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**PAPER**

# An unprecedented synthesis of γ-lactams *via* mercaptoacetylation of aziridines in water

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A highly green and expeditious route to α-mercapto-γ-lactams from masked mercapto acids *viz*. 2-phenyl-2-methyl-1,3-oxathiolan-5-ones, and tosyl aziridines in an excellent yield (82–93%) is reported. The synthetic protocol involves regioselective opening of the terminal aziridine ring and mercaptoacetylative cyclisation cascades in a one-pot procedure wherein water acts as both a catalyst as well as a solvent. These reactions were carried out in aqueous media as well as under solvent-free conditions, however, under solvent-free conditions, lower yields are obtained.

## Introduction

Since the pioneering studies by Breslow,[1] organic reactions in water have gained tremendous importance because of their green chemistry perspective. γ-Lactam motifs are ubiquitous in the natural product arena and in pharmaceuticals with interesting biological activities.[2] Many γ-lactam-based pharmaceutical ingredients have been approved for potential treatment toward many common diseases such as hepatitis, diabetes, and cancers.[3] From a chemical viewpoint, they are important intermediates in the synthesis of five-membered heterocycles *viz*. pyrazole[4] and are also excellent precursors for the synthesis of biologically active pyrrolidine derivatives such as (+)-α-allokainic acid and its analogue (–)-α-kainic acid.[5] Especially, α-substituted-γ-lactams are used in the synthesis of (–)-nakadomarin A,[6] a marine alkaloid. Furthermore, pyrrolidin-2-ones have been widely used as monomers in the assembly of polymers with semiconducting properties.[7] The presence of a thiol function in many enzymes, called –SH enzymes, is essential for their enzyme activity. Likewise, incorporation of a thiol function in heterocycles, nucleosides, or nucleotides has led to a number of analogues possessing interesting biological and therapeutic properties.[8]

Numerous methods for the synthesis of differently substituted γ-lactams are reported, which include sequential allylation of imines with 2-alkoxycarbonyl alkylboronates and cyclisation,[9] ring expansion of β-lactams,[10] cyclisation of enamides,[11] nitro-Mannich/lactamisation cascades of 3-nitropropanoate with imines,[12] reductive amination-lactamisation of piperidine and γ-amino esters,[13] cyclisation of *N*-benzylidenamide,[14] Michael reaction of glycine equivalents,[15] Heck–Matsuda arylation,[16] *N*-alkenyl-α-PhSe-β-ketoamides,[2] α-aminonitriles,[17] 3-aryl-2-diethoxyphosphoryl-4-nitroalkanoates,[18] vinyl sulfonium salts,[19] Baylis–Hillman acetates[20] and cyclisation of *N*-alkyl and *N*,*N*-dimethyl amides.[21,22] However, these methods are in disagreement with green chemistry and suffer from one or more disadvantages, such as the use of hazardous solvents, a tedious work-up, high cost, need for a large amount of catalyst or a special treatment for its activation, they are not time efficient and tend to be lengthy and cumbersome if the lactam contains any sort of substitution. Although the literature records a few reports on the synthesis of β-mercapto-γ-lactams,[23,24] no effort has been made to synthesise α-mercapto-γ-lactams, although they appear to be attractive scaffolds for exploiting chemical diversity and generating a drug-like library to screen for lead candidates.

Due to ring strain, the chemistry of aziridines is mainly dominated by nucleophilic ring-opening reactions and this strategy has been well utilised for the stereoselective synthesis of N-containing molecules.[25] In this context, Badía and coworkers have reported the synthesis of γ-lactams *via* regioselective ring opening of aziridines with enolates (Scheme 1).[26] Keeping the synthetic and pharmacological importance of the –SH group and Scheme 1 in mind, we turned our attention to utilize such a type of substituted enolisable substrates, which can introduce –SH groups at the α position into γ-lactams, which are the target molecules in the present investigation. For this purpose we utilised masked mercaptoacetic acid, as given in Fig. 1.

## Results and discussion

At the outset, we tried mercaptoacetic acid for the mercaptoacetylation of aziridines **2**, but were not successful, probably due to the presence of free –COOH and –SH groups. Instead, we turned our attention to block the –COOH and –SH groups

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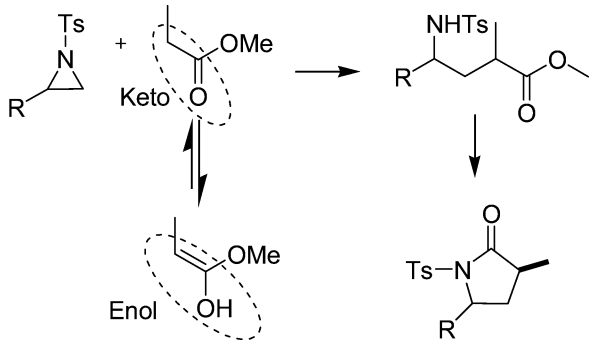



**Scheme 1** The synthesis of γ-lactams *via* aziridine ring opening.

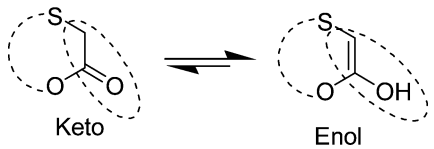
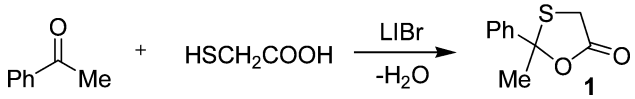
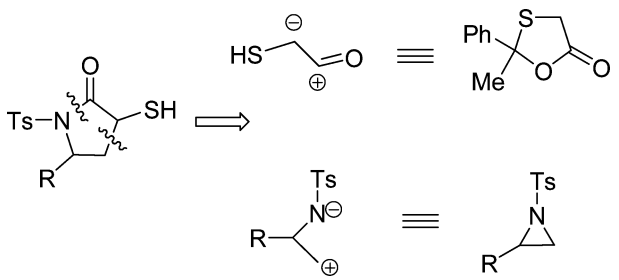



**Fig. 1** The substrate designed for introducing mercapto functional groups into γ-lactams.

of mercaptoacetic acid and thus activate its methylene group by converting it into a 1,3-oxathiolan-5-one moiety. In this regard, we examined various aldehydes and ketones, *viz*., acetaldehyde, acetone and acetophenone using LiBr in neat conditions. Amongst these, acetophenone afforded the desired product in excellent yield,[27] while the reaction did not take place using acetone and acetaldehyde. Thus, we relied upon acetophenone and converted mercaptoacetic acid to 2-methyl-2-phenyl-1,3-oxathiolan-5-one **1** (Scheme 2).[27] Compound **1** not only acts as a mercaptoacetyl transfer agent for the synthesis of α-mercapto acids, but also provides a completely new route to α-mercapto-γ-lactams and is the cornerstone of our approach, presenting its novel utility in γ-lactam chemistry (Scheme 3). Furthermore, the envisaged synthetic protocol is in continuation of our efforts for developing new synthetic routes,[28] especially using green chemistry protocols.[29]




**Scheme 2** The formation of the mercaptoacetyl transfer agent, 2-methyl-2-phenyl-1,3-oxathiolan-5-one **1**.




**Scheme 3** The disconnection approach for targeting α-mercapto-γ-lactams.

We estimated the reactivity of aziridine **2a** (2 mmol) and 2-methyl-2-phenyl-1,3-oxathiolan-5-one (2 mmol) by refluxing these in water for 3.5 h and we successfully isolated the corresponding lactam **3a** in 90% yield (Table 2, entry 1). For comparison purposes, the model experiment was also carried out at 90 °C in a microwave (Chemical Laboratory Microwave Oven, Model; BP-310/50, 230 volt, 50 Hz power input), but the reaction did not occur in the absence of a catalyst. With the aim to establish its solvent-free version and to compare the synthetic efficiency, we have examined various mineral catalysts for the formation of **3a** at 90 °C. Among the catalysts tested, K-10 clay gave the best result (Table 1, entry 1). $CeCl_3 \cdot 7H_2O$ and a $CeCl_3 \cdot 7H_2O$/NaI-system afforded the product **3a** in moderate to good yields, while poor yields of product **3a** were obtained in the case of silica gel and neutral or acidic alumina (Table 1). Moreover, the reaction did not take place using basic alumina. Thus, It was observed that a significantly lower yield of **3a** was obtained in the solvent-free version rather than its catalyst-free aqueous medium version. Therefore, we relied upon water, which not only acts as the solvent but also catalyses the reaction, in the present investigation.

**Table 1** Microwave (MW) assisted synthesis of **3a**

| | | MW | |
|---|---|---|---|
| Entry | Catalyst system | Time (min)[a] | Yield (%)[b] |
| 1 | K-10 clay | 12 | 57 |
| 2 | $CeCl_3 \cdot 7H_2O$ | 15 | 43 |
| 3 | $CeCl_3 \cdot 7H_2O$/NaI | 13 | 51 |
| 4 | Silica gel | 18 | 24 |
| 5 | Neutral alumina | 20 | 11 |
| 6 | Acidic alumina | 20 | 17 |

[a] Time for the completion of the reaction at 90 °C as indicated by TLC. [b] Yield of isolated and purified product **3a**.

The current optimised synthesis is accomplished by refluxing an equimolar mixture of aziridines **2** and 2-methyl-2-phenyl-1,3-oxathiolan-5-ones **1** in water for 3–4 h (Table 2). The isolation and purification steps are very simple and performed by filtration with a Buchner funnel, followed by washing with water (2 × 10 mL) and recrystallization from EtOH. After isolation of the product, the aqueous layer was extracted with EtOAc (3 × 10 mL) and acetophenone was easily collected from the organic phase. For the general validity of the reaction, several structurally varied aromatic and aliphatic aziridines **2** were used, employing the present optimized reaction conditions to afford the corresponding γ-lactams **3** in good to excellent yields summarized in Table 2. Furthermore, attempts to employ the more sterically hindered 2,4-dimethyl-2-phenyl-1,3-oxathiolan-5-one in place of **1** failed to produce the desired γ-lactone **3′** under similar reaction conditions, rather we isolated the corresponding intermediate **5** (Scheme 4). In this case perhaps, water catalysed only the aziridine ring opening step and failed to cyclize intermediate **5** into the corresponding γ-lactone **3′**.

In case of aziridines, the regioselective ring opening followed either electronic or kinetic control, giving different compounds. There are several reports of aziridine ring opening where nucleophilic attack took place on the benzylic carbon following electronic control. But, when the steric factor predominates over kinetic control, the nucleophile prefers to attack on the terminal carbon rather than the benzylic carbon.[25] Herein, presumably

**Table 2** One-step synthesis of α-mercapto-γ-lactam **3** in water

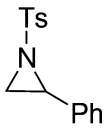
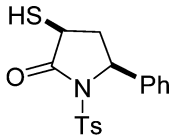
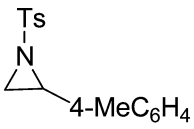
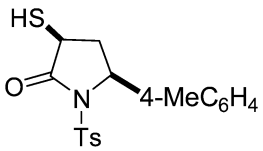
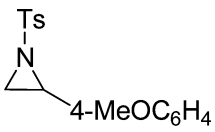
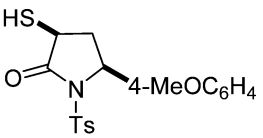
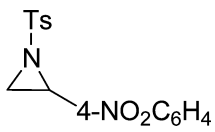
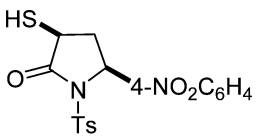
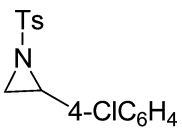
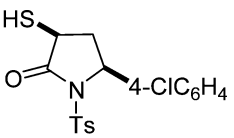
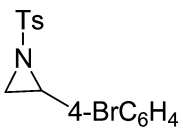
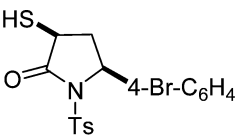
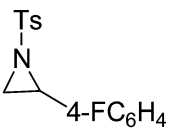
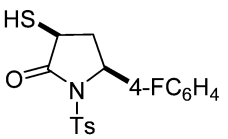
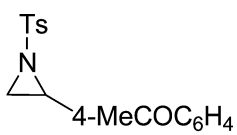
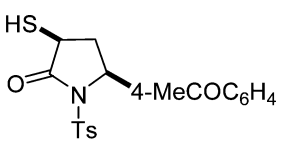
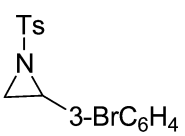
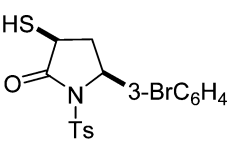
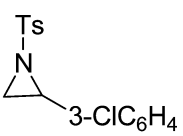
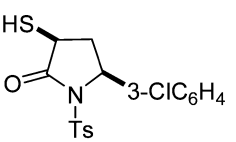
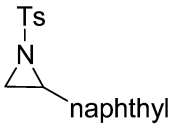
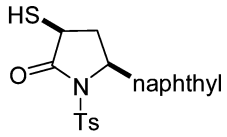
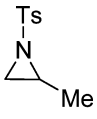
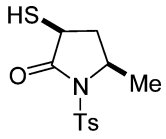
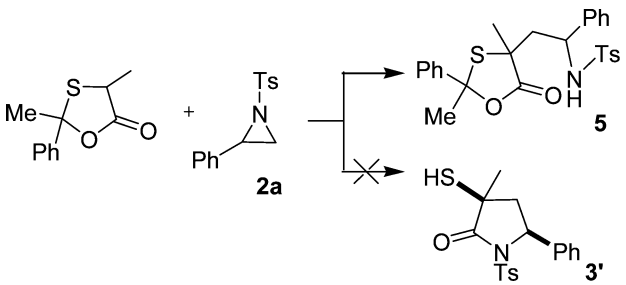
| Entry | Masked acid **1** | Aziridine **2** | Reaction time (h)[a] | γ-Lactam **3** | Yield (%)[b,c] |
|---|---|---|---|---|---|
| 1 | **1** |  **2a** | 3.5 |  **3a** | 90 |
| 2 | **1** |  **2b** | 4 |  **3b** | 91 |
| 3 | **1** |  **2c** | 3 |  **3c** | 89 |
| 4 | **1** |  **2d** | 3 |  **3d** | 93 |
| 5 | **1** |  **2e** | 3.5 |  **3e** | 82 |
| 6 | **1** |  **2f** | 3.5 |  **3f** | 88 |
| 7 | **1** |  **2g** | 4 |  **3g** | 92 |
| 8 | **1** |  **2h** | 3.5 |  **3h** | 92 |
| 9 | **1** |  **2i** | 3 |  **3i** | 86 |
| 10 | **1** |  **2j** | 3.5 |  **3j** | 91 |

**Table 2** *(Contd.)*

| Entry | Masked acid **1** | Aziridine **2** | Reaction time (h)[a] | γ-Lactam **3** | Yield (%)[b,c] |
|---|---|---|---|---|---|
| 11 | **1** |  **2k** | 4 |  **3k** | 93 |
| 12 | **1** |  **2l** | 3.5 |  **3l** | 88 |

[a] Refluxing time in water. [b] Yield of isolated and purified products. [c] All compounds gave C, H and N analyses within ± 0.37%, and satisfactory spectral (IR, $^{1}$H NMR, $^{13}$C NMR and EIMS) data.

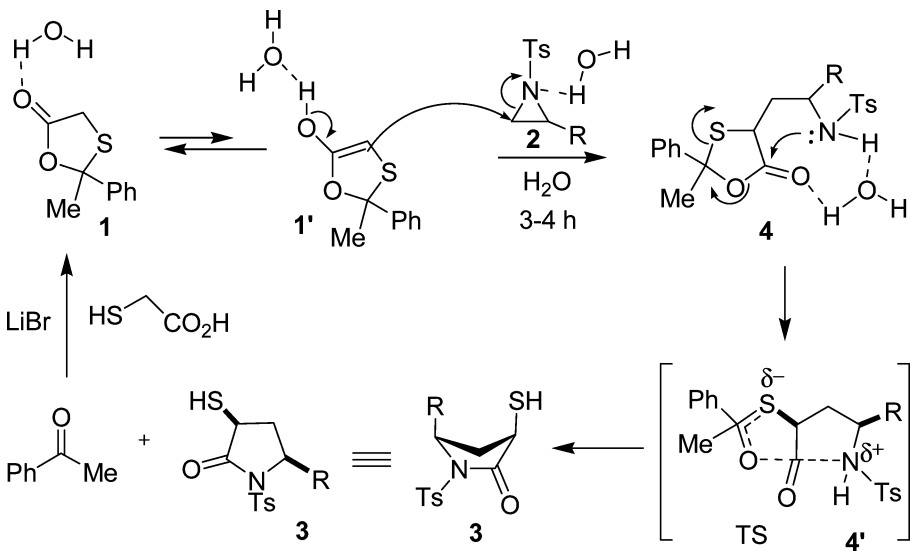




**Scheme 4** The use of masked 2-mercaptopropionic acid.

due to the bulky nature of the attacking nucleophile, the steric factor predominates over the electronic effect.

Thus, formation of **3** can be rationalized by nucleophilic attack of the active methylene carbon (C-4) of **1** on to the less-substituted carbon of tosyl aziridine **2** regioselectively, followed by protonation of the aziridine nitrogen leading to intermediate **4**. The adduct **4** undergoes intramolecular nucleophilic attack of the nitrogen atom of the NHTs group at the carbonyl carbon (C-5) of the oxathiolan-5-one moiety to yield target compounds **3** with the elimination of acetophenone (Scheme 5), which was easily recovered and reused for the preparation of the mercaptoacetyl transfer agent, 2-methyl-2-phenyl-1,3-oxathiolan-5-one **1**, by treatment with LiBr and mercaptoacetic acid as depicted in Scheme 2. This conclusion is based on the observation that the representative intermediate compounds **4a** (R = Ph), **4e** (R = 4-Cl$C_6H_4$) and **4j** (R = 3-Cl$C_6H_4$) could be isolated in 46–51% yield, these could then be converted into the corresponding lactones **3a**, **3e** and **3j** in quantitative yields, and acetophenone was formed during the reaction (Scheme 5). Since no product was formed upon MW irradiation of compound **1** and aziridine **2** without using a catalyst, it may be speculated that the role of water is a catalyst in the present synthetic protocol. Thus, the role of water in the envisaged synthetic protocol is not only as a solvent but it also catalyses the reaction. Presumably, H-bonding of $H_2O$ with the aziridine nitrogen renders the aziridine ring more susceptible to nucleophilic attack. Furthermore, $H_2O$ also may help in the enolization of **1** by hydrogen bonding with the OH of **1′** and thus increasing the nucleophilic character



**Scheme 5** A plausible mechanism for the formation of γ-lactams **3**.

of the methylene carbon (C-4) of **1**. Therefore, water activates both the steps, *i.e.* the nucleophilic opening of aziridines and the mercaptoacetylative cyclization, in the envisaged synthetic strategy (Scheme 5).

The reactions were clean and all the synthesised products were characterized by their $^{1}$H NMR, $^{13}$C NMR, IR and mass spectroscopic data. It was gratifying to find that the formation of lactams **3** was entirely diastereoselective in favour of the *cis* isomer. The *cis* stereochemistry of lactams **3** was assigned on the basis of the *J* value of the 5-H peak and the literature precedent,[30] $J_{5\text{-H},4\text{-H}_a}$ = 7.0–7.3 Hz, $J_{5\text{-H},4\text{-H}_b}$ = 6.8–6.9 Hz. Furthermore, the relative stereochemistry of lactams **3** was also established by NOE observations (Fig. 2). The strong NOE at 3-H/5-H upon irradiation of $H_a$ indicates that 4-$H_a$ and 3-H/5-H are located on the same face of the molecule, that is, lactams **3** have 3,5-*cis* configurations (Fig. 2).

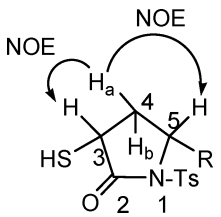



**Fig. 2** NOE observations of γ-lactams **3**.

## Conclusions

In summary, our work offers a general, efficient and green method for the preparation of synthetically and pharmaceutically important α-mercapto-γ-lactams, adopting the stringent and growing environmental regulations of green chemistry. The envisaged synthetic protocol opens up a new conceptual aspect for pyrrolidine chemistry.

## Experimental

### General

Melting points were determined by the open glass capillary method and are uncorrected. IR spectra in KBr were recorded on a Perkin–Elmer 993 IR spectrophotometer. $^{1}$H NMR spectra were recorded on a Bruker WM-40 C (400 MHz) FT spectrometer in DMSO-$d_6$ using TMS as an internal reference. $^{13}$C NMR spectra were recorded on the same instrument at 100 MHz in DMSO-$d_6$ and TMS was used as an internal reference. Mass (EI) spectra were recorded on a JEOL D-300 mass spectrometer. Elemental analyses were carried out in a Coleman automatic carbon, hydrogen and nitrogen analyzer. A Chemical Laboratory Microwave Oven (Model; BP-310/50, 230 volt, 50 Hz power input) was used. All chemicals used were reagent grade and were used as received without further purification. Silica gel-G was used for TLC.

**α-Mercapto-γ-lactam (3).** 2-Methyl-2-phenyl-1,3-oxathiolan-5-one **1** (2 mmol) and tosyl aziridine **2** (2 mmol) were mixed in 20 mL water and refluxed for 3–4 h (Table 2). After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature, filtered with a Buchner funnel and washed with water (3 × 10 mL). The crude product **3** thus obtained was recrystallized from EtOH to afford an analytically pure sample of **3**. The acetophenone was extracted from aqueous solution.

**3a.** Colourless solid (Found: C, 58.46; H, 5.11; N, 4.21%. $C_{17}H_{17}NO_3S_2$ requires C, 58.77; H, 4.93; N, 4.03%); mp 85–87 °C (from EtOH); $\nu_{max}$(KBr)/cm$^{-1}$ 3021, 2925, 2551, 1708, 1605, 1583, and 1455; $\delta_H$(400 MHz; DMSO-$d_6$/TMS) 1.59 (1 H, d, *J* 7.7 Hz), 2.28 (3 H, s), 2.83 (1 H, ddd, *J* 11.4, 7.1, 4.9 Hz), 2.92 (1 H, ddd, *J* 11.4, 9.2, 6.9 Hz), 3.65 (1 H, ddd, *J* 9.2, 7.7, 4.9 Hz), 4.97 (1 H, dd, *J* 7.1, 6.9 Hz) and 7.11–7.45 (9 $H_{arom}$, m); $\delta_C$(100 MHz; DMSO-$d_6$/TMS) 25.5, 35.3, 41.3, 50.2, 126.5, 127.8, 129.5, 130.2, 131.2, 132.0, 133.1, 133.9 and 178.2; (*m*/*z*) 347 ($M^+$).

**3b.** Colourless solid (Found: C, 59.52; H, 5.03; N, 3.95%. $C_{18}H_{19}NO_3S_2$ requires C, 59.81; H, 5.30; N, 3.87%); mp 128–130 °C (from EtOH); $\nu_{max}$(KBr)/cm$^{-1}$ 3025, 2929, 2555, 1705, 1603, 1585, and 1457; $\delta_H$(400 MHz; DMSO-$d_6$/TMS) 1.62 (1 H, d, *J* 7.5 Hz), 2.31 (3 H, s), 2.37 (3 H, s), 2.81 (1 H, ddd, *J* 11.2, 7.3, 5.1 Hz), 2.94 (1 H, ddd, *J* 11.2, 9.3, 6.8 Hz), 3.61 (1 H, ddd, *J* 9.3, 7.5, 5.1 Hz), 4.98 (1 H, dd, *J* 7.3, 6.8 Hz) and 7.19–7.61 (8 $H_{arom}$, m); $\delta_C$(100 MHz; DMSO-$d_6$/TMS) 25.8, 26.5, 35.8, 41.8, 50.7, 125.5, 126.7, 127.8, 128.3, 129.5, 130.8, 131.7, 133.0 and 177.9; (*m*/*z*) 361 ($M^+$).

**3c.** Colourless solid (Found: C, 57.49; H, 4.88; N, 3.53%. $C_{18}H_{19}NO_4S_2$ requires C, 57.27; H, 5.07; N, 3.71%); mp 146–148 °C (from EtOH); $\nu_{max}$(KBr)/cm$^{-1}$ 3021, 2928, 2556, 1702, 1607, 1581, and 1451; $\delta_H$(400 MHz; DMSO-$d_6$/TMS) 1.57 (1 H, d, *J* 7.6 Hz), 2.29 (3 H, s), 2.85 (1 H, ddd, *J* 11.2, 7.0, 5.0 Hz), 2.91 (1 H, ddd, *J* 11.1, 9.1, 6.8 Hz), 3.62 (1 H, ddd, *J* 9.1, 7.6, 5.0 Hz), 3.69 (3 H, s), 5.01 (1 H, dd, *J* 7.0, 6.8 Hz), 7.19–7.35 (6 $H_{arom}$, m) and 7.51–7.73 (2 $H_{arom}$, m); $\delta_C$(100 MHz; DMSO-$d_6$/TMS) 25.2, 35.5, 53.5, 41.5, 50.6, 125.3, 125.9, 127.1, 127.7, 129.2, 129.9, 131.2, 132.3 and 178.5; (*m*/*z*) 377 ($M^+$).

**3d.** Colourless solid (Found: C, 52.31; H, 3.81; N, 6.77%. $C_{17}H_{16}N_2O_5S_2$ requires C, 52.03; H, 4.11; N, 7.14%); mp 105–107 °C (from EtOH); $\nu_{max}$(KBr)/cm$^{-1}$ 3023, 2925, 2553, 1704, 1602, 1579, and 1453; $\delta_H$(400 MHz; DMSO-$d_6$/TMS) 1.56 (1 H, d, *J* 7.7 Hz), 2.28 (3 H, s), 2.81 (1 H, ddd, *J* 11.5, 7.1, 5.2 Hz), 2.91 (1 H, ddd, *J* 11.5, 9.2, 6.7 Hz), 3.61 (1 H, ddd, *J* 9.2, 7.7, 5.2 Hz), 5.07 (1 H, dd, *J* 7.1, 6.7 Hz), 7.22–7.59 (6 $H_{arom}$, m) and 7.71–7.89 (2 $H_{arom}$, m); $\delta_C$(100 MHz; DMSO-$d_6$/TMS) 25.1, 35.5, 41.2, 50.2, 126.1, 126.7, 127.3, 128.8, 129.6, 130.5, 131.2, 132.5 and 178.3; (*m*/*z*) 392 ($M^+$).

**3e.** Colourless solid (Found: C, 53.68; H, 4.31; N, 3.51%. $C_{17}H_{16}ClNO_3S_2$ requires C, 53.47; H, 4.22; N, 3.67%); mp 118–120 °C (from EtOH); $\nu_{max}$(KBr)/cm$^{-1}$ 3019, 2923, 2549, 1702, 1599, 1581, and 1452; $\delta_H$(400 MHz; DMSO-$d_6$/TMS) 1.63 (1 H, d, *J* 7.9 Hz), 2.32 (3 H, s), 2.80 (1 H, ddd, *J* 11.3, 7.1, 5.3 Hz), 2.92 (1 H, ddd, *J* 11.3, 9.2, 6.8 Hz), 3.63 (1 H, ddd, *J* 9.2, 7.9, 5.3 Hz), 5.05 (1 H, dd, *J* 7.1, 6.8 Hz), 7.29–7.51 (6 $H_{arom}$, m) and 7.69–7.85 (2 $H_{arom}$, m); $\delta_C$(100 MHz; DMSO-$d_6$/TMS) 25.5, 36.6, 41.6, 50.9, 125.8, 126.7, 127.5, 128.3, 130.1, 130.7, 131.5, 132.3 and 177.5; (*m*/*z*) 381, 383 (M, M + 2).

**3f.** Colourless solid (Found: C, 48.26; H, 3.49; N, 3.03%. $C_{17}H_{16}BrNO_3S_2$ requires C, 47.89; H, 3.78; N, 3.29%); mp 89–90 °C (from EtOH); $\nu_{max}$(KBr)/cm$^{-1}$ 3017, 2921, 2551, 1701, 1608, 1588, and 1455; $\delta_H$(400 MHz; DMSO-$d_6$/TMS) 1.58 (1 H, d, *J* 7.8 Hz), 2.30 (3 H, s), 2.78 (1 H, ddd, *J* 11.3, 7.0, 4.8 Hz), 2.90 (1 H, ddd, *J* 11.3, 9.1, 6.9 Hz), 3.62 (1 H, ddd, *J* 9.1, 7.8, 4.8 Hz), 4.99 (1 H, dd, *J* 7.0, 6.9 Hz), 7.25–7.56 (6 $H_{arom}$, m) and 7.73–7.83 (2 $H_{arom}$, m); $\delta_C$(100 MHz; DMSO-$d_6$/TMS) 25.2, 35.9, 41.5, 51.3, 126.2, 127.1, 127.8, 128.6, 129.3, 129.9, 130.6, 131.8 and 177.6; (*m*/*z*) 427 ($M^+$).

**3g.** Colourless solid (Found: C, 55.66; H, 4.69; N, 3.58%. $C_{17}H_{16}FNO_3S_2$ requires C, 55.87; H, 4.41; N, 3.83%); mp 93–94 °C (from EtOH); $\nu_{max}$(KBr)/cm$^{-1}$ 3019, 2920, 2555, 1707, 1605, 1580 and 1452; $\delta_H$(400 MHz; DMSO-$d_6$/TMS) 1.59 (1 H, d, *J* 7.5 Hz), 2.30 (3 H, s), 2.81 (1 H, ddd, *J* 11.2, 7.1, 4.9 Hz), 2.95 (1 H, ddd, *J* 11.2, 9.3, 6.8 Hz), 3.67 (1 H, ddd, *J* 9.3, 7.5, 4.9 Hz), 4.96 (1 H, dd, *J* 7.1, 6.8 Hz), 7.21–7.58 (6 $H_{arom}$, m) and 7.79–7.87 (2 $H_{arom}$, m); $\delta_C$(100 MHz; DMSO-$d_6$/TMS) 25.1, 37.1, 41.7, 51.5, 125.5, 126.7, 127.5, 128.4, 129.1, 129.7, 130.5, 132.7 and 178.2; (*m*/*z*) 365 ($M^+$).

**3h.** Colourless solid (Found: C, 58.32; H, 5.29; N, 3.45%. $C_{19}H_{19}NO_4S_2$ requires C, 58.59; H, 4.92; N, 3.60%); mp 121–123 °C (from EtOH); $\nu_{max}$(KBr)/cm$^{-1}$ 3022, 2928, 2552, 1708, 1602, 1585 and 1458; $\delta_H$(400 MHz; DMSO-$d_6$/TMS) 1.56 (1 H, d, *J* 7.7 Hz), 2.28 (3 H, s), 2.41 (3 H, s), 2.80 (1 H, ddd, *J* 11.1, 7.2, 4.9 Hz), 2.93 (1 H, ddd, *J* 11.1, 9.4, 6.8 Hz), 3.67 (1 H, ddd, *J* 9.4, 7.7, 4.9 Hz), 5.11 (1 H, dd, *J* 7.2, 6.8 Hz), 7.31–7.58 (6 $H_{arom}$, m) and 7.79–7.83 (2 $H_{arom}$, m); $\delta_C$(100 MHz; DMSO-$d_6$/TMS) 24.7, 25.5, 36.5, 41.6, 51.0, 126.2, 126.8, 127.6, 128.5, 129.7, 130.5, 131.2, 132.9, 177.3 and 178.1; (*m*/*z*) 389.

**3i.** Colourless solid (Found: C, 47.67; H, 3.93; N, 3.36%. $C_{17}H_{16}BrNO_3S_2$ requires C, 47.89; H, 3.78; N, 3.29%); mp 102–104 °C (from EtOH); $\nu_{max}$(KBr)/cm$^{-1}$ 3025, 2921, 2552, 1705, 1605, 1581, and 1449; $\delta_H$(400 MHz; DMSO-$d_6$/TMS) 1.57 (1 H, d, *J* 7.6 Hz), 2.29 (3 H, s), 2.83 (1 H, ddd, *J* 11.4, 7.1, 5.1 Hz), 2.92 (1 H, ddd, *J* 11.4, 9.2, 6.9 Hz), 3.62 (1 H, ddd, *J* 9.2, 7.6, 5.1 Hz), 5.03 (1 H, dd, *J* 7.1, 6.9 Hz), 7.42–7.69 (6 $H_{arom}$, m) and 7.81–7.88 (2 $H_{arom}$, m); $\delta_C$(100 MHz; DMSO-$d_6$/TMS) 25.5, 35.9, 41.2, 52.4, 125.3, 125.9, 126.6, 127.5, 128.2, 129.1, 129.8, 130.7, 131.4, 132.8 and 178.5; (*m*/*z*) 427 ($M^+$).

**3j.** Colourless solid (Found: C, 53.75; H, 4.08; N, 3.82%. $C_{17}H_{16}ClNO_3S_2$ requires C, 53.47; H, 4.22; N, 3.67%); mp 136–138 °C (from EtOH); $\nu_{max}$(KBr)/cm$^{-1}$ 3018, 2925, 2556, 1706, 1604, 1585, and 1451; $\delta_H$(400 MHz; DMSO-$d_6$/TMS) 1.58 (1 H, d, *J* 7.8 Hz), 2.28 (3 H, s), 2.82 (1 H, ddd, *J* 11.5, 7.3, 5.0 Hz), 2.91 (1 H, ddd, *J* 11.5, 9.1, 6.8 Hz), 3.63 (1 H, ddd, *J* 9.1, 7.8, 5.0 Hz), 5.05 (1 H, dd, *J* 7.3, 6.8 Hz), 7.37–7.71 (6 $H_{arom}$, m) and 7.86–7.91 (2 $H_{arom}$, m); $\delta_C$(100 MHz; DMSO-$d_6$/TMS) 25.2, 36.8, 40.9, 50.8, 124.8, 125.7, 126.5, 127.3, 128.0, 128.7, 129.4, 130.7, 132.0, 133.2 and 178.2; (*m*/*z*) 381, 383 (M, M + 2).

**3k.** Colourless solid (Found: C, 63.66; H, 5.01; N, 3.41%. $C_{21}H_{19}NO_3S_2$ requires C, 63.45; H, 4.82; N, 3.52%); mp 133–135 °C (from EtOH); $\nu_{max}$(KBr)/cm$^{-1}$ 3027, 2929, 2548, 1707, 1605, 1578, and 1453; $\delta_H$(400 MHz; DMSO-$d_6$/TMS) 1.62 (1 H, d, *J* 7.6 Hz), 2.30 (3 H, s), 2.81 (1 H, ddd, *J* 11.2, 7.3, 4.7 Hz), 2.91 (1 H, ddd, *J* 11.2, 9.2, 6.9 Hz), 3.61 (1 H, ddd, *J* 9.2, 7.6, 4.7 Hz), 5.04 (1 H, dd, *J* 7.3, 6.9 Hz) and 7.29–7.69 (11 $H_{arom}$, m); $\delta_C$(100 MHz; DMSO-$d_6$/TMS) 25.3, 36.3, 40.8, 51.5, 124.7, 125.5, 126.1, 126.9, 127.6, 128.3, 129.0, 129.7, 130.8, 132.7 and 177.8; (*m*/*z*) 397 ($M^+$).

**3l.** Colourless solid (Found: C, 50.67; H, 5.21; N, 5.26%. $C_{12}H_{15}NO_3S_2$ requires C, 50.50; H, 5.30; N, 4.91%); mp 152–154 °C (from EtOH); $\nu_{max}$(KBr)/cm$^{-1}$ 3022, 2926, 2551, 1703, 1608, 1586, and 1459; $\delta_H$(400 MHz; DMSO-$d_6$/TMS) 1.61 (1 H, d, *J* 7.7 Hz), 1.90 (3 H, d, *J* 5.6 Hz), 2.31 (3 H, s), 2.86 (1 H, ddd, *J* 11.2, 7.2, 4.8 Hz), 2.94 (1 H, ddd, *J* 11.2, 9.2, 6.9 Hz), 3.62 (1 H, ddd, *J* 9.2, 7.7, 4.8 Hz), 5.04 (1 H, m), 7.37–7.51 and (4 $H_{arom}$, m); $\delta_C$(100 MHz; DMSO-$d_6$/TMS) 25.5, 26.7, 36.1, 41.7, 50.7, 126.5, 127.9, 129.8, 130.5 and 178.1; (*m*/*z*) 285 ($M^+$).

**Isolation of 4a (R = Ph), 4e (R = 4-Cl) and 4j (R = 3-Cl) and their cyclisation into γ-lactams 3a, 3e and 3j.** The procedure followed was the same as described above for the synthesis of **3**, except that the refluxing time in this case was only 75 min instead of the 3–4 h used for **3**. The adducts **4** were recrystallised from ethanol to give an analytical sample of **4a**, **4e** and **4j**. Finally, these intermediates were refluxed in water for 2–3 h to give the corresponding cyclized products **3a**, **3e** and **3j**, quantitatively.

**4a.** Colourless solid (Found: C, 64.49; H, 5.21; N, 3.31%. $C_{25}H_{25}NO_4S_2$ requires C, 64.21; H, 5.39; N, 3.00%); mp 96–98 °C (from EtOH); $\nu_{max}$(KBr)/cm$^{-1}$ 3289, 3018, 2928, 1761, 1602, 1585 and 1451; $\delta_H$(400 MHz; DMSO-$d_6$/TMS) 2.12 (3 H, s), 2.38 (3 H, s), 2.72–2.78 (2 H, m), 3.41 (1 H, dd, *J* 8.7, 4.9 Hz), 3.81 (1 H, m), 5.21 (1 H, br, s) and 7.21–7.81 (14 $H_{arom}$, m); $\delta_C$(100 MHz; DMSO-$d_6$/TMS) 24.8, 25.3, 38.5, 48.3, 52.5, 78.1, 123.8, 124.5, 125.3, 125.9, 126.8, 127.5, 128.3, 129.0, 129.6, 130.5, 131.9, 133.4 and 185.2; (*m*/*z*) 467 ($M^+$).

**4e.** Colourless solid (Found: C, 59.96; H, 5.21; N, 2.58%. $C_{25}H_{24}ClNO_4S_2$ requires C, 59.81; H, 4.82; N, 2.79%); mp 142–144 °C (from EtOH); $\nu_{max}$(KBr)/cm$^{-1}$ 3286, 3017, 2925, 1765, 1605, 1579 and 1448; $\delta_H$(400 MHz; DMSO-$d_6$/TMS) 2.15 (3 H, s), 2.32 (3 H, s), 2.71–2.81 (2 H, m), 3.39 (1 H, dd, *J* 8.7, 4.5 Hz), 3.83 (1 H, m), 5.18 (1 H, br, s), 7.18–7.69 (11 $H_{arom}$, m) and 7.78–7.83 (2 $H_{arom}$, m); $\delta_C$(100 MHz; DMSO-$d_6$/TMS) 25.2, 26.1, 38.3, 48.6, 52.3, 78.5, 124.8, 125.5, 126.1, 126.9, 127.7, 128.5, 129.2, 130.0, 130.7, 131.5, 132.8, 134.1 and 183.4; (*m*/*z*) 501, 503 (M, M + 2).

**4j.** Colourless solid (Found: C, 59.63; H, 4.91; N, 3.16%. $C_{25}H_{24}ClNO_4S_2$ requires C, 59.81; H, 4.82; N, 2.79%); mp 165–167 °C (from EtOH); $\nu_{max}$(KBr)/cm$^{-1}$ 3288, 3017, 2922, 1762, 1605, 1581 and 1455; $\delta_H$(400 MHz; DMSO-$d_6$/TMS) 2.14 (3 H, s), 2.39 (3 H, s), 2.70–2.76 (2 H, m), 3.37 (1 H, dd, *J* 8.5, 4.8 Hz), 3.78 (1 H, m), 5.27 (1 H, br, s), 7.17–7.65 (11 $H_{arom}$, m) and 7.73–7.81 (2 $H_{arom}$, m); $\delta_C$(100 MHz; DMSO-$d_6$/TMS) 24.9, 25.5, 38.5, 48.1, 52.5, 78.4, 123.9, 124.5, 125.2, 125.9, 126.5, 127.3, 128.1, 128.7, 129.3, 130.1, 130.7, 131.3, 131.9, 133.4 and 184.9; (*m*/*z*) 501, 503 (M, M + 2).

**2,2-Dimethyl-2-phenyl-1,3-oxathiolan-5-one.** A mixture of acetophenone (20 mmol), 2-mercaptopropionic acid (20 mmol) and a catalytic amount of lithium bromide (2 mmol) was stirred for 3 h at 80 °C and kept overnight at room temperature. Water (50 mL) was added to the reaction mixture and the product thus obtained was recrystallized from water to give an analytically

pure sample. The aqueous part containing LiBr was evaporated to dryness and thus LiBr was recovered without any loss. (Found: C, 63.21; H, 5.93%. $C_{11}H_{12}O_2S$ requires C, 63.43; H, 5.81%); $\nu_{max}$ (KBr)/cm$^{-1}$ 3011, 2963, 1777, 1601, 1515, 1441 and 1019; $\delta_H$(400 MHz; DMSO-$d_6$/TMS) 1.73 (3 H, d), 1.85 (3 H, s), 3.12 (1 H, m) and 7.23–7.27 (5 $H_{arom}$, m); $\delta_C$(100 MHz; DMSO-$d_6$/TMS) 19.1, 20.8, 39.5, 89.5, 126.8, 128.3, 129.2, 135.8 and 175.2; ($m/z$) 194 ($M^+$).

**2,4-Dimethyl-2-phenyl-4-(2-phenyl-2-(tosylamino)ethyl)-1,3-oxathiolan-5-one (5).** A mixture of 2,4-dimethyl-2-phenyl-1,3-oxathiolan-5-one (2 mmol) and tosyl aziridine **2a** (2 mmol) in 20 mL water was refluxed for 4 h (Table 2). After the completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature, filtered with a Buchner funnel and washed with water (3 × 10 mL). The crude product **5** thus obtained was recrystallized from EtOH to afford an analytically pure sample of **5**. The acetophenone was extracted from aqueous solution.

**5.** Colourless solid (Found: C, 64.55; H, 5.47; N, 3.02%. $C_{26}H_{27}NO_4S_2$ requires C, C, 64.84; H, 5.65; N, 2.91%); mp 117–119 °C (from EtOH); $\nu_{max}$(KBr)/cm$^{-1}$ 3286, 3021, 2933, 1758, 1599, 1581 and 1457; $\delta_H$(400 MHz; DMSO-$d_6$/TMS) 1.89 (3H, s), 2.16 (3 H, s), 2.29 (3 H, s), 2.68 (2 H, d), 3.88 (1 H, t), 5.19 (1 H, br, s) and 7.21–7.81 (14 $H_{arom}$, m); $\delta_C$(100 MHz; DMSO-$d_6$/TMS) 21.5, 24.7, 25.9, 38.1, 48.8, 52.1, 78.5, 124.2, 124.9, 125.7, 126.3, 126.9, 127.5, 128.2, 129.0, 129.8, 130.6, 132.1, 133.7 and 185.5; ($m/z$) 481 ($M^+$).



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