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Studies towards C-3 functionalization of β-lactams using substituted allylsilanes

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Abstract. An effective and stereoselective synthesis of 3-(1′-methyl/phenylallyl)-3-phenylthio-β-lactams (**3/4**) using substituted allylsilane and Lewis acid is described. The reaction leads to the formation of a mixture of C-3 substituted allyl β-Lactams. However, these compounds on desulphurisation using tri-n-butyltinhydride and Raney Ni provide two separable diastereomers of the reduced product.

Keywords. Allylsilane; β-Lactams; Lewis acid; desulphurisation; crotylsilane; cinnamylsilane.

1. Introduction

The presence of β-lactam moiety in several widely used families of antibiotics has stimulated considerable activity directed at their stereocontrolled synthesis.[1] In recent years, various natural monocyclic β-lactams have been shown to exhibit high antibacterial activity, suggesting that a suitably substituted monocyclic β-lactam might perhaps be the minimum requirement for biological activity. Besides, the ever growing new applications of β-lactam in various fields ranging from enzyme inhibition[2] to the use of these products as starting materials to develop new synthetic methodology,[3,4] justify a renewed interest in these compounds.[5,6] In the β-lactam chemistry, introduction of allyl group at C-3 is of special interest.[7] As olefins are considered as masked ketones,[8] so the allylated β-lactams can be convenient intermediates for a variety of heterocyclic compounds. A limited number of approaches to densely functionalized α-allyl-β-lactams have been reported so far.[9] These employ appropriate substrate having carbonyl functionality at C-3 for their reactions with organometallics in organic as well as aqueous media.[10] Alternate methods to introduce allyl group at β-lactam are of immense interest even today. As a part of our ongoing research and in continuation of earlier work,[11] here we report a methodology capable of providing 3-substituted allyl/propyl β-lactams. This employs the Lewis acid promoted addition of substituted allylsilane to β-lactam carbocation equivalents of type **2**.

2. Experimental

2.1 *General Information*

Melting points (uncorrected) were determined with a Thomas-Hoover capillary melting point apparatus. Infrared spectra (IR) were recorded using Perkin-Elmer Model 1430 spectrophotometer. Only principal absorption bands of interest are reported in cm^{-1}. ^{1}H NMR spectra were recorded using JEOL FT NMR System AL 300 (300 MHz) in the Department of Chemistry and Centre of Advance Studies in Chemistry and BRUKER AVANCE II 400 (400 MHz) in the Sophisticated Analytical Instrumentation Facility (SAIF), Panjab University, Chandigarh. The chemical shift values are expressed in δ values (ppm) using tetramethylsilane (TMS) as internal standard. The coupling constant J values are given in Hertz (Hz). While reporting ^{1}H NMR data, following abbreviations have been used: s-singlet; br s-broad singlet; d-doublet; t-triplet; q-quartet and m-multiplet. Thin layer chromatography (TLC) was performed using TLC grade silica gel 'G' (Acme Synthetic Chemicals). The spots were made visible by exposing plates to iodine vapor. Column chromatography was performed with silica gel (Acme Synthetic Chemicals, 60–120 mesh) and eluted with ethyl acetate:hexanes mixture unless otherwise stated. All commercially available compounds or reagents

were used without further purification. All solvents used were of LR grade. Where necessary, the solvents were distilled and dried prior to use, when this seemed necessary by standard methods.

2.2 General procedure for the synthesis of cis-3-(1′-methyl/phenylallyl)-3-phenylthio-β-lactams (3 and 4)

To a stirred solution of *trans*-3-chloro-3-phenylthio-β-lactam **2** (1 mmol) and crotyl/ cinnamylsilane (2 mmol) in dry methylene chloride (15 mL) at 0°C was added TiCl$_4$ (2 mmol) rapidly under a nitrogen atmosphere. The resulting solution was stirred for additional 2 h at the same temperature. The reaction mixture was quenched with water, extracted with methylene chloride, washed with 5% NaHCO$_3$ solution, dried over Na$_2$SO$_4$ and filtered. The residue after solvent evaporation was purified by column chromatography.

2.2a *1-(4′-Methoxyphenyl)-3-(1′-methylallyl)-3-phenyl-thio-4-phenylazetidin-2-one (3a)*: Oil; yield 96%; IR ν_{max} (CHCl$_3$): 1752 (C=O), 1636.7, 1512.8 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.74–7.65 (m, 28H, Ph, both isomers), 6.24–6.39 (m, 1H, minor isomer), 5.95–6.05 (m, 1H, major isomer), 5.15–5.30 (m, 4H, both isomers), 5.00 (s, 1H, C4-H, major isomer), 4.97 (s, 1H, minor isomer), 3.75 (s, 6H, OCH$_3$, both isomers), 2.65–2.80 (m, 2H, both isomers), 1.40 (d, $J = 8.8$ Hz, major isomer, 3H), 1.25 (d, $J = 9.6$ Hz, minor isomer, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 165.8, 165.5, 156.3, 156.2, 138.4, 137.8, 135.4, 135.2, 133.8, 133.7, 130.9, 127.8, 118.6, 117.8, 116.0, 114.5, 114.4, 70.5, 69.9, 60.7, 60.2, 55.2, 38.3, 37.3, 14.3, 13.8. Analysis: calcd. for C$_{26}$H$_{25}$O$_2$NS: C, 75.15; H, 6.06; N, 3.37%; Found: C, 75.27; H, 6.17; N, 3.42%.

2.2b *1-(4′-Methylphenyl)-3-(1′-methylallyl)-3-phenyl-thio-4-(4′-chlorophenyl)azetidin-2-one (3b)*: Oil; yield 65%; IR ν_{max} (CCl$_4$): 1757.1 (C=O), 1637.2, 1615.2 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.00–7.64 (m, 28H, Ph, both isomers), 6.29–6.40 (m, 1H, minor isomer), 5.95–6.07 (m, 1H, major isomer), 5.13–5.33 (m, 4H, both isomers), 4.99 (s, 1H, C4-H, major isomer), 4.96 (s, 1H, C4-H, minor isomer), 2.61–2.81 (m, 2H, both isomers), 2.34 (s, 6H, CH$_3$, both isomers), 1.35 (d, $J = 8.8$ Hz, CH$_3$, major isomer, 3H), 1.23 (d, $J = 9.5$ Hz, CH$_3$, minor isomer, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 165.8, 165.5, 138.1, 137.6, 135.9, 135.2, 135.1, 135.0, 134.6, 134.5, 133.5, 133.4, 132.4, 132.2, 130.5, 130.4, 129.8, 129.7, 129.6, 129.5, 129.3, 129.2, 129.1, 129.0, 128.9, 128.8, 128.5, 128.4, 118.0, 117.5, 117.3, 116.2, 70.6, 69.8, 60.1, 59.1, 38.5, 37.2, 21.2, 14.1, 13.8. Analysis: calcd. for C$_{26}$H$_{24}$ONSCl: C, 72.03; H, 5.58; N, 3.23%; Found: C, 72.17; H, 5.67; N, 3.34%.

2.2c *1-(4′-Bromophenyl)-3-(1′-methylallyl)-3-phenyl-thio-4-phenylazetidin-2-one (3c)*: Oil; yield 81%; IR ν_{max} (CCl$_4$): 1756.9 (C=O), 1637.5, 1590.9 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.14-7.63 (m, 28H, Ph, both isomers), 6.29–6.40 (m, 1H, for minor isomer), 5.95–6.07 (m, 1H, major isomer), 5.12–5.22 (m, 4H, both isomers), 5.01 (s, 1H, C4-H, major isomer), 4.98 (s, 1H, minor isomer), 2.64–2.78 (m, 2H, both isomers), 1.35 (d, $J = 8.7$ Hz, 3H, CH$_3$, major isomer), 1.28 (d, $J = 9.6$ Hz, 3H, CH$_3$, minor isomer); ^{13}C NMR (100 MHz, CDCl$_3$): δ 166.4, 166.1, 138.0, 137.4, 136.2, 136.1, 135.5, 135.4, 135.3, 133.2, 133.0, 132.3, 132.2, 130.5, 130.4, 128.8, 128.5, 128.4, 128.2, 128.1, 128.0, 118.9, 118.3, 117.0, 116.9, 116.3, 70.8, 70.1, 60.1, 60.3, 38.2, 37.1, 14.2, 13.7. Analysis: calcd. for C$_{25}$H$_{22}$ONSBr: C, 64.78; H, 4.79; N, 3.02%; Found: C, 64.87; H, 4.83; N, 3.10%.

2.2d *1-Phenyl-3-(1′-methylallyl)-3-phenylthio-4-phenyl-azetidin-2-one (3d)*: Oil; yield 85%; IR ν_{max} (CHCl$_3$): 1757.4 (C=O), 1600.7 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.01–7.64 (m, 20H, Ph both isomers), 6.30–6.42 (m, 1H, minor isomer), 5.95–6.05 (m, 1H, major isomer), 5.16–5.31 (m, 4H, both isomers), 5.04 (s, 1H, C4-H, major isomer), 5.01 (s, 1H, C4-H, minor isomer), 2.66–2.81 (m, 2H, both isomers), 1.35 (d, $J = 8.7$ Hz, 3H, CH$_3$, major isomer), 1.25 (d, $J = 9.6$ Hz, 3H, CH$_3$, minor isomer); ^{13}C NMR (100 MHz, CDCl$_3$): δ 166.3, 166.0, 138.2, 137.6, 137.3, 137.2, 135.4, 135.3, 133.6, 133.5, 130.7, 130.6, 129.2, 129.1, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 124.0, 123.9, 117.9, 116.0, 70.5, 69.8, 60.6, 60.1, 38.4, 37.2, 14.2, 13.9. Analysis: calcd. for C$_{25}$H$_{23}$ONS: C, 77.89; H, 6.01; N, 3.63%; Found: C, 77.97; H, 6.10; N, 3.70%.

2.2e *1-(4′-Methoxyphenyl)-3-(1′-phenylallyl)-3-phenyl-thio-4-phenylazetidin-2-one (4a)*: Oil; yield 62%; IR ν_{max} (CCl$_4$): 1754 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.95–7.58 (m, 38H, Ph, both isomers), 6.50–6.70 (m, 2H, both isomers), 5.20–5.57 (m, 6H, both isomers), 4.15–4.20 (m, 2H, both isomers), 3.98 (s, 3H, OCH$_3$, major isomer), 3.94 (s, 3H, OCH$_3$, minor isomer); ^{13}C NMR (100 MHz, CDCl$_3$): δ 165.2, 164.8, 156.2, 156.0, 138.8, 138.4, 136.2, 135.5, 135.4, 135.1, 133.8, 130.8, 130.5, 129.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 118.9, 118.6, 118.4, 114.5, 114.3, 70.5, 70.1, 61.8, 61.4, 55.1, 55.0, 51.7, 51.2. Analysis: calcd. for C$_{31}$H$_{27}$O$_2$NS: C, 77.95; H, 5.69; N, 2.93%; Found: C, 78.08; H, 5.77; N, 2.99%.

2.2f *1-(4′-Methylphenyl)-3-(1′-phenylallyl)-3-phenyl-thio-4-(4′-chlorophenyl)azetidin-2one (4b)*: Oil; yield 71%; IR ν_{max} (CCl$_4$): 1761 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.45–8.00 (m, 36H, Ph, both isomers), 6.56–6.75 (m, 2H, both isomers), 5.45 (s, 2H, C4-H, both isomers), 5.23–5.66 (m, 4H, both isomers), 4.17–4.22 (m, 2H, both isomers), 2.54 (s, 3H, CH$_3$, major isomer), 2.43 (s, 3H, CH$_3$, minor isomer); ^{13}C NMR (100 MHz, CDCl$_3$)δ 165.2, 164.8, 138.6, 138.2, 136.4, 135.5, 135.2, 135.1, 133.6, 130.7, 130.2, 129.5, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 118.7, 118.5, 118.4, 114.4, 114.1, 70.3, 70.1, 61.9, 61.5, 51.5, 51.3, 21, 20.9. Analysis: calcd. for C$_{31}$H$_{26}$ONSCl: C, 75.13; H, 5.29; N, 2.83%; Found: C, 75.18; H, 5.37; N, 2.90%.

2.2g *1-(4′-Bromophenyl)-3-(1′-phenylallyl)-3-phenyl-thio-4-phenylazetidin-2-one (4c)*: Oil; yield 71%; IR ν_{max} (CCl$_4$): 1760 (C=O), 1656 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.00–7.98 (m, 38H, Ph, both isomers), 6.52–6.72 (m, 2H, both isomers), 5.40 (s, 2H, C4-H, both isomers), 5.20–5.60 (m, 4H, both isomers), 4.17–4.22 (m, 2H, both isomers); ^{13}C NMR (100 MHz, CDCl$_3$): δ 166.4, 166.1, 139.1, 138.7, 136.5, 136.4, 136.3, 136.1, 135.8, 135.7, 135.6, 133.8, 133.0, 132.9, 132.7, 132.5, 131.1, 131.0, 130.6, 130.3, 132.9, 132.7, 132.5, 131.1, 131.0, 130.6, 130.3, 130.2, 130.0, 129.8, 129.5, 129.3, 129.1, 129.0, 128.9, 128.8, 128.7, 128.6, 128.5, 128.3, 128.2, 127.9, 127.7, 120.6, 119.8, 119.7, 119.5, 119.4, 119.2, 118.4, 117.6, 117.4, 71.5, 70.9, 69.4, 62.6, 62.0, 52.4, 51.6. Analysis: calcd. for C$_{30}$H$_{24}$ONSBr: C, 68.56; H, 4.60; N, 2.66%; Found: C, 68.59; H, 4.67; N, 2.73%.

2.2h *1-Phenyl-3-(1′-phenylallyl)-3-phenylthio-4-phenylazetidin-2-one (4d)*: Oil; yield 70%; IR ν_{max} (CCl$_4$): 1755 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.00–7.90 (m, 40H, Ph, both isomers), 6.60 (m, 2H, both isomers), 5.49 (s, 2H, C4-H, both isomers), 5.18–5.68 (m, 4H, both isomers), 4.16 (m, 2H, both isomers); ^{13}C NMR (100 MHz, CDCl$_3$): δ 166.8, 166.4, 160.8, 140.0, 138.9, 137.2, 136.5, 135.9, 135.7, 134.3, 138.7, 131.5, 131.3, 131.2, 130.5, 130.3, 122.5, 121.9, 121.5, 121.4, 117.5, 117.1, 80.7, 71.2, 70.8, 69.5, 62.5, 62.2, 52.3, 52.0. Analysis: calcd. for C$_{30}$H$_{25}$ONS: C, 80.50; H, 5.63; N, 3.13%; Found: C, 80.55; H, 5.69; N, 3.23%.

2.3 General procedure for n-Bu$_3$SnH reduction

To a solution of **3/4** (1 mmol) in dry toluene (10 mL) were added *n*-Bu$_3$SnH (1 mmol) and catalytic amount of AIBN. The reaction mixture was refluxed and progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was cooled to RT and concentrated under vacuum. The residue was redissolved in DCM (20 mL) and washed with water. The residue obtained after evaporation of solvent was purified by silica gel column chromatography.

2.3a *cis-1-(4′-Methoxyphenyl)-3-(1′-methylallyl)-4-phenylazetidin-2-one (5a, 6a)*: The fast moving diastereomer **5a** was characterized by the following data: White solid; yield 24%; M.p. 125–127°C; IR ν_{max} (KBr): 1749 (C=O), 1513 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.08–7.29 (m, 9H, Ph), 5.11–5.25 (m, 1H), 5.05 (d, J = 7.6 Hz ,1H), 4.58 (d, J = 12 Hz 1H), 4.25 (d, J = 17 Hz , 1H), 3.69 (s, 3H, OCH$_3$), 3.28-3.35 (m, 1H), 2.23-2.30 (m, 1H), 1.23 (d, J = 6 Hz 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 165.5, 155.8, 140.5, 135.4, 131.4, 128.5, 128.4, 123.2, 118.3, 114.3, 113.9, 59.2, 58.7, 55.1, 34.7, 18.4. Analysis: calcd. for C$_{20}$H$_{21}$O$_2$N: C, 78.14; H, 6.88; N, 4.56%; Found: C, 78.27; H, 6.99; N, 4.69%.

The slow moving diastereomer **6a** was characterized by following data: Solid; yield 54%; M.p. 105–107°C; IR ν_{max} (KBr): 1749 (C=O), 1513.3 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.11–7.36 (m, 9H, Ph), 5.95–6.16 (m, 1H), 5.07 (d, J = 8 Hz ,1H), 4.89–5.02 (m, 2H), 3.72 (s, 3H, OCH$_3$), 3.28–3.35 (m, 1H), 2.20–2.26 (m, 1H), 0.6 (d, J = 4.4 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 165.0, 155.9, 140.2, 135.5, 131.4, 128.7, 128.5, 128.3, 127.9, 127.5, 126.9, 118.3, 114.4, 114.3, 60.6, 58.5, 55.1, 34.3, 17.6.

2.3b *cis-1-Phenyl-3-(1′-methylallyl)-4-phenylazetidin-2-one (5d, 6d)*: The fast moving diastereomer **5d** was characterized by following data: White solid; yield 28%; M.p. 86–88°C; IR ν_{max} (KBr): 1750 (C=O), 1512 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.86–7.24 (m, 10H, Ph), 5.05–5.15 (m, 1H), 5.03 (d, J = 7.6 Hz, 1H), 4.54 (d, J = 12 Hz, 1H), 4.20 (d, J = 17.2 Hz, 1H), 3.26–3.32 (m, 1H), 2.22–2.27 (m, 1H), 1.17 (d, J = 6 Hz), 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 166.1, 140.8, 140.4, 139.8, 137.7, 135.1, 129.2, 129.1, 129.0, 128.4, 128.3, 123.2, 128.1, 126.1, 126.0, 123.4, 117.1, 116.9, 115.5, 113.9, 65.1, 59.1, 58.6, 34.6, 18.4. Analysis: calcd. for C$_{19}$H$_{19}$ON: C, 82.26; H, 6.90; N, 5.05%; Found: C, 82.32; H, 6.97; N, 5.11%.

The slow moving diastereomer **6d** was characterized by following data: White solid; M.p. 126–128°C; IR ν_{max} (KBr): 1750 (C=O), 1514 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.87–7.30 (m, 9H, Ph), 5.93–6.06 (m, 1H), 5.10 (d, J = 8 Hz, 1H), 4.84–5.07 (m, 2H), 3.26–3.33 (m, 1H), 2.23–2.28 (m, 1H), 0.56

(d, $J = 4.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 165.70, 140.1, 137.8, 135.2, 129.0, 128.7, 128.6, 127.8, 123.6, 117.1, 114.4, 60.5, 58.4, 34.3, 17.6.

2.3c cis-1-(4′-Methoxyphenyl)-3-(1′-phenylallyl)-4-phenylazetidin-2-one (7a, 8a):

The fast moving diastereomer **7a** was characterized by following data: Solid; yield 49%; M.p. 112–114°C; IR ν_{max} (KBr): 1745 (C=O), 1515 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.53–7.29 (m, 14H, Ph), 6.25–6.27 (m, 1H), 5.05 (d, $J = 5$ Hz, 1H), 4.98 (d, $J = 5.4$Hz , 1H), 4.62–4.68 (m, 1H), 4.04–4.10 (m, 1H), 3.70 (s, 3H), 3.36–3.40 (m, 1H);^{13}C NMR (100 MHz, CDCl$_3$): δ 165, 156.1, 137.8, 137.4, 136, 135.5, 135.4, 135.1, 133.5, 130.4, 130.2, 129.5, 128.6, 128.2, 128.7, 128.3, 128.2, 128.1, 128.0, 118.8, 118.6, 118, 114.5, 114.2, 61, 60, 55.1, 50. Analysis: calcd for C$_{25}$H$_{23}$O$_2$N: Calcd. C, 81.27; H, 6.27; N, 3.79%; Found: C, 81.38; H, 6.39; N, 3.89%.

The slow moving diastereomer **8a** was characterized by following data: Solid; yield 25%; M.p. 182–184°C; IR ν_{max} (KBr): 1749 (C=O), 1512 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.66–7.27 (m, 14H, Ph), 5.47-5.59 (m, 1H), 5.18 (d, $J = 8$ Hz, 1H), 4.74-4.78 (m, 1H), 4.46-4.52 (m, 1H), 3.96–4.02 (m, 1H), 3.69 (s, 3H), 3.36–3.38 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 165.2, 156.0, 138.8, 138.4, 136.2, 135.5, 135.4, 135.1, 133.8, 130.8, 130.5, 129.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 118.9, 118.6, 118.4, 114.5, 114.3, 61.2, 60.5, 55.0, 51.5.

2.3d cis-1-Phenyl-3-(1′-phenylallyl)-4-phenylazetidin-2-one (7d, 8d):

The fast moving diastereomer **7d** was characterized by following data: Oil; yield 44%; IR ν_{max} (CCl$_4$): 1750 (C=O), 1512 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.97–7.30 (m, 15H, Ph), 6.27–6.29 (m, 1H), 5.03 (d, $J = 5.4$ Hz, 1H), 4.96 (d, $J = 5$ Hz, 1H), 4.65–4.70 (m, 1H), 4.04–4.10 (m, 1H), 3.35–3.40 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 166.8, 139.0, 138.6, 137.1, 136.5, 135.8, 135.7, 134.1, 132.7, 131.5, 131.1, 131.0, 130.5, 130.2, 122.2, 121.7, 121.6, 121.3, 117.3, 117.1, 61.7, 60.5, 51.0. Analysis: calcd. for C$_{24}$H$_{21}$ON: Calcd C, 84.91; H, 6.24; N, 4.13%; Found: C, 84.97; H, 6.30; N, 4.19%.

The slow moving diastereomer **8d** was characterized by following data: Solid; yield 29%; M.p. 153–160°C; IR ν_{max} (KBr): 1752 (C=O), 1513 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.45–7.32 (m, 10H, Ph), 5.43–5.52 (m, 1H), 5.22 (d, $J = 8$ Hz, 1H), 4.73–4.77 (m, 1H), 4.45–4.51 (m, 1H), 3.95–4.02 (m, 1H), 3.35–3.37 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 166.2, 139.0, 138.4, 137, 136.2, 135.8, 135.2, 134.4, 132.7, 131.7, 131.3, 131.0, 130.8, 130.6, 122.4, 121.5, 121.3, 121.1, 117.2, 117, 61.9, 60.2, 51.3.

2.4 General procedure for Raney-Ni reduction

To a suspension of Raney–Ni (15 mmol, 100% activated) in dry ethanol (20 mL) was added **3/4** (1 mmol). The suspension was refluxed for 1 h. The progress of reaction was checked by TLC. After disappearance of spot for the starting substrate and appearance of a new spot, suspension was filtered and solvent was evaporated *in vacuo*, extracted with methylene chloride (3 × 20 mL) and dried over anhydrous Na$_2$SO$_4$. The residue so obtained was purified by silica gel column chromatography.

2.4a cis-1-(4′-Methoxyphenyl)-3-(1′-methylpropyl)-4-phenylazetidin-2-one (9a):

Oil; yield 100%; IR ν_{max} (CCl$_4$): 1745.6 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.67–7.35 (m, 9H, Ph), 5.04 (d, $J = 8$ Hz, 1H), 3.69 (s, 3H), 3.00–3.20 (m, 1H), 1.06 (d, $J = 6$ Hz, 3H), 0.84 (t, $J = 10$ Hz, 2H), 0.60–0.70 (m, 1H), 0.40–0.50 (m, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 166.1, 155.7, 135.6, 131.4, 129.1, 128.6, 128.3, 127.8, 127.2, 125.9, 118.2, 117.7, 114.2, 60.8, 60.1, 58.6, 55.1, 31.6, 31.5, 27.5, 26.7, 16.9, 16.7, 10.7. 10.4. Analysis: calcd. for C$_{20}$H$_{23}$O$_2$N: C, 77.63; H, 7.49; N, 4.52%; Found: C, 77.77; H, 7.62; N, 4.61%.

2.4b cis-1-Phenyl-3-(1′-methylpropyl)-4-phenylazetidin-2-one (9d):

Oil; yield 80%; IR ν_{max} (CCl$_4$): 1745 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.80–7.25 (m, 10H, Ph), 5.00 (d, $J = 8$ Hz, 1H), 3.00–3.23 (m, 1H), 1.00 (d, $J = 6$ Hz, 3H), 0.74 (t, $J = 10$ Hz, 2H), 0.60–0.71 (m, 1H), 0.41–0.50 (m, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 166, 135.4, 131.2, 129.4, 128.5, 128.2, 127.5, 127.2, 125.7, 118.2, 117.6, 114.5, 60.6, 60.2, 58.4, 55, 31.7, 31.5, 27.4, 26.5, 16.6, 16.5, 10.8. 10.5. Analysis: calcd. for C$_{19}$H$_{20}$ON: C, 81.96; H, 7.24; N, 5.03%; Found: C, 81.99; H, 7.30; N, 5.13%.

2.4c cis-1-(4′-Methoxyphenyl)-3-(1′-phenylpropyl)-4-phenylazetidin-2-one (10a, 11a):

The fast moving diastereomer **10a** was characterized by following data: Oil; yield 32%; IR ν_{max} (CCl$_4$): 1745.3 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.35–7.21 (m, 14H, Ph), 4.83 (d, $J = 7.6$ Hz, 1H), 3.86 (dd, $J = 8$, 16 Hz, 1H), 3.63 (s, 3H), 2.40–2.49 (m, 1H), 2.24–2.32 (m, 1H), 1.40–1.50 (m, 1H), 0.55 (t, $J = 10$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 165.9, 155.8, 141.5, 135.0, 131.3, 129.1, 128.7, 128.4, 128.2, 128.1, 127.8, 127.7, 127.5, 127.0, 125.9, 118.3, 118.1, 114.3, 114.2, 65.9, 59.3, 58.3, 55.1, 47.1, 44.4, 27.9, 26.0, 12.3, 11.3.

The slow moving diastereomer **11a** was characterized by following data: Solid; yield 45%; M.p. 187–189°C; IR ν_{max} (KBr): 1746.1 (C=O) cm^{-1}; ^{1}H NMR

(400 MHz, CDCl$_3$): δ 6.72–7.40 (m, 14H, Ph), 5.23 (d, $J = 7.6$ Hz, 1H), 3.82–3.88 (m,1H), 2.40–2.52 (m, 1H), 1.34–1.40 (m, 2H), 0.39 (t, $J = 9.6$ Hz, 3H) ; ^{13}C NMR (100 MHz, CDCl$_3$): δ 165.5, 155.7, 141.3, 135.0, 131.3, 128.6, 128.3, 128.2, 127.6, 126.5, 118.2, 114.2, 60.0, 58.9, 55.3, 44.4, 27.8, 11.2. Analysis: calcd. for C$_{25}$H$_{25}$O$_2$N: C, 81.83; H, 6.78; N, 3.77%; Found: C, 81.95; H, 6.90; N, 3.89%.

2.4d *cis-1-Phenyl-3-(1′-phenylpropyl)-4-phenylazetidin-2-one (10d, 11d)*: The fast moving diastereomer **10d** was characterized by following data: Oil; yield 39%; IR ν_{max} (CCl$_4$): 1745.3 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.36–7.25 (m, 15H, Ph, both isomers), 4.87 (d, $J = 7.6$ Hz, 1H), 3.86 (dd, $J = 8, 16$ Hz, 1H), 2.41–2.50 (m, 1H), 2.25–2.33 (m, 1H), 1.41–1.51 (m, 1H), 0.54 (t, $J = 10$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 166.5, 141.5, 137.7, 134.9, 129.2, 129.0, 128.9, 128.7, 128.4, 128.3, 127.9, 127.8, 127.5, 127.1, 126.0, 125.9, 123.6, 117.2, 117.1, 116.9, 59.4, 58.3, 47.1, 44.4, 27.9, 27.0, 11.3. Analysis: calcd. for C$_{24}$H$_{23}$ON: C, 84.41; H, 6.79; N, 4.10%; Found: C, 84.45; H, 6.84; N, 4.15%.

The slow moving diastereomer **11d** was characterized by following data: Solid; yield 64%; M.p. 173–175°C; IR ν_{max} (KBr): 1745 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.90–7.37 (m, 15H, Ph), 5.21 (d, $J = 7.6$ Hz, 1H), 3.82–3.87 (m, 1H), 2.42–2.53 (m, 1H), 1.35–1.42 (m, 2H), 0.40 (t, $J = 9.6$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 166.2, 141.0, 137.0, 134.7, 128.2, 127.8, 127.6, 126.9, 126.4, 122.7, 116.2, 59.6, 57.7, 30.8, 26.8, 15.9, 9.6.
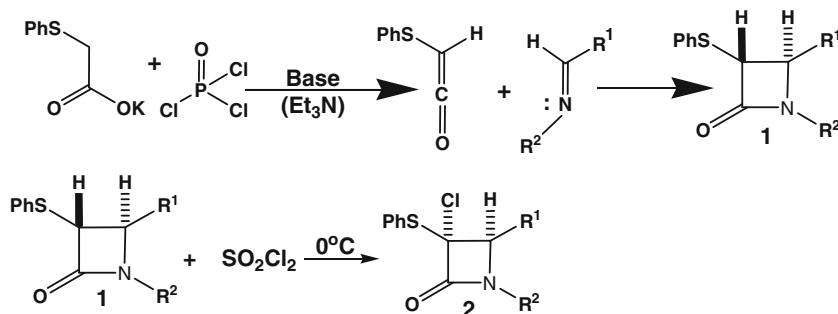
3. Results and Discussion

It has been previously reported that exposure of *trans-3-chloro-3-phenylthio-β-lactams* and allylsilane to a Lewis acid promotes a facile and stereoselective C-3 allylation to give *cis-3-allyl-3-phenylthio-β-lactams* in excellent yield.[11–13] The present work is an extension of the same methodology employing the use of substituted silanes. The starting substrates for Lewis acid mediated C-3 functionalization, *i.e.*, *trans-3-chloro-3-phenylthio-β-lactams* **2** were prepared by reacting phenylthioacetyl chloride or potassium phenylthioacetate with Schiff base in the presence of a triethylamine[8] and phoshphorus oxychloride, followed by stereospecific chlorination[9,10] at C-3 using SO$_2$Cl$_2$ (Scheme 1).

Two silanes, namely, crotylsilane and cinnamylsilane have been used for this study. It was envisaged that use of cinnamylsilane may lead to the formation of 3-(3′-phenylallyl) β-lactams very similar to biologically active ezetimibe (Zeita). Similarly, the use of crotyl silane could provide 3-(3′-methylallyl) β-lactams, another type of densely functionalized β-lactams. The studies were initiated with preparation of substituted silanes which were prepared by coupling reactions of Grignard reagent of the corresponding halide with chlorotrimethylsilane according to the procedure reported in literature.[14]

The reaction of crotyl magnesium chloride with chlorotrimethylsilane resulted in the formation of mixture of *trans-* and *cis-crotyltrimethylsilanes* and trimethyl-α-methylallylsilanes in the ratio 80:20. However, the reaction of cinnamyl chloride with magnesium and trimethylsilylchloride resulted in the formation of only *trans-cinnamyltrimethylsilane* with a trace of *cis-isomer*. These silanes were purified by distillation. However, these silanes could not be fractionated and were used for further reaction as such. The structures of these silanes were confirmed by comparison of ^{1}H-NMR data of products with the reported data in literature (Schemes 2 and 3).[14]

3.1 Studies using crotylsilanes

Initial studies were carried out using crotyl silanes as the nucleophile. Treatment of *trans-3-chloro-3-phenylthio-β-lactam* **2a** with crotyl silanes in the presence of TiCl$_4$ at 0°C in CH$_2$Cl$_2$[11] was monitored by

Scheme 1. Synthesis of starting compounds-3-phenylthioazetidin-2-ones **1** & 3-chloro-3-phenylthioazetidin-2-ones **2**.
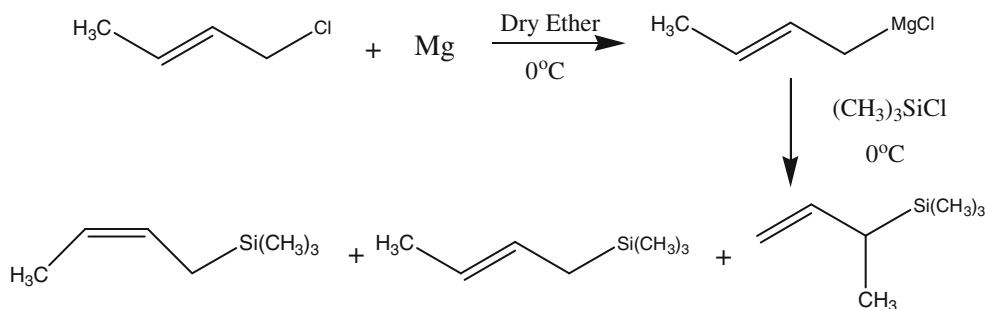
Scheme 2. Synthesis of crotyl silanes.
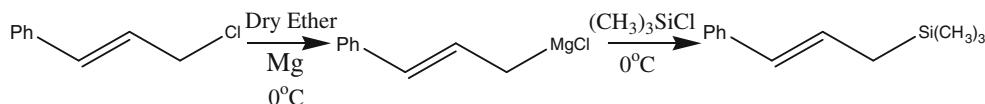
Scheme 3. Synthesis of cinnamyl silanes.

Table 1. Preparation of 3-(1′-methylallyl)-3-phenylthioazetidin-2-ones **3a–d**.

Entry	3	R^1	R^2	Diastereomeric ratio	Yield[a] (%)
1	a	C_6H_5	$C_6H_4(OMe)(4)$	1 : 1	96.15
2	b	$C_6H_4Cl(4)$	$C_6H_4(Me)(4)$	1.33 : 1	64.5
3	c	C_6H_5	$C_6H_4Br(4)$	1.14 : 1	80.6
4	d	C_6H_5	C_6H_5	1.23 : 1	85

[a]Isolated yields were determined after work up and chromatographic purification
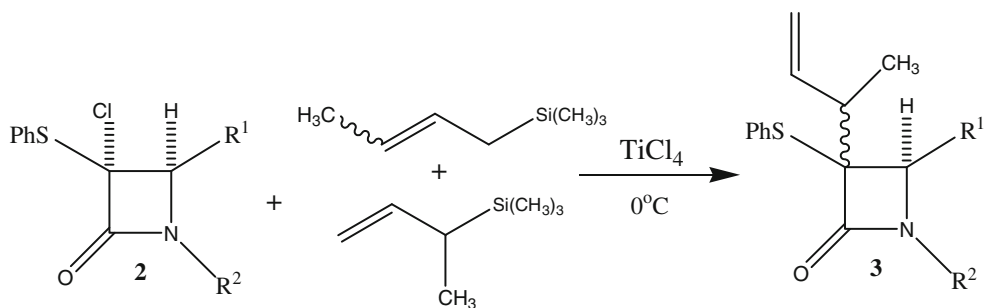
Scheme 4. Synthesis of 3-α-methylallyl-β-lactams **3**.

TLC. The reaction mixture showed the appearance of single spot having R_f slightly higher than that of the substrate. The ^{1}H NMR of the crude product indicated the formation of 3-(1′-methylallyl) β-lactams **3** instead of the expected 3-(3′-methylallyl) β-lactams. This upon purification and complete structural analysis confirmed the formation of compound **3** as mixture of two diastereomers. The diasteromeric ratio was determined by comparing peak area/integral values of multiplet of C′2–H of attached allyl group which resonated at different chemical shifts δ 6.24–6.39 (minor isomer), 5.95–6.05 (major isomer). But these isomeric diastereomers could not be separated by column chromatography, since both isomers showed a single spot and same R_f in TLC. The comparison of ^{1}H NMR data of this compound with that of *cis*-3-allyl-3-phenylthio-β-lactam,[11] whose stereochemistry has been assigned based on X-ray crystallographic data, hinted the same stereochemical placement of allyl group at C-3. However, as this compound itself could not be crystallized, so no concrete proof of its stereochemistry can be given. From the types of product obtained, it can be inferred that in this reaction, out of two isomeric silanes, only the major one *i.e.*, crotyl silane was found to be reacting. The reaction was found to be general and results are summarized in Table 1 (Scheme 4).

### 3.2 *Studies using cinnamylsilanes*

Next, the reaction of **2** with cinnamylsilane under similar conditions was studied. This reaction also resulted in formation of the product arising from allylic shift, namely, 3-(1′-phenylallyl)-3-phenylthio-β-lactams. The product of this reaction, **4** was also found to be a mixture of two inseparable diastereomers, as detected by ^{1}H NMR spectrum of the crude product. However, the diastereomeric ratio was obtained from integration of protons of the substituent attached to the benzene ring as all other protons of the two diastereomers resonated at same value of chemical shift. The

stereochemical placement of allyl group could not be assigned based on this data alone (Scheme 5, Table 2).

The transformation of *trans*-3-chloro-3-phenylthio-β-lactam **2** into 3-(1′-methyl/phenylallyl)-3-phenylthio-β-lactams seems to proceed *via* intermediate formed by addition of C-3 carbocation to double bond facilitating the cleavage of C-Si bond for formation of vinyl bond in the product as shown below (Scheme 6).

3.3 *Desulphurization studies*

Further, to prove the synthetic potential of this reaction and versatility of the products, all C-3-substituted-β-lactams
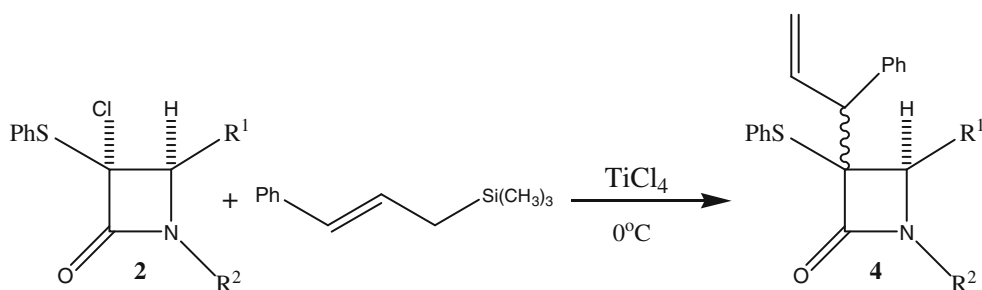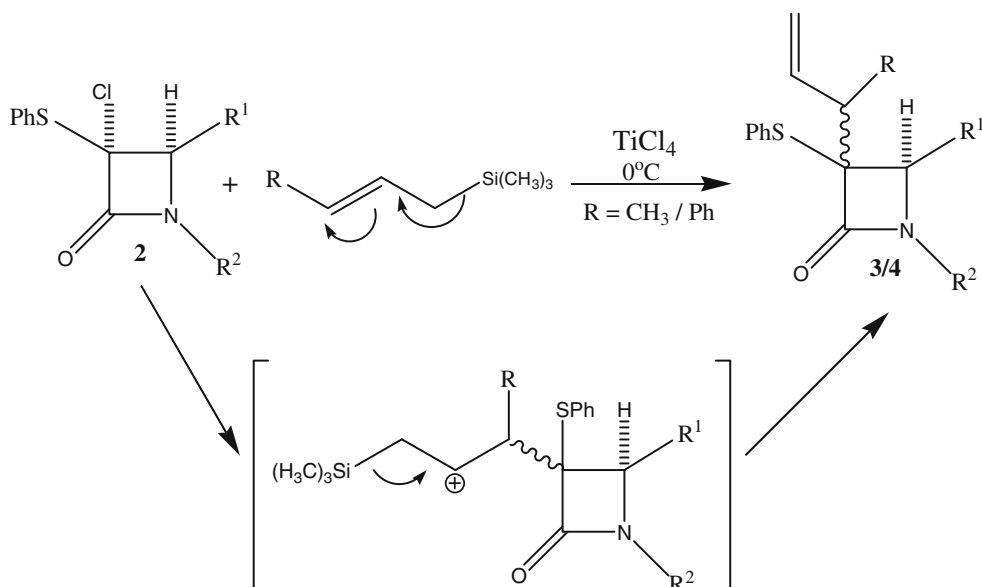

**Scheme 5.** Synthesis of 3-α-phenylallyl-β-lactams **4**.

Table 2. 3-(1′-phenylallyl)-3-phenylthioazetidin-2-ones, **4a–d**.

Entry	4	R^1	R^2	Diastereomeric ratio	Yield^a (%)
1	a	C$_6$H$_5$	C$_6$H$_4$(OMe)(4)	1.6 : 1	62
2	b	C$_6$H$_4$Cl(4)	C$_6$H$_4$(Me)(4)	1.5 : 1	71
3	c	C$_6$H$_5$	C$_6$H$_4$Br(4)	–	71
4	d	C$_6$H$_5$	C$_6$H$_5$	–	70

^{a}Isolated yields were determined after work up and chromatographic purification

Scheme 6. Plausible reaction pathway for transformation of substrate **2** to product **3/4**.
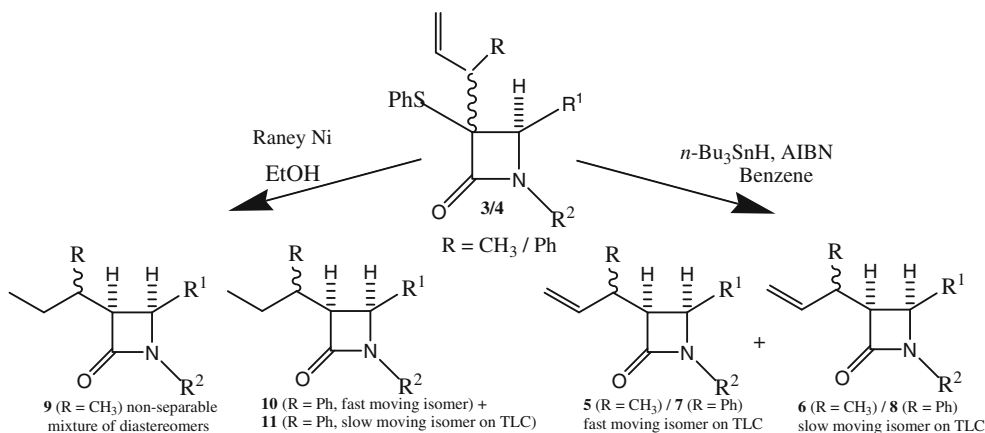
Scheme 7. Desulphurisation reactions of substrate **3** and **4**.

Table 3. Reduction of **3** and **4** using n-Bu$_3$SnH.

Entry	Substrate	Product	Yield^a (%)
1	**3a**	**5a**, **6a**	56, 24
2	**3d**	**5d**, **6d**	55, 27
3	**4a**	**7a**, **8a**	49, 25
4	**4d**	**7d**, **8d**	44, 29

^{a}Isolated yields were determined after work up and chromatographic purification.

Table 4. Reduction of **3** and **4** using Raney Ni.

Entry	Substrate	Product	Yield^a (%)
1	**3a**	**9a**	100
2	**3d**	**9d**	80
3	**4a**	**10a**, **11a**	33, 46
4	**4d**	**10d**, **11d**	31, 64

^{a}Isolated yields are determined after work up and chromatographic purification.

were subjected to desulphurization reaction. Reduction of **3** using n-Bu$_3$SnH (1 equiv.) in benzene catalysed by Azobisisobutyronitrile (AIBN) gave reduced product *cis*-3-α-methylallyl-β-lactams **5** and **6**. Interestingly, both the isomers of this reduced product were easily separable by column chromatography. The reduction reaction of **4** using the same reagent gave separable isomers of the reduced products, *cis*-3-α-phenylallyl-β-lactams **7** and **8**. The stereochemistry at C-3 of these products was confirmed by the coupling constant between C_3-H and C_4-H. However, the relative stereochemistry of the α-group of the allyl substituent to these isomers could not be assigned on the basis of spectroscopic data alone. So, the two isomers were named as 'slow moving' and 'fast moving' diastereomers based on their R_f values in TLC profile (Scheme 7, Table 3).

Reduction using Raney Nickel resulted in desulphurisation accompanied by hydrogenation of the double bond. Treatment of *cis*-3-α-methylallyl-β-lactams, **3** with Raney Nickel gave *cis*-3-α-methylpropyl-β-lactams **9**, whose two diastereomers were inseparable on TLC and column chromatography. But reaction of **4** with Raney Nickel gave two separable diastereomers of the product *cis*-3-α-phenylpropyl-β-lactam, **10** and **11** (Table 4).

4. Conclusions

In summary, this research work provides a facile and stereoselective method for the synthesis of *cis*-3-(1′-methyl/phenylallyl)-β-lactams. Although these reactions could not give the desired products, they have resulted in the synthesis of new 3-substituted-allyl β-lactams. Further, reduction using different reagents provides an easy access to two diastereomers of the products, which as such were unseparable. The synthetic potential of these compounds is under research in our lab.

Supplementary Information (SI)

All additional information pertaining to characterization of the representative compounds (**3a**, **4a**, **5a**, **6a**, **7a**, **8a**, **9a**, **10a** and **11a**) using ^{1}H NMR and ^{13}C NMR techniques (Figures S1–S8) are given in the supporting information. Supplementary Information is available at www.ias.ac.in/chemsci.

Acknowledgements

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