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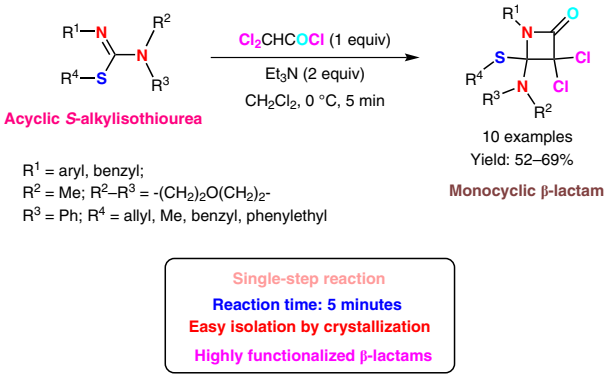
Facile Synthesis of Some Chlorinated and Heteroatom-Rich Monocyclic β-Lactams via the Staudinger Reaction of Acyclic *S*-Alkylisothioureas

Nisha Dawra [a,b]*
Ram Nath Ram [b]

[a] School of Engineering and Technology, BML Munjal University, Gurgaon, Haryana 122413, India
[b] Department of Chemistry, Indian Institute of Technology Delhi, Hauz Khas, New Delhi 110016, India
nishadawra@gmail.com



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Abstract The optimized preparation of a rare class of highly functionalized (chlorinated and heteroatom-rich) monocyclic β-lactams by the Staudinger reaction of reactive acyclic *S*-alkylisothioureas with dichloroketene is presented. The use of acyclic *S*-alkylisothioureas in the Staudinger β-lactam synthesis has been demonstrated for the first time. The present method is mild, economical and wide in scope.

Key words monocyclic β-lactams, dichloroketene, acyclic *S*-alkylisothioureas, Staudinger reaction, chlorinated, heteroatom rich

Heterocyclic compounds are of immense importance both in chemistry and biology. The majority of the natural products, drugs and biologically active compounds are rich in heteroatoms. Heteroatom-rich organic compounds, particularly those containing heteroatoms such as N, O, S and Cl, are well known to behave as reactive intermediates in organic synthesis, while a few others exhibit interesting biological activities.[1] Monocyclic β-lactams are important as antibiotics[2] and inhibitors of β-lactamases[2a,3] and other mammalian enzymes that regulate important physiological processes in human beings and other animals.[4] The synthesis of novel β-lactams is an emerging area of research in organic synthesis due to the problem of ever-increasing bacterial resistance to the existing β-lactam antibiotics.[5] The use of monocyclic β-lactams as versatile synthetic intermediates has been well documented in the literature.[6] Ring transformations of the β-lactam ring have been used as an efficient and straightforward method for the synthesis of a variety of azaheterocycles, such as 1,4-diazepanes,[6a] pyrrolidines,[6e] aziridines,[6g] piperazines[6a,h] and azetidines,[6e,g] which are promising compounds in the field of drug design.

A chlorine substituent at the α-position of the β-lactam ring is well known to enhance the chemical reactivity and it also offers a great diversity regarding the biological activity[2a,7] (Figure 1). Monocyclic β-lactams bearing different heteroatoms or heteroatom substituents at the α- or β-position of the β-lactam ring are endowed with a broad spectrum of biological activities.[8] Monocyclic β-lactams bearing a morpholinyl group at the β-position of the β-lactam ring exhibit good antibiotic activity.[9]

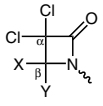


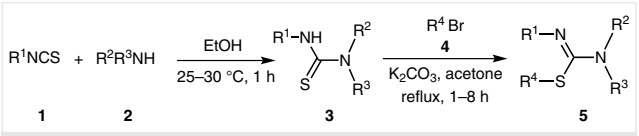
Figure 1 General structure of a heteroatom-rich monocyclic β-lactam

A literature survey revealed that the synthesis of β,β-diamino-substituted monocyclic β-lactams and α-S,β-N-disubstituted monocyclic β-lactams has been scarcely reported. The very few reported methods for the synthesis of such β-N-substituted β-lactams involve the [2+2] cycloaddition of alkenes to isocyanates,[10] the [2+2] cycloaddition of β,β-disubstituted enamines to aryl isocyanates[9] or the Staudinger reaction of amidines with ketenes.[8h,11] However, all of the aforesaid methods have some limitations with regard to the nature of substituents present on the β-lactam ring, and the low product stability and low product yields in some cases. These drawbacks prompted us to develop a more efficient method to synthesize some novel, chlorinated and heteroatom-rich β-N-substituted monocyclic β-lactams.

To the best of our knowledge, monocyclic β-lactams having the two different heteroatom substituents N and S at the same position (α or β) are not known. Furthermore, a recent search has shown that monocyclic β-lactams bearing all three of the heteroatom substituents N, S and Cl in a single molecular framework are unreported. Only a few examples of non-chlorinated bicyclic β-lactams having both a nitrogen and a sulfur substituent at the β-position of the β-lactam ring have been reported,[12] which were prepared by the [2+2] cycloaddition of ketenes across cyclic isothioureas.

Therefore, in view of the above facts, herein we disclose a simple, broader and efficient route of general applicability for the synthesis of such interesting and intriguing monocyclic β-lactams having the aforesaid unprecedented grouping and positioning of chlorine, nitrogen and sulfur heteroatom substituents. The well-documented Staudinger method was chosen for the construction of the β-lactam ring.[13] We proposed that the properly substituted acyclic *S*-alkylisothioureas containing the substituted N and S atoms could serve as excellent precursors for the synthesis of the desired α,α-dichloro-β-N,β-S-disubstituted monocyclic β-lactams. However, until now, the use of acyclic *S*-alkylisothioureas in the Staudinger reaction has not been reported.

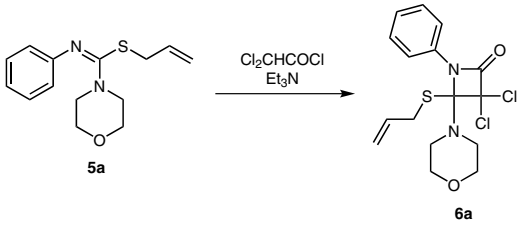
The general synthetic strategy to construct the above-mentioned persubstituted monocyclic β-lactams began with the synthesis of trisubstituted thioureas **3** (Scheme 1) which were prepared by nucleophilic addition of *sec*-amines **2** to aryl/alkyl isothiocyanates **1** in ethanol at room temperature (25–30 °C) according to a literature procedure.[14]



Scheme 1 General route for the synthesis of acyclic *S*-alkylisothioureas **5**

Purification of the crude solid products by recrystallization in ethanol afforded the trisubstituted thioureas **3** in quantitative yields. The crucial acyclic *S*-alkylisothioureas **5** were accessed by reacting the trisubstituted thioureas **3** with the appropriate alkylating agents **4** in refluxing acetone using anhydrous potassium carbonate as a base. Purification of the crude products by silica gel column chromatography furnished the desired acyclic *S*-alkylisothioureas **5** in 88–98% yield. Thereafter, the Staudinger reaction of *S*-alkylisothioureas **5** with dichloroketene was investigated. To explore the feasibility of this approach, we first attempted the reaction of isothiourea **5a** with dichloroketene generated in situ by the reaction of dichloroacetyl chloride with triethylamine. Numerous attempts at this reaction were made by varying the solvent, reaction temperature, stoichiometric ratio of the reagents and reaction time, as shown in Table 1. Disappointingly, complete decomposition of the starting material was observed in benzene at 25–30 °C (Table 1, entry 1).

Table 1 Optimization of the Staudinger Reaction of Isothiourea **5a**[a]



Entry	$Cl_2CHCOCl$ (mol equiv)	Et_3N (mol equiv)	Solvent	Temp (°C)	Time (min)	Ratio[b] **5a**/**6a**	Yield[c,d] (%)	
							Recovered **5a**	**6a**
1	2	2	benzene	25–30	120	–	extensive decomposition	–
2	2	2	Et_2O	0	120	1:0	74	–
3	2	2	Et_2O	25–30	720	1:0	76	–
4	2	2	CH_2Cl_2	0	120	–	extensive decomposition	–
5	1	2	CH_2Cl_2	0	60	1:1	partial decomposition	–
6	**1**	**2**	**CH_2Cl_2**	**0**	**5**	**0:1**	**–**	**54**
7	1	1	CH_2Cl_2	0	5	5:85	slight decomposition	–

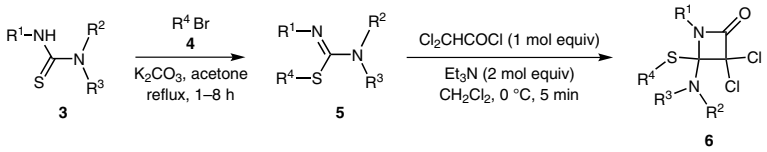
[a] All reactions were performed with isothiourea **5a** (1 mmol), under a nitrogen atmosphere.
[b] Calculated by ^1H NMR analysis of the crude reaction mixture.
[c] Isolated yield of **5a** after purification by column chromatography.
[d] Isolated yield of **6a** after purification by precipitation from EtOH.

However, neither product formation nor decomposition was observed, both at 0 °C and 25–30 °C, when diethyl ether was used as a solvent (Table 1, entries 2 and 3). Curiously, extensive decomposition of the starting material was observed in dichloromethane (CH_2Cl_2), even at 0 °C, after 2 hours (Table 1, entry 4). From these experiments, it was presumed that the reaction probably occurred in CH_2Cl_2 at 0 °C, but the β-lactam product **6a** decomposed under these reaction conditions. This may be due to a susceptibility of β-lactam product **6a** towards excess dichloroacetyl chloride and longer reaction time. In order to suppress the decomposition in CH_2Cl_2 at 0 °C, the amount of dichloroacetyl chloride was reduced to 1 equivalent and the time was reduced to 1 hour. Interestingly, after 1 hour the ^1H NMR spectrum of the crude reaction mixture indicated the presence of the β-lactam **6a** and the starting material **5a** in a 1:1 ratio, and partial decomposition was also observed (Table 1, entry 5). The reaction was indeed cleaner under these conditions, providing greater latitude for further manipulation. Thus, the influence of the reaction time and the stoichiometric ratio of dichloroacetyl chloride for the successful synthesis of the monocyclic β-lactam **6a** soon became very apparent. Pleasingly, considerable success was realized when the reaction of isothiourea **5a** with dichloroketene was performed for only 5 minutes under similar reaction conditions as used for the previous experiment. These conditions resulted in complete conversion of the starting material into product without any decomposition (Table 1, entry 6).

Further, the requirement of excess base (Et_3N) in the Staudinger reaction was also investigated by performing another experiment in which the amount of triethylamine was reduced to 1 equivalent, keeping the rest of the parameters the same. Interestingly, on monitoring the progress of the reaction by TLC after 5 minutes, the presence of a small amount of the starting material **5a** along with the product **6a** was observed (Table 1, entry 7). Decomposition was also noticed. Thus, it appears that the basic medium is quite necessary for the success of the Staudinger reaction of **5a** with dichloroketene.

Therefore, 1 equivalent of dichloroacetyl chloride, 2 equivalents of triethylamine, CH_2Cl_2 as solvent, 0 °C as reaction temperature and 5 minutes as reaction time were considered as the optimized reaction conditions for the Staudinger reaction of acyclic *S*-alkylisothioureas for the synthesis of the desired persubstituted monocyclic β-lactams. Thus, several α,α-dichloro-β-N,β-S-disubstituted monocyclic β-lactams **6** were successfully synthesized by the Staudinger reaction of acyclic *S*-alkylisothioureas **5** with dichloroketene in 52–69% yield (Table 2).

Table 2 Yields of *S*-Alkylisothioureas **5**[a] and Monocyclic β-Lactams **6**[b]



Entry	R^1	R^2	R^3	R^4	Time[c] (h)	Yield[d] (%) of **5**		Yield[e] (%) of **6**	
1	Ph	-$(CH_2)_2O(CH_2)_2$-		allyl	2	**5a**	96	**6a**	54
2	Ph	Me	Ph	allyl	2	**5b**	94	**6b**	67
3	Ph	Me	Ph	Bn	6	**5c**	96	**6c**	68
4	*p*-$MeOC_6H_4$	Me	Ph	Bn	8	**5d**	93	**6d**	69
5	*p*-ClC_6H_4	Me	Ph	Bn	7	**5e**	95	**6e**	56
6	*p*-BrC_6H_4	Me	Ph	Bn	8	**5f**	95	**6f**	56
7	*o*-MeC_6H_4	Me	Ph	Bn	6	**5g**	89	**6g**	69
8	Ph	Me	Ph	$(CH_2)_2Ph$	4	**5h**	98	**6h**	55
9	Ph	Me	Ph	Me	1	**5i**	98	**6i**	59
10	Bn	Me	Ph	Bn	10	**5j**	88[f]	**6j**	52

[a] Reaction conditions: **3** (5 mmol), **4** (5 mmol), acetone (30 mL).
[b] Reaction conditions: **5** (2 mmol), $Cl_2CHCOCl$ (2 mmol), Et_3N (4 mmol), CH_2Cl_2 (20 mL).
[c] Reaction time for the conversion of **3** into **5**.
[d] Isolated yield of **5** after purification by column chromatography.
[e] Isolated yield of **6** after purification by precipitation from EtOH.
[f] Yield of the crude product.

The structures of all new compounds synthesized in the present work were supported by IR, ^{1}H NMR and ^{13}C NMR spectroscopy, and HRMS data. The structure of the monocyclic β-lactams was further confirmed by single-crystal X-ray diffraction data of the monocyclic β-lactam **6i** (Figure 2).

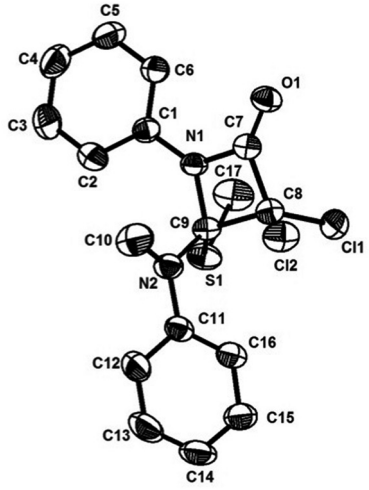


Figure 2 ORTEP diagram of the monocyclic β-lactam **6i**

In conclusion, the so-far unprecedented Staudinger reaction of acyclic *S*-alkylisothioureas with dichloroketene has been successfully accomplished for the first time for the synthesis of a variety of chlorinated and heteroatom-rich monocyclic β-lactams. The method is quite general and the starting materials used are inexpensive and readily accessible. The purification procedures are convenient and do not involve chromatographic methods. The β-lactams thus synthesized belong to a rarely reported class of highly functionalized β-lactams having high heteroatom density. These attributes make them important building blocks in organic synthesis and interesting targets for biological studies.

The entire data analysis of all the compounds synthesized in the present work was done in the Chemistry Instrumentation Lab, IIT Delhi, New Delhi. IR spectra were recorded on Nicolet Protégé 460 ES-P and Cary 600 Series FT-IR spectrometers by taking solid samples as KBr pellets and liquids as thin films on KBr discs. NMR spectra were recorded on a Bruker 300-MHz FT-NMR spectrometer as solutions in $CDCl_3$ with TMS as internal standard. Multiplicities are indicated by the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet doublet). DEPT spectra were routinely recorded to identify different types of carbons. Mass spectra were recorded on a micrOTOF-Q II, ESI-TOF/MS mass spectrometer (ESI-TOF) in the positive ion mode. Melting points were determined on a Fischer Scientific electrically heated apparatus by taking the samples in a glass capillary sealed at one end, and are uncorrected. The progress of reactions was monitored by TLC using glass plates coated with TLC-grade silica gel. Iodine was used for visualizing the spots. For column chromatography, silica gel (60–120 mesh) was used as the stationary phase with *n*-hexane/EtOAc mixtures as the mobile phase. Solvents were evaporated on a rotary evaporator under reduced pressure using an aspirator. The trisubstituted thioureas were prepared by the reaction of alkyl/aryl isothiocyanates with *sec*-amines according to a reported procedure.[14] Dichloroacetyl chloride is commercially available and was used as received. Et_3N was dried over KOH pellets overnight and distilled over CaH_2. Acetone was dried by distillation over anhydrous K_2CO_3. CH_2Cl_2 was dried by distillation over P_2O_5.

Acyclic *S*-Alkylisothioureas 5; General Procedure

To a solution of the trisubstituted thiourea **3** (5 mmol) in dried acetone (30 mL) were added anhydrous K_2CO_3 (0.829 g, 6 mmol) and an allyl/alkyl bromide **4** (5 mmol), and the reaction mixture was heated at reflux. After completion of the reaction, the reaction mixture was cooled and filtered to remove the insoluble K_2CO_3. The crude product was purified by silica gel column chromatography (*n*-hexane/EtOAc, 95:5 v/v), except for the isothiourea **5j** which was highly unstable and decomposed on column chromatography. Thus, **5j** was used as such without further purification in the Staudinger reaction. The pure acyclic *S*-alkylisothioureas **5a–i** were thus obtained in 89–98% yield as yellowish or colorless liquids or white solids.

Allyl *N*-Phenylmorpholine-4-carbimidothioate (5a)[15]

Yellowish liquid; yield: 1.259 g (96%).

IR (KBr): 3083, 2970, 1608, 1589, 1484, 1444, 1370, 1269, 1242, 1195, 1156, 1112, 1025, 767, 698, 574 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27 (t, *J* = 7.8 Hz, 2 H, Ar-H), 7.01 (t, *J* = 7.5 Hz, 1 H, Ar-H), 6.88 (d, *J* = 7.8 Hz, 2 H, Ar-H), 5.74–5.61 (m, 1 H, CH_2=C*H*-CH_2), 5.09–5.02 (m, 2 H, CH_2=CH-CH_2), 3.74 (t, *J* = 4.2 Hz, 4 H, CH_2OCH_2), 3.63 (t, *J* = 4.2 Hz, 4 H, CH_2NCH_2), 3.05 (d, *J* = 7.2 Hz, 2 H, CH_2=CH-CH_2).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 154.3, 149.5, 133.5, 128.6, 122.4, 121.6, 117.7, 66.7, 48.6, 35.3.

Allyl *N*-Methyl-*N*,*N*′-diphenylcarbamimidothioate (5b)

Yellowish liquid; yield: 1.327 g (94%); R_f = 0.59 (5% *n*-hexane/EtOAc).

IR (KBr): 3059, 2968, 1606, 1578, 1492, 1344, 1252, 1206, 1116, 1029, 920, 762, 697 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.18 (m, 7 H, Ar-H), 7.05–6.94 (m, 3 H, Ar-H), 5.61–5.48 (m, 1 H, CH_2=C*H*-CH_2), 5.00–4.95 (m, 2 H, CH_2=CH-CH_2), 3.38 (s, 3 H, NMe), 2.91 (d, *J* = 7.2 Hz, 2 H, CH_2=CH-CH_2).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 154.1, 149.5, 146.2, 133.5, 128.9, 128.7, 126.1, 125.6, 122.6, 121.6, 117.4, 41.6, 35.2.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{19}N_2S$: 283.1263; found: 283.1268.

Benzyl *N*-Methyl-*N*,*N*′-diphenylcarbamimidothioate (5c)

White solid; yield: 1.596 g (96%); mp 42–44 °C; R_f = 0.58 (5% *n*-hexane/EtOAc).

IR (KBr): 3054, 2973, 1603, 1565, 1486, 1454, 1429, 1345, 1291, 1255, 1203, 1111, 1072, 1027, 993, 902, 886, 764, 698 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.17 (m, 8 H, Ar-H), 7.14–7.09 (dd, *J* = 8.7, 1.2 Hz, 2 H, Ar-H), 7.03–6.99 (m, 3 H, Ar-H), 6.89 (dd, *J* = 8.7, 1.2 Hz, 2 H, Ar-H), 3.47 (s, 2 H, SCH_2), 3.30 (s, 3 H, NMe).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 153.9, 149.4, 146.0, 137.2, 128.8, 128.7, 128.6, 128.2, 127.0, 125.8, 125.4, 122.5, 121.5, 41.4, 36.4.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{21}N_2S$: 333.1420; found: 333.1416.

Benzyl *N*′-(4-Methoxyphenyl)-*N*-methyl-*N*-phenylcarbamimidothioate (5d)

White solid; yield: 1.686 g (93%); mp 48–50 °C; R_f = 0.58 (5% *n*-hexane/EtOAc).

IR (KBr): 3027, 2992, 2959, 2932, 1604, 1568, 1491, 1454, 1344, 1288, 1237, 1206, 1111, 1041, 891, 840, 769 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29 (t, *J* = 7.5 Hz, 2 H, Ar-H), 7.22–7.09 (m, 6 H, Ar-H), 7.02 (d, *J* = 7.2 Hz, 2 H, Ar-H), 6.83 (s, 4 H, Ar-H), 3.76 (s, 3 H, OMe), 3.50 (s, 2 H, SCH_2), 3.29 (s, 3 H, NMe).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 155.5, 154.1, 146.2, 142.7, 137.3, 128.8, 128.7, 128.2, 127.0, 125.5, 125.2, 122.4, 113.9, 55.3, 41.4, 36.5.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{23}N_2OS$: 363.1526; found: 363.1525.

Benzyl *N*′-(4-Chlorophenyl)-*N*-methyl-*N*-phenylcarbamimidothioate (5e)

White solid; yield: 1.743 g (95%); mp 85–87 °C; R_f = 0.58 (5% *n*-hexane/EtOAc).

IR (KBr): 2966, 1603, 1574, 1491, 1453, 1328, 1208, 1115, 1086, 1030, 892, 833, 764 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.33 (m, 2 H, Ar-H), 7.30–7.19 (m, 6 H, Ar-H), 7.14–7.11 (m, 2 H, Ar-H), 7.04–7.01 (m, 2 H, Ar-H), 6.78 (d, *J* = 8.7 Hz, 2 H, Ar-H), 3.49 (s, 2 H, SCH_2), 3.32 (s, 3 H, NMe).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 154.2, 148.1, 145.8, 137.1, 128.9, 128.62, 128.56, 128.3, 127.6, 127.1, 126.0, 125.7, 122.8, 41.5, 36.6.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{20}ClN_2S$: 367.1030; found: 367.1033.

Benzyl *N*′-(4-Bromophenyl)-*N*-methyl-*N*-phenylcarbamimidothioate (5f)

White solid; yield: 1.954 g (95%); mp 76–78 °C; R_f = 0.58 (5% *n*-hexane/EtOAc).

IR (KBr): 3059, 2924, 1604, 1574, 1493, 1455, 1350, 1255, 1202, 1166, 1118, 1066, 1028, 1002, 893, 766 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.30 (m, 4 H, Ar-H), 7.26–7.19 (m, 4 H, Ar-H), 7.12 (d, *J* = 7.5 Hz, 2 H, Ar-H), 7.02 (d, *J* = 7.5 Hz, 2 H, Ar-H), 6.73 (d, *J* = 8.1 Hz, 2 H, Ar-H), 3.49 (s, 2 H, SCH_2), 3.32 (s, 3 H, NMe).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 154.3, 148.6, 145.9, 137.2, 131.6, 129.0, 128.7, 128.4, 127.2, 126.2, 125.8, 123.4, 115.4, 41.6, 36.7.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{20}BrN_2S$: 411.0525; found: 411.0525.

Benzyl *N*-Methyl-*N*-phenyl-*N*′-*o*-tolylcarbamimidothioate (5g)

Yellowish liquid; yield: 1.542 g (89%); R_f = 0.58 (5% *n*-hexane/EtOAc).

IR (KBr): 3028, 1608, 1582, 1493, 1454, 1337, 1253, 1215, 1114, 1030, 893, 763, 698 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.35 (m, 2 H, Ar-H), 7.28–7.08 (m, 8 H, Ar-H), 7.02–6.93 (m, 3 H, Ar-H), 6.72 (d, *J* = 7.5 Hz, 1 H, Ar-H), 3.51 (s, 2 H, SCH_2), 3.33 (s, 3 H, NMe), 2.13 (s, 3 H, Me).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 154.1, 148.2, 146.4, 137.3, 130.0, 129.0, 128.9, 128.7, 128.3, 127.1, 126.0, 125.4, 125.2, 123.0, 120.8, 41.7, 36.6, 18.1.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{23}N_2S$: 347.1576; found: 347.1577.

2-Phenethyl *N*-Methyl-*N*,*N*′-diphenylcarbamimidothioate (5h)

Colorless liquid; yield: 1.698 g (98%); R_f = 0.59 (5% *n*-hexane/EtOAc).

IR (KBr): 2965, 1606, 1576, 1494, 1453, 1343, 1249, 1207, 1168, 1116, 996, 762, 696 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.12 (m, 10 H, Ar-H), 7.03–6.93 (m, 5 H, Ar-H), 3.37 (s, 3 H, NMe), 2.64–2.58 (m, 2 H, Ph$CH_2$$CH_2$), 2.54–2.48 (m, 2 H, Ph$CH_2$$CH_2$).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 154.6, 149.6, 146.3, 139.8, 129.0, 128.7, 128.34, 128.28, 126.3, 126.0, 125.6, 122.6, 121.5, 41.6, 36.1, 33.2.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{23}N_2S$: 347.1576; found: 347.1576.

Methyl *N*-Methyl-*N*,*N*′-diphenylcarbamimidothioate (5i)

Yellowish liquid; yield: 1.256 g (98%); R_f = 0.59 (5% *n*-hexane/EtOAc).

IR (KBr): 3057, 1606, 1576, 1492, 1342, 1246, 1206, 1116, 1029, 762, 696 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.24 (m, 6 H, Ar-H), 7.17 (t, *J* = 7.2 Hz, 1 H, Ar-H), 7.02–6.94 (m, 3 H, Ar-H), 3.37 (s, 3 H, NMe), 1.88 (s, 3 H, SMe).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 156.4, 149.5, 146.3, 128.9, 128.6, 125.6, 125.4, 122.4, 121.4, 41.7, 15.7.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{17}N_2S$: 257.1107; found: 257.1104.

Monocyclic β-Lactams 6; General Procedure

To a solution of the *S*-alkylisothiourea **5** (2 mmol) in dried CH_2Cl_2 (20 mL) was injected dried Et_3N (0.404 g, 0.557 mL, 4 mmol) at room temperature (25–30 °C) under a nitrogen atmosphere using Schlenk techniques. Then, a solution of dichloroacetyl chloride (0.295 g, 0.192 mL, 2 mmol) in dried CH_2Cl_2 (5 mL) was added dropwise via a dropping funnel with stirring over a period of 5 min at 0 °C. The reaction was quenched immediately by diluting with CH_2Cl_2 (50 mL) and washing successively with saturated $NaHCO_3$ solution (2 × 20 mL) and brine (2 × 20 mL). The CH_2Cl_2 layer was dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give the crude monocyclic β-lactam as a dark pasty mass. The crude product was prone to decomposition on column chromatography using either silica gel or neutral alumina as the stationary phase. Therefore, it was purified by dissolving in EtOH and allowing the solution to stand at 0 °C for 1–3 h. The pure monocyclic β-lactams precipitated out as white solids in 52–69% yield. Further purification by recrystallization from EtOH or benzene (in the case of **6i**) afforded the pure monocyclic β-lactams **6a–j** as colorless crystals.

4-(Allylthio)-3,3-dichloro-4-morpholino-1-phenylazetidin-2-one (6a)

Colorless needles; yield: 0.403 g (54%); mp 77–79 °C (EtOH); R_f = 0.48 (5% *n*-hexane/EtOAc).

IR (KBr): 2969, 1782, 1637, 1596, 1494, 1371, 1265, 1173, 1116, 890, 834, 798, 754 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 7.8 Hz, 2 H, Ar-H), 7.43 (t, *J* = 7.8 Hz, 2 H, Ar-H), 7.27 (t, *J* = 7.8 Hz, 1 H, Ar-H), 5.64–5.50 (m, 1 H, CH_2=CH-CH_2), 5.10–5.01 (m, 2 H, CH_2=CH-CH_2), 3.71 (t, *J* = 4.5 Hz, 4 H, CH_2OCH_2), 3.39–3.31 (m, 3 H, CH_2NCH_2 and one allylic H of CH_2=CH-CH_2), 3.19–3.05 (m, 3 H, CH_2NCH_2 and one allylic H of CH_2=CH-CH_2).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 158.2, 135.7, 131.4, 129.4, 126.5, 119.2, 119.1, 99.2, 91.3, 67.1, 47.3, 35.2.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{18}Cl_2N_2O_2SNa$: 395.0358; found: 395.0361.

4-(Allylthio)-3,3-dichloro-4-[(methyl)(phenyl)amino]-1-phenylazetidin-2-one (6b)

Colorless needles; yield: 0.527 g (67%); mp 68–70 °C (EtOH); R_f = 0.48 (5% *n*-hexane/EtOAc).

IR (KBr): 3063, 2943, 1787, 1668, 1597, 1494, 1372, 1312, 1232, 1132, 1130, 1102, 987, 790, 753, 693 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 8.1 Hz, 2 H, Ar-H), 7.45 (t, *J* = 7.8 Hz, 2 H, Ar-H), 7.35–7.23 (m, 5 H, Ar-H), 7.07 (t, *J* = 6.9 Hz, 1 H, Ar-H), 5.44–5.36 (m, 1 H, CH_2=C*H*-CH_2), 4.94–4.88 (m, 2 H, C*H*$_2$=CH-CH_2), 3.30 (dd, *J* = 11.7, 7.5 Hz, 1 H, CH_2=CH-CH*H*), 3.20 (s, 3 H, NMe), 2.88 (dd, *J* = 11.7, 7.2 Hz, 1 H, CH_2=CH-C*H*H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 158.2, 145.3, 135.8, 131.0, 129.5, 128.4, 126.4, 123.0, 122.5, 119.1, 118.8, 97.7, 92.3, 39.5, 36.0.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{18}Cl_2N_2OSNa$: 415.0409; found: 415.0430.

4-(Benzylthio)-3,3-dichloro-4-[(methyl)(phenyl)amino]-1-phenylazetidin-2-one (6c)

Colorless cubes; yield: 0.603 g (68%); mp 98–100 °C (EtOH); R_f = 0.47 (5% *n*-hexane/EtOAc).

IR (KBr): 3063, 2904, 1792, 1596, 1492, 1363, 1308, 1225, 1123, 1103, 754, 693 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 8.1 Hz, 2 H, Ar-H), 7.48 (t, *J* = 7.8 Hz, 2 H, Ar-H), 7.35–7.23 (m, 5 H, Ar-H), 7.12–7.10 (m, 3 H, Ar-H), 7.04 (t, *J* = 7.5 Hz, 1 H, Ar-H), 6.84 (d, *J* = 4.5 Hz, 2 H, Ar-H), 3.91 (d, *J* = 10.5 Hz, 1 H, SCH*H*), 3.37 (d, *J* = 10.5 Hz, 1 H, SC*H*H), 3.22 (s, 3 H, NMe).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 158.3, 145.3, 136.0, 134.6, 129.6, 129.1, 128.4, 127.5, 126.5, 123.0, 122.5, 118.9, 97.5, 92.5, 39.5, 37.5.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{20}Cl_2N_2OSNa$: 465.0566; found: 465.0551.

4-(Benzylthio)-3,3-dichloro-1-(4-methoxyphenyl)-4-[(methyl)(phenyl)amino]azetidin-2-one (6d)

Colorless needles; yield: 0.653 g (69%); mp 108–110 °C (EtOH); R_f = 0.47 (5% *n*-hexane/EtOAc).

IR (KBr): 3062, 2931, 1779, 1597, 1510, 1454, 1371, 1302, 1251, 1170, 1129, 834, 698 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 9.0 Hz, 2 H, Ar-H), 7.32–7.22 (m, 4 H, Ar-H), 7.13–7.11 (m, 3 H, Ar-H), 7.06–6.98 (m, 3 H, Ar-H), 6.87–6.85 (m, 2 H, Ar-H), 3.90–3.86 (d, 1 H, overlapped by singlet at 3.86, SC*H*H), 3.86 (s, 3 H, OMe), 3.37 (d, *J* = 10.5 Hz, 1 H, SCH*H*), 3.22 (s, 3 H, NMe).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 157.9, 157.8, 145.4, 134.7, 129.1, 129.0, 128.4, 127.5, 122.9, 122.5, 120.6, 114.7, 97.5, 92.4, 55.5, 39.5, 37.4.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{22}Cl_2N_2O_2SNa$: 495.0671; found: 495.0659.

4-(Benzylthio)-3,3-dichloro-1-(4-chlorophenyl)-4-[(methyl)(phenyl)amino]azetidin-2-one (6e)

Colorless plates; yield: 0.535 g (56%); mp 85–87 °C (EtOH); R_f = 0.47 (5% *n*-hexane/EtOAc).

IR (KBr): 3029, 2943, 1792, 1596, 1493, 1364, 1309, 1225, 1168, 1123, 1103, 1047, 838, 755 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 7.8 Hz, 2 H, Ar-H), 7.43 (d, *J* = 7.8 Hz, 2 H, Ar-H), 7.29–7.24 (m, 4 H, Ar-H), 7.13–7.05 (m, 4 H, Ar-H), 6.87 (br s, 2 H, Ar-H), 3.92 (d, *J* = 10.5 Hz, 1 H, SC*H*H), 3.35 (d, *J* = 10.5 Hz, 1 H, SCH*H*), 3.19 (s, 3 H, NMe).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 158.2, 145.2, 134.4, 132.0, 129.7, 129.0, 129.0, 128.5, 127.6, 123.3, 122.7, 120.1, 97.6, 92.5, 39.5, 37.5.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{19}Cl_3N_2OSNa$: 499.0176; found: 499.0176.

4-(Benzylthio)-1-(4-bromophenyl)-3,3-dichloro-4-[(methyl)(phenyl)amino]azetidin-2-one (6f)

Colorless plates; yield: 0.585 g (56%); mp 82–84 °C (EtOH); R_f = 0.47 (5% *n*-hexane/EtOAc).

IR (KBr): 3070, 1787, 1597, 1494, 1455, 1366, 1301, 1262, 1218, 1169, 1094, 1032, 834, 754, 693 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 8.7 Hz, 2 H, Ar-H), 7.59 (d, *J* = 8.7 Hz, 2 H, Ar-H), 7.33–7.28 (m, 2 H, Ar-H), 7.26–7.21 (m, 2 H, Ar-H), 7.15–7.10 (m, 3 H, Ar-H), 7.05 (t, *J* = 7.2 Hz, 1 H, Ar-H), 6.89–6.86 (m, 2 H, Ar-H), 3.93 (d, *J* = 10.5 Hz, 1 H, SC*H*H), 3.35 (d, *J* = 10.5 Hz, 1 H, SCH*H*), 3.19 (s, 3 H, NMe).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 158.2, 145.1, 134.9, 134.4, 132.6, 129.0, 128.5, 127.6, 123.2, 122.6, 120.3, 119.8, 97.5, 92.5, 39.5, 37.5.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{20}BrCl_2N_2OS$: 520.9851; found: 520.9820.

4-(Benzylthio)-3,3-dichloro-4-[(methyl)(phenyl)amino]-1-*o*-tolylazetidin-2-one (6g)

Colorless cubes; yield: 0.631 g (69%); mp 83–85 °C (EtOH); R_f = 0.48 (5% *n*-hexane/EtOAc).

IR (KBr): 3062, 1797, 1595, 1493, 1455, 1359, 1298, 1069, 835, 779, 759 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 7.8 Hz, 1 H, Ar-H), 7.38–7.25 (m, 7 H, Ar-H), 7.10–7.08 (m, 4 H, Ar-H), 6.58–6.56 (m, 2 H, Ar-H), 3.45 (s, 3 H, NMe), 3.29 (2 overlapping d, *J* = 16.5, 10.8 Hz, 2 H, SCH_2), 2.46 (s, 3 H, Me).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 158.2, 145.4, 139.4, 135.8, 129.5, 128.4, 128.2, 126.43, 126.39, 122.9, 122.4, 118.9, 97.8, 92.4, 39.5, 34.8, 33.8.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{23}Cl_2N_2OS$: 457.0903; found: 457.0895.

3,3-Dichloro-4-[(methyl)(phenyl)amino]-4-(2-phenethylthio)-1-phenylazetidin-2-one (6h)

Colorless needles; yield: 0.503 g (55%); mp 86–88 °C (EtOH); R_f = 0.49 (5% *n*-hexane/EtOAc).

IR (KBr): 3071, 3028, 2928, 1787, 1597, 1494, 1453, 1366, 1306, 1227, 1172, 1121, 1102, 1049, 753, 730, 695 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 7.8 Hz, 2 H, Ar-H), 7.43 (t, *J* = 7.2 Hz, 2 H, Ar-H), 7.35–7.23 (m, 5 H, Ar-H), 7.15 (d, *J* = 5.7 Hz, 3 H, Ar-H), 7.06 (t, *J* = 6.9 Hz, 1 H, Ar-H), 6.81 (d, *J* = 6.9 Hz, 2 H, Ar-H), 3.20 (s, 3 H, NMe), 2.96–2.80 (m, 1 H, CH_2CH_2Ph), 2.62–2.33 (m, 3 H, CH_2CH_2Ph).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 158.2, 145.4, 139.4, 135.8, 129.5, 128.4, 128.2, 126.43, 126.39, 122.9, 122.4, 118.9, 97.8, 92.4, 39.5, 34.8, 33.8.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{23}Cl_2N_2OS$: 457.0903; found: 457.0895.

3,3-Dichloro-4-[(methyl)(phenyl)amino]-4-(methylthio)-1-phenylazetidin-2-one (6i)

Colorless cubes; yield: 0.433 g (59%); mp 100–102 °C (benzene); R_f = 0.49 (5% *n*-hexane/EtOAc).

IR (KBr): 3026, 1787, 1597, 1493, 1430, 1367, 1301, 1218, 1169, 1132, 1095, 753, 693 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.98–7.95 (m, 2 H, Ar-H), 7.44 (t, *J* = 7.5 Hz, 2 H, Ar-H), 7.35–7.22 (m, 5 H, Ar-H), 7.07 (t, *J* = 7.2 Hz, 1 H, Ar-H), 3.19 (s, 3 H, NMe), 1.97 (s, 3 H, SMe).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 158.3, 145.4, 136.0, 129.5, 128.4, 126.3, 123.0, 122.4, 118.5, 97.2, 92.2, 39.6, 15.6.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{17}Cl_2N_2OS$: 367.0433; found: 367.0416.

1-Benzyl-4-(benzylthio)-3,3-dichloro-4-[(methyl)(phenyl)amino]azetidin-2-one (6j)

Colorless needles; yield: 0.476 g (52%); mp 102–104 °C (EtOH); R_f = 0.48 (5% *n*-hexane/EtOAc).

IR (KBr): 2829, 1792, 1596, 1495, 1454, 1429, 1382, 1306, 1226, 1101, 1067, 778, 700 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.26 (m, 9 H, Ar-H), 7.16–7.05 (m, 4 H, Ar-H), 6.72–6.70 (m, 2 H, Ar-H), 4.45 (d, *J* = 2.7 Hz, 2 H, NCH_2), 3.56 (d, *J* = 11.4 Hz, 1 H, SC*H*H), 3.37 (d, *J* = 11.4 Hz, 1 H, SCH*H*), 3.09 (s, 3 H, NMe).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 160.9, 145.6, 135.7, 134.3, 128.9, 128.8, 128.5, 128.3, 128.2, 127.5, 122.4, 122.1, 98.1, 90.9, 46.6, 39.3, 36.3.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{22}Cl_2N_2OSNa$: 479.0722; found: 479.0702.

X-ray Crystal Structure Data of 6i

Formula sum: $C_{17}H_{16}Cl_2N_2OS$; formula weight: 367.29; crystal system: monoclinic; space group: *P*2(1)/*c*; unit cell dimensions: *a* = 7.8189(18) Å, *b* = 16.387(4) Å, *c* = 13.218(3) Å, α = 90.00°, β = 93.190(4)°, γ = 90.00°; cell volume = 1691.0(7) Å^3; *Z* = 4; D_{calcd} = 1.443 g/cm^3; R_{All} = 0.0346. Detailed X-ray crystallographic data are available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, as supplementary publication no. CCDC 1009980.

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