Pergamon

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Tetrahedron Letters 44 (2003) 895–897

TETRAHEDRON LETTERS

A facile Lewis acid-promoted allylation of azetidin-2-ones

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Received 22 October 2002; revised 25 November 2002; accepted 6 December 2002

Dedicated to Professor S. V. Kessar, Senior INSA Scientist, Panjab University, Chandigarh, India on his 70th birthday

Abstract—Exposure of 3α-chloro-3-phenylthioazetidin-2-ones and allyltrimethylsilane to a Lewis acid promotes a remarkably facile and stereoselective C-3 allylation to give 3α-allyl-3-phenylthioazetidin-2-ones **4** in excellent yield. These allylated azetidin-2-ones undergo smooth desulphurization with tri-*n*-butyltin hydride or Raney-nickel producing *cis*-3-allyl- and *cis*-3-propylazetidin-2-ones.

Amongst the most fundamental and important organic reactions for creating carbon–carbon bonds, Lewis acid-promoted addition of allylsilanes and allyltributylstannanes to carbonyl compounds is by now a well established[1] synthetic approach. Likewise the synthetic potential of α-chlorosulphides has also been explored[2,3] which undergo a facile reaction with a variety of nucleophiles including allylsilanes. As a part of our ongoing studies towards C-3 functionalization[4] of azetidin-2-ones, we became interested in the incorporation of allyl groups at C-3 of azetidin-2-ones. It was envisaged to employ α-chlorosulphides, the β-lactam carbocation equivalents of type **1** (Fig. 1) for this reaction to afford valuable β-lactam synthons. α-Chlorosulphides, the azetidinones of type **1** are also precursors for azetidin-2,3-diones **2**.[5]

Recently densely substituted β-lactams[6–8] have been recognized as important intermediates as well as molecules of great practical and biological significance. A limited number of reports on allylation[9–11] of azetidin-2-ones have appeared in the literature, which employ appropriate substrates having a carbonyl functionality at C-3 for their reactions with organometallics in organic as well as aqueous media.

We wish to report here the stereoselective introduction of an allyl group at C-3 of azetidin-2-ones using the β-lactam carbocation equivalents **1** and allylmetals in the presence of a Lewis acid (Scheme 1).

The starting substrates 3α-chloro-3-phenylthio-azetidin-2-ones **1(a–d)**[2] were obtained by SO_2Cl_2 α-chlorination of 3-phenylthioazetidin-2-ones **3(a–d)** which in turn were prepared through the Staudinger reaction of phenylthioacetic acid and an appropriate imine using $POCl_3$ as the condensing agent in the presence of Et_3N in CH_2Cl_2 at 0°C. Exposure of the α-chloro-sulphide β-lactam **1a** to Lewis acids such as $TiCl_4$, $SnCl_4$, $ZnBr_2$ in the presence of allyltrimethylsilane under nitrogen in CH_2Cl_2 resulted in a facile and stereoselective C-3 allylation giving **4a** as a single isomer in excellent yield. The product after chromatographic purification was

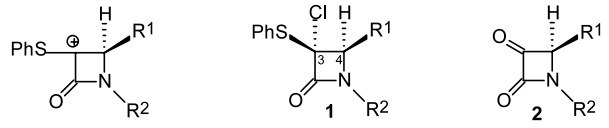
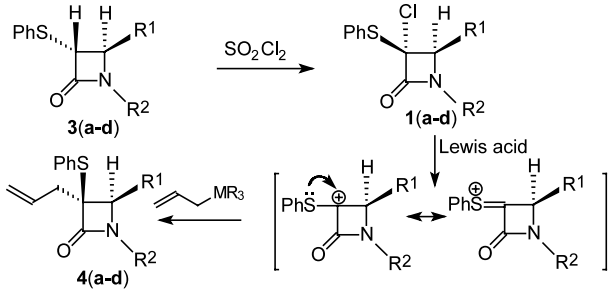


Figure 1.



Scheme 1.

Keywords: azetidinones; Lewis acid; allylation; allylsilane; allylstannane; desulphurisation.

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0040-4039/03/$ - see front matter
PII: S0040-4039(02)02775-2

Table 1. Stereoselective allylation of azetidin-2-ones **1(a–d)**

Entry	Product[a]	R^1	R^2	Lewis acid	MR_3	Temp. (°C)/time (h)	Yield[b] (%)
1	**4a**	C_6H_5	C_6H_4·OMe(*p*)	$TiCl_4$	$SiMe_3$	0/2	86
2	**4a**	C_6H_5	C_6H_4·OMe(*p*)	$SnCl_4$	$SiMe_3$	0/2	80
3	**4a**	C_6H_5	C_6H_4·OMe(*p*)	$TiCl_4$	$SnBu_3$	0/2	52
4	**4b**	C_6H_4·OMe(*p*)	C_6H_4·OMe(*p*)	$TiCl_4$	$SiMe_3$	−10/2	85
5	**4c**	C_6H_4·Cl(*p*)	C_6H_4·CH_3(*p*)	$TiCl_4$	$SiMe_3$	0/1.5	88
6	**4d**	C_6H_5	C_6H_4·Br (*p*)	$TiCl_4$	$SiMe_3$	0/2	85
7	**4a**	C_6H_5	C_6H_4·OMe(*p*)	$ZnBr_2$	$SiMe_3$	25/48	75

[a] All new compounds have been characterized by IR, NMR, MS and CHN analysis.
[b] Isolated yields after purification by column chromatography.

identified as 3-allyl-3-phenylthio-1-(4-methoxyphenyl)-4-phenylazetidin-2-one **4a**[12] on the basis of its spectroscopic data. The reaction was found to be general with several substrates and the results are summarized in Table 1. The stereochemical assignment of the allyl group at C-3 was established by single-crystal X-ray crystallographic analysis[13] of **4a** as depicted in its ORTEP diagram (Fig. 2).

Although the role of sulphur is not yet completely understood, the formation of a single isomer of **4a** may be explained in terms of the Lewis acid first coordinating the halogen at C-3 followed by abstraction leading to the formation of a C-3 carbocation stabilized by the lone pair on sulphur. Subsequent approach of the nucleophile to this carbocation from the less hindered face would lead to the observed stereoselectivity.

In an effort to demonstrate the synthetic potential of this reaction and versatility of the products, we have carried out the following transformations (Scheme 2). Tri-*n*-butyltin hydride reduction of **4a** catalyzed by AIBN in toluene at reflux led to stereoselective desulphurization to afford *cis*-3-allyl-1-(4′-methoxyphenyl)-4-phenylazetidin-2-one **5a**. The *cis* stereochemistry of the 3-allyl-azetidin-2-ones **5(a–c)** was assigned on the basis of the coupling constant J_{3H-4H} (5.6 Hz) in the ^1H

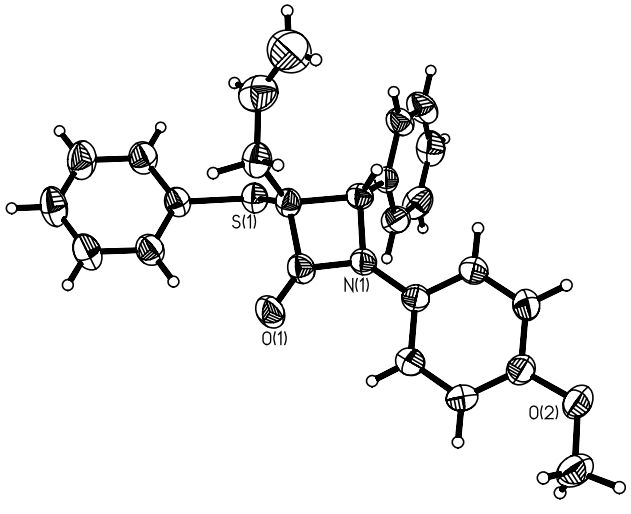
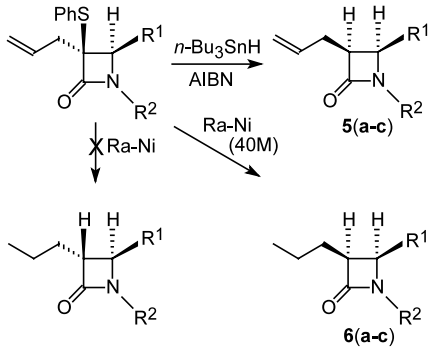


Figure 2. ORTEP representation of **4a**.



Scheme 2.

NMR spectrum and is due to donation of hydrogen to the less hindered face of the intermediate radical.

Alternatively, treatment of **4a** with Raney-nickel in refluxing acetone resulted in desulphurization accompanied by hydrogenation of the double bond giving only *cis*-3-propyl-1-(4′-methoxyphenyl)-4-phenyl-azetidin-2-one **6a**. The unexpected *cis* stereochemistry of these products **6(a–c)** was established on the basis of the coupling constant J_{3H-4H} (5.3 Hz). These reactions were carried out with different substrates **4(b,c)** and the results are summarized in Table 2. The formation of only the *cis* β-lactam accompanied by hydrogenation of the double bond is quite interesting during the reductive desulphurization[14] with Ra-Ni.

In summary this work not only provides a facile and stereoselective method for allylation of azetidin-2-ones

Table 2. Reductive desulphurization of azetidin-2-ones **4(a–c)**

Entry	Substrate	Reagent	Product[a]	Yields[b] (%)
1	**4a**	*n*-Bu_3SnH	**5a**	50
2	**4b**	*n*-Bu_3SnH	**5b**	43
3	**4c**	*n*-Bu_3SnH	**5c**	53
4	**4a**	Rn-Ni	**6a**	45
5	**4b**	Rn-Ni	**6b**	100
6	**4c**	Rn-Ni	**6c**	48

[a] All new compounds have been characterized by IR, NMR and CHN analysis.
[b] Isolated yields after purification by chromatography.

at C-3, but also extends the scope of the Lewis acid-catalyzed allylation using carbocation equivalents with allylsilanes and allylstannanes. Further elaboration of these products to potentially useful building blocks is underway in our laboratory.

Acknowledgements

We gratefully acknowledge financial support from Department of Science and Technology (DST), New Delhi, Govt. of India, Grant No. SP/S1/G-50/99. The authors are also thankful to Mr. Avtar Singh, Regional Sophisticated Instrumentation Centre, P.U. Chandigarh for recording the NMR spectra.

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12. General procedure for synthesis of **4a**: To a stirred solution of 3α-chloro-3-phenylthioazetidin-2-one (80 mg, 0.2 mmol) and allyltrimethylsilane (0.06 ml, 0.4 mmol) in dry methylene chloride (10 ml) at 0°C was added $TiCl_4$ (0.044 ml, 0.4 mmol) rapidly under a nitrogen atmosphere. The resulting solution was stirred for an additional 2 h at the same temperature. The reaction was quenched with water, extracted with methylene chloride, washed with 5% $NaHCO_3$ solution, dried over Na_2SO_4 and filtered. The residue after solvent evaporation was purified by column chromatography (8% EtOAc/hexane). The product on recrystallization from EtOAc/hexane furnished colorless crystals of **4a** (70 mg, 86%), mp 130–132°C; FTIR(KBr): 1745, 1510 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 2.68 (d, 2H, $J=7.25$ Hz), 3.78 (s, 3H), 5.15 (s, 1H), 5.26 (m, 1H), 5.3 (bs, 1H), 6.01 (m, 1H), 6.83–7.62 (m, 14H, aromatic protons); ^{13}C NMR (300 MHz, $CDCl_3$) δ: 38.06, 55.11, 63.50, 65.96, 114.38, 118.56, 119.44, 126.38, 128.02, 128.23, 128.63, 130.70, 130.91, 132. 85, 133.68, 135.24, 156.2, 165.7; MS(EI): 401M^+. Anal. calcd for $C_{25}H_{23}O_2NS$: C, 74.78; H, 5.77; N, 3.48. Found: C, 74.64; H, 5.66; N, 3.39.
13. Crystal data for **4a**: monoclinic, $P2_1/n$, $a=12.692(1)$, $b=10.453(1)$, $c=17.003(1)$ Å, $\beta=110.48(1)°$, $V=2113.2(3)$ Å^3, $Z=4$, $\rho_{calcd}=1.262$ Mg/m^3, μ(Mo-Kα)$=0.174$ mm^{-1}, full matrix least-square on F^2, $R_1=0.0478$, $wR_2=0.1288$ for 2644 reflections [$I>2\sigma(I)$].
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