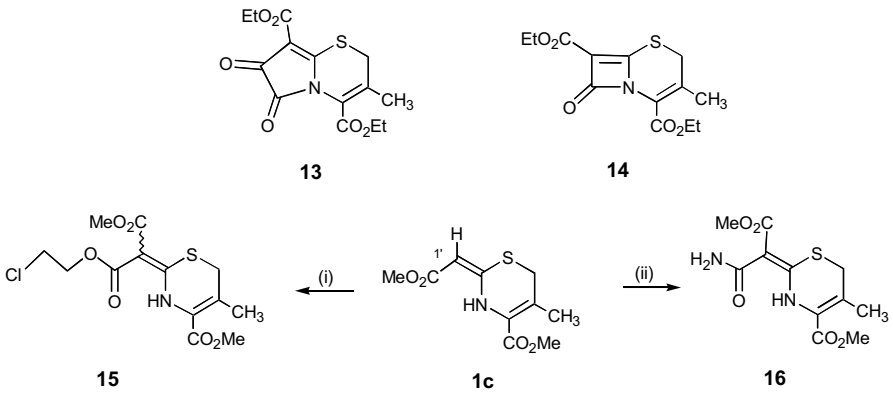
Scheme 3 *Reagents and conditions:* (i) $Cl_2CHCOCl$, Et_3N, CH_2Cl_2, rt, overnight

The thiazine **1a**[5] was now reacted with dichloroacetyl chloride in dichloromethane containing triethylamine (Scheme 3) to give the C-acylated compound **11**. This exhibited no olefinic signal in the ^{1}H NMR spectrum and appeared to exist as a single geometric isomer. The equivalent reaction of the thiazolidine **2a** gave the *N*-acylated product **12** with sharp signals at δ 6.66 ppm for the olefinic proton and at δ 6.35 ppm for the COC*H*CCl_2 proton in the ^{1}H NMR spectrum at 50°C. At –50°C, these split into pairs of signals at δ 6.15 ppm and δ 6.71 ppm for the olefinic proton, and at δ 6.0 ppm and δ 7.06 ppm for COC*H*CCl_2. Variable temperature ^{1}H NMR spectral experiments gave a coalescence temperature of 265 ± 3 K and suggested $\Delta G^{\ddagger}$ 51.6 ± 0.6 kJmol^{-1}. In an NOE experiment at –70°C, irradiation of the signal at δ 6.00 ppm caused a 6% enhancement of the olefinic signal at δ 6.71 ppm, indicating that the major rotamer was **12a** and the minor was **12b**. There was therefore a clear-cut distinction when dichloroacetyl chloride was used as electrophile, *C*-acylation occurring in the thiazine series and *N*-acylation in the thiazolidine series.

We have prepared the reactive lactam analogue **13** of cephalosporin by reacting the reduced thiazine **1c** with oxalyl chloride, and so it was of interest to see whether reaction of **1c** with phosgene might give the very strained β-lactam **14**, a compound which would be anti-aromatic in one of its amide resonance forms. We therefore treated **1c** with phosgene at room temperature and at –78°C, but observed no reaction. When the reaction was repeated in the presence of ethylene oxide, a product was obtained which, from its spectroscopic data, was the *C*-acylated product **15** (Scheme 4).

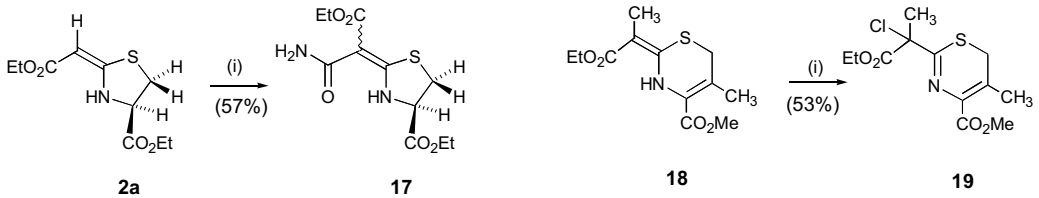
When chlorosulfonyl isocyanate was reacted with the thiazine **1c**, the *C*-acylated amide **16** was obtained in 50% yield. (Scheme 4) With the thiazolidine **2a**, this reaction also resulted in *C*-acylation (Scheme 5) and the product **17** was obtained as two geometric isomers. The ^{1}H NMR spectrum exhibited two broad exchangeable NH signals at δ 7.08 ppm and δ 9.16 ppm and no olefinic signal.

To see whether *N*-acylation might occur when the thiazine exomethylene group was fully substituted, the "blocked" thiazine **18**[6] was treated with chlorosulfonyl isocyanate.



13 **14** **15** **1c** **16**

Scheme 4 *Reagents and conditions:* (i) Cl_2CO, CH_2Cl_2, ethylene oxide, rt, overnight (88%); (ii) $ClSO_2N{=}C{=}O$, CH_2Cl_2, rt, 6 h (50%).



2a **17** **18** **19**

Scheme 5 *Reagents and conditions:* (i) $ClSO_2N{=}C{=}O$, CH_2Cl_2, rt, 6 h.

The product had λ_{max} 236 nm, compared to λ_{max} 348 nm of the original thiazine and the absorption at 1750 cm^{-1} in the IR was typical of a saturated ester. No NH signal was observed in either IR or ^1H NMR spectra. From these data and the molecular ion, the structure **19** was tentatively assigned to the product. Thus, rather than *N*-acylation, chlorosulfonyl isocyanate has acted as a source of Cl^+.

C-Acylation of the vinylogous urethane seems to be a general consequence in reactions of thiazines **1** which have the alternative possibility of the nitrogen participating in enamine resonance, whereas the thiazolidine **2** undergoes either *C*-acylation or *N*-acylation depending on the acylating agent used.

Experimental

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Infrared spectra were recorded on Perkin-Elmer 157G, 577 and PE1710FT and Pye-Unicam SP3-100 spectrometers and ultraviolet spectra using Pye-Unicam SP800 and Philips PU8720 spectrometers. ^1H NMR spectra were recorded on Bruker WH360 (360 MHz) and WP80 (80 MHz) spectrometers. *J* values are in Hz. ^{13}C NMR spectra were recorded on a Bruker WH360 (90.5 MHz) spectrometer. *J*-Modulated spin echo experiments were used to help characterise ^{13}C NMR spectra where necessary. Mass spectra were recorded on Kratos MS80 or MS25 spectrometers. Combustion analyses and other spectra were provided by the staff of AstraZeneca. Column chromatography was carried out using silica gel PF 254 60. Petroleum ether refers to that fraction of hexanes boiling between 60 and 80°C.

*Ethyl2-(1-ethoxy-1,3-dioxopropan-2-ylidene)-5-methyl-3,6-dihydro-2H-1,3-thiazine-4-carboxylate (**5**):* Ethyl 2-(2-ethoxy-2-oxoethylidene)-5-methyl-3,6-dihydro-2*H*-1,3-thiazine-4-carboxylate[3] (**1b**) (100 mg, 0.37 mmol) was stirred overnight in formic acetic anhydride (2 ml) at room temperature. The solvent was removed *in vacuo* to yield a gum which was chromatographed on silica gel using diethyl ether as eluent to give the aldehydo-ester **5** as a solid, which was recrystallised from ethanol (108 mg, 97%); m.p. 111–112°C. IR: ν_{max} (KBr)/cm^{-1} 1701, 1662 and 1627 (carbonyl). UV: λ_{max} (MeOH)/nm 234 and 350 (ε 7380 and 7520). NMR: δ_H (80 MHz, C^2HCl_3, two conformers, ratio 7: 2) 1.28 (3H, t, *J* = 7.1, CH_3), 1.36 (3H, t, *J* = 7.1, CH_3), 2.33 (3H, s, CH_3), 3.18 and 3.25 (2H, 2 s, CH_2S), 4.21 (2H, q, *J* = 7.1, OCH_2), 4.29 (2H, q, *J* = 7.1, OCH_2), 9.7 and 9.9 (1H, 2 s, CHO), and 13.1 and 14.7 (1H, 2 s, br, NH); at 80°C a saturation transfer experiment of the aldehyde region (9.94 and 10.17 ppm in a ratio of 5: 2 at this temperature) gave an increase in intensity of the signal at 9.94 ppm (ratio 11: 1); δ_C (90.5 MHz, C^2HCl_3) 14.05 (CH_3), 14.4 (CH_3), 19.7 (CH_2S), 30.7 (CH_3C=), 60.1 (OCH_2), 62.0 (OCH_2) and 187.8 (CHO); quaternary carbon signals were not distinguished from noise. MS: *m/z* (CI) 300 ([M + H]$^+$). Found: C, 51.8; H, 5.7; N, 4.7. $C_{13}H_{17}NO_5S$ requires C, 52.2; H, 5.7; N, 4.7%.

*Ethyl 2-(1-ethoxy-1,3-dioxopropan-2-ylidene)-thiazolidine-4-carboxylate (**6**):* Ethyl 2-(2-ethoxy-2-oxoethylidene)-thiazolidine-4-carboxylate[3] (**2a**) (100 mg, 0.41 mmol) in formic acetic anhydride (2 ml) was stirred overnight at room temperature. The solvent was removed *in vacuo* to give a solid which was chromatographed on silica gel using diethyl ether as eluant to give the aldehydo-ester **6** as a solid, which was recrystallised from ethanol (102 mg, 92%); m.p. 44–46°C. IR: ν_{max} (KBr)/cm^{-1} 1737, 1698 and 1680 (carbonyl). UV: λ_{max} (MeOH)/nm 244 and 290 (ε 4230 and 6610); λ_{max} (pH>7)/ nm 285 (ε 7790). NMR: δ_H (360 MHz, C^2HCl_3, two conformers, ratio 9: 4) 1.12 (6H, m, *J* = = 7.1, CH_3), 3.31 (2H, m, CH_2S), 4.11 (4H, m, *J* = 7.1, OCH_2), 4.67 and 4.76 (1H, 2t, $J_{4,5}$ 6.5, H-4), 9.59 and 9.70 (1H, 2 s, CHO), and 10.15 and 11.7 (1H, 2 s, br, NH). MS: *m/z* (EI) 273 (M^+). Found: C, 48.1; H, 5.7; N, 4.9. $C_{11}H_{15}NO_5S$ requires C, 48.3; H, 5.5; N, 5.1%.

3-Benzyl 4-ethyl 2-(2-ethoxy-2-oxoethylidene)-thiazolidine-3,4-dicarboxylate (**7**): Potassium carbonate (170 mg, 1.23 mmol) in water (50 ml) was added to ethyl 2-(2-ethoxy-2-oxoethylidene)-thiazolidine-4-carboxylate[3] (**2a**) (100 mg, 0.4l mmol) in diethyl ether (50 ml). Benzyl chloroformate (140 mg, 0.82 mmol) was added and the mixture was shaken vigorously for 6 h at room temperature. The aqueous layer was extracted with diethyl ether and the combined ether extracts were dried (Na_2SO_4). The solvent was removed *in vacuo* to give a solid which was chromatographed on silica gel using diethyl ether-petroleum ether (1: 1) as eluent. The 3-benzyloxy-carbonyl derivative **7** was recrystallised from ethanol (87 mg, 56%); m.p. 68–71°C. NMR: δ_H (360 MHz, C^2HCl_3) 1.15 (3H, t, *J* = 7.2, CH_3), 1.23 (3H, t, *J* = 7.2, CH_3), 3.23 (1H, ddd, J_{AB} 12.4, $J_{5,4}$ 2, $J_{5,7}$ 0.7, SCHA), 3.30 (1H, dd, J_{BA} 12.4, $J_{5,4}$ 7, SCHB), 4.15 (4H, 2q, *J* = 7.2, OCH_2), 5.18 (1H, dd $J_{4,5}$ 2 & 7, H-4), 5.22 (2H, 2d, J_{AB} = 12.1, $ArCH_2O$), 6.87 (1H, s, br, HC=) and 7.33 (5H, m, ArH); at –60°C the broad signal at 6.87 ppm at 25°C appeared as two sharp singlets at 6.97 and 6.43 ppm (ratio 8: 1); δ_C (90.5 MHz, C^2HCl_3) 13.75 (CH_3), 14.2 (CH_3), 29.7 (CH_2S), 59.7 (OCH_2), 62.1 (CH), 62.7 (OCH_2), 68.45 ($PhCH_2O$), 96.5 (HC=), 128.1, 128.4 and 134.8 (Ar), 151.3 (NC=), 154.5 (urethane), 168.5 and 168.9 (ester). MS: *m/z* (CI) 380 ([M + H]$^+$). Found: C, 57.2; H, 5.7; N, 3.7. $C_{18}H_{21}NO_6S$ requires C, 57.0; H, 5.6; N, 3.7%.

*Ethyl 2-(2-ethoxy-2-oxoethylidene)-3-formylthiazolidine-4-carboxylate (**8**):* 3-Benzyl 4-ethyl 2-(2-ethoxy-2-oxoethylidene)thiazolidin e-3,4-dicarboxylate **7** (70 mg, 0.18 mmol) was stirred overnight in formic acetic anhydride (2 ml) at room temperature. The solvent was removed *in vacuo* to yield a gum which was chromatographed on silica gel using diethyl ether – petroleum ether (1: 1) as eluant to yield the *N*-formyl product **8** (34 mg, 67%), m.p. 103–104°C. IR: ν_{max} (KBr)/cm^{-1} 1737, 1698 and 1680 (carbonyl). [αl_D –277.4 (EtOH). UV: λ_{max} (MeOH)/nm 244 and 290 (ε 4230 and 6610). NMR: δ_H (360 MHz, C^2HCl_3) 1.24 (3H, t, *J* = 7.1, CH_3), 1.25 (3H, t, *J* = 7.1, CH_3), 3.25 (2H, m, CH_2S), 4.17 (4H, m, OCH_2), 5.33 (1H, d, $J_{4,5}$ 6.9, CH), 5.88 (1H, s, HC=) and 8.83 (1H, s, CHO); δ_C (90.5 MHz, C^2HCl_3) 14.0 (CH_3), 14.3 (CH_3), 30.8 (CH_2S), 59.4 (CH), 60.3 (OCH_2), 62.5 (OCH_2), 91.9 (CH=) and 157.5 (CHO); no other carbon signals were observed above noise. MS: *m/z* (EI) 273 ([M]$^+$). Found: C, 48.5; H, 5.6; N, 4.9. $C_{11}H_{15}NO_5S$ requires C, 48.3; H, 5.5; N, 5.1%.

*Reaction of ethyl 2-(2-ethoxy-2-oxoethylidene)-thiazolidine-4-carboxylate (**2a**) with acetyl chloride*

Triethylamine (114 µl, 0.82 mmol) and acetyl chloride (64 mg, 0.82 mmol) were added to a solution of ethyl 2-(2-ethoxy-2-oxoethylidene)-thiazolidine-4-carboxylate **2**[3] (200 mg, 0.82 mmol) in methylene chloride (30 ml). The solution was stirred at room temperature overnight and washed with water. The organic layer was dried (Na_2SO_4) and the solvent was removed *in vacuo* to yield a gum which was crystallised from diethyl ether. This contained two components by TLC and was chromatographed on silica gel using diethyl ether-petroleum ether (1: 1) as eluent. *Ethyl 3-acetyl-2-ethoxy-2-oxoethylidene)-thiazolidine-4-carboxylate* **9** eluted first and was recrystallised from ethanol (98 mg, 42%), m.p. 66–70°C. [α]$_D$ -228.3 (EtOH). λ_{max} (MeOH)/nm 244 and 293 (ε 5880 and 7830). NMR: δ_H (360 MHz, C^2HCl_3) 1.23 (3H, t, *J* = 7.1, CH_3), 1.24 (3H, t, *J* = 7.1, CH_3), 2.33 (3H, s, $COCH_3$), 3.22 (1H, 2d, $J_{5\alpha,5\beta}$ 11, $J_{5\alpha,4}$ 7.3, H-5α), 3.31 (1H, d, $J_{5\beta,5\alpha}$ 11, H-5β), 4.14 (2H, q, *J* = 7.1, OCH_2), 4.18 (2H, q, *J* = 7.1, OCH_2) 5.31 (1H, br d, $J_{4,5\alpha}$ = 7.2, H-4) and 6.39 (1H, br, HC=); δ_C (90.5 MHz, C^2HCl_3) 13.98 (CH_3),14.32 (CH_3), 24.64 (CS), 29.97 (CH_3CO), 60.09 (C-4), 62.51 (OCH_2), 62.53 (OCH_2), 99.10 (HC=), 155.07 (C-2), and 167.07, 168.45 and 168.69 (3 × C=O). MS: *m/z* (EI) 287 ([M]$^+$) and 288 ([M + H]$^+$). *Ethyl 2-(1-ethoxy-1,3-dioxobutan-2-ylidene)-thiazolidine-4-carboxylate* **10** eluted second (105 mg, 45%), m.p. 51–52°C. IR: ν_{max} (KBr)/cm^{-1} 1731 and 1666 (esters and ketone). [α]$_D$ –136.2 (EtOH). UV: λ_{max} (MeOH)/nm 237 and 295 (ε 7670 and 9160). NMR: δ_H (360 MHz, C^2HCl_3) 1.28 (6H, m, 2 × CH_3), 2.42 and 2.45 (3H, 2 s, CH_3CO), 3.28 and 3.33 (2H, m, CH_2S), 4.25 (4H, m, OCH_2), 4.69 and 4.78 (1H, 2dt, $J_{4,5\beta}$ 7.8, $J_{4,NH}$ 1, H-4), and 8.15 and 10.06 (1H, br, NH); δ_C (90.5 MHz, C^2HCl_3)) 14.04 (CH_3), 14.36 and 14.42 (CH_3), 30.76, and 31.23 (CH_3), 31.75 (CH_2S), 60.26 and 61.48 (H-4), 62.33 and 63.11 (OCH_2); no other carbon signals were observed above noise. MS: *m/z* (EI) 287 ([M]$^+$) and 288 ([M + H]$^+$).

*Treatment of ethyl 2-(2-ethoxy-2-oxoethylidene)-thiazolidine-4-carboxylate (**2a**) with acetic anhydride*

Ethyl 2-(2-ethoxy-2-oxoethylidene)-thiazolidine-4-carboxylate **2**[3] (125 mg, 0.51 mmol) was stirred in acetic anhydride (2 ml) at room temperature overnight. The solvent was removed *in vacuo* to give a solid which was chromatographed on silica gel using diethyl ether-petroleum ether (1: 1) as eluant to yield two products. The first product (**9**) was a gum (14 mg, 9%); the second product (**10**) was a solid, recrystallised from ethanol (128 mg, 87%), m.p. 51–52°C. Both products had spectra identical to the samples prepared above.

Benzyl 2-(1-benzyloxy-4,4-dichloro-1,3-dioxobutan-2-ylidene)-5-methyl-3,6-dihydro-2H-1,3-thiazine-4-carboxylate (**11**): Triethylamine (30 µl, 0.2l mmol) and dichloroacetyl chloride (31 mg, 0.21 mmol) were added to a solution of benzyl 2-(2-benzyloxy-2-oxoethylidene)-5-methyl-3,6-dihydro-2*H*-1,3-thiazine-4-carboxylate

1a[5] (85 mg, 0.2l mmol) in methylene chloride (25 ml). The solution was stirred at room temperature for 4 h and washed with water. The organic layer was dried (Na_2SO_4) and the solvent was removed *in vacuo* to give an oil which was chromatographed on silica gel, using diethyl ether-petroleum ether (1: 1) as eluent to give *benzyl 2-(1-benzyloxy-4,4-dichloro-1,3-dioxobutan-2-ylidene)-5-methyl-3,6-dihydro-2H-1,3-thiazine-4-carboxylate* (**11**) as a solid which was recrystallised from ethanol (79 mg, 73%), m.p. 146–150°C. IR: ν_{max} (KBr)/cm^{-1} 1728 and1660 (ester/ketone). UV: λ_{max} (MeOH)/nm 237, 314 and 348 (ε 1200, 1000 and 600). NMR: δ_H (360 MHz, C^2HCl_3) 2.36 (3H, *s*, CH_3), 3.18 (2H, 2 s, CH_2S), 5.29 (2H, *s*, $ArCH_2O$), 5.33 (2H, *m,* $ArCH_2O$), 6.91 and 7.01 (1H, 2 s, $CHCl_2$) and 7.38 (10H, *m*, ArH), and 132.3 and 14.7 (1H, NH); δ_C (90.5 MHz, C^2HCl_3) 19.89 (CH_3), 31.30 (CH_2S), 67.00 ($ArCH_2O$), 67.78 ($ArCH_2O$) and 70.19 ($CHCl_2$); no other carbon signals were observed above noise. MS: *m/z* (EI) 435.1146. $C_{24}H_{21}NO_5S$ ([M-Cl_2]$^+$) requires 435.1140; *m/z* (CI/NH_3) 506, 508 and other isotopes ([M + H]$^+$).

*Ethyl 3-(2,2-dichloroacetyl)-2-(2-ethoxy-2-oxoethylidene)-thiazolidine-4-carboxylate (***12***):* Triethylamine (57 μl, 0.4l mmol) and dichloroacetyl chloride (60 mg, 0.41 mmol) were added to a solution of ethyl 2-(2-ethoxy-2-oxoethylidene)-thiazolidine-4-carboxylate **2a**[3] (100 mg, 0.4l mmol) in methylene chloride (25 ml). The solution was stirred at room temperature overnight and washed with water. The organic layer was dried (Na_2SO_4) and the solvent was removed *in vacuo* to give a solid which was chromatographed on silica gel using diethyl ether-petroleum ether (1: 1) as eluent. The product, *ethyl 3-(2,2-dichloroacetyl)-2-(2-ethoxy-2-oxoethylidene)-thiazolidine-4-carboxylate* (**12**) was recrystallised from ethanol (138 mg, 95%), m.p. 120–122°C. IR: ν_{max} (KBr)/cm^{-1} 1735 (ester), 1724 (unsaturated ester) and 1683 (ketone). $[\alpha]_D$ –231.5 (EtOH). UV: λ_{max} (MeOH)/nm 246 and 292 (ε 8160 and 9320). NMR: δ_H (360 MHz, C^2HCl_3) 1.26 (3H, t, J = 7.1, CH_3), 1.28 (3H, t, J = 7.1, CH_3), 3.31 (1H, dd, $J_{2\alpha,2\beta}$ 11.5, $J_{2\alpha,4}$ 6.9, H-2α), 3.44 (1H, *d*, $J_{2\beta,2\alpha}$ = 11.5, H-2β), 4.20 (2H, *q*, J = 7.1, OCH_2), 4.24 (2H, *q*, J = 7.1, OCH_2), 5.47 (1H, *d*, $J_{4,5}$ = 6.9, H-4), 6.35 (1H, *s*, HC=) and 6.66 (1H, *s*, Cl_2CHC=O); at –50°C the HC= signal (6.35 ppm at 25°C) appeared as two singlets at δ 6.15 and 6.71 ppm and the Cl_2CHCO signal (δ 6.66 ppm at 25°C) as two singlets at δ 6.00 ppm and δ 7.06 ppm in a ratio of 4: 3; δ_C (90.5 MHz, C^2HCl_3) 13.97 (CH_3), 14.32 (CH_3), 30.53 (CH_2S), 60.53 (OCH_2), 62.63 (OCH_2), 62.97 (OCH_2), 64.46 (Cl_2CHC=O) and 101.69 (HC=); no other carbon signals were observed above noise. Found C, 39.4; H, 4.1; N, 3.6. $C_{12}H_{15}Cl_2NO_5S$ requires C, 40.5; H, 4.2; N, 3.9%.

*Methyl 2-(3-(2-chloroethoxy)-1-methoxy-1,3-dioxopropan-2-ylidene)-5-methyl-3,6-dihydro-2H-1,3-thiazine-4-carboxylate (***15***):* Ethylene oxide (23 mg, 0.52 mmol) was added to a solution of methyl 2-(2-methoxy-2-oxoethylidene)-5-methyl-3,6-dihydro-2*H*-1,3-thiazine-4-carboxylate[3] (**1c**) (120 mg, 0.50 mmol) in methylene chloride (25 ml). Phosgene (*ca* 0.1M in benzene, 5.2 ml, 0.52 mmol) was added *via* syringe and the solution was stirred overnight at room temperature under nitrogen. The solution was washed with water and the organic layer was dried (Na_2SO_4). The solvent was removed *in vacuo* to give *methyl 2-(3-(2-chloroethoxy)-1-methoxy-1,3-dioxopropan-2-ylidene)-5-methyl-3,6-dihydro-2H-1,3-thiazine-4-carboxylate* (**15**) as a solid which was recrystallised from ethanol (154 mg, 88%), m.p. 129.5–130.5°C. IR: ν_{max} (KBr)/cm^{-1} 1736 (saturated ester), 1657 and 1627 (unsat. esters). UV: λ_{max} (MeOH)/nm 223 and 335 (ε 9950 and 12040). NMR: δ_H (80 MHz, C^2HCl_3) 2.31 (3H, s, CH_3), 3.17 (2H, s, CH_2S), 3.66 (2H, *t*, J = 4.6, CH_2Cl), 3.77 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 4.37 (2H, t, J = 4.6, OCH_2), 12.45 (0.5H, br, NH) and 12.61 (0.5H, br, NH); δ_C (90.5 MHz, C^2HCl_3) 19.59 (CH_3), 31.37 (CH_2S), 41.34 (CH_2Cl), 51.57 (OCH_3), 52.34 (OCH_3), 63.71 (OCH_2), 92.15 (C), 125.50 (NC=), 162.47 (NCS), 165.12 ($NCCO_2CH_3$), and 166.15, 167.35 and 168.32 (ester). MS: *m/z* (EI) 351 and 349 (1: 3, [M]$^+$). Found: C, 44.1; H, 4.5; N, 3.9; Cl, 10.0. $C_{13}H_{16}ClNO_6S$ requires C, 44.6; H, 4.6; N, 4.0; Cl, 10.1%.

*Methyl 2-(1-amino-3-methoxy)-1,3-dioxopropan-2-ylidene)-5-methyl-3,6-dihydro-2H-1,3-thiazine-4-carboxylate (***16***):* Chlorosulfonyl isocyanate (76 mg, 0.54 mmol) was added to a solution of methyl 2-(2-methoxy-2-oxoethylidene)-5-methyl-3,6-dihydro-2*H*-1,3-thiazine-4-carboxylate **1c**[3] (125 mg, 0.51 mmol) in methylene chloride (30 ml). The solution was stirred at room temperature under nitrogen for 6 h and shaken with water for 5 min. The organic layer was dried (Na_2SO_4) and the solvent was removed *in vacuo* to yield a gum which was chromatographed on silica gel, eluting with diethyl ether-petroleum ether (2: 1) to give *methyl 2-(1-amino-3-methoxy)-1,3-dioxopropan-2-ylidene)-5-methyl-3,6-dihydro-2H-1,3-thiazine-4-carboxylate* (**16**) as a solid which was recrystallised from ethanol (73 mg, 50%), m.p. 125–126°C. IR: ν_{max} (KBr)/cm^{-1} 3168, 3028 (NH_2), 1707, 1672 (ester) and 1635 (amide). UV: λ_{max} (MeOH)/nm 344 (ε 2900). NMR: δ_H (360 MHz, C^2HCl_3) 2.33 (3H, s, CH_3), 3.18 (2H, s, CH_2S), 3.80 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 5.23 (1H, br, NH), 8.22 (1H, br, NH) and 14.94 (1H, br, CONH); δ_C (90.5 MHz, C^2HCl_3) 19.17 (CH_3), 30.72 (CH_2S), 52.16 (OCH_3), 57.99 (OCH_3), 124.31 (C), 127.06 (NC) and 169.80 (ester). Other carbon signals could not be distinguished from noise. MS: *m/z* (EI) 286 ([M]$^+$).

Ethyl 2-(1-amino-3-ethoxy-1,3-dioxopropan-2-ylidene)-thiazolidine-4-carboxylate (**17**): Chlorosulfonyl isocyanate (115 mg, 0.82 mmol) was added to a solution of ethyl 2-(2-ethoxy-2-oxoethylidene)-thiazolidine-4-carboxylate[3] (**2a**) (200 mg, 0.82 mmol) in methylene chloride (50 ml). The solution was stirred at room temperature under nitrogen for 6 h and shaken with water for 5 min. The organic layer was dried (Na_2SO_4) and the solvent was removed *in vacuo* to yield a gum which was chromatographed on silica gel, eluting with diethyl ether-petroleum ether (2: 1) as eluent to give *ethyl 2-(1-amino-3-ethoxy-1,3-dioxopropan-2-ylidene)-thiazolidine-4-carboxylate* (**17**) as a solid which was recrystallised from ethanol (135 mg, 57%), m.p. 156–159°C. IR: ν_{max} (KBr)/cm^{-1} 3010 (NH_2), 1729, 1661 (ester) and 1622 (amide). UV: λ_{max} (MeOH)/nm 229 and 287 (ε 1370 and 2690). NMR: δ_H (360 MHz, C^2HCl_3)/($^2H_3C)_2SO$) 1.25 (3H, t, J 7.1, CH_3), 1.33 (3H, t, J = 7.1, CH_3), 3.45 (2H, m, J = 9 and 6.4, OCH_2), 4.22 (2H, q, J = 7.1, CH_2S), 4.25 (2H, q, J = 7.1, OCH_2), 4.89 (1H, t, $J_{4,5}$ = 6.4, H-4), 7.08 (1H, br, NH) and 9.16 (1H, s, CONH); δ_C (90.5 MHz, C^2HCl_3) 13.59 (CH_3), 17.47 (CH_3), 30.67 (CH_2S), 56.45 (OCH_2), 59.55 (OCH_2), 61.71 (CH), 86.62 (NC=), 166.42 (NCS), 169.60, 170.31 and 175.10 (carbonyl). MS: *m/z* (CI) 289 ([M + H]$^+$).

Methyl 2-(2-chloro-1-ethoxy-1-oxopropan-2-yl)-5-methyl-6H-1,3-thiazine-4-carboxylate (**19**)

Chlorosulfonyl isocyanate (78 mg, 0.55 mmol) was added to a solution of methyl2-(1-ethoxy-1-oxopropan-2-ylidene)-5-methyl-3,6-dihydro-2*H*-1,3-thiazine-4-carboxylate[6] (**18**) (150 mg, 0.55 mmol) in methylene chloride (40 ml). The solution was stirred at room temperature under nitrogen for 6 h and then shaken with water for 5 min. The organic layer was dried (Na_2SO_4) and the solvent was removed *in vacuo* to yield an oil which was chromatographed on silica gel, eluting with diethyl ether-petroleum ether (1: 1) to yield *methyl 2-(2-chloro-1-ethoxy-1-oxopropan-2-yl)-5-methyl-6*H*-1,3-thiazine-4-carboxylate* (**19**) as a gum (89 mg, 53%). IR: ν_{max} (film)/cm^{-1} 1750 (ester), 1723 (ester) and 1583 (SC=N). UV: λ_{max} (MeOH)/(nm) 236 (ε 3160); λ_{max} (pH>7 (irreversible)/(nm) 240, 293, 344 and 426 (ε 3720, 1800, 980 and 910). NMR: δ_H (360 MHz, C^2HCl_3) 1.17 (3H, t, J = 7.1, CH_3), 1.91 (3H, s, CH_3), 2.18 (3H, s, CH_3), 3.20 (2H, 2d, J_{AB} = 15, CH_2S), 3.66 (3H, s, OCH_3) and 4.16 (2H, q, J = 7, OCH_2); δ_C (90.5 MHz, C^2HCl_3) 13.61 (CH_3), 19.91 (CH_3), 26.50 (CH_3C=), 31.06 (CH_2S), 51.47 (OCH_3), 62.52 (OCH_2), 71.95 (C–Cl), 126.88 (C=), 134.76 (C=), 160.73 (N=CS), 164.83 and 168.10 (ester). MS (CI): *m/z* 306 and 308 (ratio 3: 1 [M + H]$^+$).

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References

1 S.H. Bhattia, G.M. Davies, P.B. Hitchcock, D. Loakes and D.W. Young, *J. Chem. Soc., Perkin Trans. 1*, 1999, 2449.
2 N.K. Capps, G.M. Davies, D. Loakes and D.W. Young, *J. Chem. Soc., Perkin Trans. 1*, 2000, 4373.
3 N.K. Capps, G.M. Davies, D. Loakes, R.W. McCabe and D.W. Young, *J. Chem. Soc., Perkin Trans. 1,* 1991, 3077.
4 I.O. Sutherland, *Annual Reports on NMR Spectroscopy*, ed. E.F. Mooney, vol. 4, Academic Press, 1971, 82.
5 S.H. Eggers, V.V. Kane and G. Lowe, *J. Chem. Soc.*, 1965, 1262.
6 G.M. Davies, P.B. Hitchcock, R.W. McCabe and D.W. Young, *J. Chem. Soc., Perkin Trans. 1*, 1992, 3391.