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Facile stereoselective synthesis of *cis*- and *trans*-3-alkoxyazetidin-2-ones

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Abstract—A highly stereoselective synthesis of *cis*- and *trans*-3-alkoxy-3-phenyl/benzylthioazetidin-2-ones is described. The reaction of α-chlorosulfide-β-lactams with various alcohols catalyzed by a Lewis acid such as $ZnCl_2$ in the presence of molecular sieves (3–4 Å) leads to *cis*-3-alkoxy-3-phenyl/benzylthio-β-lactams whereas treatment of potassium 2-alkoxy-2-phenylthioethanoate with appropriate Schiff's base using $POCl_3$ in the presence of triethylamine leads to the formation of *trans*-3-alkoxy-3-phenylthioazetidin-2-ones as major products.

1. Introduction

Apart from being the sub-structure of widely used antibiotics[1–3] such as penicillins, cephalosporins and monobactams, β-lactams have emerged as an important class of heterocycles. There is a considerable activity directed at the stereocontrolled synthesis of this heterocycle.[4] Besides this, the unique feature of these strained molecules is that these heterocycles are also important building blocks for the stereoselective synthesis of a variety of biologically important compounds.[5] For example, suitably substituted hydroxy β-lactams have been used in the semi-synthesis of paclitaxel (Taxol) and docetaxel (Taxotere).[6] The need for potent effective β-lactam antibiotics as well as new β-lactamase inhibitors has motivated synthetic organic and medicinal chemists to design new functionalized azetidin-2-ones. Some of the synthetic azetidin-2-ones are reported to be biologically active as inhibitors of cholesterol acyl transferase,[7] thrombin,[8] human cytomegalovirus protease,[9] human leukocyte elastase[10] and cysteine protease.[11]

Further interest in the development of synthetic methodology for 3-alkoxy-β-lactams was sparked by the discoveries of 2-isocephem,[12] 2-oxa-isocephem,[12] 7-methoxycephalosporins[13] and PS-5,[14] possessing an alkoxy group at the C-3 position of azetidin-2-ones. The potential use of *cis*-3-alkoxy-β-lactams in the preparation of the Taxol C-13 side chain has also been well documented.[15] More recently, a novel 3-methoxy-β-lactam **1** (Fig. 1) has been found to have apoptotic activity against human leukaemia, breast, prostate and head–neck cancer cells, thus exhibiting antitumour activity.[16] Besides this, 3-methoxy spiro-β-lactam **2** (Fig. 1) has also been found to be an inhibitor of both poliovirus and human rhinovirus 3C-proteinases.[17]

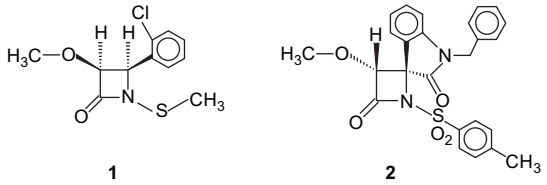

Figure 1. Biologically active 3-methoxyazetidin-2-ones.

The biological activity of the particular β-lactam ring is influenced by the type of substitution attached to the basic nucleus.[6–17] So, keeping in view the importance of relationship between biological activity and structural diversity as an essential component, we wish to report here a stereoselective synthesis of *cis*- and *trans*-3-alkoxyazetidin-2-ones. Synthesis of *cis*-3-alkoxy-3-phenyl/benzylthio-β-lactams has been achieved via transformation at C-3 of cationic β-lactam equivalents **3** using Lewis acid catalyzed reaction of various alcohols in the presence of silica gel and zinc chloride. However, both *trans*- and *cis*-3-alkoxy-3-phenylthio-β-lactams are obtained via direct annelation of potassium 2-alkoxy-2-phenylthioethanoate (**11**) with appropriate Schiff's base (**12**) using $POCl_3$ as the condensing reagent in the presence of triethylamine.

Keywords: Azetidin-2-ones; *cis*-3-Alkoxy-β-lactams; *trans*-3-Alkoxy-β-lactams; Lewis acid catalysis; Ethyl 2-alkoxy-2-phenylthioethanoate; Potassium 2-alkoxy-2-phenylthioethanoate.
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2. Results and discussion

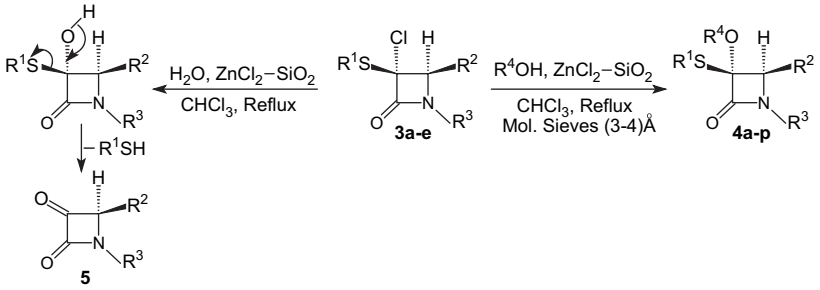
2.1. *cis*-3-Alkoxy-3-phenyl/benzylthio-β-lactams

In continuation of our efforts towards the synthesis of C-3 substituted β-lactams,[18–20] we became interested in studies towards the synthesis of C-3 alkoxy-β-lactams. Our earlier study, reporting[21] the preparation of α-methoxy-β-lactams was re-examined with a view to using it for the synthesis of other *cis*-3-alkoxy-β-lactams. We report here a modification of this procedure, which has now been successfully employed for the synthesis of various *cis*-3-alkoxy-β-lactams.

The starting substrates, *trans*-3-chloro-3-phenyl/benzylthioazetidin-2-ones (**3a–e**) were prepared from *trans*-3-phenyl/benzylthioazetidin-2-ones according to the procedure, reported in our earlier publication.[20] The reported reaction conditions,[21] when applied for the synthesis of other 3-alkoxy-β-lactams using various alcohols, invariably failed to produce the desired products. In some cases, the reaction did not even take place, whereas in others, it produced some amount of 3-keto-β-lactams (**5**)[22] only (Scheme 1). However, it was found that the addition of dry molecular sieves (3–4 Å) to the reaction mixture, containing anhydrous $ZnCl_2$, alcohol and SiO_2 in chloroform prior to the addition of substrate β-lactam (**3**) produced very satisfactory results and provided *cis*-3-alkoxy-3-phenyl/benzylthioazetidin-2-ones (**4**) in very high yields (Scheme 1, Table 1).

Initial studies were carried out by treating **3a** with absolute ethyl alcohol as the nucleophile in the presence of dry molecular sieves (3–4 Å), SiO_2 and a sub-stoichiometric amount of anhydrous $ZnCl_2$ in refluxing chloroform. This reaction resulted in the exclusive formation of *cis*-3-ethoxy-3-phenylthioazetidin-2-one (**4b**) in quantitative yield (Scheme 1). The reaction was carried out successfully with a number of substrates (**3a–e**) using various alcohols (R^4OH) and the results are summarized in Table 1. However, this reaction failed to give the anticipated products with benzyl alcohol and chiral alcohols such as (*R*)-(+)-*sec*-phenethyl alcohol. Lewis acids such as $TiCl_4$ and $SnCl_4$ were found to give unsatisfactory results. Only anhydrous $ZnCl_2$ brought about this transformation effectively.

The structures of these *cis*-3-alkoxy-β-lactams **4** were confirmed on the basis of their spectral data (IR, ^1H NMR and



Scheme 1. Synthesis of *cis*-3-alkoxy-3-phenyl/benzylthioazetidin-2-ones **4a–p**.

Table 1. *cis*-3-Alkoxy-3-phenyl/benzylthio-β-lactams **4a–p**

Entry	**3** (substrate)	R^4OH (nucleophile)	R^1	R^2	R^3	Product **4** (% yield)[a]
1	**3a**	CH_3OH	C_6H_5	C_6H_5	$C_6H_4OCH_3(p)$	**4a** (91)
2	**3a**		C_6H_5	C_6H_5	$C_6H_4OCH_3(p)$	**4b** (83)
3	**3a**		C_6H_5	C_6H_5	$C_6H_4OCH_3(p)$	**4c** (76)
4	**3a**		C_6H_5	C_6H_5	$C_6H_4OCH_3(p)$	**4d** (74)
5	**3a**		C_6H_5	C_6H_5	$C_6H_4OCH_3(p)$	**4e** (64)
6	**3a**		C_6H_5	C_6H_5	$C_6H_4OCH_3(p)$	**4f** (78)
7	**3b**	CH_3OH	C_6H_5	$C_6H_4OCH_3(p)$	$C_6H_4OCH_3(p)$	**4g** (81)
8	**3b**		C_6H_5	$C_6H_4OCH_3(p)$	$C_6H_4OCH_3(p)$	**4h** (80)
9	**3b**		C_6H_5	$C_6H_4OCH_3(p)$	$C_6H_4OCH_3(p)$	**4i** (70)
10	**3b**		C_6H_5	$C_6H_4OCH_3(p)$	$C_6H_4OCH_3(p)$	**4j** (66)
11	**3b**		C_6H_5	$C_6H_4OCH_3(p)$	$C_6H_4OCH_3(p)$	**4k** (61)
12	**3c**	CH_3OH	C_6H_5	C_6H_5	$CH_2C_6H_5$	**4l** (89)
13	**3d**	CH_3OH	$CH_2C_6H_5$	C_6H_5	$C_6H_4OCH_3(p)$	**4m** (90)
14	**3d**		$CH_2C_6H_5$	C_6H_5	$C_6H_4OCH_3(p)$	**4n** (81)
15	**3e**	CH_3OH	$CH_2C_6H_5$	$C_6H_4OCH_3(p)$	$C_6H_4OCH_3(p)$	**4o** (79)
16	**3e**		$CH_2C_6H_5$	$C_6H_4OCH_3(p)$	$C_6H_4OCH_3(p)$	**4p** (63)

[a] Yields quoted are for the isolated products.

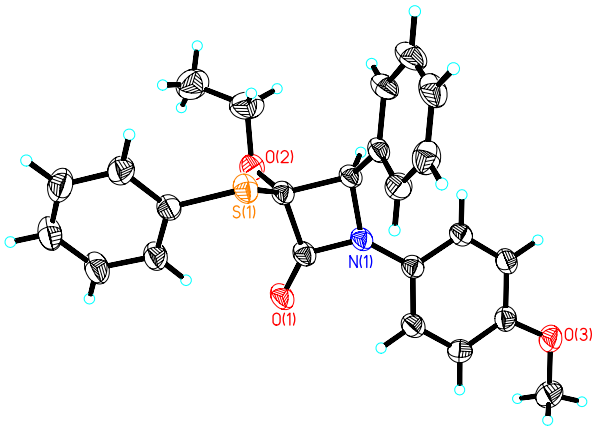


Figure 2. ORTEP diagram for compound **4b**.

^{13}C NMR). The stereochemistry at C-3 of *cis*-3-alkoxy-β-lactams was established through single crystal X-ray crystallographic studies of **4b**[23] (Fig. 2) and **4m**[24] (Fig. 3).

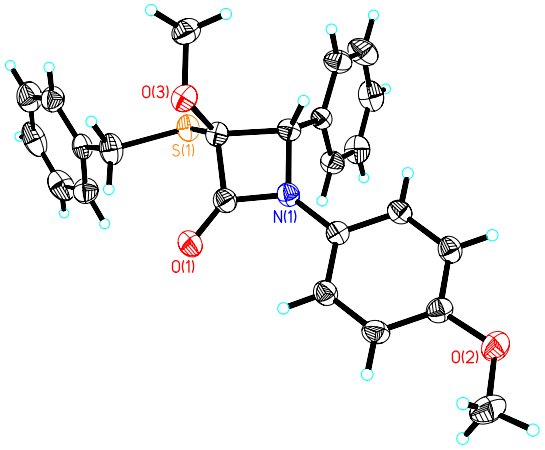
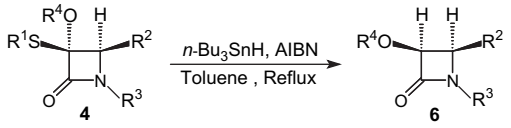


Figure 3. ORTEP diagram for compound **4m**.

In order to propose a plausible explanation for the transformation of *trans*-3-chloro-3-phenyl/benzylthioazetidin-2-ones (**3**) into *cis*-3-alkoxy-3-phenyl/benzylthioazetidin-2-ones (**4**), a schematic reaction pathway is shown in Scheme 2.

It is likely that the reaction first involves the co-ordination by chlorine at C-3 to $ZnCl_2$ and the latter being a Lewis acid, it results in the formation of intermediate carbocation at C-3, which is further resonance stabilized by lone pair of electrons on sulfur. Subsequent approach of the nucleophile (R^4OH) to this carbocation from the side of hydrogen atom at C-4, which is less hindered, results in the formation of *cis*-β-lactam **4**.

In an effort to demonstrate the synthetic potential of this reaction and versatility of the products, the *cis*-3-alkoxy-3-phenyl/benzylthioazetidin-2-ones were subjected to a desulfurization reaction. Initially, tri-*n*-butyltinhydride reduction of **4a**, catalyzed by AIBN in toluene at reflux temperature, led to stereoselective desulfurization to afford *cis*-3-methoxyazetidin-2-one (**6a**) (Scheme 3).



Scheme 3. *n*-Bu_3SnH desulfurization of *cis*-3-alkoxy-3-phenyl/benzylthio-β-lactams **4**.

The cis stereochemistry of the product **6a** was assigned on the basis of coupling constant (J=5.1 Hz, C3–H and C4–H) in the ^{1}H NMR spectrum.[20,25] The reaction was found to be general with several substrates and the results are summarized in Table 2. The exclusive formation of the cis product is due to the donation of hydrogen from the less hindered face of the intermediate radical.

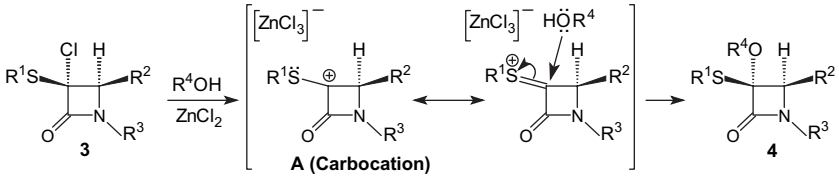
Table 2. *cis*-3-Alkoxyazetidin-2-ones **6**

Entry	**4** (substrate)	Product **6** (% yield)[a]
1	**4a**	**6a** (88)
2	**4b**	**6b** (83)
3	**4c**	**6c** (72)
4	**4g**	**6g** (71)
5	**4m**	**6a** (81)
6	**4o**	**6g** (74)

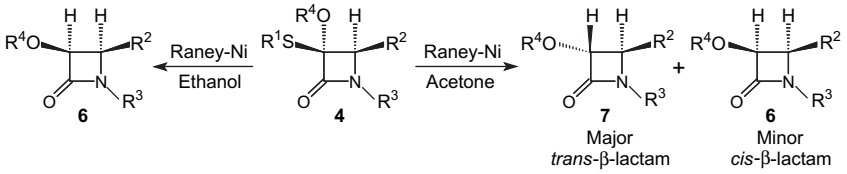
[a] Yields quoted are for the isolated products.

The stereospecific Raney-nickel desulfurization[26] of *cis*-3-alkoxy-3-phenyl/benzylthioazetidin-2-ones (**4**) was carried out in different solvents to ascertain its effect on the product stereochemistry. Initially, treatment of **4a** with Raney-nickel in refluxing ethanol resulted in the exclusive formation of *cis*-3-methoxyazetidin-2-one (**6a**). However, when desulfurization was performed in acetone, it produced a mixture of two compounds, which were separated by column chromatography and identified as *trans*-3-methoxyazetidin-2-one (**7a**) and *cis*-3-methoxyazetidin-2-one (**6a**), respectively, in the ratio of 3:1 on the basis of their spectroscopic data (Scheme 4, Table 3).

Thereafter, the reaction was carried out successfully with a number of substrates using different solvents and the results are summarized in Table 3. Variable ratio of *trans*-3-alkoxyazetidin-2-ones (**7**) and *cis*-3-alkoxyazetidin-2-ones (**6**) was observed when desulfurization was performed



Scheme 2. Plausible reaction pathway for the formation of *cis*-3-alkoxy-3-phenyl/benzylthioazetidin-2-ones (**4**).



Scheme 4. Raney-nickel desulfurization of *cis*-3-alkoxy-3-phenyl/benzylthio-β-lactams **4**.

Table 3. Raney-nickel desulfurization of azetidin-2-ones **4**

Entry	**4** (substrate)	Solvent	Products of type (% yield)[a]	
			7 (*trans*-β-lactam)	**6** (*cis*-β-lactam)
1	**4a**	Ethanol	—	**6a** (79)
2	**4b**	Ethanol	—	**6b** (74)
3	**4c**	Ethanol	—	**6c** (69)
4	**4d**	Ethanol	—	**6d** (70)
5	**4g**	Ethanol	—	**6g** (75)
6	**4m**	Ethanol	—	**6a** (68)
7	**4a**	Acetone	**7a** (63)	**6a** (20)
8	**4b**	Acetone	**7b** (55)	**6b** (28)
9	**4c**	Acetone	**7c** (49)	**6c** (30)
10	**4d**	Acetone	**7d** (65)	**6d** (22)
11	**4g**	Acetone	**7g** (46)	**6g** (27)
12	**4m**	Acetone	**7a** (52)	**6a** (16)
13	**4n**	Acetone	**7c** (53)	**6c** (21)
14	**4o**	Acetone	**7g** (43)	**6g** (24)

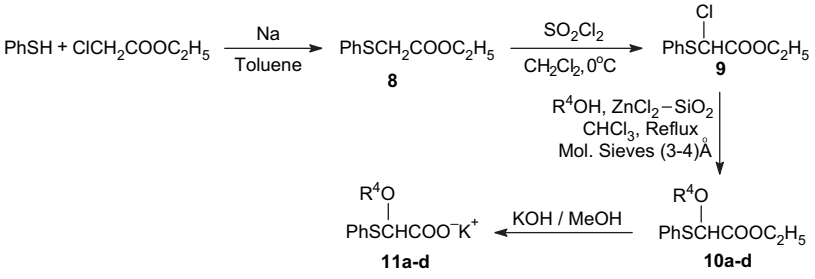
[a] Yields quoted are for the isolated products.

in acetone. The spatial juxtaposition of the C3–H and C4–H was assigned cis in product **6** and trans in product **7** on the basis of coupling constant values (J=4.8–5.1 Hz, C3–H and C4–H) and (J=1.8–2.1 Hz, C3–H and C4–H), respectively, in ^{1}H NMR spectrum.[20,25] The structures of these 3-alkoxy-β-lactams (**6** and **7**) were confirmed on the basis of their spectral data (IR, ^{1}H NMR and ^{13}C NMR).

2.2. *trans*-3-Alkoxy-3-phenylthio-β-lactams

Our interest in the stereodivergent construction of the β-lactam ring with alkoxy substituents at C-3 led us to examine the preparation of *trans*-3-alkoxy-3-phenylthio-β-lactams (**13**) also. A convenient procedure for the synthesis of the β-lactam ring skeleton is the [2+2] cyclocondensation of ketenes to imines, a process known as the Staudinger reaction.[28,29] In particular, this method has provided useful and economic entries to β-lactams, mainly due to ready availability of both Schiff's bases and ketenes. It was envisaged to study the synthesis of *trans*-3-alkoxy-β-lactams via direct annelation of alkoxy-substituted potassium phenylthioacetate (**11**) with appropriate Schiff's base (**12**) using phosphorus oxychloride ($POCl_3$) as the condensing reagent in the presence of triethylamine. The desired substrates **11**(**a**–**d**) were prepared from ethyl 2-chloro-2-phenylthioethanoate (**9**) (Scheme 5). To the best of our knowledge, no such alkoxy-substituted phenylthioacetates have been reported so far.

The reaction of ethyl chloroacetate with thiophenol in the presence of sodium in toluene at refluxing temperature gave a quantitative yield of thiophenoxy ethylacetate (**8**). This ester was further treated with 1 equiv of SO_2Cl_2 in methylene chloride at 0 °C, to yield ethyl 2-chloro-2-phenylthioethanoate (**9**). Treatment of ethyl 2-chloro-2-phenylthioethanoate



Scheme 5. Synthesis of potassium 2-alkoxy-2-phenylthioethanoate **11a**–**d**.

The variation in the stereochemistry of 3-alkoxy-β-lactams formed with Raney-nickel desulfurization in acetone or ethanol can be rationalized on the basis of the availability of surface hydrogen on the catalyst. Thus, the greater the hydrogen availability, the greater is the tendency for an inversion[27] to take place at C-3. Retention of configuration at C-3 in acetone solvent may be attributed to depletion in the supply of surface bound hydrogen due to the reducible character of the carbonyl function of acetone. In contrast, ethanol as a solvent enhances the supply of surface hydrogen due to its capability of initiating dehydrogenation in the presence of Raney-nickel under reflux conditions and thus favours the inversion of configuration at C-3.

(**9**) with various alcohols catalyzed by $ZnCl_2$–SiO_2, resulted in the formation of ethyl 2-alkoxy-2-phenylthioethanoate (**10a**–**d**) efficiently and the results are summarized in Table 4. Ethyl 2-alkoxy-2-phenylthioethanoate (**10a**–**d**) on hydrolysis

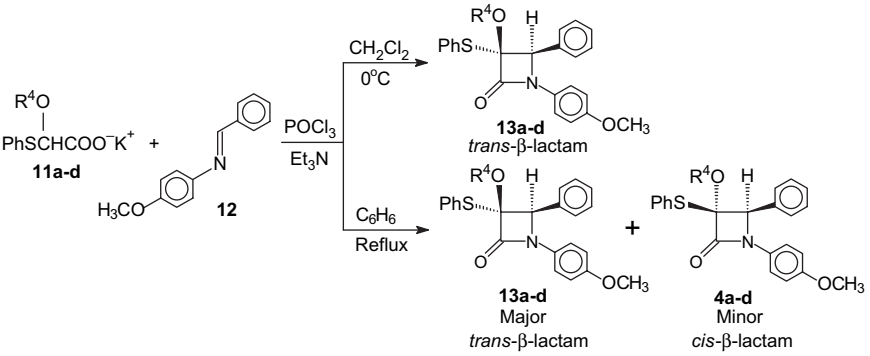
Table 4. Ethyl 2-alkoxy-2-phenylthioethanoate **10a**–**d**

Entry	R^4OH (nucleophile)	Product **10** (% yield)[a]
1	CH_3OH	**10a** (90)
2		**10b** (87)
3		**10c** (81)
4		**10d** (84)

[a] Yields quoted are for the isolated products.

using KOH in methanol afforded potassium 2-alkoxy-2-phenylthioethanoate (**11a–d**).

Initial studies were carried out by treating **11a** with appropriate Schiff's base (**12**) using methylene chloride at 0 °C. This reaction resulted in the exclusive formation of *trans*-3-methoxy-3-phenylthioazetidin-2-one (**13a**) in quantitative yield (Scheme 6). The reaction was carried out successfully with a number of substrates **11b–d** and the results are summarized in Table 5. Interestingly, all the substrates produced exclusively *trans*-3-alkoxy-3-phenylthio-β-lactams.



Scheme 6. Synthesis of *trans*- and *cis*-3-alkoxy-3-phenylthioazetidin-2-ones.

Table 5. Synthesis of *trans*-3-alkoxy-3-phenylthio-β-lactams (**13a–d**) using CH_2Cl_2 at 0 °C

Entry	**11** (substrate)	Product **13** (% yield)[a]
1	**11a**	**13a** (85)
2	**11b**	**13b** (80)
3	**11c**	**13c** (71)
4	**11d**	**13d** (74)

[a] Yields quoted are for the isolated products.

On the other hand, when this reaction was performed in refluxing benzene (Scheme 6), instead of leading to the exclusive formation of the expected *trans*-3-methoxy-3-phenylthioazetidin-2-one (**13a**), a mixture of *trans*- and *cis*-3-alkoxy-β-lactams was formed in a ratio of 3:1, respectively, and the β-lactams were separated by column chromatography. The reaction was found to be general for various substrates (**11b–d**) and the results are summarized in Table 6. The structures of these *trans*-3-alkoxy-β-lactams (**13a–d**) and *cis*-3-alkoxy-β-lactams (**4a–d**) were confirmed on the basis of their spectral data (IR, ^{1}H NMR and ^{13}C NMR).

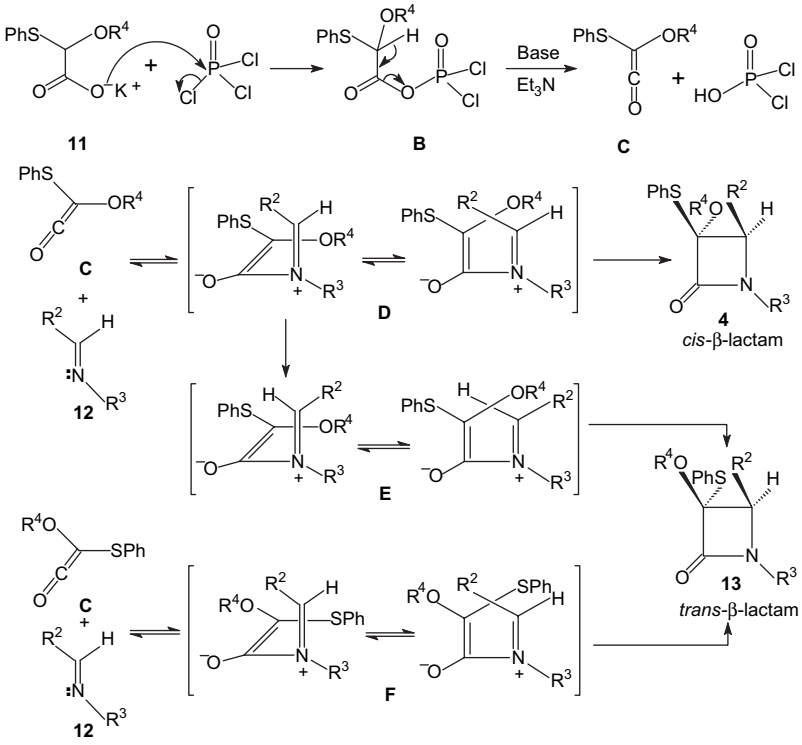
A variety of factors, such as structure and size of the substituents of the acid and imine components, sequence of addition of reactants, nature of solvent and temperature play an important role in the stereochemical outcome of the Staudinger reaction.[30,31] The formation of *trans*- and *cis*-3-alkoxy-β-lactams in this case can be rationalized on the basis of the mechanism, which is presented in Scheme 7.

Here, first an active ester **B** is formed by the reaction of potassium 2-alkoxy-2-phenylthioethanoate (**11**) and $POCl_3$, which furnishes the ketene **C** by undergoing elimination under the influence of a base. It has been postulated that LUMO of the ketene carbonyl group, which is coplanar to the substituents of the ketene, is attacked by imine in an orthogonal approach.[30] *E* imines gave preferentially *cis*-β-lactams and *Z* imines gave predominantly the corresponding *trans*-β-lactams.[31] The literature studies reveal that most of the starting acyclic imines employed in the Staudinger reaction exist in *E* configuration exclusively.[31,32] Considering this, the formation of *trans*-β-lactams can be proposed initially by the *exo* attack of the *E* imine to the ketene **C**, generating the zwitterionic intermediate **D**. Further, the isomerization of the *E* imine to less favoured *Z* imine gives the zwitterionic intermediate **E**, which, on conrotatory electrocyclization generates the thermodynamically more stable *trans*-3-alkoxy-β-lactams (**13**). The literature findings conclude that the reaction of ketene with cyclic imines also gives *trans*-β-lactams exclusively.[31] Since the cyclic imines cannot undergo the isomerization in the reaction,[30,31,33] the possibility of formation of *trans*-β-lactams through isomerization of the *E* imine moiety to less favoured *Z* imine or reaction with inversion of imine configuration is not feasible. So, in this case, it is believed that the attack of the *E* imine on the face of the ketene **C** brings the PhS group closure to imine, thus generating the zwitterionic intermediate **F**, which on direct ring closure or conrotatory electrocyclization produces exclusively the *trans*-3-alkoxy-β-lactams (**13**).[34] It has been proposed that the competition between the direct ring closure and the isomerization controls the relative stereoselectivity of β-lactam formation, which can be further explained in terms of rate constant. It has been reported[31] that the lower rate constant for direct ring closure process is the real reason for the exclusive formation of the *trans*-β-lactams. The rate constant of the direct ring closure process has been found to be quite small when the R^1 in ketene **C** is PhS.[31] This can also be rationalized through the experimental classification as proposed by Georg and Ravikumar.[30] 'Moore ketenes' possessing very weak electron-donating substituents R^1 (such as *S*-alkyl, *S*-aryl, alkyl and

Table 6. Synthesis of *trans*- and *cis*-3-alkoxy-3-phenylthio-β-lactams using C_6H_6 at reflux temperature

Entry	**11** (substrate)	Products of type (% yield)[a]	
		13 (*trans*-β-lactam)	**4** (*cis*-β-lactam)
1	**11a**	**13a** (69)	**4a** (21)
2	**11b**	**13b** (60)	**4b** (18)
3	**11c**	**13c** (54)	**4c** (15)
4	**11d**	**13d** (57)	**4d** (17)

[a] Yields quoted are for the isolated products.



Scheme 7. A plausible mechanism for the formation of *trans*- and *cis*-3-alkoxy-3-phenylthioazetidin-2-ones.

aryl) have a strong preference for *trans*-β-lactam formation due to small rate constant of the direct ring closure (k_1, $_{rel}<1$). However, the formation of almost 30% *cis*-3-alkoxy-β-lactams (**4**) at high temperature in refluxing benzene indicates the involvement of high energy zwitterionic intermediate **D** as shown, which undergoes further conrotatory electrocyclization to form *cis*-β-lactam.

The *trans*-3-alkoxy-3-phenylthioazetidin-2-ones (**13a–d**) were also subjected to stereospecific Raney-nickel desulfurization[25] in different solvents. When **13a** was treated with Raney-nickel in refluxing acetone, *cis*-3-methoxyazetidin-2-one **6a** was formed exclusively, whereas, it undergoes reductive desulfurization with inversion of configuration in ethanol, leading to the exclusive formation of *trans*-3-methoxyazetidin-2-one **7a** (Scheme 8). The reaction was found to be general with several substrates (**13b–d**) and the results are summarized in Table 7.

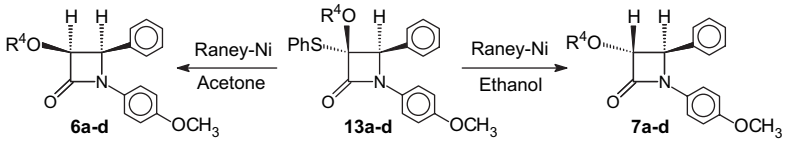
The assignment of stereochemistry to *trans*- and *cis*-3-alkoxy-β-lactams is also based on ^{1}H NMR spectroscopy. The alkoxy signal in the ^{1}H NMR spectrum of *trans*-3-alkoxy-β-lactams is shifted to higher field by about 0.35–0.50 ppm as compared to *cis*-3-alkoxy-β-lactams.[21] This upfield shift is due to the shielding effect of the *cis*-4-phenyl group on the 3-alkoxy protons. Support for this

Table 7. Reductive desulfurization of *trans*-3-alkoxy-3-phenylthio-β-lactams **13**

Entry	**13** (substrate)	Solvent	Products of type (% yield)[a]	
			6 (*cis*-β-lactam)	**7** (*trans*-β-lactam)
1	**13a**	Acetone	**6a** (85)	—
2	**13b**	Acetone	**6b** (82)	—
3	**13c**	Acetone	**6c** (78)	—
4	**13d**	Acetone	**6d** (81)	—
5	**13a**	Ethanol	—	**7a** (75)
6	**13b**	Ethanol	—	**7b** (72)
7	**13c**	Ethanol	—	**7c** (63)
8	**13d**	Ethanol	—	**7d** (68)

[a] Yields quoted are for the isolated products.

configurational assignment is provided by taking into consideration the comparison of spectroscopic data of **13a** and **4a**. The stereochemistry of **4a** was confirmed by single crystal X-ray crystallographic studies of **4b**[23] (Fig. 2) and **4m**[24] (Fig. 3) and further, the comparison of spectroscopic data of **13a** with **4a**, confirmed the stereochemistry of **13a** as well. The methoxy group in *trans*-β-lactam **13a**, in which, it is cis to phenyl group, resonates at higher field (3.41 ppm) than the methoxy group in *cis*-β-lactam **4a**, in which, it is trans to phenyl group, resonating at 3.77 ppm (Fig. 4).



Scheme 8. Raney-nickel desulfurization of *trans*-3-alkoxy-3-phenylthio-β-lactams **13a–d**.

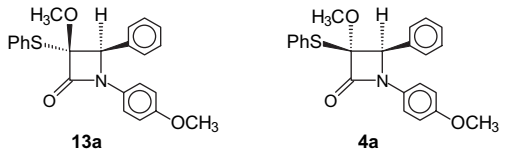


Figure 4. *trans*- and *cis*-3-Methoxy-azetidin-2-ones (**13a** and **4a**).

3. Conclusion

In conclusion, it is thus possible to achieve the stereoselective synthesis of *cis*-3-alkoxy-3-phenyl/benzylthioazetidin-2-ones by reacting *trans*-3-chloro-3-phenyl/benzylthioazetidin-2-ones (**3a–e**) with various alcohols in silica gel mediated by Lewis acid such as $ZnCl_2$ using molecular sieves (3–4 Å) in refluxing chloroform. The X-ray crystallographic analysis of compounds **4b** and **4m** allowed establishment of the stereochemistry at C-3 of *cis*-3-alkoxy-β-lactams **4**. Additionally, we have also shown that direct annelation of potassium 2-alkoxy-2-phenylthioethanoate (**11a–d**) and appropriate Schiff's base (**12**) using phosphorous oxychloride ($POCl_3$) as condensing reagent in the presence of triethylamine as the base provides an easy access to *trans*-3-alkoxy-3-phenylthioazetidin-2-ones. Further elaboration of these products to potentially useful building blocks is underway in our laboratory.

4. Experimental

4.1. General

General experimental has been described previously.[20] Crystallographic data (excluding structure factors) of compounds **4b**[23] and **4m**[24] in CIF format have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internet.) +44 1223/336 033; e-mail: deposit@ccdc.cam.ac.uk]. All other relevant information regarding the data and supplementary publication CCDC number is presented in respective references.

Compounds **3a–e**[20] were prepared by the procedures described in the cited reference. The spectroscopic data of compounds **3a–e**[20] were also reported in the cited reference.

4.2. General procedure for the synthesis of *cis*-3-alkoxy-3-phenyl/benzylthio-β-lactams (4a–p)

A mixture containing silica gel (1.00 g, 100–200 mesh), alcohol (4.68 mmol), anhydrous chloroform (10 mL), molecular sieves (3–4 Å) and anhydrous zinc chloride (0.03 mmol) was stirred for 25–30 min, followed by the addition of a solution of *trans*-3-chloro-3-phenylthio-β-lactam (**3**) (0.13 mmol) in 1 mL of $CHCl_3$. The reaction mixture was refluxed for 2 h with constant stirring. The progress of the reaction was monitored by TLC. Disappearance of the starting β-lactam was considered as the completion of the reaction. The reactants were filtered, washed with water (2×5 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and filtered. The residue after solvent evaporation in vacuo, was purified by silica gel column chromatography (10% EtoAc/hexane).

4.2.1. *cis*-1-(4′-Methoxyphenyl)-3-methoxy-3-phenylthio-4-phenylazetidin-2-one (4a). Colourless crystalline solid (0.045 g, 91%); mp 141–142 °C [Found: C, 70.49; H, 5.36; N, 3.52. $C_{23}H_{21}NO_3S$ requires C, 70.57; H, 5.40; N, 3.58%]; IR (cm^{-1}, KBr): 1755 (C=O); δ_H (300 MHz, $CDCl_3$) 7.33–6.76 (14H, m, Ph), 5.10 (1H, s, C4-*H*), 3.77 (6H, s, 2×OCH_3); δ_C (75 MHz, $CDCl_3$) 160.8, 156.4, 133.7, 132.2, 130.6, 130.5, 128.6, 128.3, 128.2, 128.1, 127.2, 118.9, 114.3, 99.9, 68.5, 55.1, 53.4.

4.2.2. *cis*-1-(4′-Methoxyphenyl)-3-ethoxy-3-phenylthio-4-phenylazetidin-2-one (4b). Colourless crystalline solid (0.042 g, 83%); mp 113–114 °C [Found: C, 71.05; H, 5.67; N, 3.34. $C_{24}H_{23}NO_3S$ requires C, 71.09; H, 5.71; N, 3.45%]; IR (cm^{-1}, KBr): 1757 (C=O); δ_H (300 MHz, $CDCl_3$) 7.65–6.75 (14H, m, Ph), 5.15 (1H, s, C4-*H*), 4.16 (1H, m, OCH_aH$_b$), 4.05 (1H, m, OCH$_a$$H_b$), 3.71 (3H, s, OC$H_3$), 1.35 (3H, t, C$H_3$); δ_C (75 MHz, $CDCl_3$) 162.0, 156.4, 132.9, 130.3, 128.6, 128.4, 128.2, 128.1, 127.5, 119.1, 114.3, 96.7, 68.4, 61.7, 55.4, 14.9.

4.2.3. *cis*-1-(4′-Methoxyphenyl)-3-isopropyloxy-3-phenylthio-4-phenylazetidin-2-one (4c). Colourless crystalline solid (0.040 g, 76%); mp 112–113 °C [Found: C, 77.54; H, 6.03; N, 3.24. $C_{25}H_{25}NO_3S$ requires C, 77.57; H, 6.00; N, 3.33%]; IR (cm^{-1}, KBr): 1750 (C=O); δ_H (300 MHz, $CDCl_3$) 7.23–6.61 (14H, m, Ph), 5.00 (1H, s, C4-*H*), 4.52 (1H, m, OC*H*), 3.62 (3H, s, OCH_3), 1.23 (3H, d, *J* 6.0 Hz, CH_3), 1.13 (3H, d, *J* 6.0 Hz, CH_3); δ_C (75 MHz, $CDCl_3$) 161.7, 156.4, 133.2, 132.1, 131.4, 130.5, 128.6, 128.4, 128.2, 127.9, 126.5, 119.0, 114.3, 98.9, 70.0, 69.8, 55.1, 23.8, 23.7.

4.2.4. *cis*-1-(4′-Methoxyphenyl)-3-propyloxy-3-phenylthio-4-phenylazetidin-2-one (4d). White crystalline solid (0.039 g, 74%); mp 114–116 °C [Found: C, 77.52; H, 5.91; N, 3.24. $C_{25}H_{25}NO_3S$ requires C, 77.57; H, 6.00; N, 3.33%]; IR (cm^{-1}, KBr): 1756 (C=O); δ_H (300 MHz, $CDCl_3$) 7.25–6.69 (14H, m, Ph), 5.05 (1H, s, C4-*H*), 4.01 (1H, m, OCH_aH$_b$), 3.89 (1H, m, OCH$_a$$H_b$), 3.71 (3H, s, OC$H_3$), 1.67 (2H, m, C$H_2CH_3$), 0.91 (3H, t, C$H_3$); δ_C (75 MHz, $CDCl_3$) 161.2, 156.4, 133.2, 132.5, 130.9, 130.6, 128.6, 128.2, 128.1, 127.8, 118.9, 114.3, 99.0, 68.5, 67.7, 55.1, 22.9, 10.9.

4.2.5. *cis*-1-(4′-Methoxyphenyl)-3-butyloxy-3-phenylthio-4-phenylazetidin-2-one (4e). Yellow solid (0.035 g, 64%); mp 72–74 °C [Found: C, 71.95; H, 6.24; N, 3.17. $C_{26}H_{27}NO_3S$ requires C, 72.03; H, 6.27; N, 3.23%]; IR (cm^{-1}, $CHCl_3$): 1757 (C=O); δ_H (300 MHz, $CDCl_3$) 7.25–6.69 (14H, m, Ph), 5.04 (1H, s, C4-*H*), 4.04 (1H, m, OCH_aH$_b$), 3.92 (1H, m, OCH$_a$$H_b$), 3.70 (3H, s, OC$H_3$), 1.61 (2H, m, OCH$_2CH_2$), 1.39 (2H, m, CH$_2CH_2CH_3$), 0.91 (3H, t, C$H_3$); δ_C (75 MHz, $CDCl_3$) 161.2, 156.4, 133.2, 132.4, 130.9, 130.6, 128.6, 128.3, 128.2, 128.1, 127.0, 118.9, 114.3, 99.0, 68.5, 65.9, 55.1, 31.7, 19.4, 14.1.

4.2.6. *cis*-1-(4′-Methoxyphenyl)-3-(prop-2-ynyloxy)-3-phenylthio-4-phenylazetidin-2-one (4f). Yellow oil (0.041 g, 78%) [Found: C, 72.24; H, 5.02; N, 3.31.

$C_{25}H_{21}NO_3S$ requires C, 72.27; H, 5.09; N, 3.37%]; IR (cm^{-1}, $CHCl_3$): 1758 (C=O); δ_H (300 MHz, $CDCl_3$) 7.25–6.69 (14H, m, Ph), 5.27 (1H, s, C4-*H*), 4.87 (1H, dd, *J* 2.4, 2.4 Hz, OCH_aH$_b$), 4.57 (1H, dd, *J* 2.4, 2.4 Hz, OCH$_a$$H_b$), 3.71 (3H, s, OC$H_3$), 2.47 (1H, t, *H*C≡); δ_C (75 MHz, $CDCl_3$) 160.3, 156.5, 133.0, 132.9, 132.9, 130.4, 129.8, 128.7, 128.4, 128.3, 128.2, 127.5, 119.1, 119.0, 114.4, 99.2, 79.4, 75.4, 68.4, 55.1, 53.9; δ_C (DEPT-135) (75 MHz, $CDCl_3$) 133.0 (+), 132.9 (+), 132.9 (+), 128.7 (+), 128.4 (+), 128.3 (+), 128.2 (+), 127.5 (+), 119.1 (+), 119.0 (+), 114.4 (+), 79.4 (+), 75.4 (+), 68.4 (+), 55.1 (+), 53.9 (−).

4.2.7. *cis*-1-(4′-Methoxyphenyl)-3-methoxy-3-phenylthio-4-(4′-methoxyphenyl)azetidin-2-one (4g). Yellowish-brown oil (0.040 g, 81%) [Found: C, 68.36; H, 5.40; N, 3.28. $C_{24}H_{23}NO_4S$ requires C, 68.39; H, 5.49; N, 3.32%]; IR (cm^{-1}, $CHCl_3$): 1745 (C=O); δ_H (300 MHz, $CDCl_3$) 7.49–6.60 (13H, m, Ph), 4.98 (1H, s, C4-*H*), 3.76 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 3.70 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 161.2, 159.8, 156.2, 132.5, 130.9, 130.5, 129.2, 128.1, 127.0, 124.7, 118.9, 114.5, 113.7, 98.8, 68.1, 55.0, 54.7, 52.8.

4.2.8. *cis*-1-(4′-Methoxyphenyl)-3-ethoxy-3-phenylthio-4-(4′-methoxyphenyl)azetidin-2-one (4h). Colourless crystalline solid (0.040 g, 80%); mp 114–115 °C [Found: C, 68.91; H, 5.71; N, 3.19. $C_{25}H_{25}NO_4S$ requires C, 68.95; H, 5.78; N, 3.22%]; IR (cm^{-1}, KBr): 1756 (C=O); δ_H (300 MHz, $CDCl_3$) 7.31–6.65 (13H, m, Ph), 4.99 (1H, s, C4-*H*), 4.09 (1H, m, OCH_aH$_b$), 3.99 (1H, m, OCH$_a$$H_b$), 3.73 (3H, s, OC$H_3$), 3.66 (3H, s, OC$H_3$), 1.23 (3H, t, C$H_3$); δ_C (75 MHz, $CDCl_3$) 161.3, 159.9, 156.2, 132.5, 130.9, 130.5, 129.3, 128.2, 127.0, 124.8, 118.9, 114.2, 113.5, 99.3, 68.1, 61.5, 55.0, 54.9, 15.1.

4.2.9. *cis*-1-(4′-Methoxyphenyl)-3-isopropyloxy-3-phenylthio-4-(4′-methoxyphenyl)azetidin-2-one (4i). Colourless crystalline solid (0.037 g, 70%); mp 87–88 °C [Found: C, 69.50; H, 6.01; N, 3.07. $C_{26}H_{27}NO_4S$ requires C, 69.47; H, 6.05; N, 3.12%]; IR (cm^{-1}, $CHCl_3$): 1755 (C=O); δ_H (300 MHz, $CDCl_3$) 7.29–6.59 (13H, m, Ph), 4.99 (1H, s, C4-*H*), 4.57 (1H, m, OC*H*), 3.73 (3H, s, OCH_3), 3.70 (3H, s, OCH_3), 1.29 (3H, d, *J* 6.0 Hz, CH_3), 1.19 (3H, d, *J* 6.0 Hz, CH_3); δ_C (75 MHz, $CDCl_3$) 161.6, 159.9, 156.3, 132.3, 131.3, 130.6, 129.5, 128.1, 126.5, 124.9, 119.1, 114.3, 113.5, 99.1, 69.9, 69.4, 55.1, 54.9, 23.8, 23.6.

4.2.10. *cis*-1-(4′-Methoxyphenyl)-3-propyloxy-3-phenylthio-4-(4′-methoxyphenyl)azetidin-2-one (4j). White solid (0.035 g, 66%); mp 75–76 °C [Found: C, 69.39; H, 6.00; N, 3.05. $C_{26}H_{27}NO_4S$ requires C, 69.47; H, 6.05; N, 3.12%]; IR (cm^{-1}, $CHCl_3$): 1756 (C=O); δ_H (300 MHz, $CDCl_3$) 7.27–6.66 (13H, m, Ph), 4.99 (1H, s, C4-*H*), 3.95 (1H, m, OCH_aH$_b$), 3.86 (1H, m, OCH$_a$$H_b$), 3.74 (3H, s, OC$H_3$), 3.70 (3H, s, OC$H_3$), 1.65 (2H, m, C$H_2CH_3$), 0.92 (3H, t, C$H_3$); δ_C (75 MHz, $CDCl_3$) 161.4, 160.0, 156.3, 132.4, 131.1, 130.6, 129.3, 128.2, 127.0, 124.9, 119.0, 114.3, 113.6, 99.3, 68.1, 67.6, 55.1, 55.0, 22.9, 10.8.

4.2.11. *cis*-1-(4′-Methoxyphenyl)-3-butyloxy-3-phenylthio-4-(4′-methoxyphenyl)azetidin-2-one (4k). Yellowish-brown oil (0.033 g, 61%) [Found: C, 69.91; H, 6.22; N, 2.93. $C_{27}H_{29}NO_4S$ requires C, 69.96; H, 6.30; N, 3.02%]; IR (cm^{-1}, $CHCl_3$): 1756 (C=O); δ_H (300 MHz, $CDCl_3$) 7.21–6.60 (13H, m, Ph), 4.92 (1H, s, C4-*H*), 3.94 (1H, m, OCH_aH$_b$), 3.83 (1H, m, OCH$_a$$H_b$), 3.69 (3H, s, OC$H_3$), 3.63 (3H, s, OC$H_3$), 1.55 (2H, m, OCH$_2CH_2$), 1.31 (2H, m, CH$_2CH_2CH_3$), 0.84 (3H, t, C$H_3$); δ_C (75 MHz, $CDCl_3$) 161.4, 160.0, 156.3, 132.4, 131.1, 130.6, 129.3, 128.2, 127.0, 125.0, 119.0, 114.3, 113.6, 99.3, 68.2, 65.8, 55.1, 55.0, 31.7, 19.4, 14.1.

4.2.12. *cis*-1-Benzyl-3-methoxy-3-phenylthio-4-phenylazetidin-2-one (4l). Colourless crystalline solid (0.044 g, 89%); mp 101–102 °C [Found: C, 73.55; H, 5.64; N, 3.70. $C_{23}H_{21}NO_2S$ requires C, 73.57; H, 5.63; N, 3.73%]; IR (cm^{-1}, KBr): 1752 (C=O); δ_H (300 MHz, $CDCl_3$) 7.22–6.94 (15H, m, Ph), 4.87 (1H, d, *J* 15.0 Hz, CH_aH$_b$Ph), 4.40 (1H, s, C4-*H*), 3.83 (1H, d, *J* 14.7 Hz, CH$_a$$H_b$Ph), 3.54 (3H, s, OC$H_3$); δ_C (75 MHz, $CDCl_3$) 164.5, 135.0, 133.3, 132.4, 130.6, 128.9, 128.6, 128.5, 128.2, 128.1, 127.9, 127.1, 100.6, 67.7, 53.4, 44.1.

4.2.13. *cis*-1-(4′-Methoxyphenyl)-3-methoxy-3-benzylthio-4-phenylazetidin-2-one (4m). Colourless crystalline solid (0.044 g, 90%); mp 128–129 °C [Found: C, 71.05; H, 5.62; N, 3.41. $C_{24}H_{23}NO_3S$ requires C, 71.09; H, 5.71; N, 3.45%]; IR (cm^{-1}, KBr): 1762 (C=O); δ_H (300 MHz, $CDCl_3$) 7.39–6.74 (14H, m, Ph), 5.13 (1H, s, C4-*H*), 4.02 (1H, d, *J* 12.0 Hz, CH_aH$_b$S), 3.77 (1H, d, *J* 12.0 Hz, CH$_a$$H_b$S), 3.75 (3H, s, OC$H_3$), 3.56 (3H, s, OC$H_3$); δ_C (75 MHz, $CDCl_3$) 161.1, 156.4, 137.6, 133.2, 130.6, 129.2, 128.8, 128.5, 128.3, 128.0, 126.9, 118.9, 114.4, 97.8, 67.9, 55.1, 52.5, 32.2.

4.2.14. *cis*-1-(4′-Methoxyphenyl)-3-isopropyloxy-3-benzylthio-4-phenylazetidin-2-one (4n). Colourless crystalline solid (0.043 g, 81%); mp 115–116 °C [Found: C, 72.10; H, 6.24; N, 3.20. $C_{26}H_{27}NO_3S$ requires C, 72.13; H, 6.27; N, 3.22%]; IR (cm^{-1}, KBr): 1760 (C=O); δ_H (300 MHz, $CDCl_3$) 7.35–6.70 (13H, m, Ph), 5.04 (1H, s, C4-*H*), 4.46 (1H, m, OC*H*), 3.96 (1H, d, *J* 12.0 Hz, CH_aH$_b$S), 3.71 (3H, s, OCH_3), 3.51 (1H, d, *J* 12.0 Hz, CH$_a$$H_b$S), 1.36 (3H, d, *J* 6.0 Hz, CH_3), 1.31 (3H, d, *J* 6.0 Hz, CH_3); δ_C (75 MHz, $CDCl_3$) 162.1, 156.3, 137.0, 133.4, 130.6, 129.2, 128.9, 128.5, 128.4, 128.3, 127.0, 118.9, 114.3, 97.6, 69.4, 69.1, 55.1, 32.5, 24.0, 23.8.

4.2.15. *cis*-1-(4′-Methoxyphenyl)-3-methoxy-3-benzylthio-4-(4′-methoxyphenyl)azetidin-2-one (4o). Colourless crystalline solid (0.039 g, 79%); mp 101–102 °C [Found: C, 68.90; H, 5.77; N, 3.19. $C_{25}H_{25}NO_4S$ requires C, 68.95; H, 5.78; N, 3.22%]; IR (cm^{-1}, KBr): 1762 (C=O); δ_H (300 MHz, $CDCl_3$) 7.12–6.62 (13H, m, Ph), 4.92 (1H, s, C4-*H*), 3.86 (1H, d, *J* 12.3 Hz, CH_aH$_b$S), 3.68 (3H, s, OCH_3), 3.64 (3H, s, OCH_3), 3.63 (1H, d, *J* 12.6 Hz, CH$_a$$H_b$S), 3.42 (3H, s, OC$H_3$); δ_C (75 MHz, $CDCl_3$) 162.0, 160.0, 156.3, 137.6, 130.5, 129.2, 128.3, 126.9, 124.7, 118.9, 114.3, 113.8, 98.6, 67.3, 55.1, 54.9, 52.4, 32.2.

4.2.16. *cis*-1-(4′-Methoxyphenyl)-3-isopropyloxy-3-benzylthio-4-(4′-methoxyphenyl)azetidin-2-one (4p). Yellow oil (0.033 g, 63%) [Found: C, 69.92; H, 6.27; N, 2.99. $C_{27}H_{29}NO_4S$ requires C, 69.96; H, 6.30; N, 3.02%]; IR

(cm^{-1}, $CHCl_3$): 1764 (C=O); δ_H (300 MHz, $CDCl_3$) 7.25–6.70 (13H, m, Ph), 4.90 (1H, s, C4-*H*), 4.43 (1H, m, OC*H*), 4.00 (1H, d, *J* 12.0 Hz, CH_aH$_b$S), 3.77 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 3.57 (1H, d, *J* 12.0 Hz, CH$_a$$H_b$S), 1.35 (3H, d, *J* 6.0 Hz, CH_3), 1.25 (3H, d, *J* 6.0 Hz, CH_3); δ_C (75 MHz, $CDCl_3$) 160.1, 156.3, 137.9, 130.8, 129.6, 129.3, 129.2, 128.4, 128.3, 126.9, 125.0, 119.0, 118.9, 114.3, 113.9, 113.8, 98.0, 67.7, 60.9, 55.1, 55.0, 32.4, 24.0, 23.8.

4.3. General procedure for *n*-Bu_3SnH reduction

n-Bu_3SnH (0.14 mmol) was added dropwise via a syringe in the mixture of **4** (0.13 mmol) and catalytic amount of AIBN in toluene (4 mL). The reaction mixture was refluxed for 1 h. The progress of the reaction was checked by TLC. After the completion of reaction, the solvent was evaporated in vacuo. The residue was redissolved in methylene chloride (20 mL), washed with water (2×5 mL) and dried over anhydrous Na_2SO_4. The residue after solvent evaporation in vacuo, was purified by silica gel column chromatography (8% EtOAc/hexane).

4.3.1. *cis*-1-(4′-Methoxyphenyl)-3-methoxy-4-phenylazetidin-2-one (6a). Colourless crystalline solid (0.027 g, 88%); mp 165–166 °C [Found: C, 85.62; H, 7.14; N, 5.84. $C_{17}H_{17}NO_3$ requires C, 85.68; H, 7.18; N, 5.87%]; IR (cm^{-1}, KBr): 1747 (C=O); δ_H (300 MHz, $CDCl_3$) 7.35–6.68 (9H, m, Ph), 5.09 (1H, d, *J* 5.1 Hz, C3-*H*), 4.73 (1H, d, *J* 5.1 Hz, C4-*H*), 3.73 (3H, s, OCH_3), 3.22 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 163.5, 156.3, 133.5, 130.7, 128.6, 128.5, 128.0, 118.7, 114.3, 84.8, 61.8, 58.3, 55.3.

4.3.2. *cis*-1-(4′-Methoxyphenyl)-3-ethoxy-4-phenylazetidin-2-one (6b). White solid (0.030 g, 83%); mp 127–128 °C [Found: C, 72.60; H, 6.37; N, 4.65. $C_{18}H_{19}NO_3$ requires C, 72.71; H, 6.43; N, 4.71%]; IR (cm^{-1}, KBr): 1757 (C=O); δ_H (300 MHz, $CDCl_3$) 7.29–6.63 (9H, m, Ph), 5.04 (1H, d, *J* 4.8 Hz, C3-*H*), 4.79 (1H, d, *J* 4.8 Hz, C4-*H*), 3.63 (3H, s, OCH_3), 3.39 (1H, m, OCH_aH$_b$), 3.10 (1H, m, OCH$_a$$H_b$), 0.82 (3H, t, C$H_3$); δ_C (75 MHz, $CDCl_3$) 163.5, 156.2, 133.6, 130.7, 128.4, 128.3, 128.0, 118.6, 114.2, 83.6, 66.2, 62.0, 55.2, 14.7.

4.3.3. *cis*-1-(4′-Methoxyphenyl)-3-isopropyloxy-4-phenylazetidin-2-one (6c). Colourless crystalline solid (0.026 g, 72%); mp 122–123 °C [Found: C, 77.21; H, 6.72; N, 4.43. $C_{19}H_{21}NO_3$ requires C, 73.29; H, 6.79; N, 4.49%]; IR (cm^{-1}, KBr): 1750 (C=O); δ_H (300 MHz, $CDCl_3$) 7.28–6.65 (14H, m, Ph), 5.03 (1H, d, *J* 4.5 Hz, C3-*H*), 4.90 (1H, d, *J* 4.8 Hz, C4-*H*), 3.65 (3H, s, OCH_3), 3.39 (1H, m, OC*H*), 1.03 (3H, d, *J* 6.0 Hz, CH_3), 0.60 (3H, d, *J* 6.0 Hz, CH_3); δ_C (75 MHz, $CDCl_3$) 164.2, 156.2, 134.5, 130.8, 128.4, 128.3, 118.4, 114.3, 82.1, 72.7, 62.6, 55.3, 22.1, 21.3.

4.3.4. *cis*-1-(4′-Methoxyphenyl)-3-methoxy-4-(4′-methoxyphenyl)azetidin-2-one (6g). Colourless oil (0.026 g, 71%) [Found: C, 68.81; H, 5.98; N, 4.38. $C_{18}H_{19}NO_4$ requires C, 68.99; H, 6.10; N, 4.47%]; IR (cm^{-1}, $CHCl_3$): 1751 (C=O); δ_H (300 MHz, $CDCl_3$) 7.37–6.71 (8H, m, Ph), 4.78 (1H, d, *J* 5.1 Hz, C3-*H*), 4.41 (1H, d, *J* 5.1 Hz, C4-*H*), 3.72 (3H, s, OCH_3), 3.68 (3H, s, OCH_3), 3.31 (3H, s, OCH_3).

4.4. General procedure for Raney-nickel desulfurization

Compounds **6** and **7**[20] were prepared by the procedure described in the cited reference.

4.4.1. *cis*-1-(4′-Methoxyphenyl)-3-propyloxy-4-phenylazetidin-2-one (6d). Colourless crystalline solid (0.026 g, 70%); mp 112–113 °C [Found: C, 73.18; H, 6.82; N, 4.43. $C_{19}H_{21}NO_3$ requires C, 73.29; H, 6.89; N, 4.49%]; IR (cm^{-1}, $CHCl_3$): 1760 (C=O); δ_H (300 MHz, $CDCl_3$) 6.85–6.21 (9H, m, Ph), 4.61 (1H, d, *J* 4.8 Hz, C3-*H*), 4.34 (1H, d, *J* 4.8 Hz, C4-*H*), 3.21 (3H, s, OCH_3), 2.89 (1H, m, OCH_aH$_b$), 2.56 (1H, m, OCH$_a$$H_b$), 0.82 (2H, m, C$H_2CH_3$), 0.52 (3H, t, C$H_3$); δ_C (75 MHz, $CDCl_3$) 163.7, 156.3, 133.7, 130.7, 128.5, 128.4, 128.1, 118.7, 114.3, 83.8, 72.5, 62.2, 55.3, 22.5, 10.2.

4.4.2. *trans*-1-(4′-Methoxyphenyl)-3-methoxy-4-phenylazetidin-2-one (7a). Yellow oil (0.019 g, 63%) [Found: C, 85.60; H, 7.11; N, 5.81. $C_{17}H_{17}NO_3$ requires C, 85.68; H, 7.18; N, 5.87%]; IR (cm^{-1}, $CHCl_3$): 1757 (C=O); ^1H NMR ($CDCl_3$) δ: 7.36–6.45 (9H, m, Ph), 4.80 (1H, d, *J* 1.8 Hz, C3-*H*), 4.31 (1H, d, *J* 1.8 Hz, C4-*H*), 3.71 (3H, s, OCH_3), 3.57 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 168.3, 156.3, 136.6, 130.7, 129.2, 128.7, 127.9, 126.0, 118.8, 114.3, 91.3, 63.2, 58.0, 55.3.

4.4.3. *trans*-1-(4′-Methoxyphenyl)-3-ethoxy-4-phenylazetidin-2-one (7b). Colourless oil (0.020 g, 55%) [Found: C, 72.58; H, 6.39; N, 4.61. $C_{18}H_{19}NO_3$ requires C, 72.71; H, 6.43; N, 4.71%]; IR (cm^{-1}, $CHCl_3$): 1761 (C=O); δ_H (300 MHz, $CDCl_3$) 7.33–6.56 (9H, m, Ph), 5.10 (1H, d, *J* 4.8 Hz, C3-*H*), 4.76 (1H, d, *J* 4.8 Hz, C4-*H*), 3.68 (1H, m, OCH_aH$_b$), 3.62 (3H, s, OCH_3), 3.57 (1H, m, OCH$_a$$H_b$), 1.06 (3H, t, C$H_3$); δ_C (75 MHz, $CDCl_3$) 163.7, 156.2, 133.4, 130.5, 129.1, 128.4, 128.0, 125.3, 118.7, 114.2, 80.2, 69.3, 61.8, 55.3, 14.9.

4.4.4. *trans*-1-(4′-Methoxyphenyl)-3-isopropyloxy-4-phenylazetidin-2-one (7c). Pinkish-yellow oil (0.018 g, 49%) [Found: C, 77.16; H, 6.66; N, 4.38. $C_{19}H_{21}NO_3$ requires C, 73.29; H, 6.79; N, 4.49%]; IR (cm^{-1}, $CHCl_3$): 1759 (C=O); δ_H (300 MHz, $CDCl_3$) 6.96–6.29 (14H, m, Ph), 4.35 (1H, d, *J* 2.1 Hz, C3-*H*), 4.01 (1H, d, *J* 1.8 Hz, C4-*H*), 3.43 (1H, m, OCH), 3.29 (3H, s, OCH_3), 0.89 (3H, d, *J* 6.0 Hz, CH_3), 0.77 (3H, d, *J* 6.0 Hz, CH_3); δ_C (75 MHz, $CDCl_3$) 164.2, 156.2, 133.0, 132.7, 131.2, 130.3, 128.6, 128.4, 128.2, 126.7, 126.1, 119.1, 114.3, 89.1, 70.1, 64.9, 55.3, 24.8, 24.6.

4.4.5. *trans*-1-(4′-Methoxyphenyl)-3-propyloxy-4-phenylazetidin-2-one (7d). Colourless oil (0.024 g, 65%) [Found: C, 73.15; H, 6.78; N, 4.37. $C_{19}H_{21}NO_3$ requires C, 73.29; H, 6.89; N, 4.49%]; IR (cm^{-1}, $CHCl_3$): 1767 (C=O); δ_H (300 MHz, $CDCl_3$) 7.28–6.66 (9H, m, Ph), 4.77 (1H, d, *J* 4.8 Hz, C3-*H*), 4.41 (1H, d, *J* 4.8 Hz, C4-*H*), 3.74 (1H, m, OCH_aH$_b$), 3.62 (3H, s, OCH_3), 3.54 (1H, m, OCH$_a$$H_b$), 1.62 (2H, m, C$H_2CH_3$), 0.91 (3H, t, C$H_3$); δ_C (75 MHz, $CDCl_3$) 163.9, 156.3, 133.9, 130.8, 128.5, 128.1, 126.0, 118.8, 114.3, 90.4, 72.7, 63.7, 55.3, 23.0, 10.5.

4.4.6. *trans*-1-(4′-Methoxyphenyl)-3-methoxy-4-(4′-methoxyphenyl)azetidin-2-one (7g). Brownish-yellow oil

(0.017 g, 46%) [Found: C, 68.83; H, 5.95; N, 4.36. $C_{18}H_{19}NO_4$ requires C, 68.99; H, 6.10; N, 4.47%]; IR (cm^{-1}, $CHCl_3$): 1762 (C=O); δ_H (300 MHz, $CDCl_3$) 7.37–6.51 (8H, m, Ph), 4.43 (1H, d, *J* 2.1 Hz, C3-*H*), 4.15 (1H, d, *J* 2.1 Hz, C4-*H*), 3.70 (3H, s, OCH_3), 3.66 (3H, s, OCH_3), 3.55 (3H, s, OCH_3).

4.5. General procedure for the preparation of ethyl 2-phenylthioethanoate (8)

A mixture of thiophenol (27.50 g, 250 mmol) and molecularized sodium (5.75 g, 250 mmol) in toluene (250 mL) was refluxed for 10 h. To the resulting sodium thiophenoxide (33.00 g, 250 mmol) was added dropwise ethyl chloroacetate (33.68 g, 275 mmol) and the reaction mixture was refluxed. Progress of the reaction was monitored by TLC. The reaction mixture was washed with water and dried over anhydrous Na_2SO_4. After evaporation of the solvent in vacuo, the residue was vacuum distilled to furnish the *title compound* **8** (41.45 g, 85%) as colourless oil [Found: C, 61.12; H, 2.51. $C_{10}H_{12}O_2S$ requires C, 61.20; H, 2.58%]; IR (cm^{-1}, $CHCl_3$): 1755 (C=O); δ_H (300 MHz, $CDCl_3$) 7.37–7.13 (5H, m, Ph), 4.14 (2H, q, OCH_2), 3.54 (2H, s, CH_2), 1.19 (3H, t, CH_3); δ_C (75 MHz, $CDCl_3$) 166.8, 133.7, 132.1, 128.8, 128.7, 128.2, 128.1, 84.6, 61.0, 14.1.

4.6. General procedure for the synthesis of ethyl 2-chloro-2-phenylthioethanoate (9)

This compound was prepared by using the same method as for **3a–c**, starting from ethyl 2-phenylthioethanoate (**8**). Colourless oil (0.044 g, 75%) [Found: C, 51.96; H, 4.77. $C_{10}H_{11}O_2SCl$ requires C, 52.04; H, 4.80%]; IR (cm^{-1}, $CHCl_3$): 1744 (C=O); δ_H (300 MHz, $CDCl_3$) 7.51–7.27 (5H, m, Ph), 5.39 (1H, s, C*H*), 4.14 (2H, q, OCH_2), 1.19 (3H, t, CH_3); δ_C (75 MHz, $CDCl_3$) 165.4, 134.1, 133.2, 130.8, 129.4, 129.3, 129.2, 129.1, 65.5, 62.5, 14.0.

4.7. General procedure for the synthesis of ethyl 2-alkoxy-2-phenylthioethanoate (10a–d)

Compounds **10a–d** were prepared by using the same method as for **4**, starting from ethyl 2-chloro-2-phenylthioethanoate (**9**).

4.7.1. Ethyl 2-methoxy-2-phenylthioethanoate (10a). Colourless oil (0.044 g, 90%) [Found: C, 58.35; H, 6.18. $C_{11}H_{14}O_3S$ requires C, 58.39; H, 6.23%]; IR (cm^{-1}, $CHCl_3$): 1755 (C=O); δ_H (300 MHz, $CDCl_3$) 7.39–7.16 (5H, m, Ph), 4.96 (1H, s, C*H*), 4.03 (2H, q, OCH_2), 3.45 (3H, s, OCH_3), 1.09 (3H, t, CH_3); δ_C (75 MHz, $CDCl_3$) 166.3, 133.5, 131.7, 128.5, 128.3, 128.1, 128.0, 86.2, 60.8, 55.2, 14.0.

4.7.2. Ethyl 2-ethoxy-2-phenylthioethanoate (10b). Colourless oil (0.045 g, 87%) [Found: C, 59.91; H, 6.63. $C_{12}H_{16}O_3S$ requires C, 59.98; H, 6.70%]; IR (cm^{-1}, $CHCl_3$): 1753 (C=O); δ_H (300 MHz, $CDCl_3$) 7.42–7.19 (5H, m, Ph), 5.05 (1H, s, C*H*), 4.08 (2H, q, OCH_2), 3.97 (1H, m, OCH_aH_b), 3.53 (1H, m, OCH_aH_b), 1.25 (3H, t, CH_3), 1.15 (3H, t, CH_3); δ_C (75 MHz, $CDCl_3$) 167.1, 133.8, 131.9, 129.9, 128.8, 128.3, 84.8, 61.8, 61.2, 14.7, 14.1.

4.7.3. Ethyl 2-isopropyloxy-2-phenylthioethanoate (10c). Yellow oil (0.044 g, 81%) [Found: C, 61.03; H, 7.05. $C_{13}H_{18}O_3S$ requires C, 61.14; H, 7.12%]; IR (cm^{-1}, $CHCl_3$): 1756 (C=O); δ_H (300 MHz, $CDCl_3$) 7.40–7.20 (5H, m, Ph), 5.07 (1H, s, C*H*), 4.21 (2H, q, OCH_2), 4.07 (1H, m, OC*H*), 1.14 (3H, t, CH_3), 1.07 (3H, d, *J* 6.0 Hz, CH_3), 0.97 (3H, d, *J* 6.0 Hz, CH_3).

4.7.4. Ethyl 2-propyloxy-2-phenylthioethanoate (10d). Yellow oil (0.046 g, 84%) [Found: C, 61.09; H, 7.14. $C_{13}H_{18}O_3S$ requires C, 61.14; H, 7.12%]; IR (cm^{-1}, $CHCl_3$): 1753 (C=O); δ_H (300 MHz, $CDCl_3$) 7.46–7.21 (5H, m, Ph), 5.09 (1H, s, C*H*), 4.11 (2H, q, OCH_2), 3.85 (1H, m, OCH_aH_b), 3.47 (1H, m, OCH_aH_b), 1.70 (2H, m, CH_2CH_3), 1.18 (3H, t, CH_3), 0.95 (3H, t, CH_3); δ_C (75 MHz, $CDCl_3$) 167.1, 133.7, 132.0, 128.8, 128.7, 128.3, 128.2, 84.7, 61.7, 61.2, 22.5, 14.1, 10.7.

4.8. General procedure for the synthesis of *trans*-3-alkoxy-3-phenylthio-β-lactams (13a–d)

Compounds **13a–d** were prepared by using the same procedure as for *trans*-3-phenyl/benzylthioazetidin-2-ones,[20] reported in cited reference, starting from potassium 2-alkoxy-2-phenylthioethanoate (**11a–d**).

4.8.1. *trans*-1-(4′-Methoxyphenyl)-3-methoxy-3-phenylthio-4-phenylazetidin-2-one (13a). White solid (0.042 g, 85%); mp 112–114 °C [Found: C, 70.52; H, 5.32; N, 3.54. $C_{23}H_{21}NO_3S$ requires C, 70.57; H, 5.40; N, 3.58%]; IR (cm^{-1}, KBr): 1755 (C=O); δ_H (300 MHz, $CDCl_3$) 7.49–6.73 (14H, m, Ph), 4.97 (1H, s, C4-*H*), 3.64 (3H, s, OCH_3), 3.41 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 160.6, 156.4, 133.6, 133.5, 131.9, 130.7, 128.9, 128.6, 128.3, 128.1, 118.8, 114.3, 97.2, 69.1, 55.1, 53.7.

4.8.2. *trans*-1-(4′-Methoxyphenyl)-3-ethoxy-3-phenylthio-4-phenylazetidin-2-one (13b). White solid (0.040 g, 80%); mp 114–115 °C [Found: C, 71.06; H, 5.74; N, 3.50. $C_{24}H_{23}NO_3S$ requires C, 71.09; H, 5.71; N, 3.45%]; IR (cm^{-1}, KBr): 1754 (C=O); δ_H (300 MHz, $CDCl_3$) 7.56–6.66 (14H, m, Ph), 4.98 (1H, s, C4-*H*), 3.92 (1H, m, OCH_aH_b), 3.67 (3H, s, OCH_3), 3.62 (1H, m, OCH_aH_b), 0.93 (3H, t, CH_3); δ_C (75 MHz, $CDCl_3$) 161.2, 156.3, 133.4, 133.1, 131.7, 130.5, 128.9, 128.7, 128.2, 118.9, 114.1, 98.9, 68.7, 61.7, 55.0, 14.7.

4.8.3. *trans*-1-(4′-Methoxyphenyl)-3-isopropyloxy-3-phenylthio-4-phenylazetidin-2-one (13c). White solid (0.037 g, 71%); mp 115–116 °C [Found: C, 77.51; H, 5.91; N, 3.28. $C_{25}H_{25}NO_3S$ requires C, 77.57; H, 6.00; N, 3.33%]; IR (cm^{-1}, KBr): 1757 (C=O); δ_H (300 MHz, $CDCl_3$) 7.08–6.18 (14H, m, Ph), 4.52 (1H, s, C4-*H*), 4.39 (1H, m, OC*H*), 3.57 (3H, s, OCH_3), 1.17 (3H, d, *J* 6.0 Hz, CH_3), 0.87 (3H, d, *J* 6.0 Hz, CH_3).

4.8.4. *trans*-1-(4′-Methoxyphenyl)-3-propyloxy-3-phenylthio-4-phenylazetidin-2-one (13d). White solid (0.039 g, 74%); mp 118–119 °C [Found: C, 77.50; H, 6.03; N, 3.29. $C_{25}H_{25}NO_3S$ requires C, 77.57; H, 6.00; N, 3.33%]; IR (cm^{-1}, KBr): 1753 (C=O); δ_H (300 MHz, $CDCl_3$) 7.13–6.25 (14H, m, Ph), 4.58 (1H, s, C4-*H*), 3.39 (1H, m, OCH_aH_b), 3.26 (3H, s, OCH_3), 3.17 (1H, m,

OCH_aH_b), 0.91 (2H, m, CH_2CH_3), 0.23 (3H, t, CH_3); δ_C (75 MHz, $CDCl_3$) 161.6, 156.4, 133.3, 133.2, 131.6, 130.5, 128.9, 128.6, 128.2, 128.1, 128.0, 118.9, 114.3, 96.3, 69.2, 67.8, 55.3, 22.5, 10.5.

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23. Crystal data for **4b**: monoclinic; $P2_1/n$; a=12.7209(2) Å, b=10.0018(2) Å, c=17.7900(3) Å; α=90°, β=110.1480(10)°, γ=90 °C; V=2124.95(6) Å^3; Z=4; ρ_{calcd}=1.267 mg/m^3; μ(Mo Kα)=0.177 mm^{-1}; full matrix least-square on F^2; R_1=0.0456, wR_2=0.1239 for 2805 reflections [$I>2\sigma$ (I)]; T=293(2) K; GOF=1.042. Crystallographic data (excluding structure factors) for the structure **4b** in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 292949.
24. Crystal data for **4m**: monoclinic; $P2_1/c$; a=10.2813(4) Å, b=18.5745(8) Å, c=11.9227(5) Å; α=90°, β=110.335(2)°, γ=90°; V=2134.98(15) Å^3; Z=4; ρ_{calcd}=1.262 mg/m^3; μ(Mo Kα)=0.176 mm^{-1}; full matrix least-square on F^2; R_1=0.0480, wR_2=0.1066 for 2447 reflections [$I>2\sigma$ (I)]; T=293(2) K; GOF=1.011. Crystallographic data (excluding structure factors) for the structure **4m** in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 292948.
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