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The synthesis, N-alkylation and epimerisation study of a phthaloyl derived thiazolidine

Emma B. Veale *, John E. O'Brien, Thomas McCabe, Thorfinnur Gunnlaugsson *

School of Chemistry, Center for Synthesis and Chemical Biology, Trinity College Dublin, Dublin 2, Ireland

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ABSTRACT

The synthesis of the phthaloyl protected thiazolidine, *N*-phthaloyl-methyl-2(*R*)-thiazolidine-4(*R*)-methyl ester, **2**, and a study of its susceptibility to epimerise in a range of solvents, using ^{1}H NMR spectroscopy, are described. Compound **2** was further reacted to yield the thiazole amino acid derivative, **3**, and an *N*-alkylated thiazolidine derivative, **6**, as a single diastereoisomer. The N-alkylation of **2**, using mild bases, resulted in the formation of a mixture of diastereoisomers of **2** (2*R*,4*R*) and (2*S*,4*R*). Successful cleavage of the methyl ester and the phthaloyl protecting groups was achieved, giving rise to the formation of the two heterocyclic building blocks, **4** and **5**.

1. Introduction

The heterocycles oxazole and thiazole are found in many naturally based peptides and peptolides isolated from marine organisms such as fungi, algae, etc. Many of these natural products have been found to be cytotoxic substances and consequently are potential therapeutic agents.[1] Their activities, including cytotoxicity, multiple drug resistance, as well as their metal binding and transport properties, have been investigated in detail.[2] Because of this, there currently exists a significant interest in the syntheses of such products and their analogues.[2] For instance, the total synthesis of lyngbyabellin A, isolated from the marine cyanobacterium *Lyngbya majuscula*, has been achieved by Yokokawa et al.,[3] where several functionalized thiazole carboxylic acids were synthesised via the oxidation of the corresponding thiazolidines. The thiazolidine ring is of significant medicinal importance, being found in many biological structures such as penicillin[4] while its formation, form the amino acid cysteine, also occurs in many important biological processes.[5] However, thiazolidine based carboxylic acids are known to epimerise in solution[6] an issue, which is of significant importance for the use of such structures in potential therapeutic reagents. As part of an ongoing anticancer drug discovery programme in our laboratory, we were interested in synthesising and incorporating thiazole containing amino acid derivatives into well-known DNA binding compounds. Our synthetic strategy involved the preparation of the orthogonally *N*-protected phthaloyl-based thiazolidine amino acid **2**, which upon oxidation gave the desired thiazole derivative **3**. We also carried out the N-alkylation of the thiazolidine ring with the aim of forming other novel functionalised thiazole based amino acids, which could then be incorporated into many of the DNA binding motifs developed within our laboratory. This paper describes the synthesis and the characterisation of these compounds, as well as the epimerisation studies carried out on compound **2** using ^{1}H NMR and X-ray crystallography diffraction analysis.

2. Results and discussion

2.1. Synthesis

The synthesis of the phthaloyl derived thiazolidine **2** and the three thiazole containing heterocyclic building blocks **3**–**5** is shown in Scheme 1. A number of methods for the synthesis of amino acid-derived thiazoles are known and include: (i) condensation of an amino acid-derived thioamide with ethyl bromopyruvate (a modification of the Hantzsch reaction);[7] (ii) condensation of enantiopure *N*-protected α-amino aldehydes or glyoxals with L-cysteine esters;[8] (iii) condensation between cysteine esters and *N*-protected imino esters;[2a,b] and (iv) cyclodehydration of β-hydroxythioamides using Burgess reagent.[9] Thiazolidines synthesised by the last three procedures are readily converted into thiazoles by oxidation.

In our endeavour, the second reaction method shown above was chosen for the preparation of the thiazole derivative **3**, Scheme 1. The phthaloyl protecting group was utilised as it is stable to both acid and base and can usually be cleaved by reaction with hydrazine in ethanol.[10] Moreover, we have in the past used related diimides quite successfully in our development of anticancer agents, and it has not been used previously in the synthesis of targets such as **5**. Hence, the synthesis of **5** involved the initial hydrolysis of

* Corresponding authors.
E-mail addresses: vealeem@tcd.ie (E.B. Veale), gunnlaut@tcd.ie (T. Gunnlaugsson).

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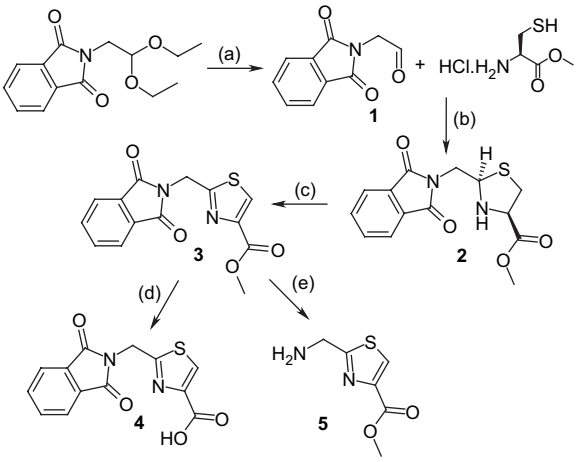


Scheme 1. Synthesis of thiazolidine **2** and thiazoles **4** and **5**. (a) TFA, $CHCl_3$, rt; (b) $KHCO_3$, $EtOH/H_2O$, rt; (c) MnO_2, pyridine, CH_2Cl_2, reflux; (d) HCl, acetone/H_2O (7:1), reflux; (e) H_2NNH_2 (2 equiv), EtOH, rt.

phthalimidoacetaldehyde diethyl acetal using a mixture of TFA and chloroform, which gave **1** in quantitative yield as a white solid without the need for further purification. The cyclocondensation reaction between the HCl salt of L-cysteine methyl ester and **1**, at rt for 5 h, gave the thiazolidine **2** in 79% yield, after a recrystallisation from methanol. The ^{1}H NMR ($CDCl_3$, 600 MHz) spectrum of **2** is shown in Figure 1 and shows that the compound was obtained as a single diastereoisomer. Analysis of the spectrum showed that the **Ha** and **Ha′** protons are diastereotopic appearing as two dd at 4.15 and 4.05 ppm, respectively, with a coupling constant of 14.5 Hz. They are also coupled to **Hz**, which appears as a dd at 4.86 ppm. The second geminal pair **Hb** and **Hb′** appeared as a dd and a t at 3.33 and 2.92 ppm, respectively. Each proton is coupled to each other as well as **Hx**, which shows as a triplet at 3.82 ppm. The NH proton appears as a broad singlet at 2.61 ppm while the protons of the methyl ester appear as a sharp singlet at 3.80 ppm. Similar NMR studies were also performed using DMSO-d_6. The resulting spectrum showed that the NH proton appeared as a triplet at 3.39 ppm (located using ^{15}N HSQC NMR), because of its coupling to both adjacent chiral protons, **Hx** and **Hz**.

Single off-white crystals of **2** were grown by the slow evaporation of CH_2Cl_2 overnight from a suspension of the compound in MeOH. They were suitable for X-ray diffraction analysis. The resulting crystal structure is shown in Figure 2 (see Section 4 for further details[11]) showing that the phthaloyl group is faced over top of the thiazolidine ring. The unit cell showed only the presence of a single molecule, and hence a single diastereoisomer was observed. This compliments the results observed in the solution studies. Assuming that the reaction was stereospecific at the C-2 position, the stereochemistry of **2** was assigned as (2*R*,4*R*).

The orthogonally protected thiazole **3** was formed by oxidising **2** using activated MnO_2 for 5 days in the presence of pyridine in dry CH_2Cl_2 at reflux temperature, in 63% yield without the need for

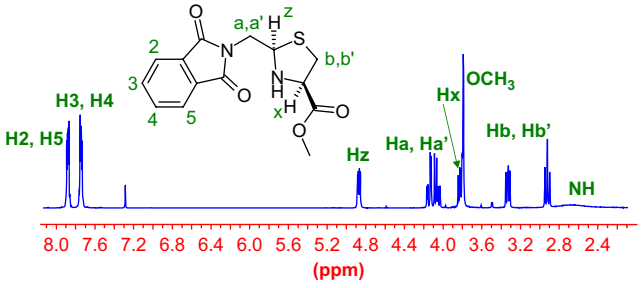


Figure 1. ^{1}H NMR ($CDCl_3$, 600 MHz) spectrum of **2**.

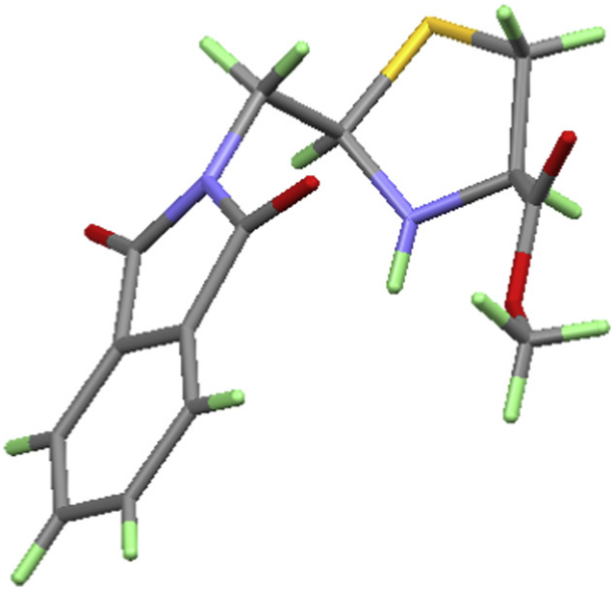


Figure 2. Crystal structure of **2**, hydrogen atoms are shown in green.

further purification. Carrying out this reaction in the absence of pyridine did not give **3** in high purity. Compound **3** was characterised using conventional methods. Additionally, crystals were grown of **3** by slow evaporation from a 3:1 mixture of MeOH and CH_2Cl_2 that were suitable for X-ray crystallography diffraction analysis. The resulting crystal structure is shown in Figure 3, showing the fully oxidised ring system.

The removal of the orthogonal protecting groups was achieved to give **4** and **5**, respectively. Cleavage of the methyl ester group was achieved by an acid-catalysed hydrolysis using HCl in a 7:1 mixture of acetone and H_2O. This gave **4** as fine colourless needles in 55% yield, without the need for further purification.[12] For the cleavage of the phthaloyl protecting group a number of hydrazinolysis reactions were attempted. When the deprotection was carried out at reflux temperature using small excess of $H_2NNH_2\cdot H_2O$, the thiazole ring decomposed. This resulted in the formation of **5**, which was, however, difficult to separate from the phthaloylhydrazide byproduct and unreacted **3**, using column chromatography on flash silica. The hydrazinolysis was, however, achieved by the slow addition of 2 equiv H_2NNH_2 to a boiling suspension of **3** in EtOH, followed by stirring the resulting clear mixture at rt for 4 h, after which the phthaloylhydrazide was removed by suction filtration. This gave the thiazole **5** in 53% yield following an acid–base extraction of the filtrate. The ^{1}H NMR ($CDCl_3$, 400 MHz) spectrum showed that **5** was formed in high purity and the successful formation of **5** was also further confirmed by X-ray crystallography diffraction analysis, Figure 4, from crystals grown by slow evaporation of CH_2Cl_2 from a saturated solution of **5** in MeOH.

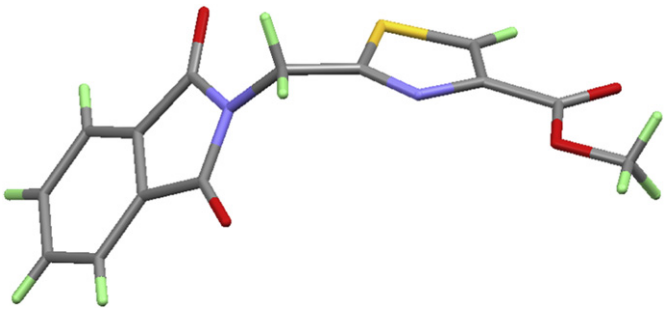


Figure 3. Crystal structure of **3**.

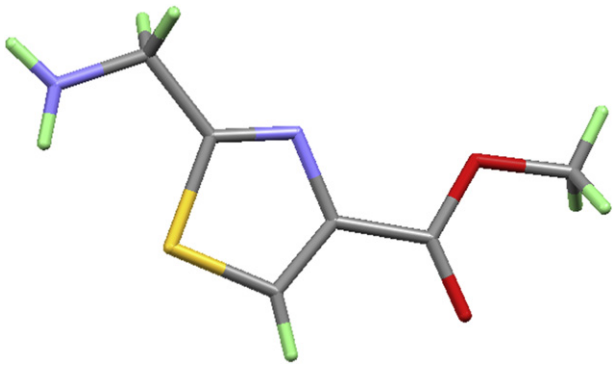
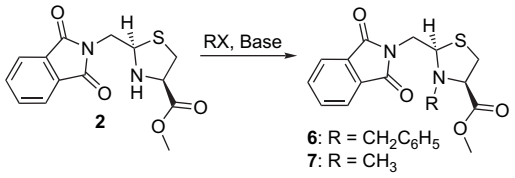


Figure 4. Crystal structure of **5**.

2.2. N-Alkylation of the thiazolidine 2

For the N-alkylation of thiazolidine **2**, Scheme 2, a number of reactions were carried out by varying the nature of the base and the reaction conditions. These are summarised in Table 1. The two first attempts involved the use of NEt_3 as a base and benzylchloride as the alkylating agent in either CH_2Cl_2 or CH_3CN, respectively. However, ^1H NMR analysis of the resulting products demonstrated that both reactions had been unsuccessful in giving the desired alkylated product. Instead, both spectra showed the presence of a mixture of diastereoisomers of **2**.



Scheme 2. Synthesis of **6** and **7** (see Table 1) from **2**.

By comparing these spectra with that observed for **2** (Fig. 1) the ratio of these two diastereoisomers were approximately 50:50, Figure 5. From the ^1H NMR we were able to assign the absolute stereochemistry of one of these diastereoisomers as (2*R*,4*R*). As it has been reported previously in the literature that thiazolidine rings are susceptible to epimerisation, and that this process may occur at the C-2 chiral centre of the thiazolidine ring,[6] we speculated that the stereochemistry of the other diastereoisomer might be (2*S*,4*R*). In an attempt to verify this, the two products were separated by column chromatography on flash silica using a mixture of ethyl acetate, CH_2Cl_2 and hexane (3:2:3). This method of purification was successful and the ^1H NMR spectrum ($CDCl_3$, 400 MHz) of the 50:50 mixture, **2** and **2a**, is shown in Figure 5. As means of determining the stereochemistry of **2a**, an attempt was made at growing crystals of the compound by the slow evaporation from a solution mixture containing CH_2Cl_2 and MeOH. This resulted in the formation of off-white single crystals, which were suitable for X-ray crystallography diffraction analysis. The crystal structure of **2a** is shown in Figure 6, from which the absolute stereochemistry was indeed assigned as (2*S*,4*R*), confirming that the epimerisation of **2** must have occurred at the C-2 position of the thiazolidine ring. The possible mechanism for this base-catalysed epimerisation is shown in Scheme 3, which would involve the deprotonation of the acidic NH proton causing the thiazolidine ring to open, and the formation of a Schiff base intermediate. This system then undergoes a ring closure, which gives rise to changing stereochemistry of the C-2 chiral centre,[6d,e] which further supports the suggested mechanism shown in Scheme 3. While such mechanism has been proposed by strong bases before, then, to the best of our knowledge, the deprotonation by a weak base such as NEt_3 has not been reported within the literature.

Table 1
N-Alkylation of **2**

	Base	RX	Condition	Product
A	Et_3N	$PhCH_2Cl$	Δ, 24 h	R=H; *R*,*R*/*S*,*S* 95:5
B	Et_3N	$PhCH_2Cl$	Δ, 21 h	R=H; *R*,*R*/*S*,*S* 95:5
C	K_2CO_3	$PhCH_2Cl$	Δ, 18 h	R=H; *R*,*R*/*S*,*S* 50:50
D	K_2CO_3	$PhCH_2Cl$	Δ, 18 h	R=CH_2Ph
E	K_2CO_3	CH_3Cl	Δ, 48 h	R=CH_3; *S*,*R* 45% R=H; *R*,*R* 55%

Attempt A was carried out in CH_2Cl_2 while all other attempts were carried out in CH_3CN. Attempt D was carried out in the presence of KI.

Other attempts to alkylate **2** using bases such as K_2CO_3 (1 equiv) in CH_3CN, only lead to the formation of a 50:50 mixture of **2** and **2a**. However, by carrying out the reaction in the presence of KI and increasing the relevant concentration of K_2CO_3 and benzylchloride to 1.5 and 1.2 equiv, respectively, seem to overcome this epimerization. Hence, compound **6** (ESMS analysis gave m/z=419 for [M+Na]) was obtained as an off-white solid in 69% yield, following purification by column chromatography on neutral flash silica (ethyl acetate/hexane 98:2→50:50 and 1% NEt_3). According to ^1H NMR ($CDCl_3$, 400 MHz) analysis of **6**, it was also formed as a single diastereoisomer, Figure 7. However, we were unable to determine the absolute stereochemistry of this new product. Compound **6** was further characterised by other conventional methods. Here, the ^{13}C NMR ($CDCl_3$, 400 MHz) showed the presence of the three methylene carbons at 61.8, 42.8 and 33.4 ppm, respectively, while the seven resonances for the aromatic rings appeared between 137.8 and 122.6 ppm.

The alkylation reaction was also carried out by using CH_3I. This again, gave rise to the formation of a 55:45 mixture of the successfully alkylated (2*R*,4*R*) diastereoisomer **7** and the (2*S*,4*R*) diastereoisomer **2a**. The successful formation of **7** was confirmed by ^1H NMR analysis as well as by ESMS analysis, which gave m/z=434 and 329 for $[M+Na]^+$ of **7** and **2a**, respectively. Instead of separating these products, the mixture was oxidised by employing activated MnO_2, which resulted in the cleavage of the *N*-methyl group and in the formation of **3** according to the ^1H and ^{13}C NMR ($CDCl_3$, 400 MHz).

2.3. Epimerisation studies of 2

With the aim of further investigating the above epimerisation process, we carried out detailed NMR studies on **2**. As shown in Figure 5, the apparent difference between the chemical shifts of the C-2 protons of the (2*R*,4*R*) and the (2*S*,4*R*) diastereoisomers would allow the process to be easily followed. The rate of epimerisation was monitored by recording the ^1H NMR spectra of **2** at 300 K immediately after dissolving the compound in the appropriate solvent until the process reached equilibrium. The solvents used in these studies were $CDCl_3$, $(CD_3)_2SO$, $(CD_3)_2CO$ and $C_2D_4O_2$. The epimerisation of **2** was also followed using $CDCl_3$ in the presence of a small amount of $(C_2H_5O)BF_3$, to determine if the process was also acid-catalysed. Furthermore, as the crystals of **2** shown in Figure 6 were grown by the slow evaporation of CH_2Cl_2 from a saturated solution of **2** in MeOH, we also monitored this process in (1:3) mixture of $CDCl_3$ and MeOD. The chemical shifts of the C-2, C-4 and NH protons are shown in Table 2 for all of the systems investigated.

The stack plot of the ^1H NMR spectra ($CDCl_3$, 600 MHz) of **2** after recording the sample over 5 days is shown in Figure 8. The change in the resonance for the **Hz** proton at 4.87 ppm was followed. After 6 h, the signal for the **Hz** proton of the (2*S*,4*R*) diastereoisomer was observed at 5.14 ppm. Upon integrating both signals, it was determined that there was approximately a 4:1 ratio of the (2*R*,4*R*)/

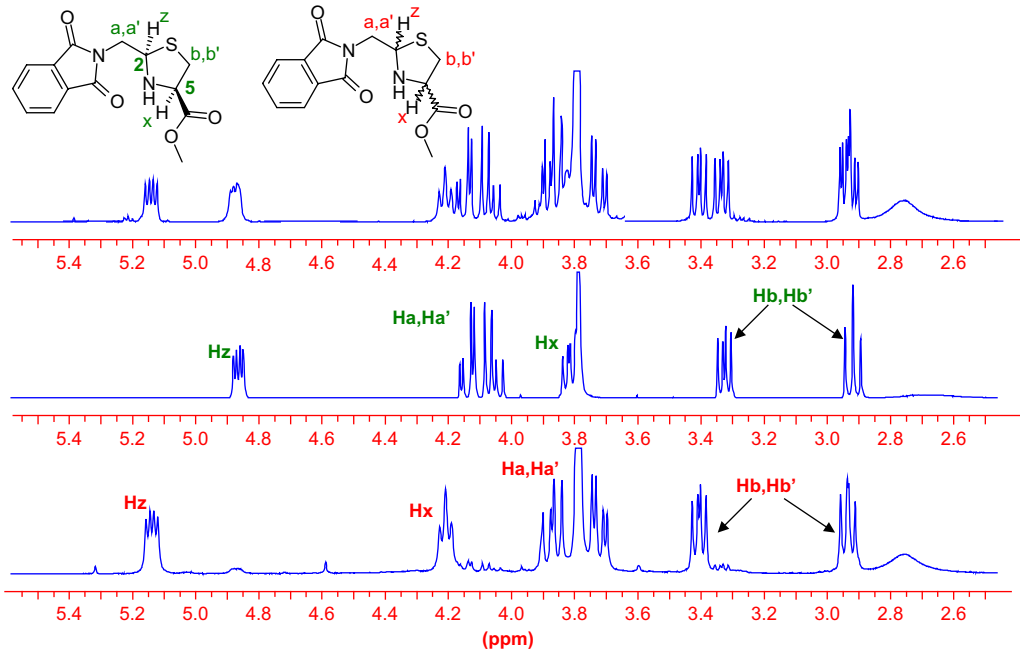


Figure 5. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of (A) the 50:50 mixture of diastereoisomers (B) **2** and (C) **2a**.

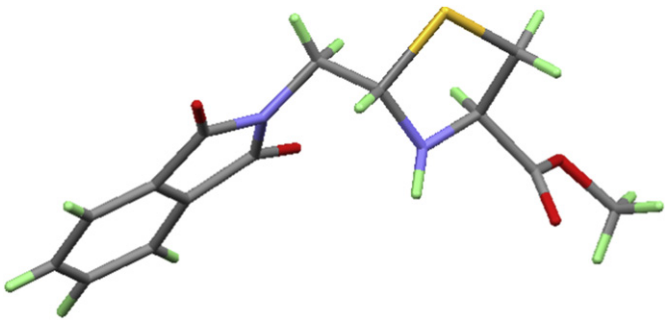


Figure 6. Crystal structure of **2a**.

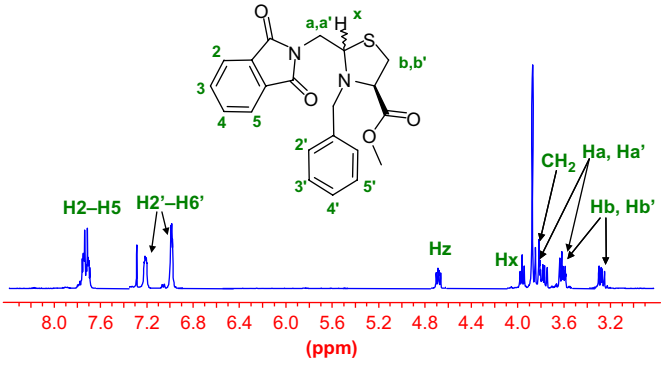


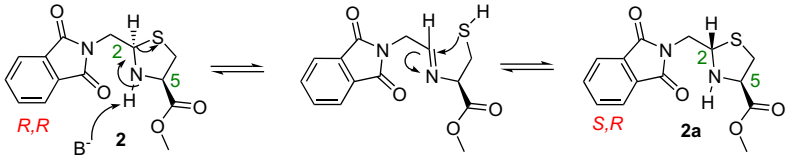
Figure 7. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of **6**.

(2*S*,4*R*) diastereoisomers present in solution. This process, while being slow, reaches equilibrium after 5 days with a (2*R*,4*R*)/(2*S*,4*R*) ratio of 1:2. When the above experiment was repeated in the presence of a small amount of $(C_2H_5O)BF_3$, the epimerisation of **2** also came to equilibrium after 5 days. However, unlike that seen above, after 3 h there was 3:1 ratio of (2*R*,4*R*)/(2*S*,4*R*) and upon reaching equilibrium there was a (2*R*,4*R*)/(2*S*,4*R*) ratio of 1:4 present in solution. This would indicate that the process is also acid-catalysed. Further evidence for this was given by the fact that the epimerisation process in $(CD_3)_2CO$ did not occur, even though the polarities of $CDCl_3$ and $(CD_3)_2CO$ are quite similar. With this in mind, the epimerisation of **2** was followed in $C_2D_4O_2$ and was found to reach equilibrium after 1.5 days with a (2*R*,4*R*)/(2*S*,4*R*) ratio of 1:1 and remained unchanged even after 4 days.

When the spectrum was recorded in $(CD_3)_2SO$, the process came to equilibrium after 6 days with a (2*R*,4*R*)/(2*S*,4*R*) ratio of 1:2. Typical first order kinetics was observed for this process and the rate constant was determined to be 3×10^{-6} S^{-1}. Strangely, it was found that the epimerisation of **2** in all of the other solvents did not obey first order or second order kinetics, and consequently a rate constant could not be determined. The final study undertaken involved following the epimerisation of **2** in a mixture of $CDCl_3$ and MeOD (1:3).

Table 2
Chemical shifts of the C-2, C-4 and NH protons of **2** and **2a**, in a number of different deuterated solvents

Solvent	C-2 (**Hz**)	C-4 (**Hx**)	NH
$CDCl_3$	4.86 (2*R*,4*R*)	3.82 (2*R*,4*R*)	2.61 (2*R*,4*R*)
	5.50 (2*S*,4*R*)	4.21 (2*S*,4*R*)	2.75 (2*S*,4*R*)
$(CD_3)_2SO$	4.82 (2*R*,4*R*)	3.96 (2*R*,4*R*)	3.39 (2*R*,4*R*)
	4.96 (2*S*,4*R*)	4.07 (2*S*,4*R*)	3.55 (2*S*,4*R*)
$(CD_3)_2CO$	4.88 (2*R*,4*R*)	3.90 (2*R*,4*R*)	2.98 (2*R*,4*R*)
CD_3CO_2D	4.90 (2*R*,4*R*)	4.14 (2*R*,4*R*)	—
	5.16 (2*S*,4*R*)	4.38 (2*S*,4*R*)	—



Scheme 3. Possible mechanism for the C-2 epimerisation of **2** via a Schiff base intermediate to give **2a**.

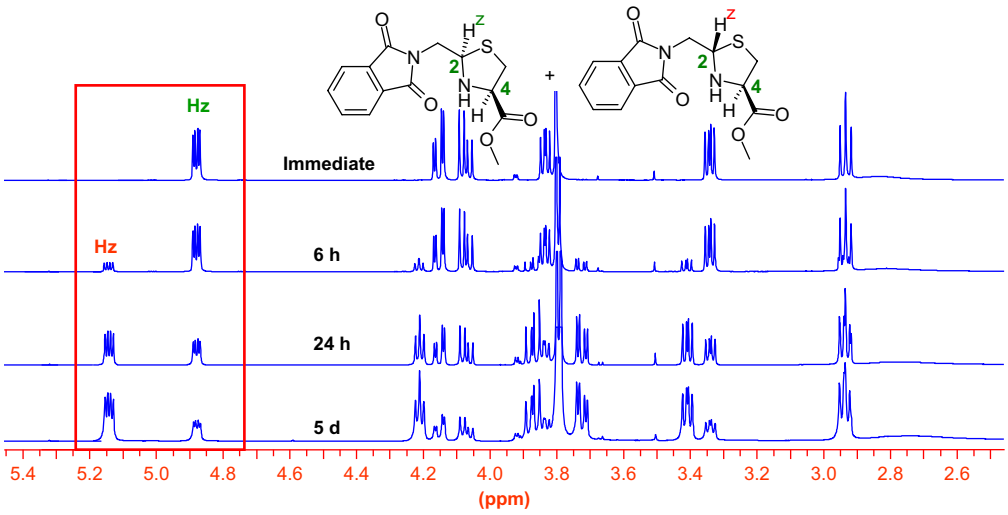


Figure 8. Stack plot of the ^{1}H NMR spectra ($CDCl_3$, 600 MHz) of **2**.

After 12 h, formation of the (2*S*,4*R*) diastereoisomer was not observed. Moreover, it was only after 8 days that the signal pertaining to the **Hz** proton of the (2*S*,4*R*) diastereoisomer was observed and an integration of each of the signals for the protons of the C-2 centre gave a (2*R*,4*R*)/(2*S*,4*R*) ratio of 6:1. This indicated that the presence of a protic solvent significantly reduces the rate of epimerisation, perhaps through hydrogen bonding interactions with the NH of **2**.

3. Conclusion

In conclusion, the phthaloyl-based thiazolidine containing amino acid **2** and the corresponding thiazole **3** were synthesised. Deprotection of **3**, whereby the methyl ester and the phthaloyl protecting groups were removed to give the corresponding free acid **4** and the free amine **5**, respectively. Both deprotection steps required efficient synthetic modification and the thiazole ring was found to be sensitive to the conditions under which the hydrazinolysis reaction was conducted.

Single crystals of **2**, **2a** and **3** were successfully grown by the slow evaporation of CH_2Cl_2 from a saturated solution of the compound in MeOH, while single crystals of **5** were obtained by a crystallisation from EtOH. All were found to be suitable for X-ray crystallography diffraction analysis. The crystal structures of **2** and **2a** allowed for their absolute stereochemistry to be assigned as (2*R*,4*R*) and (2*S*,4*R*), respectively, for these products.

A series of attempts were made at N-alkylating the thiazolidine intermediate **2**, and the synthesis was achieved by using K_2CO_3 as a base in the presence of KI. This gave the alkylated product, **6**, as a single diastereoisomer. All other attempts resulted in the formation of a mixture of the (2*R*,4*R*) and the (2*S*,4*R*) diastereoisomers of **2**. The rate of epimerisation of **2** was monitored in a range of solvents by ^{1}H NMR. It was found that the rate of epimerisation increased in the presence of acid whereas it decreased in polar solvents. From these results we can conclude that when L-cysteine methyl ester is reacted with a phthaloyl protected aldehyde a single diastereoisomer, as the kinetic product, is obtained in the solid state. However, over time, selective inversion occurs to give a mixture of C-2 epimeric thiazolidines.

4. Experimental

4.1. General

All chemicals were obtained from Sigma–Aldrich, Fluka, or Lancaster and unless specified, were used without further purification. Deuterated solvents for NMR use were purchased from Apollo Ltd. NMR spectra were recorded using a Bruker Avance III spectrometer, operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR and a Bruker Avance II 600 MHz for ^{1}H NMR and 150 MHz for ^{13}C NMR. Shifts are referenced relative to the internal solvent signals. NMR data were processed using Bruker Win-NMR 5.0 software. Electrospray mass spectra were recorded on a Mass Lynx NT V 3.4 on a Waters 600 controller connected to a 996 photodiode array detector with HPLC-grade methanol, water or acetonitrile as carrier solvents. Accurate molecular weights were determined by a peak-matching method, using leucine enkephaline (H–Tyr-Gly-Gly-Phe-Leu–OH) as the standard internal reference (*m*/*z*=556.2771); all accurate mass were calculated to $\leq$5 ppm. Melting points were determined using an Electrothermal IA9000 digital melting point apparatus. Infrared spectra were recorded on a Mattson Genesis II FTIR spectrometer equipped with a Gateway 2000 4DX2-66 workstation and on a Perkin Elmer Spectrum One FT-IR Spectrometer equipped with Universal ATR sampling accessory. Solid samples were dispersed in KBr and recorded as clear pressed discs or as neat samples. Elemental analysis was carried out at the Microanalysis Laboratory, School of Chemistry and Chemical Biology, University College Dublin. X-ray diffraction studies were carried out by Dr. T. McCabe, School of Chemistry, Trinity College Dublin, Dublin, Ireland.

4.2. *N*-[(Formyl)methyl]phthalimide (1)

Compound **1** was prepared by stirring phthalimido-acetaldehydediethylacetal (26.0 g, 98 mmol) in a mixture of TFA (175 mL) and $CHCl_3$ (350 mL) in an ice/water bath, under an argon atmosphere, for 1 h. The reaction mixture was stirred at rt for a further 5 h. The solvent was removed in vacuo and co-evaporated with CH_2Cl_2 several times, to remove the remaining traces of TFA. This yielded the product as an off-white solid (18.78 g, 100%). No purification was necessary. m.p. 102–103 °C. Found: C, 63.23; H, 3.02; N, 6.58%. $C_{10}H_7NO_3$ requires C, 63.49; H, 3.73; N, 7.40%; δ_H (400 MHz, $CDCl_3$) 9.67 (1H, s, CHO), 7.90 and 7.78 (4H, AA′BB′ system, Phth), 4.58 (2H, s, CH_2); δ_c (100 MHz, $CDCl_3$) 193.2 (CH), 167.1, 133.9, 131.4, 123.2, 46.9; *m*/*z*: 190 $(M+H)^+$; ν_{max} (KBr)/cm^{-1} 3100, 2965, 2850, 1580.

4.3. *N*-Phthaloyl-methyl-2(*R*)-thiazolidine-4(*R*)-methyl ester (2)

Compound **2** was prepared by adding a solution of L-cysteine methyl ester hydrochloride (32.47 g, 189.0 mmol, 2 equiv) in H_2O (250 mL) to the aldehyde **1** (18.0 g, 94.6 mmol, 1 equiv) suspended

in EtOH (500 mL). $KHCO_3$ (18.9 g, 189.0 mmol, 2 equiv) was then added and the resulting mixture was stirred under argon at rt for 5 h with thiazolidine **2** gradually precipitating from the reaction medium. The reaction was allowed to sit overnight at 0 °C. The crude product **2** (27.0 g, 93% yield) was collected by suction filtration and washed several times with EtOH. Recrystallisation from MeOH yielded **2** as a white crystalline fibrous solid (22.7 g, 79%). m.p. 81–82 °C; $[\alpha]_D^{23}$ −39.4 (c=5.3 mgcg^{-3}, $CHCl_3$). Found: C, 54.08; H, 4.23; N, 8.79%. $C_{14}H_{14}N_2O_4S$ requires C, 54.89; H, 4.61; N, 9.14%; HRMS: 329.0562 ($[M+Na]^+$ $C_{14}H_{14}N_2O_4NaS$ requires 329.0572); δ_H (400 MHz, $CDCl_3$) 7.87 and 7.74 (4H, AA′BB′ system, Phth), 4.86 (1H, dd, J=8.5 and 4.0 Hz, Hz), 4.14 (1H, dd, J=14.5, 4.0 Hz, Ha), 4.06 (1H, dd, J=14.0, 8.5 Hz, Ha′), 3.82 (1H, dd, J=9.5, 7.6 Hz, Hx), 3.80 (3H, s, OCH_3), 3.33 (1H, dd, J=14.0, 6.5 Hz, Hb), 2.92 (1H, dd, J=10.0, 8.0 Hz, Hb′), 2.53 (1H, br s, NH); δ_c (100 MHz, $CDCl_3$) 170.9 (CO), 168.1 (CO), 134.1 (CH), 131.7 (CH), 123.5 (CH), 68.2 (CH), 65.5 (CH), 52.5 (CH_3), 41.1 (CH_2), 38.2 (CH_2); m/z: 329 $(M+Na)^+$; ν_{max} (KBr)/cm^{-1} 3500, 3180, 2901, 2850, 1603.

4.4. *N*-Phthaloyl-methyl-thiazole-4-methyl ester (3)

Compound **3** was prepared by stirring **2** (22.50 g, 73.9 mmol, 1 equiv), activated MnO_2 (224.9 g, 2580 mmol, 35 equiv) and pyridine (6.60 g, 6.7 mL, 83.5 mmol, 1.13 equiv) at reflux in dry CH_2Cl_2 under an argon atmosphere for 5 days. The reaction mixture was filtered hot through celite, washing several times with CH_2Cl_2. The filtrate and washings were evaporated to dryness and the white residue was redissolved in CH_2Cl_2 and washed three times with HCl (0.1 M) and once with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated to dryness to give the product as a white solid (13.39 g, 63% yield) after recrystallisation from MeOH. m.p. 164–164 °C. Found: C, 54.99; H, 2.76; N, 8.68%. $C_{14}H_{10}N_2O_4S$ requires C, 55.62; H, 3.33; N, 9.27%; HRMS: 325.0265 ($[M+Na]^+$ $C_{14}H_{10}N_2O_4NaS$ requires 325.0259); δ_H (400 MHz, $CDCl_3$) 8.15 (1H, s, CH), 7.93 and 7.77 (4H, AA′BB′ system, Phth), 5.25 (2H, s, CH_2), 3.95 (3H, s, OCH_3); δ_c (100 MHz, $CDCl_3$) 166.7 (C=O), 165.6 (C=O), 161.1 (C), 146.3 (C), 134.4 (CH), 131.3 (C), 128.3 (CH), 123.7 (CH), 52.0 (CH_3), 38.7 (CH_2); m/z: 325 $(M+Na)^+$; ν_{max} (KBr)/cm^{-1} 3260, 3150, 2701, 2650, 1589.

4.5. *N*-Phthaloyl-methyl-thiazole-4-carboxylic acid (4)

Compound **4** was prepared by adding **2** (1.68 g, 5.5 mmol, 1 equiv) to a mixture of acetone (28 mL), H_2O (17 mL) and concentrated HCl (8.5 mL). The suspension was stirred at reflux for 48 h. The reaction mixture was allowed to cool and any precipitate present was collected by suction filtration and washed with a little acetone. The filtrate and washings were evaporated under reduced pressure. The residue was dissolved in K_2CO_3 (1.2 M). The solution was filtered and brought to pH 1 by adding concentrated HCl. A small amount of EtOH was added and the mixture was gradually heated to dissolve the precipitate. On cooling the product separated and was collected by suction filtration, washed with a little EtOH and dried to yield **4** as fine colourless needles (0.87 g, 55%). m.p. 102–103 °C; HRMS: 311.0114 ($[M+Na]^+$ $C_{13}H_8N_2O_4NaS$ requires 311.0102); δ_H (400 MHz, $(CD_3)_2SO$) 8.42 (1H, s, CH), 7.95 and 7.90 (4H, AA′BB′ system, Phth), 5.12 (2H, s, CH_2); δ_c (100 MHz, $CDCl_3$) 16.1 (C=O), 165.3 (C=O), 161.3 (C), 146.6 (C), 134.8 (CH), 131.4 (C), 12.6 (CH), 123.5 (CH), 39.2 (CH_2); m/z: 311 $(M+Na)^+$; ν_{max} (KBr)/cm^{-1} 3260, 3150, 2650, 1589, 1360.

4.6. 2-Aminomethyl-thiazole-4-carboxylate (5)

Compound **5** was prepared by adding hydrazine monohydrate (3.9 g, 3.8 mL, 79.4 mmol, 2 equiv) to a suspension of **2** (12 g, 39.7 mmol, 1 equiv) in boiling EtOH (180 mL). The resulting solution was stirred at rt for 4 h. A white precipitate was produced as the reaction progressed, indicating the formation of phthalhydrazide side-product. The reaction was allowed sit at rt overnight. The voluminous white precipitated phthalhydrazide (6.24 g, 97% yield) was collected by suction filtration and washed with a little EtOH (^1H, ^{13}C NMR and MS confirmed the structure to be $C_8H_6O_2$). The filtrate and washings were evaporated under reduced pressure. The white residue was redissolved in EtOH and any remaining precipitate was collected by suction filtration and washed with a little EtOH. The filtrate and washings were evaporated under reduced pressure. This procedure was repeated until an oil-like residue was obtained. The residue was then dissolved in H_2O and extracted three times with $CHCl_2$. The combined chloroform layers were washed three times with HCl (0.1 M) and the combined aqueous phases were extracted two times with CH_2Cl_2. The aqueous phase was brought to pH 12 by adding NaOH (0.1 M) and extracted three times with $CHCl_2$. The solvent was removed in vacuo to give **5** as an off-white solid (3.6 g, 53% yield). m.p. 162–163 °C; HRMS: 195.0125 ($[M+Na]^+$. $C_6H_8N_2O_2NaS$ requires 195.0229); δ_H (400 MHz, $CDCl_3$) 8.13 (1H, s, CH), 4.22 (2H, s, CH_2), 3.94 (3H, s, OCH_3); δ_c (100 MHz, $CDCl_3$) 175.4 (CO), 161.5 (C), 146.3 (C), 128.3 (CH), 51.9 (CH_3), 43.52 (CH_2); m/z: 195 $(M+Na)^+$; ν_{max} (KBr)/cm^{-1} 2957, 2843, 2810, 1650.

4.7. *N*-Phthaloyl-methyl-3-benzyl-2(*R*)-thiazolidine-4(*R*)-carboxylate (6)

Compound **6** was prepared by treating **2** (0.15 g, 0.49 mmol, 1 equiv) with K_2CO_3 (0.102 g, 0.74 mmol, 1.5 equiv) in dry acetonitrile at 40 °C for 1 h. Benzylchloride (0.067 ml, 0.59 mmol, 1.2 equiv) and KI (0.098 g, 0.59 mmol, 1.2 equiv) were then added and the reaction mixture was stirred at 80 °C for 3 days. The solvent was then removed in vacuo and the residue was dissolved in CH_2Cl_2 and washed twice with water. The organic layer was dried over $MgSO_4$, filtered and evaporated to dryness to give the product (0.13 g, 69%) as a light yellow solid following purification by column chromatography on neutral flash silica (ethyl acetate/hexane 98:2 → 50:50 and 1% NEt_3). m.p. 94–96 °C; HRMS: 419.1023 ($[M+Na]^+$ $C_{21}H_{20}N_2O_4NaS$ requires 419.1041); δ_H (400 MHz, $CDCl_3$) 7.72 and 7.68 (4H, AA′BB′ system, Phth), 7.19 (2H, br s, H2′, H6′), 7.02–6.97 (3H, m, H3′, H4′, H5′), 4.67 (1H, dd, J=8.5, 6.0 Hz, Hz), 3.82 (1H, t, J=7.5 Hz, Hx), 3.85 (3H, s, OCH_3), 3.83 (1H, dd, J=14.0, 4.5 Hz, Ha), 3.75 (1H, dd, J=14.0, 8.0 Hz, Ha′), 3.60 (1H, dd, J=14.0, 6.0 Hz, Hb), 2.92 (1H, dd, J=12.0, 7.5 Hz, Hb′); δ_c (100 MHz, $CDCl_3$) 171.9 (CO), 167.2 (CO), 137.8 (C), 133.2 (CH), 131.6 (C), 128.6 (CH), 127.7 (CH), 126.8 (CH), 122.6 (CH), 71.6 (CH), 70.6 (CH), 61.8 (CH_2), 52.1 (CH_3), 42.8 (CH_2), 33.4 (CH_2); m/z: 419 $(M+Na)^+$; ν_{max} (KBr)/cm^{-1} 3500, 3180, 2901, 2850, 1603.

4.8. Crystal data (2)

$C_{14}H_{14}N_2O_4S$, M=306.33, monoclinic, a=9.673(3), b=5.2263(13), c=14.1444(4) Å, α=90°, β=109.251(4)°, γ=90°, U=675.1(3) Å^3, T=123 K, space group $P2(1)$, Z=2, μ(Mo Kα)=0.26 mm^{-1}, 4434 reflections collected, 1944 unique, (R_{int}=0.0241), R=0.0274, $wR2[I>2\sigma(I)]$=0.0787, Flack=0.11(13). CCDC deposition number: 677805.

4.9. Crystal data (2a)

$C_{28}H_{28}N_4O_8S_2$, M=612.66, monoclinic, a=13.6914(11), b=8.6680(7), c=23.5487(18) Å, α=90°, β=90.4720(10)°, γ=90°, U=2789.2(4) Å^3, T=123 K, space group $C2$, Z=4, μ(Mo Kα)=0.25 mm^{-1}, 6585 reflections collected, 6384 unique, (R_{int}=0.0178), R=0.0328, $wR2[I>2\sigma(I)]$=0.0876, Flack=0.03(4). CCDC deposition number: 677802.

4.10. Crystal data (3)

$C_{14}H_{10}N_2O_4S$, M=302.3, triclinic, a=5.8552(13), b=7.8771(17), c=14.112(3) Å, α=84.814(4)°, β=89.300(4)°, γ=82.239(4)°, U=642.3(2) Å^3, T=123 K, space group P-1, Z=2, μ(Mo Kα)=0.27 mm^{-1}, 6399 reflections collected, 3095 unique, (R_{int}=0.0191), R=0.0365, $wR2[I>2\sigma(I)]$=0.0994. CCDC deposition number: 677804.

4.11. Crystal data (5)

$C_6H_8N_2O_2S$, M=172.20, monoclinic, a=5.8172(98), b=13.3627(19), c=9.7714(14) Å, α=90°, β=97.06°, γ=90°, U=753.81(18) Å^3, T=123 K, space group $P2(1)/n$, Z=4, μ(Mo Kα)=0.38 mm^{-1}, 7652 reflections collected, 1858 unique, (R_{int}=0.0217), R=0.0568, $wR2[I>2\sigma(I)]$=0.1403. CCDC deposition number: 677803.

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References and notes

1. (a) Williams, A. B.; Jacobs, R. S. *Cancer Lett.* **1993**, *71*, 97–102; (b) Faulkner, D. J. *Nat. Prod. Rep.* **1998**, *15*, 113–158; (c) Ogino, J.; Moore, R. E.; Patterson, G. M. L.; Smith, C. D. *J. Nat. Prod.* **1996**, *59*, 581–586; (d) Davidson, B. S. *Chem. Rev.* **1993**, *93*, 1771–1791; (e) Wipf, P. *Chem. Rev.* **1995**, *95*, 2115–2134.
2. (a) North, M.; Pattenden, G. *Tetrahedron* **1990**, *46*, 8267–8290; (b) Boden, C. D. J.; Pattenden, G.; Ye, T. *Synlett* **1995**, 417–419; (c) Boden, C. D. J.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 875–882; (d) Boden, C. D. J.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 883–888; (e) Kigoshi, H.; Yamada, S. *Tetrahedron* **1999**, *55*, 12301–12308; (f) Downing, S. V.; Aguilar, E.; Meyers, A. I. *J. Org. Chem.* **1999**, *64*, 826–831; (g) Michael, J. P.; Pattenden, G. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1–23; (h) Bertram, A.; Blake, A. J.; de Turiso, F. G.-L.; Hannam, J. S.; Jolliffe, K. A.; Pattenden, G.; Skae, M. *Tetrahedron* **2003**, *59*, 6979–6990; (i) Moody, C. J.; Bagley, M. C. *J. Chem. Soc., Perkin Trans. 1* **1998**, 601–607; (j) Xia, Z.; Smith, C. D. *J. Org. Chem.* **2001**, *66*, 3459–3466.
3. Yokokawa, F.; Sameshima, H.; Shioiri, T. *Tetrahedron Lett.* **2001**, *42*, 4171–4174.
4. (a) Sheehan, J. C.; Henery-Logan, K. R. *J. Am. Chem. Soc.* **1957**, *79*, 1262–1263; (b) Sheehan, J. C.; Henery-Logan, K. R. *J. Am. Chem. Soc.* **1959**, *81*, 3089–3094.
5. (a) Kallen, R. G. *J. Am. Chem. Soc.* **1971**, *93*, 6236–6248; (b) Abbott, E. H.; Martell, A. E. *J. Am. Chem. Soc.* **1970**, *92*, 1754–1759; (c) Yang, I. Y.; Khomutov, R. M.; Metzler, D. E. *Biochemistry* **1974**, *13*, 3877–3884; (d) Rinaldi, A.; DeMarco, C. *Arch. Biochem. Biophys.* **1970**, *138*, 697–699; (e) Buell, M. V.; Hansen, R. E. *J. Am. Chem. Soc.* **1960**, *82*, 6042–6049; (f) Nagasawa, H. T.; Goon, D. J. W.; de Master, E. B. *J. Med. Chem.* **1978**, *21*, 1274–1279; (g) Nagasawa, R. E.; Goon, D. J. W.; Zera, R. T.; Yuzon, D. L. *J. Med. Chem.* **1984**, *27*, 591–596.
6. (a) Pesek, J. J.; Frost, J. H. *Tetrahedron* **1975**, *31*, 907–913; (b) Refouvelet, B.; Robert, J.-F.; Couquelet, J.; Tronche, P. *J. Heterocycl. Chem.* **1994**, *31*, 77–80; (c) Chiarino, D.; Ferrario, F.; Pellacini, F.; Sala, A. *J. Heterocycl. Chem.* **1989**, *26*, 589–593; (d) Ponticelli, F.; Marinello, E.; Missale, M. C. *Org. Magn. Reson.* **1982**, *20*, 138–140; (e) Nagasawa, H. T.; Goon, D. J. W.; Shirota, F. N. *J. Heterocycl. Chem.* **1981**, *18*, 1047–1051; (f) Szilagyi, L.; Gyorgydeak, Z. *J. Am. Chem. Soc.* **1979**, *101*, 427–432.
7. (a) Schmidt, U.; Utz, R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 725–726; (b) Schmidt, U.; Gleich, P. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 569–571; (c) Schmidt, U.; Utz, A.; Lieberknecht, H.; Griesser, B.; Potzolli, B.; Bahr, J.; Wagner, K.; Fischer, P. *Synthesis* **1987**, 233–236.
8. (a) Hamada, Y.; Shibata, M.; Sugiuri, T.; kato, S.; Shioro, T. *J. Org. Chem.* **1987**, *52*, 1252–1255; (b) Groarke, M.; McKervey, M. A.; Moncrieff, H. M.; Nieuwenhuyzen, M. *Tetrahedron Lett.* **2000**, *41*, 1279–1282.
9. Wipf, P.; Fritch, P. C. *Tetrahedron Lett.* **1994**, *35*, 5397–5400.
10. Curley, S. O. M.; McCormick, J. E.; McElhinney, S. R.; McMurry, B. T. H. *ARKIVOC* **2003**, *7*, 180–183.
11. The data were collected on a Bruker Smart Apex Diffractometer. Each crystal was mounted on a 0.30 mm quartz fibre and immediately placed on the goniometer head in a 150 K N_2 gas stream. The data sets were collected using Smart Version 5.625 software run in multi-run mode and for each data set 2400 frames in total, at 0.3° per frame, were recorded. Data integration and reduction was performed using Bruker Saint+ Version 6.45 software and corrected for absorption and polarization effects using Sadabs Version 2.10 software. Space group determinations, structure solutions and refinements were obtained using Bruker Shelxtl Ver. 6.14 software. *SMART Software Reference Manual, Version 5.625*; Bruker Analytical X-Ray Systems: Madison, WI, 2001; Sheldrick, G. M. *SHELXTL, An Integrated System for Data Collection, Processing, Structure Solution and Refinement*; Bruker Analytical X-Ray Systems: Madison, WI, 2001.
12. Cross, D. F. W.; Kennerr, G. W.; Shepparda, R. C.; Stehr, C. E. *J. Chem. Soc.* **1963**, 2143–2150.