Pergamon

Tetrahedron Letters 41 (2000) 5577–5581

TETRAHEDRON LETTERS

A new synthetic approach for novel C-3 substituted β-lactams

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Received 13 March 2000; accepted 23 May 2000

Abstract

An effective route to novel C-3 substituted β-lactams is described. This involves reaction of a β-lactam carbocation equivalent with active aromatic nucleophiles in the presence of a Lewis acid. The stereospecificity of the formation of mono-substituted products may be rationalised on the basis of the $SnCl_4$ mediated intermediate complex **A** that reacts via an S_N2 mechanism.

β-Lactams are well-acknowledged structural elements of the widely used penicillins, cephalosporins, thienamycins and other monocyclic β-lactam antibiotics[1] such as monobactams. New routes for the synthesis of monocyclic β-lactams with different appendages at C-3 and C-4 continue to present a challenge for the synthetic organic chemist. More recently, C-3 aryl substituted monocyclic β-lactams have been shown to be potential inhibitors of cholesterol acyl transferase[2] which is mainly responsible for atherosclerotic coronary heart disease.

Transformations at the C-3 carbon of β-lactams leading to the formation of diverse molecules involving anionic and cationic β-lactam equivalents **1** and **2**, respectively (Fig. 1) are an important area of research.[3] The potential of the anionic β-lactam equivalent of type **1** has been explored by many groups[4] for the preparation of different β-lactam synthons.

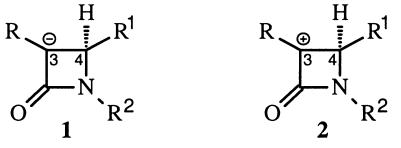

Figure 1.

However, the chemistry involving the cationic β-lactam equivalent **2** is not fully explored. A related study involving S_N2' substitution at C-3 has recently been reported.[5] Hence, our attention

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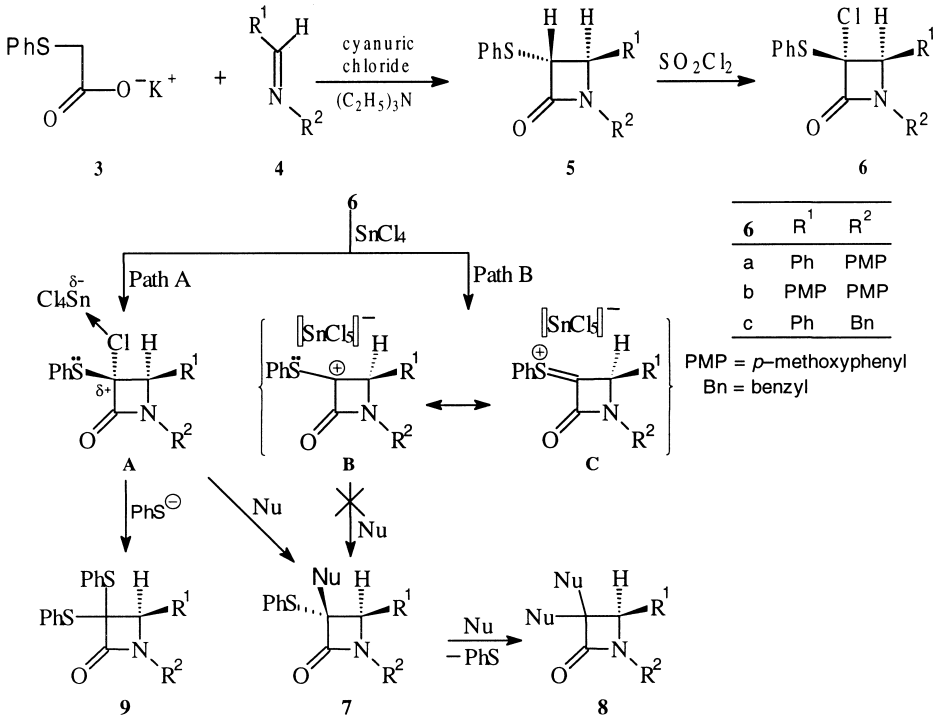
0040-4039/00/$ - see front matter
PII: S0040-4039(00)00865-0

was focused on the use of the cationic β-lactam equivalent type **2** and the exploration of its potential in synthetically useful transformations. We report here a new strategy for the synthesis of novel C-3 substituted β-lactams involving an easily available[6] α-chloro-α-phenylthio-β-lactam **6**. This β-lactam is capable of functioning as a C-3 carbocation equivalent in the presence of a Lewis acid.

Thus, in the presence of the Lewis acid[7] $SnCl_4$, β-lactam **6** reacts with a number of active aromatic nucleophiles to produce a variety of substituted β-lactams. A number of interesting C-3 mono-substituted as well as disubstituted β-lactams which may not be easily prepared via the classical routes using an acid chloride-imine cycloaddition[8] approach, are accessible using this strategy (Scheme 1).



6	R^1	R^2
a	Ph	PMP
b	PMP	PMP
c	Ph	Bn

Scheme 1.

β-Lactams **5**, suitable for this study, were prepared from potassium phenylthioacetate **3** and appropriate Schiff bases **4** by the reported procedure.[6] These β-lactams **5** were converted to the corresponding 3-chloro-3-phenylthioazetidin-2-ones **6(a–c)** by reacting with SO_2Cl_2.[9] Initial studies were carried out by reacting **6a** with anisole as the nucleophile[10] in the presence of 1 equivalent of $SnCl_4$ at –78°C. Instead of leading to the formation of the expected monosubstituted product of type **7**, surprisingly, the product was found to be a mixture of two compounds. These products, after chromatographic purification, were identified as 3,3-bis(4-methoxyphenyl)-1-(4-methoxyphenyl)-4-phenylazetidin-2-one **8a** and 3,3-bis(phenylthio)-1-(4-methoxyphenyl)-4-phenylazetidin-2-one **9a** on the basis of their spectroscopic data and by X-ray crystallography. The reaction was found to be general for several active aromatic nucleophiles and the results obtained are summarised in Table 1.

Table 1
Reaction of cationic β-lactam equivalents **6** with various active aromatic nucleophiles using $SnCl_4$ as Lewis acid

Entry	Substrate	Nucleophile	Products[a] of type (% yield)[b]		
			7	**8**	**9**
1	**6a**	C_6H_5OMe	-	**8a**(47)	**9a**(42)
2	**6b**	C_6H_5OMe	-	**8b**(42)	**9b**(39)
3	**6c**	C_6H_5OMe	**7c**(45)	**8c**(35)	**9c**(16)
4	**6a**	1,3-$C_6H_4(OMe)_2$	-	**12a**(43)	**9a**(35)
5	**6b**	1,3-$C_6H_4(OMe)_2$	-	**13b**(39)	**9b**(32)
6	**6a**	1,4-$C_6H_4(OMe)_2$	-	**14a**(38)	**9a**(43)
7	**6b**	C_6H_5OH	-	**15b**(36)	**9b**(26)
8	**6a**	$C_{10}H_7OMe(2)$	**7a**(48)	-	**9a**(29)
9	**6c**	$C_{10}H_7OMe(2)$	**11c**(42)	-	**9c**(20)

[a]All new compounds gave satisfactory CHN analysis.
[b]Yields quoted are for the isolated products characterised by IR, ^{1}H NMR, ^{13}C NMR and MS.

Most of the activated aromatic nucleophiles produce the 3,3-disubstituted azetidin-2-ones of type **8**, along with varying amounts of 3,3-diphenylthioazetidin-2-ones of type **9**. However, it is interesting to note that the monosubstituted products of type **7** were formed along with disubstituted ones in the case of β-lactams **6a** and **6c** (entries 3, 8 and 9). The spatial juxtaposition of the C-4 hydrogen and nucleophile at C-3 in **7a** was assigned *trans* on the basis of its transformation to the *cis*-β-lactam ($J = 6.2$ Hz, C_3-H and C_4-H) on stereospecific[11] Raney-nickel desulphurisation. This was further confirmed by the X-ray crystallographic analysis[12] of monosubstituted β-lactam **7a** (Fig. 2).

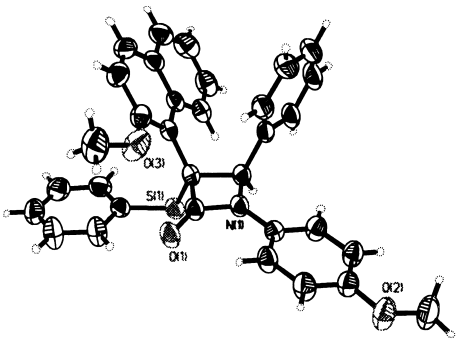
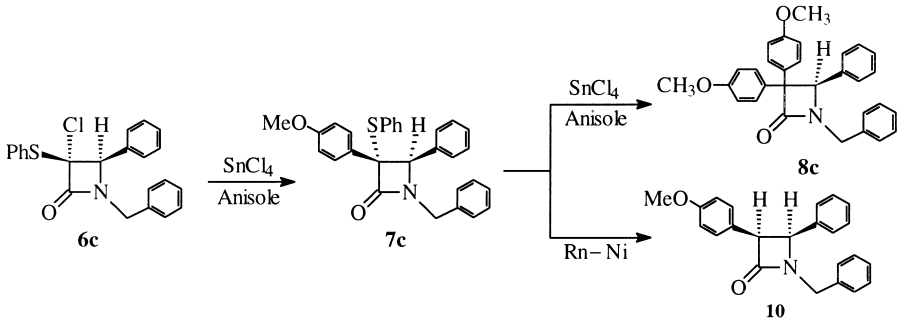


Figure 2. Ortep representation of **7a**

The same result was established for **7c** via its Raney-nickel desulphurisation leading to the formation of *cis*-β-lactam **10** (Scheme 2) ($J = 5.6$ Hz, C_3-H and C_4-H). Similarly, **11c** also produced the *cis*-β-lactam on desulphurisation. The reaction proceeds well in CH_2Cl_2 at –78 to –5°C using 1 equivalent of $SnCl_4$.



Scheme 2.

It is interesting to note that the monosubstituted products are formed by approach of the nucleophile to the more hindered face of the β-lactam. A possible explanation is that the Lewis acid forms complex **A** (Scheme 1) thus preventing the approach of the incoming nucleophile from the same side. The reaction probably follows *Path A* and proceeds via an S_N2 mechanism. The intermediate formation of carbocation **B** would have led to the opposite configuration of β-lactams **7a** and **7c**. This is supported by the fact that benzene and toluene, being milder nucleophiles, failed to react to give corresponding products.

The possible role of **7** as an intermediate in the formation of the disubstituted products **8** was supported by the conversion of monosubstituted β-lactam **7c**, into the disubstituted β-lactam **8c** on treatment with anisole, in the presence of $SnCl_4$.

The formation of **9a** (Scheme 1) was totally unexpected. The ambiphilic behaviour of -SPh as a leaving group (leading to **8**) and at the same time acting as a nucleophile (leading to **9**) is remarkable. The role of $SnCl_4$ in these processes as a complexing agent may be involved (complex **A**) and **9** may be formed by the approach of the nucleophilic -SPh from the opposite side to the Lewis acid in complex **A**. However, the exact mechanism may be quite complex. Further studies using heterocycles and trimethyl silyl enol ethers as nucleophiles are in progress in our laboratory.

In summary, the reaction of a β-lactam cation equivalent **6** with active aromatic nucleophiles provides access to novel C-3 monocyclic substituted β-lactams. The starting β-lactams are easily available and the reaction procedure, workup and the product purification are also easy to carry out.

Acknowledgements

We thank the Department of Science and Technology, Government of India, for financial support of this work, Grant No. SP/S1/G-29/94 and Professor S. V. Kessar, Senior Scientist, Indian National Science Academy (INSA) for helpful discussions.

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10. General procedure for the synthesis of **8a**: To a stirred mixture of 3-chloro-3-phenylthioazetidin-2-one **6a** (80 mg, 0.2 mmol) and anisole (0.02 mL, 0.2 mmol) in dry methylene chloride (10 mL) cooled at –78°C was added $SnCl_4$ (0.026 mL, 0.22 mmol) rapidly under a nitrogen atmosphere and the resulting solution was stirred for an additional 2 h at the same temperature. The reaction mixture was cooled to rt, quenched with water, extracted with methylene chloride, washed with a 5% $NaHCO_3$ solution, dried over $MgSO_4$ and then purified using column chromatography (15% EtOAc–hexanes). The product was recrystallised from CH_2Cl_2/hexanes to furnish colorless crystals of **8a** (44 mg, 47%), mp 136–138°C; FTIR (KBr) 1736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.54–6.53 (m, 17H), 5.67 (s, 1H), 3.79 (s, 3H), 3.73 (s, 3H), 3.65 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 167.05, 158.80, 158.15, 156.12, 135.18, 133.36, 131.16, 129.74, 129.56, 128.43, 128.39, 128.10, 127.65, 118.78, 114.28, 114.15, 113.25, 71.23, 67.57, 55.43, 55.34, 55.08; MS (EI): 465.5397 M^+.
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12. Crystal data for $[C_{33}H_{27}NO_3S]$: MW = 517.62, monoclinic, $P2_1/c$, $a = 10.546(1)$ Å, $b = 21.341(2)$ Å, $c = 12.501(1)$ Å, $\beta = 108.60(1)^\circ$, $V = 2666.5(4)$ $Å^3$, $Z = 4$, $T = 293(2)$ K, μ(Mo-Kα) = 1.57 cm^{-1}, $D_{calcd} = 1.289$ mg/m^3, refinement on F^2, $R_1 = 0.0407$ and $wR_2 = 0.1115$ for 3655 observed reflections [$I > 2\sigma(I)$].