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Facile synthesis of (*Z*)- and (*E*)-3-allylidene-β-lactams via thermal β-elimination of *trans*-3-allyl-3-sulfinyl-β-lactams

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ABSTRACT

A competent synthetic route for the synthesis of novel (*Z*)- and (*E*)-3-allylidene-β-lactams is described. The strategy involves oxidation of *trans*-3-allyl-3-phenylthio-β-lactams **1** using sodium metaperiodate ($NaIO_4$) to diastereomeric *trans*-3-allyl-3-phenylsulfinyl-β-lactams **2** and **3**, which further undergo thermal β-elimination in refluxing carbon tetrachloride to furnish (*Z*)- and (*E*)-3-allylidene-β-lactams **5** and **6** in good to excellent yields. The molecular structure of **3b** has been established with the help of single crystal X-ray analysis.

β-Lactams have attracted continued interest not only for their diverse and powerful antibiotic activity[1] but also for their utility as versatile synthetic intermediates.[2] The need for potent and effective β-lactam antibiotics as well as effective β-lactamase inhibitors has motivated chemists world over to design new β-lactams.[3] In addition, the relevance of β-lactams in many other significant non-antibiotic uses, such as cholesterol acyl transferase inhibitors, thrombin inhibitors, human cytomegalovirus protease inhibitors, matrix-metallo protease inhibitors, human leukocyte elastase, cysteine protease, apoptosis inductors, gene activators, and β-turn nucleator continues to expand at a surprising rate.[4]

α-Alkylidene-β-lactams are well-acknowledged structural elements of ene-type β-lactamase inhibitors such as asparenomycins, Ro 15-1903, 6-[(*Z*)-methoxymethylidene]penicillanic acid, and 6-(2′-pyridyl)methylene penem sulfone.[5] Moreover, 6-alkylidenepenicillianate sulfoxides and sulfones have been shown to possess antitumor properties.[6] Recently, 4-alkylidene-β-lactams have been reported to exhibit activity against human leukocyte elastase, gelatinase MMP-2, and MMP-9.[7] Besides this, α-alkylidene-β-lactams are valuable synthetic intermediates for α-keto-β-lactams, spiro-β-lactams, bicyclic-β-lactams,[8] and β-amino alcohols and acids.[9]

Recognition of the importance of α-alkylidene-β-lactams and in persistence to our earlier studies[4,10–19] intended toward the synthesis of novel thio/seleno-β-lactams and their functionalization, renewed efforts have been made in the present work to achieve the synthesis of 3-allylidene-β-lactams from 3-allyl-3-sulfinyl-β-lactams.

Several synthetic methods have been listed in the literature for the synthesis of α-alkylidene-β-lactams.[5,6] Mahajan and co-workers have reported the diastereoselective synthesis of *trans*-3-allylidene-β-lactams and their further elaboration to Diels–Alder adducts on reaction with variety of dienophiles.[20] Keeping in view that sulfoxide can undergo a facile β-elimination leading to the introduction of unsaturation in the target molecule,[21] we envisaged the synthesis of 3-allylidene-β-lactams via thermal β-elimination of *trans*-3-allyl-3-sulfinyl-β-lactams, prepared by the oxidation of *trans*-3-allyl-3-phenylthio-β-lactams using sodium metaperiodate.

Starting substrates, *trans*-3-allyl-3-phenylthio-β-lactams **1(a–d)** were prepared through Lewis acid-promoted C-3 allylation of 3α-chloro-3-phenylthio-β-lactams with allyltrimethylsilane according to our earlier reported synthetic route.[11] The *trans*-3-allyl-3-phenylthio-β-lactams **1(a–d)** were submitted to the oxidation using sodium metaperiodate to provide *trans*-3-allyl-3-phenylsulfinyl-β-lactams **2(a–d)** and **3(a–d)** in good to excellent yields (Scheme 1, Table 1, entries 1–4). Initial studies were carried out by the treatment of **1a** with 2 equiv of $NaIO_4$ in MeOH–H_2O (10:1) at room temperature. The progress of the reaction was monitored by thin-layer chromatography (TLC). The reaction resulted in the formation of a mixture of two diastereomeric 3-phenylsulfinyl-β-lactams **2a** and **3a** as the major products in 1:1 ratio, as was evident from ^{1}H NMR spectroscopy, along with 3-phenylsulfonyl-β-lactam **4a** as a minor one (Scheme 1, Table 1, entry 1).[22] The sulfinyl- (**2a, 3a**) and sulfonyl-β-lactams, (**4a**) with different R_f values were separable through

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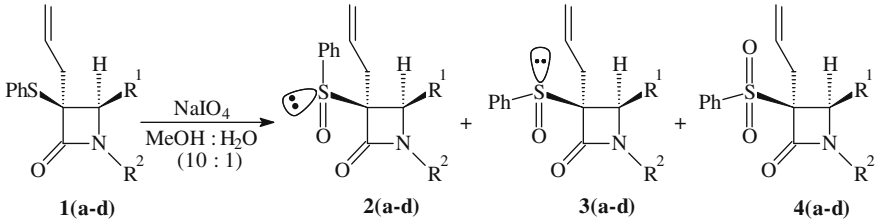


Scheme 1. Synthesis of *trans*-3-allyl-3-phenylsulfinyl-β-lactams **2**(**a**–**d**) and **3**(**a**–**d**).

Table 1
Synthesis of *trans*-3-allyl-3-phenylsulfinyl-β-lactams **2**(**a**–**d**) and **3**(**a**–**d**)

Entry	Substrate **1**	R^1	R^2	Products of type[a] (% yield)		
				2	**3**	**4**
1	**1a**	Ph	4-$MeOC_6H_4$	**2a** (36)	**3a** (46)	**4a** (9)
2	**1b**	4-$MeOC_6H_4$	4-$MeOC_6H_4$	**2b** (30)	**3b**[b] (41)	**4b** (12)
3	**1c**	4-ClC_6H_4	4-MeC_6H_4	**2c** (28)	**3c** (37)	**4c** (14)
4	**1d**	Ph	Ph	**2d** (32)	**3d** (40)	**4d** (7)

[a] Isolated yields after purification by column chromatography.
[b] The structure of this molecule was also established from single crystal X-ray data (Fig. 1).

column chromatography on silica gel eluting with EtOAc/hexane (7:93) and were identified as *trans*-3-allyl-3-phenylsulfinyl-β-lactam **2a** (R_f = 0.53), *trans*-3-allyl-3-phenylsulfinyl-β-lactam **3a** (R_f = 0.43), and *trans*-3-allyl-3-phenylsulfonyl-β-lactam **4a** (R_f = 0.66), respectively.[22] The reaction was found to be general with other substrates **1**(**b**–**d**) (Scheme 1) and the results are summarized in Table 1 (entries 2–4). Although in the present reaction the diastereoselectivity was not improved using different temperature conditions, the good yields of the two diastereomeric 3-phenylsulfinyl-β-lactams **2** and **3** were attained.

The structures of these β-lactams **2–4**(**a–d**) were established by spectroscopic studies such as FT-IR, ^{1}H NMR, ^{13}C NMR, mass spectrometry, and elemental (CHN) analyses.[22] The stereochemistry of the major *trans*-3-allyl-3-phenylsulfinyl-β-lactam **3** was confirmed through single crystal X-ray structure analysis of **3b**[23] (Fig. 1). The stereochemistry of the other isomer, that is, *trans*-3-allyl-3-phenylsulfinyl-β-lactam **2** was tentatively assigned in relation to the stereochemistry of **3b**.

The *trans*-3-allyl-3-phenylsulfinyl-β-lactams **2**(**a**–**d**) were further subjected to thermolysis reaction using different solvents such as $CHCl_3$, CCl_4, and toluene (Scheme 2). Initially, **2a** underwent facile thermolysis giving isomeric 3-allylidene-β-lactams **5a** and **6a** in 1:1 ratio, as was evident from ^{1}H NMR spectroscopy (Table 2, entry 1).[25] These two dienes were separated by column chromatography on silica gel eluting with EtOAc/hexane (7:93) and were identified as (*Z*)-3-allylidene-β-lactam **5a** (R_f = 0.60) and (*E*)-3-allylidene-β-lactam **6a** (R_f = 0.57), respectively, on the basis of spectroscopic studies. This reaction was also performed successfully with other substrates **2**(**b**–**d**) and goes to nearly 80% completion without any further rearrangement of the diene products (Scheme 2, Table 2, entries 2–4). It was observed that CCl_4 is the best solvent for this reaction as compared to $CHCl_3$ and toluene which produce undesired rearranged products from diene.

The structures of 3-allylidene-β-lactams **5–6**(**a–d**) were confirmed by spectroscopic means such as UV–vis, FT-IR, ^{1}H NMR, ^{13}C NMR, ^{13}C NMR (DEPT–135), and elemental (CHN) analyses. The stereochemistry (*Z*)- and (*E*)- of 3-allylidene-β-lactams was established on the basis of chemical shift of olefin multiplet for γ-proton and doublet for β-proton in ^{1}H NMR (Fig. 2). The γ-proton resonated downfield at δ 7.10 ppm for the *Z*-isomer (**5**) due to deshielding anisotropic effect of β-lactam carbonyl. The doublet for β-proton of this isomer was observed at δ 5.88 (*J* = 10.5 Hz) ppm. Whereas, in *E*-isomer (**6**), the multiplet for γ-proton resonated upfield at δ 5.95 ppm and the doublet for β-proton appeared downfield at δ 6.52 (*J* = 10.5 Hz) ppm due to deshielding effect of β-lactam carbonyl. Additionally, the disappearance of doublet for methylene protons of allyl moiety of **2**(**a**–**d**) provides evidence indicating the formation of (*Z*)- and (*E*)-3-allylidene-β-lactams. Further, the mass spectra (EI-MS) of **3a** and **4a** show peaks at

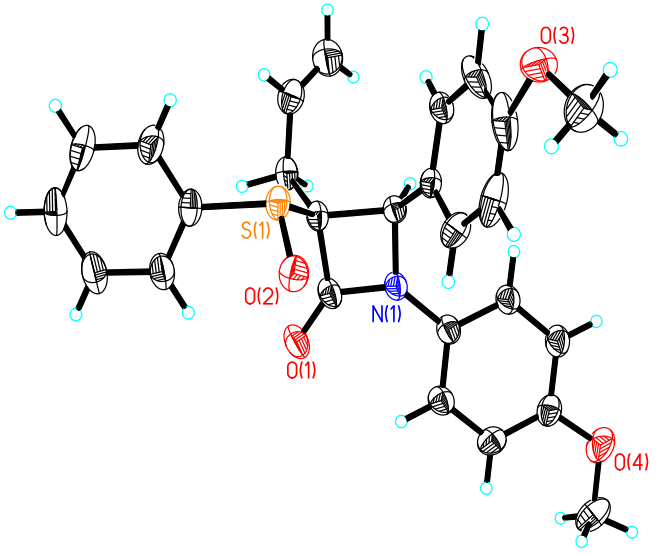
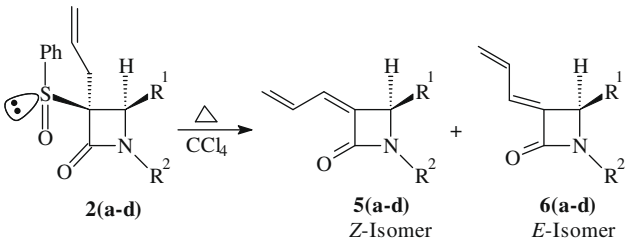


Figure 1. ORTEP diagram of *trans*-3-allyl-3-sulfinyl-β-lactam **3b**.[24]



Scheme 2. Synthesis of (*Z*)- and (*E*)-3-allylidene-β-lactams **5**(**a**–**d**) and **6**(**a**–**d**) via thermolysis of *trans*-3-allyl-3-phenylsulfinyl-β-lactams **2**(**a**–**d**).

Table 2
Synthesis of (*Z*)- and (*E*)-3-allylidene-β-lactams **5** and **6** via thermolysis of *trans*-3-allyl-3-phenylsulfinyl-β-lactams **2**

Entry	**2**	R^1	R^2	Time (h)	Products of type[a] (% yield)		Unreacted **2** (% yield)
					5 (*Z*-isomer)	**6** (*E*-isomer)	
1	**2a**	Ph	4-$MeOC_6H_4$	24	**5a** (30)	**6a** (32)	**2a** (12)
2	**2b**	4-$MeOC_6H_4$	4-$MeOC_6H_4$	45	**5b** (29)	**6b** (34)	**2b** (14)
3	**2c**	4-ClC_6H_4	4-MeC_6H_4	40	**5c** (27)	**6c** (36)	**2c** (18)
4	**2d**	Ph	Ph	12	**5d** (31)	**6d** (37)	**2d** (15)

[a] Isolated yields after purification by column chromatography.

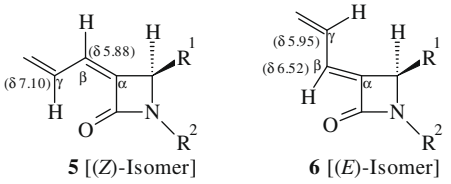
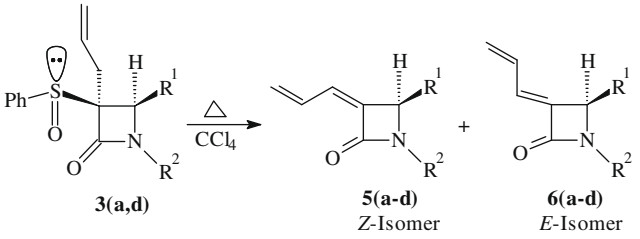


Figure 2. (*Z*)- and (*E*)-3-allylidene-β-lactams **5** and **6**.



Scheme 3. Synthesis of (*Z*)- and (*E*)-3-allylidene-β-lactams **5**(**a**–**d**) and **6**(**a**–**d**) via thermolysis of *trans*-3-allyl-3-phenylsulfinyl-β-lactams **3**(**a**,**d**).

m/*z* 291 (78, [(*E*)-3-allylidene-β-lactam **6a**]$^+$) and 291 (13, [(*E*)-3-allylidene-β-lactam **6a**]$^+$) indicate the thermolysis affording more stable (*E*)-3-allylidene-β-lactam.

Next, we examined the behavior of *trans*-3-allyl-3-phenylsulfinyl-β-lactams **3(a,d)** under the similar reaction conditions (Scheme 3, Table 3, entries 1–2). This reaction proceeds more slowly, leaving the unreacted substrate (**3**) even after prolonged refluxing. Surprisingly, thermolysis of **3(a,d)** strongly favors the formation of (*E*)-isomer of 3-allylidene-β-lactams **6**(**a**,**d**) over (*Z*)-isomer **5(a,d)**.

This can be rationalized on the basis of the formation of benzenesulfenic (PhSOH) acid in the reaction which highlights the proximity of sulfoxide oxygen to the two β-hydrogens of allyl group of **2** and **3** determining the reactivity toward thermal β-elimination. The ORTEP diagram of **3b** shows the minimum steric repulsion between the S=O, allyl group at C-3, and phenyl group at C-4 and hence explains the greater stability with respect to **2**. However, in **2** the S=O group is much closer to the β-hydrogens of allyl group, facilitating thermolysis rapidly. Moreover, thermolysis favors the formation of (*E*)-isomer **6**(**a**,**d**) over (*Z*)-isomer **5**(**a**,**d**) which may be due to the higher stability of (*E*)-isomer because of less steric interference and this could be attributed to the electronic repulsion of the carbonyl group and the terminal ethylene in the case of (*Z*)-isomer. Thermolysis of *trans*-3-allyl-3-phenylsulfonyl-β-lactam **4a** did not furnish any diene product under similar reaction conditions.

In conclusion, a facile route to novel (*Z*)- and (*E*)-3-allylidene-β-lactams has been explored and developed via thermal β-elimination of *trans*-3-allyl-3-phenylsulfinyl-β-lactams. Further elaboration of these novel 3-allylidene-β-lactams to Diels–Alder adducts using variety of dienophiles is underway in our laboratory.

Table 3
Synthesis of (*Z*)- and (*E*)-3-allylidene-β-lactams **5** and **6** via thermolysis of *trans*-3-allyl-3-phenylsulfinyl-β-lactams **3**

Entry	**3**	R^1	R^2	Time (h)	Products of type[a] (% yield)		Unreacted **3** (% yield)
					5 (*Z*-isomer)	**6** (*E*-isomer)	
1	**3a**	Ph	4-$MeOC_6H_4$	90	**5a** (14)	**6a** (40)	**3a** (30)
2	**3d**	Ph	Ph	90	**5d** (10)	**6d** (36)	**3d** (35)

[a] Isolated yields after purification by column chromatography.

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22. *General procedure for the synthesis of* ***2–4***: A solution of **1** (1.0 mmol) in MeOH (10 mL) and THF (1 mL) was stirred with $NaIO_4$ (2.7 mmol) and dissolved in H_2O (1 mL) at room temperature. The progress of the reaction was checked by TLC, which showed the appearance of three new spots, all of them having R_f lower than the substrate **1**. The solvent was evaporated under reduced pressure and the reaction mixture was extracted with dichloromethane (5 × 20 mL), washed with H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4, and then filtered. The solvent was evaporated under reduced pressure to give the crude products. β-Lactams **2–4**(**a–d**) were purified by column chromatography on silica gel eluting with EtOAc/hexane (7:93). *trans-1-(4′-Methoxyphenyl)-3-allyl-3-phenylsulfinyl-4-phenylazetidin-2-one (***2a***):* Yield 36%, R_f (7:93, EtOAc/hexane): 0.53; FT-IR ($CHCl_3$) cm^{-1}: 1753 (C=O), 1638 (C=C); ^1H NMR (300 MHz, $CDCl_3$) δ 2.19–2.26 (–C*H*$_2$–, m, 1H), 2.81–2.89 (–C*H*$_2$–, m, 1H), 3.63 (OC*H*$_3$, s, 3H), 5.10–5.24 (*H*$_2$C=, m, 2H), 5.16 (C4–*H*, s, 1H), 5.66–5.67(=C*H*–, m, 1H), 6.63–7.55 (Ar*H*, m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.1 (–CH_2–), 55.3 (OCH_3), 61.7 (C-4), 78.6 (C-3), 114.5–156.7 (C=C, ArC), 160.4 (C=O); Anal. Calcd for $C_{25}H_{23}NO_3S$: C, 71.91; H, 5.55; N, 3.35. Found: C, 71.80; H, 5.46; N, 3.28. *trans-1-(4′-methoxyphenyl)-3-allyl-3-phenylsulfinyl-4-phenylazetidin-2-one* (**3a**). Yield 46%, R_f (7:93, EtOAc/hexane): 0.43; mp: 161–162 °C; FT-IR ($CHCl_3$) cm^{-1}: 1748 (C=O), 1640 (C=C); ^1H NMR (300 MHz, $CDCl_3$) δ 2.22–2.30 (–C*H*$_2$–, m, 1H), 2.59–2.66 (–C*H*$_2$–, m, 1H), 3.73 (OC*H*$_3$, s, 3H), 5.20 (C4–*H*, s, 1H), 5.25–5.28 (*H*$_2$C=, m, 2H), 5.75–5.78 (=C*H*–, m, 1H), 6.76–7.56 (Ar*H*, m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 33.7 (–CH_2–), 55.4 (OCH_3), 62.3 (C-4), 80.4 (C-3), 114.2–156.4 (C=C, ArC), 160.7 (C=O); EI-MS *m*/*z* (R.I.%, [assignment]$^+$): 417 (03, $[M]^+$), 291 (78, [(*E*)-3-allylidene-β-lactam **6a**]$^+$), 211 (51, $[C_6H_5CH{=}NC_6H_4(OCH_3)]^+$), 149 (100, $[O{=}C{=}NC_6H_4(OCH_3)]^+$); Anal. Calcd for $C_{25}H_{23}NO_3S$: C, 71.91; H, 5.55; N, 3.35. Found: C, 71.85; H, 5.48; N, 3.29. *trans-1-(4′-Methoxyphenyl)-3-allyl-3-phenylsulfonyl-4-phenylazetidin-2-one* (**4a**). Yield 9%, R_f (7:93, EtOAc/hexane): 0.66; FT-IR ($CHCl_3$) cm^{-1}: 1760 (C=O), 1639 (C=C); ^1H NMR (300 MHz, $CDCl_3$) δ 2.52–2.60 (–C*H*$_2$–, m, 1H), 2.66–2.73 (–C*H*$_2$–, m, 1H), 3.60 (OC*H*$_3$, s, 3H), 5.08 (C4–*H*, s, 1H), 5.14–5.23 (*H*$_2$C=, m, 2H), 5.72–5.75 (=C*H*–, m, 1H), 6.59–7.64 (Ar*H*, m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.4 (–CH_2–), 55.1 (OCH_3), 61.9 (C-4), 80.1 (C-3), 115.2–155.3 (C=C, ArC), 161.1 (C=O); EI-MS *m*/*z* (R.I.%, [assignment]$^+$): 433 (44, $[M]^+$), 291 (13, [(*E*)-3-allylidene-β-lactam **6a**]$^+$), 211 (100, $[C_6H_5CH{=}NC_6H_4(OCH_3)]^+$), 149 (65, $[O{=}C{=}NC_6H_4(OCH_3)]^+$); Anal. Calcd for $C_{25}H_{23}NO_4S$: C, 69.26; H, 5.35; N, 3.23. Found: C, 69.22; H, 5.31; N, 3.20.
23. *Crystal data for* **3b***:* Monoclinic; $P2_1/n$; a = 11.9440(10) Å, b = 11.4770(10) Å, c = 17.757(2) Å; α = 90°, β = 107.25°, γ = 90 °C; V = 2324.7(4) Å^3; Z = 4; ρ Calcd = 1.279 mg/m^3; μ (Mo Kα = 0.171 mm^{-1}; full matrix least-square on F^2; R_1 = 0.0570, wR_2 = 0.1355 for 2184 observed reflections [$I > 2\sigma$ (I)] and R_1 = 0.0900, wR_2 = 0.1554 for all 3226 reflections; GOF = 1.011. Crystallographic data (excluding structure factors) for the structure **3b** in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 642730. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internet) +44 1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
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25. *General procedure for the synthesis of 3-allylidene-β-lactams* ***5***, ***6***: A solution of **2** or **3** (1.0 mmol) in CCl_4 (10 mL) was refluxed and the progress of the reaction was monitored by TLC. The TLC profile of the reaction mixture showed the appearance of two new spots, having R_f higher than the substrate **2** or **3**. Refluxing was continued until no change in TLC profile was observed. The solvent was evaporated under reduced pressure to give the crude products. 3-Allylidene-β-lactams **5**, **6**(**a–d**) were purified by column chromatography on silica gel eluting with EtOAc/hexane (7:93). *(Z)-1-(4′-Methoxyphenyl)-3-allylidene-4-phenylazetidin-2-one (***5a***):* Yield 30%, R_f (7:93, EtOAc/hexane): 0.60; FT-IR ($CHCl_3$) cm^{-1}: 1746 (C=O), 1695, 1649 (C=C); ^1H NMR (300 MHz, $CDCl_3$) δ 3.66 (OC*H*$_3$, s, 3H), 5.20 (C4–*H*, s, 1H), 5.23–5.30 (*H*$_2$C=, m, 2H), 5.88 (–C*H*=C–, d, 1H, J = 10.5), 6.66–7.29 (Ar*H* and $H_2C{=}CH$–, m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) (DEPT–135) δ 55.1 [+, (OCH_3)], 62.6 [+, (C-4)], 122.4 [–, (H_2C=)], 114.4–156.1 (C=C, ArC), 159.6 (C=O); Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.32; H, 5.88; N, 4.80. Found: C, 78.24; H, 5.81; N, 4.73. *(E)-1-(4′-Methoxyphenyl)-3-allylidene-4-phenylazetidin-2-one (***6a***):* Yield 32%, R_f (7:93, EtOAc/hexane): 0.57; UV–vis (THF) λ_{max} (ε) nm: 312 (14357); FT-IR ($CHCl_3$) cm^{-1}: 1736 (C=O), 1686, 1609 (C=C); ^1H NMR (300 MHz, $CDCl_3$) δ 3.64 (OC*H*$_3$, s, 3H), 5.21 (*H*$_2$C=, d, 1H, J = 10.2), 5.32 (C4–*H*, s, 1H), 5.34 (*H*$_2$C=, d, 1H, J = 10.2), 5.95–6.07 ($H_2C{=}CH$–, m, 1H), 6.52 (–C*H*=C–, d, 1H, J = 11.7), 6.62–7.37 (Ar*H*, m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) (DEPT–135) δ 55.1 [+, (OCH_3)], 63.1 [+, (C-4)], 124.5 [–, (H_2C=)], 114.4–156.1 (C=C, ArC), 160.2 (C=O); Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.32; H, 5.88; N, 4.80. Found: C, 78.27; H, 5.83; N, 4.77.