



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

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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 $\text{S}_{\text{N}}2$ mechanism. © 2000 Elsevier Science Ltd. All rights reserved.

β -Lactams are well-acknowledged structural elements of the widely used penicillins, cephalosporins, thienamycins and other monocyclic β -lactam antibiotics¹ 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 transferase² 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 groups⁴ for the preparation of different β -lactam synthons.

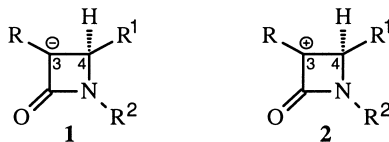


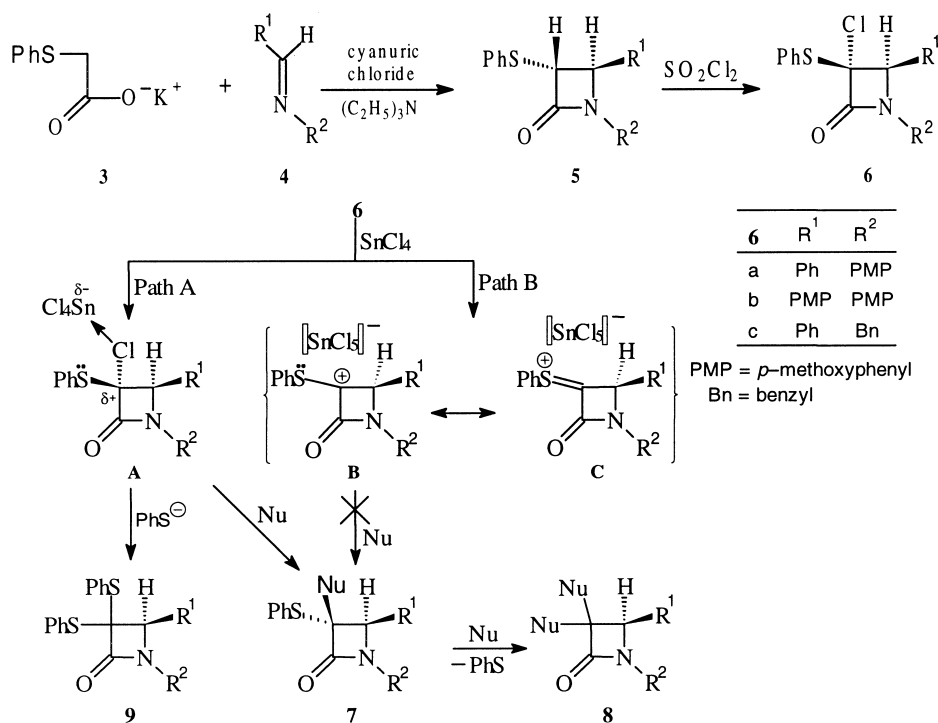
Figure 1.

However, the chemistry involving the cationic β -lactam equivalent **2** is not fully explored. A related study involving $\text{S}_{\text{N}}2'$ substitution at C-3 has recently been reported.⁵ Hence, our attention

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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 available⁶ 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 acid⁷ 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 cycloaddition⁸ approach, are accessible using this strategy (Scheme 1).



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-phenylthioazetid-2-ones **6(a-c)** by reacting with SO_2Cl_2 .⁹ Initial studies were carried out by reacting **6a** with anisole as the nucleophile¹⁰ 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-phenylazetid-2-one **8a** and 3,3-bis(phenylthio)-1-(4-methoxyphenyl)-4-phenylazetid-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	$\text{C}_6\text{H}_5\text{OMe}$	-	8a (47)	9a (42)
2	6b	$\text{C}_6\text{H}_5\text{OMe}$	-	8b (42)	9b (39)
3	6c	$\text{C}_6\text{H}_5\text{OMe}$	7c (45)	8c (35)	9c (16)
4	6a	$1,3\text{-C}_6\text{H}_4(\text{OMe})_2$	-	12a (43)	9a (35)
5	6b	$1,3\text{-C}_6\text{H}_4(\text{OMe})_2$	-	13b (39)	9b (32)
6	6a	$1,4\text{-C}_6\text{H}_4(\text{OMe})_2$	-	14a (38)	9a (43)
7	6b	$\text{C}_6\text{H}_5\text{OH}$	-	15b (36)	9b (26)
8	6a	$\text{C}_{10}\text{H}_7\text{OMe}(2)$	7a (48)	-	9a (29)
9	6c	$\text{C}_{10}\text{H}_7\text{OMe}(2)$	11c (42)	-	9c (20)

^aAll new compounds gave satisfactory CHN analysis.

^bYields quoted are for the isolated products characterised by IR, ^1H 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, $\text{C}_3\text{-H}$ and $\text{C}_4\text{-H}$) on stereospecific¹¹ Raney-nickel desulphurisation. This was further confirmed by the X-ray crystallographic analysis¹² of monosubstituted β -lactam **7a** (Fig. 2).

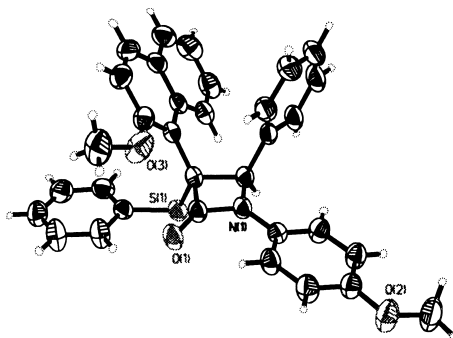
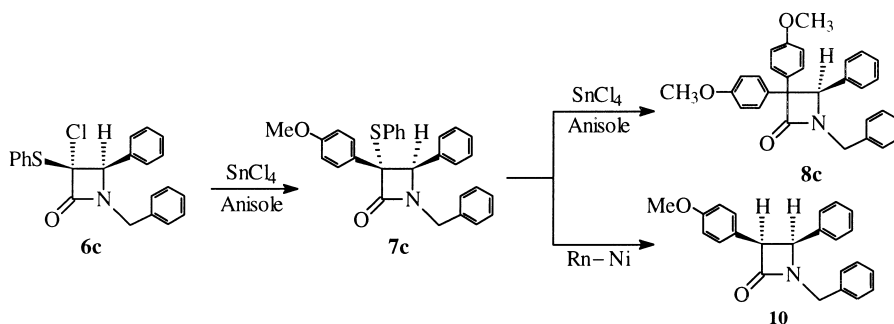


Figure 2. Ortep representation of **7a**

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, $\text{C}_3\text{-H}$ and $\text{C}_4\text{-H}$). 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 $\text{S}_{\text{N}}2$ 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

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References

- (a) Dürckheimer, W.; Blumbach, J.; Lattrell, R.; Scheunemann, K. H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 180.
(b) Chu, D. T. W.; Plattner, J. J.; Katz, L. *J. Med. Chem.* **1996**, *39*, 3853. (c) Morin, R. B.; Gorman, M., Eds.; *Chemistry and Biology of β-Lactam Antibiotics*; Academic Press: New York, 1982.
- Burnett, D. A.; Caplen, M. A.; Davis Jr., H. R.; Burrier, R. E.; Clader, J. W. *J. Med. Chem.* **1994**, *37*, 1733.

3. (a) Wild, H. In *The Organic Chemistry of β -Lactams*; Georg, G. I., Ed.; VCH: New York, 1992; pp. 53–64. (b) O'Donnell, M. J.; Bennett, W. D. *Tetrahedron* **1988**, *44*, 5389.
4. (a) d'Angelo, J.; Pecquet-Dumas, F. *Tetrahedron Lett.* **1983**, *24*, 1403. (b) Roe, J. M.; Thomas, E. J. *Synlett* **1990**, 727. (c) Yamashita, H.; Minami, N.; Sakakibara, K.; Kobayashi, S.; Ohno, M. *Chem. Pharm. Bull.* **1988**, *36*, 69. [DOC1]
5. (a) Bellettini, J. R.; Miller, M. J. *J. Org. Chem.* **1996**, *61*, 7959. (b) Teng, M.; Miller, M. J. *J. Am. Chem. Soc.* **1993**, *115*, 548.
6. van der Veen, J. M.; Bari, S. S.; Krishnan, L.; Manhas, M. S.; Bose, A. K. *J. Org. Chem.* **1989**, *54*, 5758.
7. Arai, K.; Ohara, Y.; Iizumi, T.; Takakuwa, Y. *Tetrahedron Lett.* **1983**, *24*, 1531.
8. Manhas, M. S.; van der Veen, J. M.; Wagle, D. R.; Hegde, V. R.; Bari, S. S.; Kosarych, Z.; Ghosh, M.; Krishnan, L. *Indian J. Chem.* **1986**, *25B*, 1095.
9. Chu, D. T. W. *J. Org. Chem.* **1983**, *48*, 3571.
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 $136\text{--}138^{\circ}\text{C}$; FTIR (KBr) 1736 cm^{-1} ; $^1\text{H NMR}$ (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); $^{13}\text{C NMR}$ (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^+ .
11. Ireland, R. E.; Marshall, J. A. *J. Org. Chem.* **1962**, *27*, 1615.
12. Crystal data for $[\text{C}_{33}\text{H}_{27}\text{NO}_3\text{S}]$: MW = 517.62, monoclinic, $P2_1/c$, $a = 10.546(1)\text{ \AA}$, $b = 21.341(2)\text{ \AA}$, $c = 12.501(1)\text{ \AA}$, $\beta = 108.60(1)^{\circ}$, $V = 2666.5(4)\text{ \AA}^3$, $Z = 4$, $T = 293(2)\text{ K}$, $\mu(\text{Mo-K}\alpha) = 1.57\text{ cm}^{-1}$, $D_{\text{calcd}} = 1.289\text{ mg/m}^3$, refinement on F^2 , $R_1 = 0.0407$ and $wR_2 = 0.1115$ for 3655 observed reflections [$I > 2\sigma(I)$].