A General and Versatile Synthesis of 3-Phenylthio β-Lactams as Lead Molecules for 3-Methyl-2-Azetidinones

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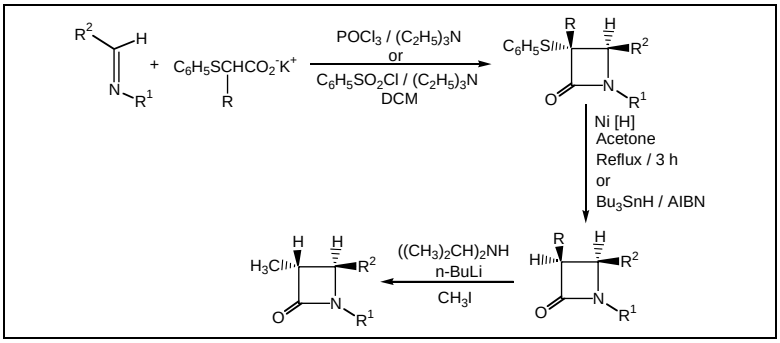

Ketene-imine cycloaddition using phosphorus oxychloride and benzenesulfonyl chloride under the described reaction conditions yielded *trans* 3-phenylthio 2-azetidinones in good yields. Desulfurization using Raney nickel and alkylation finally afforded *trans* 3-methyl-2-azetidinones in a stereoselective manner.

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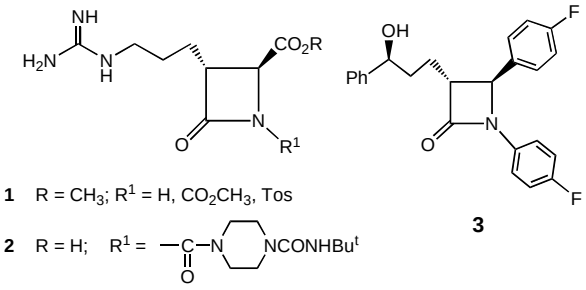
INTRODUCTION

The synthesis of β-lactams has witnessed a resurgence of interest since the discovery that several representatives of this class of compounds can effectively inhibit proteases [1,2]. In particular azetidinone **1** was identified [3] as a powerful and selective inhibitor of thrombin, a serine protease involved in both venous and arterial thrombotic episodes [4]. More recently, β-lactam **2** was found to display inhibition of tryptase at the subnanomolar level and suppress induced inflammation in animal lungs [5] and **3** as cholesterol absorption inhibitor (Figure 1).



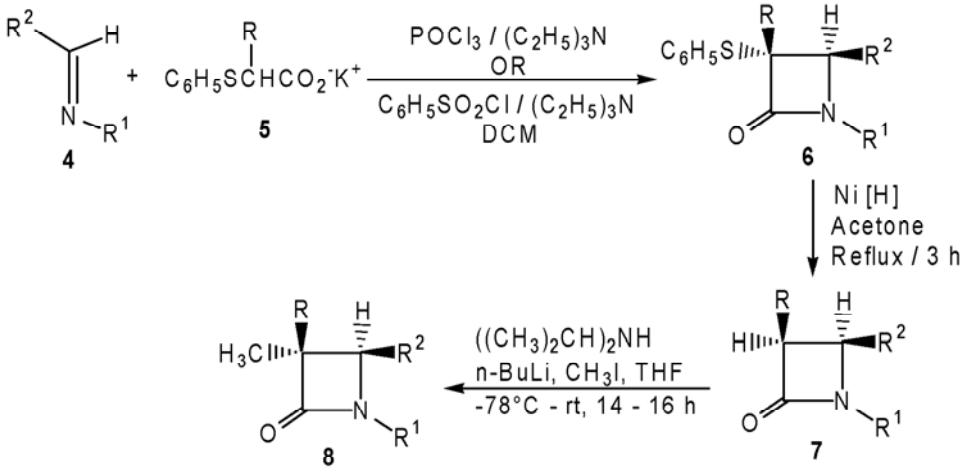
(**Figure 1**)

The structural features of these new types of β-lactams are (a) the presence of an alkyl group at the C - 3 position of the β-lactam ring; (b) the presence of diverse substitutents at C - 4 and N - 1; and (c) the relative stereochemistry at C - 3 and C - 4 positions. Among numerous methods for the synthesis of substituted monocyclic β-lactams [6], the annulation of acid chlorides or equivalents with imines (a variant of the Staudinger Reaction [7]) has proved to be a convenient procedure for the construction of 2-azetidinone ring. This strategy is potentially quite versatile since the needed substrates, acetic acids and Schiff bases are easily accessible, and as a result a number of β-lactams with latent functional group at the three positions can be prepared. Although from this method the steric course of the β-lactam formation does not appear to be predictable, it can be controlled by the experimental conditions used [8,9] and by the choice of Schiff bases with bulky substitutents [10].

α-Unsubstituted β-lactams can serve as synthons for 3-alkylazetidin-2-ones antibiotics. β-Lactams of this type have a single chiral center at C-4 and the question of *cis* and *trans* isomers is absent. The activated methylene group at C-3 can undergo base catalyzed alkylation and condensation reactions, the steric course of which is usually controlled by the bulk of the substituents at C-4. These 3-unsubstituted 2-azetidinones, therefore, can undergo a variety of chemical transformations of immense interest [11].

The utility of the α-bromoester-imine condensation to the synthesis of appropriately substituted 3-alkyl β-lactams had been reported by Palomo *et al* in 1989 [12]. Among many other methods for the synthesis of monocyclic β-lactams [13], however, the direct preparation of 3-alkyl β-lactams from monoalkylketenes, generated from their corresponding acid chlorides, is often limited in scope [14]. Although some exception has appeared [15], no general method to the synthesis of 3-

alkyl β-lactam from the ketene-imine approach has been described. Given the strategic and tactical significance of 3-unsubstituted β-lactams, it was imperative to secure an efficient and highly stereoselective synthetic route to prepare these compounds. The fulcrum of our synthetic plan was a stereoselective synthesis of 3-phenylthio-2-azetidinones derived from Schiff bases and phenylthioacetic acids using readily available benzenesulfonyl chloride and phosphorus oxychloride as the acid activating agents for the construction of β-lactam ring which in analogous systems, is well-precedented in the literature employing Staudinger reaction between appropriately substituted acid chloride and imines [16].



Entry	R^1	R^2	R
a.	C_6H_5	C_6H_5	H
b.	C_6H_5	Piperonyl	H
c.	$C_6H_4OCH_3(p)$	$C_6H_4OCH_3(p)$	H
d.	C_6H_5	$C_6H_4OCH_3(p)$	H
e.	$C_6H_4OCH_3(p)$	$CH{=}CHC_6H_5$	H
f.	$C_6H_4CO_2H$	$C_6H_4OCH_3(p)$	H

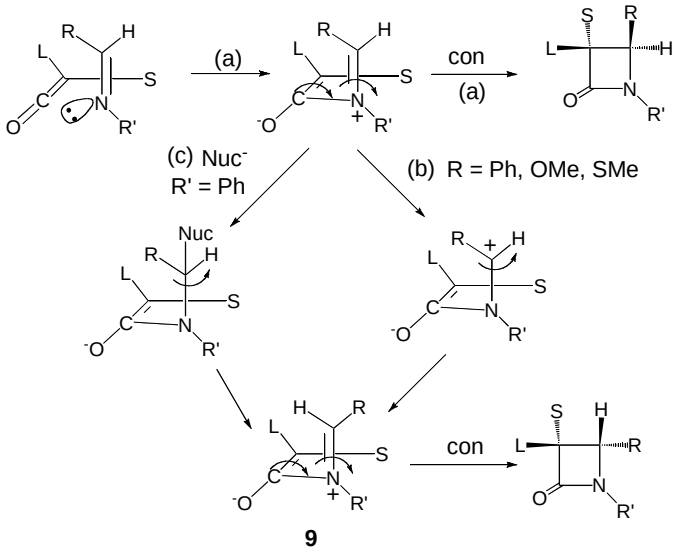
Scheme 1

RESULTS AND DISCUSSION

Though we have already reported the use of $PhSO_2Cl$ as well as $POCl_3$ [17] for the synthesis of β-lactams, we have observed that these reagents work in a cleaner fashion when potassium salts of the requisite acid components were used instead of the acids themselves. A large number of 3-phenylthio β-lactams were prepared using this technique as precursors of 3-unsubstituted β-lactams (Scheme 1). Synthesis of such β-(phenylthio) azetidine-2-ones as an isomeric mixture of *cis* and *trans* have already been reported [18,19] in the literature using methyl-(phenylthio)ketene. Even the β-thiophenoxy ester-enolates react with N-trimethylsilylimines to afford mixture of stereoisomeric β-lactams [20,21].

In the present work, we have substantially improved the synthesis of 3-phenylthio-2-azetidinones and shown that these reagents ($POCl_3$ and $PhSOCl_2$) under the described reaction conditions undergo clean and efficient cycloaddition to provide a concise, high yielding and stereoselective synthesis of *trans* 3-phenylthio-2-azetidinones. The thiophenoxyacetic acid after converting to its potassium salt was reacted with a variety of imines in presence of benzenesulfonyl chloride as well as phosphorous oxychloride and triethylamine to yield the corresponding *trans* β-lactams in good yields which were purified using column chromatography. In all of these β-lactams the 2 Hz coupling constant between the C-3 and C-4 protons were indicative of the *trans* stereochemistry.

No trace of *cis* isomer was detected by NMR spectroscopy. This method display a general scope since various carboxylic acids, as their potassium salt and imines were readily cyclized to their corresponding β-lactams yields being in the range 75-80% (Table 1). To explain the stereoselectivity associated with the reaction involving imines and aryl/alkyl thioacetic acids using $C_6H_5SO_2Cl/(C_2H_5)_3N$ and $POCl_3/(C_2H_5)_3N$ it seems quite



Scheme 2

probable that the groups on the bond forming carbons C-3 and C-4 orient themselves on the diene dipolar intermediates **9** as shown in Scheme 2. This intermediate is the favored one due to absence of any interaction of C_3-SPh vs C_4–R^2. Conrotation of the overlapping orbitals for bond formation leads to the exclusive formation of the *trans* β-lactams.

A key feature of these β-lactams is shown by their use as potential precursors of 3-unsubstituted β-lactams where as these last are recognized as valuable starting materials for the introduction of several groups at the α-position of the β-lactam carbonyl [22]. The phenylthio group at C-3 of the β-lactam ring is chosen as a convenient vehicle for introducing the alkyl group. Cleavage of the C - S bond has been most conveniently done under mild conditions using desulfurization reaction with Raney nickel chemisorbed with hydrogen [23], the reaction is generally performed in ethanol or acetone. Thus when the 3-thio-

Table 1

Characterization Data of 3-Phenylthio-2-azetidinones

Compd.	Yield (%)	mp (°C)	Molecular formula (molecular weight)	Analytical data Found (calculated) (%) C	H	N	Spectral data FT-IR (NaCl plates, ν, cm^{-1}) ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm) ^{13}C NMR (300 MHz, $CDCl_3$, δ, ppm)
6a	70	67-68	$C_{21}H_{17}NOS$ (331)	75.92 (75.73)	5.12 (5.24)	4.41 (4.22)	1750 4.44 (d, 1H, C_3H, J = 1.6 Hz), 4.85 (d, 1H, C_4H, J = 1.6 Hz), 7.01-7.72 (m, 15H, ArH) 52.2, 61.9, 120.4, 124.9, 126.6, 127.1, 128.7, 135.6, 140.8, 142.4, 170.9
6b	72	175-176	$C_{22}H_{17}NO_3S$ (375)	70.20 (70.40)	4.49 (4.53)	3.86 (3.73)	1760 4.25 (d, 1H, C_3H, J = 2.2 Hz), 4.65 (d, 1H, C_4H, J = 2.2 Hz), 6.85 (s, 2H, OCH_2O) 7.31-7.82 (m, 13H, ArH) 53.2, 62.2, 91.5, 112.1, 115, 120, 124, 126.6, 128.7, 135, 140.8, 145.6, 147.4, 170.9
6c	70	Oil	$C_{23}H_{21}NO_3S$ (391)	70.49 (70.59)	5.01 (5.27)	3.71 (3.58)	1747 3.79 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.21 (d, 1H, C_3H, J = 2.2 Hz), 4.71 (d, 1H, C_4H, J = 2.2 Hz), 6.76-7.62 (m, 8H, ArH), 7.35 (s, 5H, ArH) 55.33, 55.41, 61.4, 63.01, 114.3, 114.63, 118.7, 127.42, 127.82, 128.19, 129.17, 130.70, 131.99, 132.52, 156.28, 160.06, 162.81
6d	69	141-142	$C_{22}H_{19}NO_2S$ (361)	72.92 (72.73)	5.17 (5.26)	3.91 (3.88)	1743 3.75 (s, 3H, OCH_3), 4.27 (d, 1H, C_3H, J = 2.3 Hz), 4.79 (d, 1H, C_4H, J = 2.3 Hz), 6.75-7.66 (m, 14H, ArH) 55.46, 61.52, 63.17, 114.33, 118.68, 126.12, 128.05, 128.55, 129.26, 130.58, 132.30, 132.60, 134.93, 136.38, 156.43, 162.79

Table 1 (continued)

Compd.	Yield (%)	mp (°C)	Molecular formula (molecular weight)	Analytical data Found (calculated) (%) C	H	N	Spectral data FT-IR (NaCl plates, ν, cm^{-1}) ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm) ^{13}C NMR (300 MHz, $CDCl_3$, δ, ppm)
6e	75	127-128	$C_{24}H_{21}NO_2S$ (387)	74.20 (74.42)	5.29 (5.43)	3.75 (3.62)	1752, 1600 3.87 (s, 3H, OCH_3), 4.99 (d, 1H, C_3H, J = 2 Hz), 5.47 (dd, 1H, C_4H, J = 7.0, 2.0 Hz), 6.32 (dd, 1H, NCHCH, J = 15.0, 7.0 Hz), 6.79 (d, 1H, CHC_6H_5, J = 15 Hz), 6.81-7.72 (m, 14H, ArH) 51.5, 56.0, 59.5, 114, 121.4, 123.3, 124.9, 126.6, 127.7, 128.4, 133.1, 134, 135.6, 157.6, 170.9
6f	73	140-142	$C_{23}H_{19}NO_4S$ (405)	68.00 (68.15)	4.51 (4.69)	3.75 (3.56)	3200, 1755, 1600 3.81 (s, 3H, OCH_3), 4.21 (d, 1H, C_3H, J = 1.8 Hz), 4.72 (d, 1H, C_4H, J = 1.8 Hz), 6.65-7.00 (m, 13H, Ar-H) 52.2, 56.0, 61.9, 113.9, 120.3, 122.5, 124.0, 125.1, 126.6, 128.7, 130.3, 133.9, 134.7, 135.6, 142.2, 160.0, 170.9, 172.0
6g	71	157-153	$C_{24}H_{23}NO_2S$ (389)	73.99 (73.84)	5.89 (5.91)	3.89 (3.60)	1756 2.89 (t, 2H, $CH_2C_6H_5$), 3.60 (t, 2H, NCH_2), 3.92 (s, 3H, OCH_3), 4.32 (d, 1H, C_3H, J = 2.0 Hz), 4.61 (d, 1H, C_4H, J = 2 Hz), 6.85-7.85 (m, 14H, ArH) 25.0, 48.8, 56.0, 59.8, 113.9, 124.9, 125.7, 126.4, 127.9, 128.7, 129.5, 135.6, 140.7, 160.3, 173.6
6h	68	130-132	$C_{19}H_{21}NO_3S$ (343)	66.23 (66.47)	6.09 (6.12)	4.11 (4.08)	3460, 1756 1.32 (d, 3H, CH_3, J = 7 Hz), 3.25 (m, 1H, CHOH), 3.53 (m, 2H, NCH_2), 3.88 (s, 3H, OCH_3), 4.19 (d, 1H, C_3H, J = 1.5 Hz), 4.23 (d, 1H, C_4H, J = 1.5 Hz), 6.85-7.73 (m, 9H, ArH) 20.4, 52.6, 56.5, 60.1, 67.6, 113.9, 124.9, 126.6, 128.7, 129.5, 135.6, 160.3, 173.6
6i	72	125-127	$C_{20}H_{21}NO_2S$ (339)	69.99 (69.81)	6.00 (6.19)	4.27 (4.13)	3381, 1739, 1650 1.23 (d, 3H, CH_3, J = 7.0 Hz), 3.25 (m, 1H, CHOH), 3.45 (m, 2H, NCH_2), 4.09 (d, 1H, C_3H, J = 1.8 Hz), 4.23 (dd, 1H, C_4H, J = 6.0, 1.8 Hz), 6.25 (dd, 1H, NCHCH, J = 14.0, 6.0 Hz), 6.75 (d, 1H, CHC_6H_5, J = 14.0 Hz), 7.41 and 7.51 (s each, 10H, ArH) 20.4, 50.5, 57.0, 57.7, 67.7, 123.3, 124.9, 126.2, 127.7, 128.4, 134.0, 135.6, 173.6
6j	60	Oil	$C_{19}H_{19}NO_4S$ (357)	63.75 (63.87)	5.30 (5.42)	4.01 (3.92)	1756, 1731 1.32 (t, 3H, CH_2CH_3,), 3.81 (s, 3H, OCH_3), 4.25 (q, 2H, CH_2CH_3), 4.41 (d, 1H, C_3H, J = 2.2 Hz), 4.85 (d, 1H, C_4H, J = 2.2 Hz), 6.85-7.73 (m, 9H, ArH) 13.6, 45.2, 56.0, 59.5, 62.2, 114.3, 121.4, 124.9, 126.6, 128.7, 133.1, 135.6, 137.6, 170.0, 172.0
6k[17]	62	121-122	$C_{22}H_{19}NO_2S$ (361)	73.01 (73.13)	5.19 (5.26)	3.95 (3.88)	1745 3.77 (s, 3H, OCH_3), 4.05 (d, 1H, C_3H, J = 2.0 Hz), 4.08 (d, 1H, C_4H, J = 2.0 Hz), 6.80-7.41 (m, 14H, ArH)

phenoxy β-lactams **6a-k** were refluxed with freshly prepared Raney nickel in acetone furnished the corresponding β-lactams **7a-k** in good yields. The characterization data of all the compounds prepared is given in Table 2.

Transformation at the C - 3 carbon of β-lactams leading to the formation of diverse molecules involving anionic and cationic β-lactam equivalents **a** and **b** respectively (Figure 2) are an important area of research [24,25]. The potential of the cationic β-lactam equivalent of type **b** has been explored by many groups [26-28] for

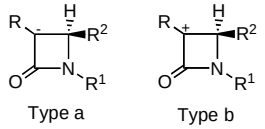


Figure 2

the preparation of different β-lactam synthons. However, the chemistry involving the anionic β-lactam equivalents has not been extensively studied. Hence, our attention was focused on the use of anionic β-lactam equivalent type **a**. If the C_4 substitution is bulky, the *trans* β-lactam is often the only substitution product and that is essential for the molecule to show antimicrobial property.

Thus, when we subjected the anion, generated *in situ* from 3-unsubstituted β-lactam **7a-k** and LDA, to alkylation with methyl iodide, and obtained exclusively the *trans* 3-methyl β-lactam **8a-k** in high yields. Significantly, no bis-methylated lactam or *cis* isomer was detected in the reaction. The structure was confirmed by analytical as well as spectral data (Table 3). As a model for our work the synthesis of **7b** was studied first. The starting material, Schiff base **4b** was prepared by the reaction of aniline and piperonal in refluxing methylene

Table 2

Characterization data of 3-Unsubstituted-2-Azetidinones

Compd.	Yield (%)	mp (°C)	Molecular formula (molecular weight)	Analytical data Found (calculated) (%) C	H	N	Spectral Data FT-IR (NaCl plates, ν, cm^{-1}) ^1H NMR (60 MHz, $CDCl_3$, δ, ppm)
7a	62	67-68	$C_{15}H_{13}NO$ (223)	80.52 (80.72)	5.70 (5.83)	6.35 (6.27)	1751 2.82 (dd, 1H, C_3H, J = 12.9, 2.4 Hz), 3.35 (dd, 1H, C_3H, J = 12.9, 5.1 Hz), 4.41 (dd, 1H, C_4H, J = 5.1, 2.4 Hz), 7.01-7.5 (m, 10H, ArH)
7b	59	145	$C_{16}H_{13}NO_3$ (267)	71.80 (71.91)	4.75 (4.87)	5.31 (5.24)	1757 3.22 (dd, 1H, C_3H, J = 15, 2.7 Hz), 3.40 (dd, 1H, C_3H, J = 15, 4.5 Hz), 4.52 (dd, 1H, C_4H, J = 4.5, 2.7 Hz), 5.99 (s, 2H, OCH_2O), 6.52-6.91 (m, 8H, ArH)
7c	61	134-136	$C_{17}H_{17}NO_3$ (283)	71.99 (72.08)	5.81 (6.00)	4.99 (4.95)	1750 2.85 (dd, 1H, C_3H, J = 14.1, 2.5 Hz), 3.55 (dd, 1H, C_3H, J = 14.1, 5.0 Hz), 3.71 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.85 (dd, 1H, C_4H, J = 5.0, 2.5 Hz), 6.73 and 6.85 (d each, 4H, ArH, J = 9.1 Hz), 7.16 and 7.35 (d each, 4H, ArH, J = 9.3 Hz)
7d	60	Oil	$C_{16}H_{15}NO_2$ (253)	75.71 (75.89)	6.01 (5.93)	5.62 (5.53)	1745 3.15 (dd, 1H, C_3H, J = 15.2, 3.0 Hz), 3.23 (dd, 1H, C_3H, J = 15.2, 5.5 Hz), 3.75 (s, 3H, OCH_3), 4.52 (dd, 1H, C_4H, J = 5.5, 3.0 Hz), 6.91-7.52 (m, 9H, ArH)
7e	61	134-136	$C_{18}H_{17}NO_2$ (279.3)	77.20 (77.40)	6.00 (6.13)	5.21 (5.01)	1750 2.81 (dd, 1H, C_3H, J = 14.1, 2.5 Hz), 3.23 (dd, 1H, C_3H, J = 14.1, 5.0 Hz), 3.76 (s, 3H, OCH_3), 4.63 (dd, 1H, C_4H, J = 5.0, 2.5 Hz), 6.04 (dd, 1H, C_4HC=, J = 15.3, 2.5 Hz), 6.61 (d, 1H, CH=CHPh, J = 15.3 Hz) 6.88 and 7.35 (d each, 4H, ArH, J = 9.4 Hz), 6.73 and 6.85 (d each, 4H, ArH, J = 9.1 Hz), 7.16 and 7.35 (d each, 4H, ArH, J = 9.3 Hz), 7.20 – 7.40 (m, 5H, ArH)
7f	55	77 - 79	$C_{17}H_{15}NO_4$ (297.31)	68.47 (68.68)	4.91 (5.09)	4.50 (4.71)	1752 2.27 (dd, 1H, C_3H, J = 15.2, 2.7 Hz), 2.95 (dd, 1H, C_3H, J = 15.2, 5.7 Hz), 3.75 (s, 3H, OCH_3), 5.07 (dd, 1H, C_4H, J = 3.0, 2.70 Hz), 6.84 and 7.25 (d each, 4H, ArH, J = 8.4 Hz), 7.27–7.96 (m, 4H, ArH)
7g	57	89 - 91	$C_{18}H_{19}NO_2$ (281.35)	76.66 (76.84)	6.70 (6.81)	4.71 (4.98)	1748 2.75 (dd, 1H, C_3H, J = 15, 2.2 Hz), 2.89 (m, 2H, CH_2Ph), 3.23 (m, 1H, $NHCH_2$), 3.30 (dd, 1H, C_3H, J = 15, 5.1 Hz), 3.45 (m, 1H, $NHCH_2$), 3.76 (s, 3H, OCH_3), 5.10 (dd, 1H, C_4H, J = 3.0, 2.7 Hz), 6.85 and 7.24 (d each, 4H, ArH, J = 8.5 Hz), 7.20 – 7.50 (m, 5H, ArH)
7h	56	101 - 103	$C_{13}H_{17}NO_3$ (237.29)	66.15 (66.36)	7.0 (7.28)	5.85 (5.95)	1751 1.21 (d, 3H, $CHCH_3$, J = 6.60 Hz), 2.52 (dd, 1H, C_3H, J = 14.0, 2.2 Hz), 3.05 (dd, 1H, NCHCH, J = 13.3, 3.6 Hz), 3.1 (dd, 1H, C_3H, J = 14.0, 5.1 Hz), 3.47 (dd, 1H, NCHCH, J = 13.3, 8.6 Hz), 3.76 (s, 3H, OCH_3), 3.83 (m, 1H, CHOH), 4.22 (dd, 1H, C_4H, J = 5.10, 2.2 Hz), 4.36 (br s, 1H, OH), 6.86 and 7.24 (d each, 4H, ArH, J = 8.5 Hz)
7i	54	77 - 79	$C_{14}H_{17}NO_2$ (231.29)	72.60 (72.70)	7.21 (7.41)	6.26 (6.06)	1751 1.22 (d, 3H, $CHCH_3$, J = 6.7 Hz), 2.76 (dd, 1H, C_3H, J = 14.9, 4.4 Hz), 2.82 (dd, 1H, NCHCH, J = 13.3 3.6 Hz), 3.16 (dd, 1H, C_3H, J = 14.9, 4.4 Hz), 3.22 (dd, 1H, NCHCH, J = 13.3, 8.6 Hz), 3.95 (m, 1H, CHOH), 4.15 (m, 1H, C_4H), 4.36 (br s, 1H, OH), 6.46 (dd, 1H, >CH-CH=, J = 15.3, 7.6 Hz), 6.58 (d, 1H, =CHPh, J = 15.3 Hz), 7.16 – 7.27 (m, 5H, ArH)
7j	58	72 - 74	$C_{13}H_{15}NO_4$ (249.26)	62.44 (62.64)	6.27 (6.07)	5.82 (5.62)	1751 1.27 (t, 3H, CH_2CH_3), 3.04 (dd, 1H, C_3H, J = 14.6, 2.6 Hz), 3.34 (dd, 1H, C_3H, J = 14.6, 4.6 Hz), 3.73 (s, 3H, OCH_3), 4.16 (q, 2H, CH_2CH_3), 4.68 (dd, 1H, C_4H, J = 4.6, 2.6 Hz), 6.88 and 7.32 (d, 4H, ArH, J = 9.40 Hz)
7k	59	81 - 83	$C_{16}H_{15}NO_2$ (253.29)	75.69 (75.87)	5.81 (5.97)	5.41 (5.53)	1753 2.88 (dd, 1H, C_3H, J = 15.2, 2.7 Hz), 3.55 (dd, 1H, C_3H, J = 15.2, 5.7 Hz), 3.72 (s, 3H, OCH_3), 4.99 (dd, 1H, C_4H, J = 2.7, 5.7 Hz), 6.93 and 7.16 (d each, 4H, ArH, J = 9.4 Hz), 7.28 – 7.41 (m, 5H, ArH)

Table 3

Characterization data of 3-Methyl-2-Azetidinones prepared

Compd.	Yield (%)	mp (°c)	Molecular formula (molecular weight)	Analytical data Found (calculated) (%) C	H	N	Spectral Data IR (NaCl plates, ν, cm^{-1}) ^1H NMR (60 MHz, $CDCl_3$, δ, ppm)
8a	62	99-100	$C_{16}H_{15}NO$ (237)	79.89 (81.01)	6.13 (6.33)	5.89 (5.91)	1748 1.25 (d, 3H, CH_3, J = 7.2 Hz), 3.21 (m, 1H, C_3H), 4.30 (d, 1H, C_4H, J = 2 Hz), 6.95-7.45 (m, 10H, ArH)
8b	61	130-135	$C_{17}H_{15}NO_3$ (281)	72.38 (72.60)	5.22 (5.34)	4.87 (4.98)	1750 1.32 (d, 3H, CH_3, J = 6.5 Hz), 3.35 (m, 1H, C_3H), 4.42 (d, 1H, C_4H, J = 2.1 Hz), 6.01 (s, 2H, OCH_2O), 6.69-7.12 (m, 8H, ArH)
8c	59	122-124	$C_{18}H_{19}NO_3$ (297)	72.51 (72.73)	6.28 (6.39)	4.69 (4.71)	1750 1.30 (d, 3H, CH_3, J = 7.0 Hz), 3.30 (m, 1H, C_3H), 3.75 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.51 (d, 1H, C_4H, J = 2.2 Hz), 6.63-7.30 (m, 8H, ArH)
8d	58	110-112	$C_{17}H_{17}NO_2$ (267)	76.38 (76.40)	6.35 (6.37)	5.11 (5.24)	1755 1.39 (d, 3H, CH_3, J = 6.5 Hz), 3.21 (m, 1H, C_3H), 3.75 (s, 3H, OCH_3), 4.50 (d, 1H, C_4H, J = 2.3 Hz), 7.00-7.60 (m, 9H, ArH)
8e	60	101-104	$C_{19}H_{19}NO_2$ (293.36)	77.58 (77.79)	6.42 (6.53)	4.82 (4.77)	1750 1.17 (d, 3H, $CHCH_3$, J = 7.42 Hz), 3.16 (m, 1H, C_3H), 3.77 (s, 3H, OCH_3), 4.88 (dd, 1H, C_4H, J = 2.3, 8.3 Hz), 6.46 (dd, 1H, >C-CH=, J = 8.3, 16.0 Hz), 6.57 (d, 1H, =CHPh, J = 16.0 Hz), 6.82 & 7.26 (d each, 4H, ArH, J = 9.40 Hz), 7.19–7.35 (m, 5H, ArH)
8f	57	112-114	$C_{18}H_{17}NO_4$ (311.33)	69.27 (69.44)	5.35 (5.50)	4.31 (4.50)	1754 1.04 (d, 3H, $CHCH_3$, J = 7.5 Hz), 3.32 (m, 1H, C_3H), 3.76 (s, 3H, OCH_3), 4.95 (d, 1H, C_4H, J = 2.3 Hz), 6.90 and 6.95 (d each, 4H, ArH, J = 8.48 Hz), 7.41 and 8.00 (d each, 4H, ArH, J = 8.7 Hz), 12.19 (br s, 1H, COOH)
8g	61	89 - 91	$C_{19}H_{21}NO_2$ (295.38)	77.11 (77.26)	7.29 (7.17)	4.53 (4.74)	1752 1.01 (d, 3H, $CHCH_3$, J = 7.5 Hz), 2.89 (t, 2H, CH_2Ph), 3.26 (m, 1H, C_3H), 3.28 (m, 1H, NCH), 3.50 (m, 1H, NCH), 3.76 (s, 3H, OCH_3), 4.13 (d, 1H, C_4H, J = 2.3 Hz), 6.92 and 6.99 (d each, 4H, ArH, J = 8.5 Hz), 7.08-7.41 (m, 5H, ArH)
8h	56	95 -97	$C_{14}H_{19}NO_3$ (249.31)	67.27 (67.45)	7.51 (7.68)	5.50 (5.62)	1755 1.04 (d, 3H, $CHCH_3$, J = 7.5 Hz), 1.22 (d, 3H, $HC(OH)CH_3$, J = 6.6 Hz), 3.03 (dd, 1H, NHCH, J = 13.3 and 3.6 Hz), 3.10 (m, 1H, C_3H), 3.45 (dd, 1H, NHCH, J = 13.3 and 8.6 Hz), 3.76 (s, 3H, OCH_3), 4.00 (dd, 1H, CHOH, J = 8.6 and 3.6 Hz), 4.10 (d, 1H, C_4H, J = 2.1 Hz), 4.36 (br s, 1H, OH), 6.91 and 6.99 (d each, 4H, ArH, J = 8.5 Hz)
8i	57	107 - 108	$C_{15}H_{19}NO_2$ (245.32)	73.30 (73.44)	7.60 (7.81)	5.61 (5.71)	1750 1.13 (d, 3H, $CHCH_3$, J = 7.4 Hz), 1.25 (d, 3H, $HC(OH)CH_3$, J = 6.6 Hz), 2.98 (dd, 1H, NHCH, J = 13.3 and 3.6 Hz), 3.14 (m, 1H, C_3H), 3.38 (dd, 1H, NHCH, J = 13.3 and 8.6 Hz), 4.00 (dd, 1H, CHOH, J = 8.6 and 3.6 Hz), 4.36 (br s, 1H, OH), 4.42 (dd, 1H, C_4H, J = 8.3 and 2.3 Hz), 6.49 (d, 1H, =CHPh, J = 16.0 Hz), 6.56 (dd, 1H, CHCH=, J = 16.0 and 8.3 Hz), 7.16–7.35 (m, 5H, ArH)
8j	60	125 - 127	$C_{14}H_{17}NO_4$ (263.29)	63.61 (63.87)	6.40 (6.51)	5.11 (5.32)	1751 1.26 (t, 3H, CH_2CH_3), 1.31 (d, 3H, $HCCH_3$, J = 7.5 Hz), 3.54 (m, 1H, $CHCH_3$), 3.70 (s, 1H, OCH_3), 4.15 (q, 1H, CH_2CH_3), 4.59 (d, 1H, C_4H, J = 2.3 Hz), 6.85 and 7.33 (d each, 4H, ArH, J = 9.4 Hz)
8k	58	130 - 132	$C_{17}H_{17}NO_2$ (267.32)	76.18 (76.38)	6.20 (6.41)	5.01 (5.24)	1754 1.04 (d, 3H, $CHCH_3$, J = 7.5 Hz), 3.38 (m, 1H, $HCCH_3$), 3.70 (s, 1H, OCH_3), 4.82 (d, 1H, C_4H, J = 2.25 Hz), 6.89 and 7.16 (d each, 4H, ArH, J = 9.4 Hz), 6.95–7.32 (m, 5H, ArH)

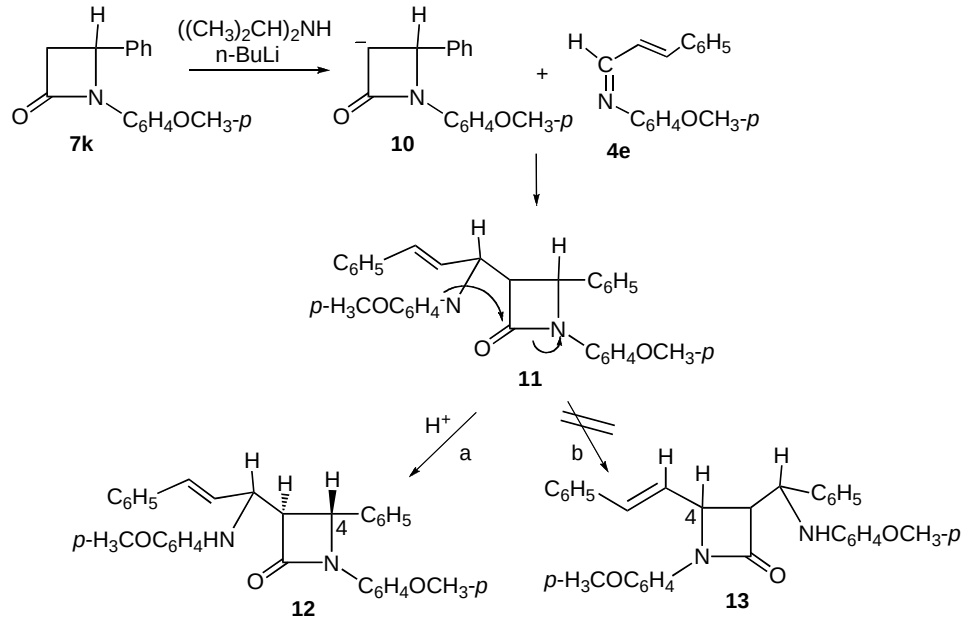
chloride. Compound **4b** was then treated with the potassium salt of thiophenoxy acetic acid **5b** and triethylamine followed by $POCl_3$ and $PhSO_2Cl$ to yield **6b** in 72 % yield. Treatment of **6b** with Raney nickel in refluxing acetone resulted in desulfurization yielding the expected 3-unsubstituted product **7b** in 59% yield. Compound **7b** could also be obtained in high yield from **6b** when treated with a slight excess of tributyltin hydride with azoisobutyronitrile (AIBN) catalyst [29] in refluxing toluene for 3 hours, to efficiently produce **7b** in 80% yield. Although both methods were successful, the first one proved to be more convenient and less expensive. Finally, methylation of 3-unsubstituted β-lactam **7b** using methyl iodide yielded the corresponding *trans* 3-methyl β-lactam **8b** in 61% yield.

We would like to describe here another very interesting reaction of the β-lactam enolate **10** with the Schiff base **4e** in a manner similar to an ester enolate-imine condensation in the hope of getting a new β-lactam structure. Below is given the probable two-step course of the reaction, which can lead to the product **12** or the desired 3-alkylated β-lactam **13** *via* **11** (Scheme 3).

Finally, these *trans* β-lactam compounds can be further elaborated according to the known methodology to give the corresponding *trans* PS-5 and *trans* PS-6 precursors. It is interesting to note that this procedure only leads to *trans* isomers. Therefore, it appears to be superior to the earlier route in terms of overall yield and stereocontrol. This synthesis of *trans* 3-alkyl-2-azetidinones, alongside previous known routes, represents a useful application of the [2+2] cycloaddition reaction and illustrates the value of phosphrous oxychloride and benzenesulfonyl chloride as efficient and readily available reagents.

EXPERIMENTAL

All melting points (mp, °C) are uncorrected. The FT-IR spectra were calibrated against polystyrene. Only the principal peaks of interest are reported and expressed in cm^{-1}. ^1H NMR chemical shifts are expressed as δ values (ppm) downfield from tetramethylsilane (TMS). Thin layer chromatography was performed using TLC grade silica gel (G) and was developed in an atmosphere of iodine vapors. The characterization data are given in Table 1-3**.**



Scheme 3

Compound **12** could not be obtained in pure form and therefore a tentative assignment had to be gleaned from the crude product. The FT-IR and ^1H NMR data undoubtly confirmed the product to be **12**. ^1H NMR showed the C - 4 proton as doublet with J = 2 Hz, indicating the *trans* orientation of β-lactam protons. In the alternative structure **13** this proton should have shown a double doublet due to coupling with adjacent C - 3 and cinnamyl proton.

General Procedure for the Formation of 3-Phenyl sulfanyl-2-azetidinones 6. Phosphorous oxychloride or benzenesulfonyl chloride (0.1 mmol) in dry dichloromethane (6 mL) was added dropwise to a well stirred solution of potassium salt of thiophenoxyacetic acid (0.12 mmol), appropriate Schiff base (0.1 mmol) and triethylamine (0.2 mmol) in dry dichloromethane (10 mL) at 0-5 °C and the reaction mixture was then stirred overnight at 25 – 30 °C. The mixture was washed with dilute hydrochloric acid (10 mL), followed by brine (10 mL) and water (10 mL). The organic layer was dried over

anhydrous sodium sulfate and the solvent removed under vacuum to obtain the final 2-azetidinones which were purified by recrystallization from suitable solvents or through column chromatography using 15% ethyl acetate in hexane as eluent.

Preparation of Raney Nickel Catalyst. To an aqueous solution of sodium hydroxide (0.1 *M*; 2 mL), 0.6 g of Ni-Al alloy was added in fractions maintaining the temperature up to 20 °C and the contents digested for 1 h at 60 °C, cooled and allowed to settle. The water was decanted off and the residue washed several times with water. It was filtered through G-4 sintered glass crucible and finally washed with alcohol (5 mL × 3) to drain off the moisture and used instantly for desulfurization reactions.

General Procedure for Desulfurization of 3-Phenylthio 2-azetidinones 7. Using Raney Nickel: A solution of appropriate phenylthio 2-azetidinone (0.1 mmol) in acetone (10 mL) was stirred and heated under reflux for 3 h with four teaspoons of Raney nickel catalyst. The catalyst was filtered and washed with acetone (2 mL). Removal of solvent from the filtrate afforded the final compound as a thick oily liquid, which was chromatographed over neutral alumina using petroleum ether as eluent and was then crystallized from *n*-hexane.

Using Bu_3SnH/AIBN: To a solution of phenylthio-2-azetidinone (5.96 mmol) in THF (30 mL) under nitrogen atmosphere was added Bu_3SnH (3.0 mL; 11.15 mmol; 1.9 equiv.). The reaction mixture was heated to reflux to get a clear homogenous solution. The reaction mixture was then cooled slightly and AIBN (300 mg) was added. The mixture as then cooled to 25 °C and concentrated to give a residue. The residue was purified by silica gel column chromatography (Silica gel 60, 230 – 400 mesh, using ethyl acetate/hexane as eluent) or by hexane trituration to afford final product **7**.

General Procedure for the Preparation of 3-Methyl-2-azetidinone 8. To diisopropylamine (0.18 mmol) in dry THF (9 mL) under nitrogen atmosphere was added *n*-BuLi in hexane (0.18 mmol, 0.5 N) at –78 °C and the solution was stirred for 15 min. This was followed by the addition of the 3-unsubstituted-2-azetidinone (0.15 mmol) in THF (9 mL) at such a rate that the temperature did not exceed –60 °C. The solution was stirred at the same temperature for 50 min followed by the addition of the methyl iodide (0.20 mmol) in THF (5 mL). The mixture was stirred at –78 °C for 1 h, the cold bath was removed and the mixture was warmed to 25 – 30 °C and was stirred for additional 14-16 h. The reaction progress was monitored by TLC. The reaction mixture was quenched with saturated ammonium chloride solution (6 mL) and extracted with ether (15 mL). The organic layer was separated, washed with water (7 mL) and brine (7 mL). The solvent was removed to afford the crude product that was purified by chromatography using light petroleum ether:ethyl acetate (4:1) to obtain pure 3-methyl 2-azetidinone.

Reaction of 3-Unsubstituted-2-Azetidinone 7k with Schiff Base 4e. To diisopropylamine (0.18 mmol) in dry THF (5 mL) under nitrogen atmosphere was added *n*-BuLi in hexane (0.18 mmol, 0.5 *N*) at –78 °C and the solution was stirred for 15 min. This was followed by the addition of the 3-unsubstituted-2-azetdidinone (0.15 mmol) in THF (5 mL) at such a rate that the temperature did not exceed –60 °C. The solution was stirred at the same temperature for 50 min followed by the addition of the Schiff base (0.20 mmol) in THF (5 mL). The mixture was stirred at –78 °C for 1 h, the cold bath was removed and the mixture was warmed to 25 – 30 °C and stirred for additional 48 h. The reaction progress was monitored by TLC. The reaction mixture was quenched with saturated ammonium chloride solution (8 mL) and extracted with ether (10 mL). The organic layer was separated, washed with water (5 mL) and brine (5 mL). The solvent was removed to afford crude **12**. FT-IR ($CHCl_3$, ν, cm^{-1}): 3200, 1748, and 1630. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 3.23 (dd, 1H, NHCH, J = 7, 6 Hz), 3.75 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.32 (dd, 1H, C_3H, J = 7, 2 Hz), 4.95 (d, 1H, C_4H, J = 2 Hz), 6.25 (dd, 1H, $CHCHC_6H_5$, J = 14, 6 Hz), 6.73 (d, 1H, CHC_6H_5, J = 14 Hz), 6.95-7.52 (m, 18H, ArH).

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