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Synthesis of some (*E*)-3-arylidene-7-methylazepan-2-ones *via* Beckmann rearrangement

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Abstract: In the present study, synthesis of some (*E*)-3-arylidene-7-methylazepan-2-ones (**6**) derived from 2-methylcyclohexanone (**1**) *via* thionyl chloride/dry dioxane mediated Beckmann rearrangement in moderate yields has been described. The structural elucidation of the synthesized compounds was confirmed on the basis of spectral (IR, NMR and mass) as well as elemental analysis results.

Keywords: Beckmann rearrangement; 2-methylcyclohexanone; oximes; thionyl chloride.

1. Introduction

Azaheterocyclic compounds have gained the attention of researchers worldwide and are of continued interest due to their presence in numerous natural products and synthetic compounds which exhibit important chemical, biological, and medicinal properties [1]. Azepine and its derivatives fall into this class. Some examples of biologically active azepinone-based natural products are like debromohymenialdisine, which acts as checkpoint kinase 2 (Chk2) inhibitor, the marine sponge constituent CID755673, which is a highly selective inhibitor of proteinkinase D (PKD), and the matrix metalloproteinase inhibitor (-)-cobactin T [2]. Similarly, benzazepines such as ribasine, isolated from Fumariaceae plants, and homoprotoberberines alkaloids that are known to show antimalarial and antibacterial properties [3]. In addition, azepinones and their saturated and unsaturated analogues play a significant role in medicinal chemistry [4] including in drugs (e.g. benazepril [5], ivabradine [6], telcagepant [7]), antibiotic research (e.g. capuramycin [8]), and as simple models of cyclic peptides [9] and many more [10]. Further, azepinone derivatives are also known for their industrial applications e.g. ε-Caprolactam, or hexahydro-2-azepinone, is an important starting material in polymer chemistry which is used in nylon preparation [11], and as such is the basis for the manufacturing of many useful products. Derivatives of ε-caprolactam are of importance for the manufacture of modified nylons [12] and nanogels [13]. As

a consequence, extensive research has been focused on the development of efficient routes towards azepine derivatives [14]. Beckmann rearrangement [15] finds various applications in the synthesis of *N*-substituted amides and lactams [16], a variety of heterocyclic compounds [17] and aza steroids [18]. The pioneering reports on Beckmann rearrangement have been published by groups of researchers [19]. Despite wide interest in the Beckmann rearrangement, chemists in the past have taken sporadic interest in Beckmann rearrangement of alicylic and cyclic *α,β*-unsaturated ketones [20]. Considering the biological interest of azepinone derivatives and synthetic utility of Beckmann rearrangement, and pursuing our interest in synthetic methodology development for heterocycle synthesis [21], herein, we wish to report the synthesis of some (*E*)-3-arylidene-7-methylazepan-2-ones (**6**) *via* thionyl chloride/ dry dioxane mediated Beckmann rearrangement with an aim to study whether (i) *O*-tosyl oximes (**5**) undergo alkyl or vinyl migration, and (ii) the rearrangement is escorted by the migration of double bond from exocyclic to endocyclic position or not.

2. Materials and methods

2.1 General: The chemicals used in the present investigation were procured from commercial sources and were used as such or after necessary purification as per standard literature procedures. Melting points (°C) of the synthesized compounds were determined on an electrothermal apparatus (Labco Co., India) in open head capillaries and are uncorrected. Purity of the synthesized compounds and progress of the reactions were monitored by thin layer chromatography (TLC) using commercially available precoated silica gel (HF_{254}, 200 mesh) plates as stationary phase and different combinations of solvents as mobile phase. The developed TLC plates were examined under UV light or using iodine staining for visualization of the spots. The synthesis of compounds was done by stirring with the aid of a magnetic stirrer and/or heating at desired temperature on a water bath and structures of all the synthesized compounds were corroborated by employing different spectral (FTIR, NMR, Mass) and elemental analytical techniques. IR spectra were scanned on Perkin Elmer Spectrum, BX II FTIR spectrometer in the range of 400–4000 cm^{-1} using potassium bromide (KBr) pellets and intensity of absorption bands are assigned as follows: s, strong; m, medium; w, weak; and br, broad. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Advance 300/400/500 MHz spectrometer at 300/400/500 MHz and 75/100/125 MHz, respectively using $CDCl_3$/ DMSO-d_6 as solvents. Chemical shift values (δ) are reported in parts per million (ppm) and tetramethylsilane (TMS) was used as an internal standard. The peak patterns are assigned as follows: *s*, singlet; *br s*, broad singlet; *d*, doublet; *m*, multiplet, and coupling constant (*J*) values are given in Hertz (Hz). Mass spectra were recorded on Agilent 6310 LCMS ION TRAP spectrometer. The figure given in the parentheses represents relative intensities corresponding to the base peak taken as 100. Elemental analysis was carried out using Vario Micro Cube Elementar CHNS analyzer and analytical results for C, H and N were found within ±0.4% of the theoretical values.

2.2 General procedure for the synthesis of (*E*)-2-arylidene-6-methylcyclohexanones (3): To a solution of 2-methylcyclohexanone (**1**, 2.24 g, 0.02 mole) and an appropriate benzaldehyde (**2**, 0.024 mole) in methanol (50 mL) was added 15% aqueous KOH (33 mL) dropwise while stirring with the aid of a magnetic stirrer and the reaction mixture was heated at reflux while stirring on a water bath for 2–3h. Thereafter, the reaction mixture was poured in cold water and extracted with chloroform (3×20 mL). The organic layer was washed with dil. HCl followed by water, dried over anhydrous $MgSO_4$, and chloroform was removed under reduced pressure. The residue

thus obtained was crystallized from ethanol to give the corresponding (*E*)-2-arylidene-6-methylcyclohexanones (**3**) in good yields. Their physical data are given as follows:

(*E*)-2-benzylidene-6-methylcyclohexanone (3a): Obtained by stirring for 2h; white crystals, yield 62%; mp 59–60 °C (Lit. mp [22,23] 61–62 °C).

(*E*)-2-(4-methylbenzylidene)-6-methylcyclohexanone (3b): Obtained by stirring for 2.5h; white crystals, yield 55%; mp 117–120 °C (Lit. mp [23] 120–124 °C).

(*E*)-2-(4-methoxybenzylidene)-6-methylcyclohexanone (3c): Obtained by stirring for 3h; white crystals, yield 53%; mp 68–69 °C (Lit. mp [22] 69–71 °C).

(*E*)-2-(4-chlorobenzylidene)-6-methylcyclohexanone (3d): Obtained by stirring for 2h; white crystals, yield 61%; mp 59–60 °C (Lit. mp [24] 61–62.5 °C).

2.3 General procedure for the synthesis of (1*E*,2*E*)-2-arylidene-6-methylcyclohexanone oximes (4): A mixture of an appropriate (*E*)-2-arylidene-6-methylcyclohexanone (**4**, 0.009 mole), $NH_2OH.HCl$ (0.70 g, 0.01 mole) and NaOH (4.0 g) in methanol (150 mL) was heated at reflux on a water bath for 2–4h. Thereafter, the hot mixture was filtered, filtrate was concentrated *in vacuuo*, water was added and solid thus obtained was collected by filtration which upon crystallization from a suitable solvent furnished the corresponding (1*E*,2*E*)-2-arylidene-6-methylcyclohexanone oximes (**4**) in high yields (79.3–86%). Their spectral parameters and other characteristics are given below:

(1*E*,2*E*)-2-benzylidene-6-methylcyclohexanone oxime (4a): Obtained by refluxing for 3h; white crystals (methanol), yield 85%; mp 145–147 °C (Lit. mp [24] 147–149 °C); IR (KBr, cm^{-1}): 3225 (br, O–H, stretch), 1630 (m, C=N, stretch), 1590 (s, C=C, stretch), 1558, 1422, 1161, 1117, 972, 885, 789, 672, 515; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.12 (*d*, *J* = 7.2 Hz, 3H, 6-CH_3), 1.53–1.79 (*m*, 4H, 4-H, 5-H), 2.27–2.99 (*m*, 3H, 3-H, 6-H), 6.82 (*s*, 1H, H_β), 7.23–7.37 (*m*, 5H, 2′-H, 3′-H, 4′-H, 5′-H, 6′-H), 8.08 (*br s*, 1H, OH, exchangeable with D_2O); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.15 (C_6-$\underline{CH_3}$), 21.60, 30.06, 30.98 (C_3, C_4, C_5), 26.92 (C_6), 127.63 ($C_{3'}$ & $C_{5'}$), 127.99 ($C_{2'}$ & $C_{6'}$), 128.17 ($C_{1'}$), 128.90 ($C_{4'}$), 135.03 (C_β), 137.91 (C_2), 163.16 (C_1); *Anal.* Calcd. for $C_{14}H_{17}NO$ (215.13): C, 78.10; H, 7.96; N, 6.51. Found: C, 77.92; H, 7.84; N, 6.66.

(1*E*,2*E*)-2-(4-methylbenzylidene)-6-methylcyclohexanone oxime (4b): Obtained by refluxing for 4h; yellow crystals (benzene), yield 86%; mp 100–102 °C; IR (KBr, cm^{-1}): 3298 (br, O–H, stretch), 1636 (m, C=N, stretch), 1599 (s, C=C, stretch), 1558, 1422, 1161, 1117, 972, 885, 789, 672, 515; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.09 (*d*, *J* = 7.2 Hz, 3H, 6-CH_3), 1.42–1.93 (*m,* 4H, 4-H, 5-H), 2.29–2.89 (*m*, 6H, 3-H, 6-H, 4′-CH_3), 6.76 (*s*, 1H, H_β), 7.13 (*d*, *J* = 8.1 Hz, 2H, 3′-H & 5′-H), 7.20 (*d, J* = 8.1 Hz, 2H, 2′-H & 6′-H), 10.05 (*br s*, 1H, OH, exchangeable with D_2O); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.23 (C_6-$\underline{CH_3}$), 21.40 ($C_{4'}$-$\underline{CH_3}$), 21.82, 29.73, 30.53 (C_3, C_4, C_5), 27.12 (C_6), 128.79 ($C_{3'}$ & $C_{5'}$), 129.06 ($C_{2'}$ & $C_{6'}$), 131.19 ($C_{1'}$), 133.78 ($C_{4'}$), 134.92 (C_β), 137.14 (C_2), 163.64 (C_1); *Anal.* Calcd. for $C_{15}H_{19}NO$ (229.15): C, 78.56; H, 8.35; N, 6.11. Found: C, 78.41; H, 8.49; N, 6.03.

(1*E*,2*E*)-2-(4-methoxybenzylidene)-6-methylcyclohexanone oxime (4c): Obtained by refluxing for 2.5h; white crystals (methanol), yield 83%; mp180–182 °C; IR (KBr, cm^{-1}): 3218 (br, O–H, stretch), 1632 (m, C=N, stretch), 1605 (s, C=C, stretch), 1511, 1461, 1370, 1112, 938, 872, 830, 532; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.14 (*d*, *J* = 7.2 Hz, 3H, 6-CH_3), 1.57–1.85 (*m*, 4H, 4-H, 5-H), 2.23–2.84 (*m*, 3H, 3-H, 6-H), 3.80 (*s*, 3H, 4′-OCH_3), 6.78 (*s*, 1H, H_β), 6.94 (*d*, *J* = 8.4 Hz, 2H, 3′-H & 5′-H), 7.45

(*d*, *J* = 8.4 Hz, 2H, 2′-H & 6′-H), 8.95 (*br s*, 1H, OH, exchangeable with D_2O); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.06 (C_6-$\underline{CH_3}$), 22.13, 29.55, 30.75 (C_3, C_4, C_5), 27.05 (C_6), 55.16 ($C_{4'}$-$\underline{OCH_3}$), 113.60 ($C_{3'}$ & $C_{5'}$), 128.67 ($C_{2'}$ & $C_{6'}$), 131.03 ($C_{1'}$), 133.17 (C_β), 136.53 (C_2), 158.90 ($C_{4'}$), 163.17 (C_1); *Anal.* Calcd. for $C_{15}H_{19}NO_2$ (245.14): C, 73.44; H, 7.81; N, 5.71. Found: C, 73.75; H, 7.53; N, 5.99.

(1*E*,2*E*)-2-(4-chlorobenzylidene)-6-methylcyclohexanone oxime (4d): Obtained by refluxing for 3h; white crystals (methanol), yield 79.3%; mp 146 °C (lit. mp [24] 147–150 °C); IR (KBr, cm^{-1}): 3282 (br, O–H, stretch), 1625 (m, C=N, stretch), 1601 (s, C=C, stretch), 1515, 1466, 1257, 1185, 957, 822, 734,673, 525; ^1H NMR (300 MHz, $CDCl_3$): δ 1.12 (*d*, *J* = 7.0 Hz, 3H, 6-CH_3), 1.43–1.81 (*m*, 4H, 4-H, 5-H), 2.41–2.98 (*m*, 3H, 3-H, 6-H), 6.80 (*s*, 1H, H_β), 7.26-7.47 (*m*, 4H, 2′-H, 3′-H, 5′-H, 6′-H), 8.06 (*br s*, 1H, OH, exchangeable with D_2O); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.20 (C_6-$\underline{CH_3}$), 22.53, 29.40, 30.69 (C_3, C_4, C_5), 26.72 (C_6), 128.43 ($C_{3'}$ & $C_{5'}$), 129.11 ($C_{2'}$ & $C_{6'}$), 131.46 ($C_{1'}$), 132.88 ($C_{4'}$), 134.54 (C_β), 136.18 (C_2), 164.13 (C_1); *Anal.* Calcd. for $C_{14}H_{16}ClNO$ (249.09): C, 67.33; H, 6.46; N, 5.61. Found: C, 67.39; H, 6.38; N, 5.75.

2.4 General procedure for the synthesis of (1*E*,2*E*)-2-arylidene-6-methylcyclohexanone *O*-tosyl oximes (5): A solution of *p*-toluenesulphonyl chloride (1.90 g, 0.01 mole) in pyridine (7 mL) was added to a solution of an appropriate (1*E*,2*E*)-2-arylidene-6-methylcyclohexanone oxime (0.01 mole) in pyridine (7 mL) at 0 °C and the reaction mixture was stirred for 2–3h while maintaining the temperature of reaction mixture 0 °C. After stirring for further 45 min. at room temperature, poured the contents onto crushed ice containing 5 mL of dil. H_2SO_4. The solid thus obtained was collected by filtration and recrystallized from a suitable solvent to afford the corresponding (1*E*,2*E*)-2-arylidene-6-methylcyclophexanone *O*-tosyl oximes (**5**) in high yields (85–90.2%). Their spectral parameters and other characteristics are given below:

(1*E*,2*E*)-2-benzylidene-6-methylcyclohexanone *O*-tosyl oxime (5a): Obtained by stirring for 3h; white crystals (methanol), yield 88%; mp 141–143 °C; IR (KBr, cm^{-1}): 1611 (m, C=N, stretch), 1528, 1393, 1321, 1196, 903, 795, 689, 617, 569; ^1H NMR (300 MHz, $CDCl_3$): δ 1.14 (*d*, *J* = 7.2 Hz, 3H, 6-CH_3), 1.47–1.86 (*m*, 4H, 4-H, 5-H), 2.31–2.86 (*m*, 6H, 3-H, 6-H, 4″-CH_3), 6.94 (*s*, 1H, H_β), 7.20–7.47 (*m*, 7H, 2′-H, 3′-H, 4′-H, 5′-H, 6′-H, 3″-H, 5″-H), 7.93 (*d*, *J* = 8.4 Hz, 2H, 2″-H & 6″-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.15 (C_6-$\underline{CH_3}$), 20.18 ($C_{4''}$-$\underline{CH_3}$), 21.82, 27.75, 30.86, 31.53 (C_3, C_4, C_5, C_6), 127.18, 127.83, 128.06, 128.32, 128.45, 129.15, 131.23 ($C_{1''}$, $C_{2''}$, $C_{3''}$, $C_{4''}$, $C_{5''}$, $C_{6''}$, $C_{2''}$, $C_{3''}$, $C_{4''}$, $C_{5''}$, $C_{6''}$), 133.84 (C_β), 136.83 (C_2), 143.73 ($C_{1''}$), 160.49 (C_1); *Anal.* Calcd. for $C_{21}H_{23}NO_3S$ (369.14): C, 68.27; H, 6.27; N, 3.79. Found: C, 68.39; H, 6.11; N, 3.96.

(1*E*,2*E*)-2-(4-methylbenzylidene)-6-methylcyclohexanone *O*-tosyl oxime (5b): Obtained by stirring for 2.5h; white crystals (methanol), yield 90.2%; mp 160–162 °C; IR (KBr, cm^{-1}): 1599 (m, C=N, stretch), 1523, 1435, 1268, 1156, 1037, 1025, 967, 884, 645; ^1H NMR (300 MHz, $CDCl_3$): δ 1.11 (*d*, *J* = 7.2 Hz, 3H, 6-CH_3), 1.57–1.96 (*m*, 4H, 4-H, 5-H), 2.33–2.98 (*m*, 9H, 3-H, 6-H, 4′-CH_3, 4″-CH_3), 6.91 (*s*, 1H, H_β), 7.16 (*d*, 2H, *J* = 7.5 Hz, 3′-H & 5′-H), 7.35 (*d*, *J* = 7.5 Hz, 2H, 2′-H & 6′-H), 7.48 (*d*, *J* = 8.4 Hz, 2H, 3″-H & 5″-H), 7.94 (*d*, *J* = 8.4 Hz, 2H, 2″-H & 6″-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.03 (C_6-$\underline{CH_3}$), 20.33 ($C_{4''}$-$\underline{CH_3}$), 21.06 (C_4-$\underline{CH_3}$), 22.36, 27.93, 30.12, 31.95 (C_3, C_4, C_5, C_6), 127.16, 128.64, 129.25, 129.49, 130.83, 131.32, 132.87 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$, $C_{6'}$, $C_{2''}$, $C_{3''}$, $C_{4''}$, $C_{5''}$, $C_{6''}$), 134.75 (C_β), 136.12 (C_2), 143.14 ($C_{1''}$), 159.96 (C_1); *Anal.* Calcd. for $C_{22}H_{25}NO_3S$ (383.16): C, 68.90; H, 6.57; N, 3.65. Found: C, 68.81; H, 6.46; N, 3.83.

(1*E*,2*E*)-2-(4-methoxybenzylidene)-6-methylcyclohexanone *O*-tosyl oxime (5c): Obtained by stirring for 2h; light brown crystals (benzene), yield 85%; mp 125–127 °C; IR (KBr, cm^{-1}): 1606 (m, C=N, stretch), 1538, 1471, 1393, 1327, 1138, 1088, 842, 756, 611; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.12 (*d*, *J* = 7.2 Hz, 3H, 6-CH_3), 1.49–1.90 (*m*, 4H, 4-H, 5-H), 2.28–2.96 (*m*, 6H, 3-H, 6-H, 4″-CH_3), 3.80 (*s*, 3H, 4′-OCH_3), 6.94 (*s*, 1H, H_β), 7.11 (*d*, *J* = 8.7 Hz, 2H, 3′-H & 5′-H), 7.33–7.48 (*m*, 4H, 2′-H, 6′-H, 3″-H, 5″-H), 7.90 (*d*, *J* = 8.4 Hz, 2H, 2″-H & 6″-H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.58 (C_6-$\underline{CH_3}$), 20.25 ($C_{4''}$-$\underline{CH_3}$), 21.78, 27.95, 30.45, 31.73 (C_3, C_4, C_5, C_6), 55.10 ($C_{4'}$-$\underline{OCH_3}$), 113.15 ($C_{3'}$ & $C_{5'}$), 127.37, 127.93, 128.48, 130.61, 131.25 ($C_{1''}$, $C_{2''}$, $C_{4''}$, $C_{6'}$, $C_{2''}$, $C_{3''}$, $C_{4''}$, $C_{5''}$, $C_{6''}$), 133.94 (C_β), 137.73 (C_2), 143.05 ($C_{1''}$), 158.60 ($C_{4'}$), 161.10 (C_1); *Anal.* Calcd. for $C_{22}H_{25}NO_4S$ (399.15): C, 66.14; H, 6.31; N, 3.51. Found: C, 66.38; H, 6.43; N, 3.67.

(1*E*,2*E*)-2-(4-chlorobenzylidene)-6-methylcyclohexanone *O*-tosyl oxime (5d): Obtained by stirring for 3h; white crystals (methanol), yield 88%; mp 165–168 °C; IR (KBr, cm^{-1}): 1609 (m, C=N, stretch), 1542, 1462, 1310, 1258, 1065, 1024, 983, 823, 654; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.11 (*d*, *J* = 7.2 Hz, 3H, 6-CH_3), 1.55–1.91 (*m*, 4H, 4-H, 5-H), 2.29–2.92 (*m*, 6H, 3-H, 6-H, 4″-CH_3), 6.90 (*s*, 1H, H_β), 7.29–7.49 (*m*, 7H, 2′-H, 3′-H, 4′-H, 5′-H, 6′-H, 3″-H, 5″-H), 7.93 (*d*, *J* = 8.4 Hz, 2H, 2″-H & 6″-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.12 (C_6-$\underline{CH_3}$), 20.47 ($C_{4''}$-$\underline{CH_3}$), 22.68, 27.77, 29.87, 31.75 (C_3, C_4, C_5, C_6), 124.67, 127.23, 127.93, 128.72, 129.67, 131.75, 133.87 ($C_{1''}$, $C_{2'}$, $C_{3'}$, $C_{4''}$, $C_{5'}$, $C_{6'}$, $C_{2''}$, $C_{3''}$, $C_{4''}$, $C_{5''}$, $C_{6''}$), 134.67 (C_β), 136.50 (C_2), 143.56 ($C_{1''}$), 160.52 (C_1); *Anal.* Calcd. for $C_{21}H_{22}ClNO_3S$ (403.10): C, 62.45; H, 5.49; N, 3.47. Found: C, 62.71; H, 5.41; N, 3.73.

2.5 General procedure for the synthesis of (*E*)-3-arylidene-7-methylazepan-2-ones (6): A solution of an appropriate (1*E*,2*E*)-2-arylidene-6-methylcyclophexanone *O*-tosyl oxime (**5**, 0.00146 mole), $SOCl_2$ (0.521 mL) in dry dioxane (30 mL) was stirred with the aid of a magnetic stirrer at room temperature for 10–11h. Thereafter, water (50 mL) was added to the reaction mixture and extracted with diethyl ether (3×20 mL). The combined extracts were washed with 5% aq. $NaHCO_3$ solution followed by water, and dried over anhydrous Na_2SO_4. Rotaevaporation of the solvent furnished a solid that upon crystallization from a suitable solvent furnished the corresponding (*E*)-3-arylidene-7-methylazepan-2-ones (**6**) in moderate yields (56–64%). Their spectral parameters and other characteristics are given below:

(*E*)-3-benzylidene-7-methylazepan-2-one (6a): Obtained by stirring for 10h; pale yellow crystals (ethanol), yield 62%; mp 97–101 °C; IR (KBr, cm^{-1}): 3274 (m, N–H, stretch), 1673 (s, C=O, stretch), 1601 (s, C=C, stretch), 1496, 1450, 1376, 1263, 1196, 1048, 764, 757, 701; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.18 (*d*, *J* = 6.6 Hz, 3H, 7-CH_3), 1.61–2.01 (*m*, 4H, 5-H, 6-H), 2.43–2.60 (*m*, 2H, 4-H), 3.43 (*m*, 1H, 7-H), 6.62 (*br s*, 1H, NH, exchangeable with D_2O), 7.18–7.34 (*m*, 5H, 2′-H, 3′-H, 4′-H, 5′-H, 6′-H), 7.45 (*s*, 1H, H_β); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.13 (C_7-$\underline{CH_3}$), 27.84, 29.71, 33.52 (C_4, C_5, C_6), 56.32 (C_7), 128.12, 128.78, 129.35, 130.38 ($C_{1''}$, $C_{2''}$, $C_{3''}$, $C_{4''}$, $C_{5''}$, $C_{6''}$), 133.57 (C_β), 136.93 (C_3), 165.20 (C_2); ESI-MS m/z: 215 ($M^{+\cdot}$, 54%), 214 (60%), 187 (63%), 116 (32%), 115 (100%), 91 (6.9%), 77 (5.1%); *Anal.* Calcd. for $C_{14}H_{17}NO$ (215.13): C, 78.10; H, 7.96; N, 6.51. Found: C, 77.82; H, 7.73; N, 6.83.

(*E*)-7-methyl-3-(4-methylbenzylidene) azepan-2-one (6b): Obtained by stirring for 11h; brown crystals (benzene-hexane), yield 62%; mp 163–165 °C; IR (KBr, cm^{-1}): 3163 (m, N–H, stretch), 1666 (s, C=O, stretch), 1612 (s, C=C, stretch), 1465, 1379, 1278, 1176, 1072, 956, 857, 833, 725, 696; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.14 (*d*, *J* = 6.6 Hz, 3H, 7-CH_3), 1.57–1.96 (*m*, 4H, 5-H, 6-H), 2.33–2.51 (*m*, 5H, 4-H,

4′-CH_3), 3.46 (*m*, 1H, 7-H), 5.74 (*br s*, 1H, NH, exchangeable with D_2O), 7.14 (*d*, *J* = 7.8 Hz, 2H, 3′-H & 5′-H), 7.38 (*d*, *J* = 7.8 Hz, 2H, 2′-H & 6′-H), 7.50 (*s*, 1H, H_β); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.03 (C_7-$\underline{CH_3}$), 21.94 ($C_{4'}$-$\underline{CH_3}$), 27.46, 29.55, 34.09 (C_4, C_5, C_6), 57.37 (C_7), 129.78, 130.57, 131.86, 134.94 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$, $C_{6'}$), 135.32 (C_β), 137.26 (C_3), 165.59 (C_2); ESI-MS m/z: 229 ($M^{+\cdot}$, 58.4%), 228 (53%), 214 (5.3%), 201 (63.4%), 130 (35%), 129 (71.2%), 115 (100%), 105 (5.4%), 91 (3.1%), 77 (0.6%); *Anal.* Calcd. for $C_{15}H_{19}NO$ (229.15): C, 78.56; H, 8.35; N, 6.11. Found: C, 78.28; H, 8.63; N, 6.38.

(*E*)-3-(4-methoxybenzylidene)-7-methylazepan-2-one (6c): Obtained by stirring for 10h; pale yellow crystals (methanol), yield 56%; mp 180–182 °C; IR (KBr, cm^{-1}): 3289 (m, N–H, stretch), 1670 (s, C=O, stretch), 1604 (s, C=C, stretch), 1460, 1384, 1321, 1249, 1160, 946, 864, 803, 690; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.12 (*d*, *J* = 7.0 Hz, 3H, 7-CH_3), 1.58–2.05 (*m*, 4H, 5-H, 6-H), 2.48–2.71 (*m*, 2H, 4-H), 3.44 (*m*, 1H, 7-H), 3.78 (s, 3H, 4′-OCH_3), 5.90 (*br s*, 1H, NH, exchangeable with D_2O), 7.03 (*d*, *J* = 8.4 Hz, 2H, 3′-H & 5′-H), 7.45 (*d*, *J* = 8.4 Hz, 2H, 2′-H & 6′-H), 7.62 (*s*, 1H, H_β); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 20.97 (C_7-$\underline{CH_3}$), 27.11, 29.32, 33.22 (C_4, C_5, C_6), 55.13 ($C_{4'}$-$\underline{OCH_3}$), 56.74 (C_7), 113.58 ($C_{3'}$ & $C_{5'}$), 128.83, 131.27 ($C_{1'}$, $C_{2'}$ & $C_{6'}$), 134.83 (C_β), 137.05 (C_3), 160.22 ($C_{4'}$), 165.37 (C_2); ESI-MS m/z: 245 ($M^{+\cdot}$, 59.1%), 244 (63%), 230 (7.4%), 217 (59.2%), 202 (26%), 186 (3.6%), 145 (73%), 121 (6.1%), 115 (100%), 91 (4.9%); *Anal.* Calcd. for $C_{15}H_{19}NO_2$ (245.14): C, 73.44; H, 7.81; N, 5.71. Found: C, 73.18; H, 7.57; N, 6.02.

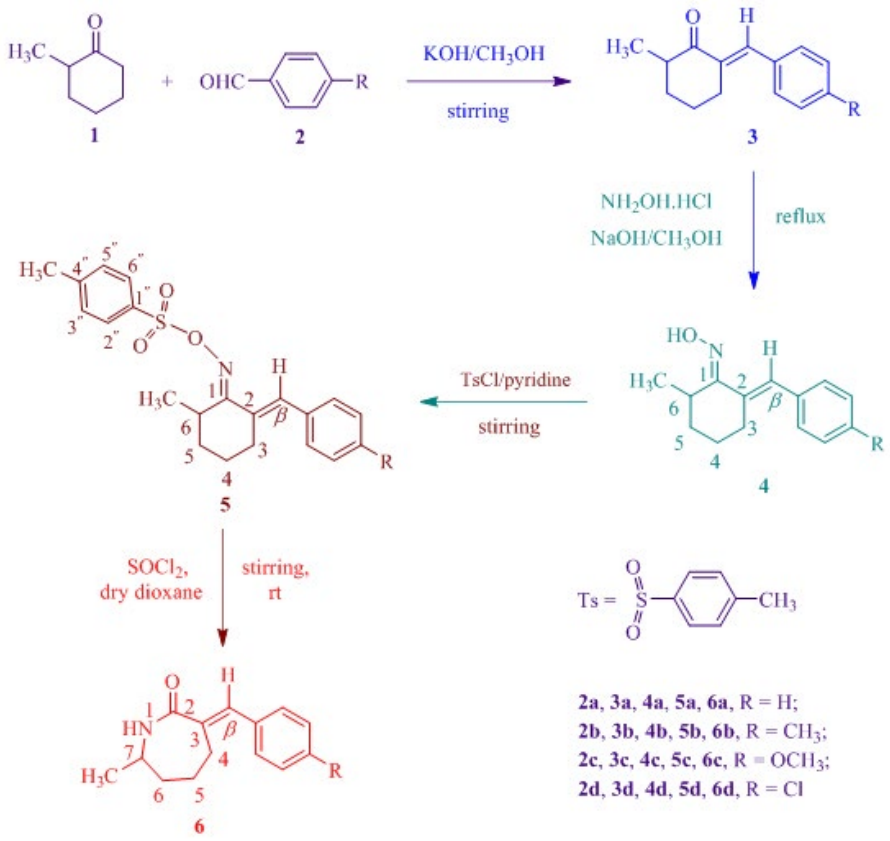
(*E*)-3-(4-chlorobenzylidene)-7-methylazepan-2-one (6d): Obtained by stirring for 10.5h; pale yellow crystals (methanol), yield 64%; mp 110–112 °C; IR (KBr, cm^{-1}): 3181 (m, N–H, stretch), 1662 (s, C=O, stretch), 1595 (s, C=C, stretch), 1490, 1453, 1330, 1244, 1163, 1093, 1014, 827, 731, 671, 559; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.12 (*d*, *J* = 7.0 Hz, 3H, 7-CH_3), 1.43–1.97 (*m*, 4H, 5-H, 6-H), 2.41–2.64 (*m*, 2H, 4-H), 3.49 (*m*, 1H, 7-H), 6.51 (*br s*, 1H, NH, exchangeable with D_2O), 7.26 (*d*, *J* = 8.5 Hz, 2H, 3′-H & 5′-H), 7.35 (*d*, *J* = 8.5 Hz, 2H, 2′-H & 6′-H), 7.58 (*s*, 1H, H_β); ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.65 (C_7-$\underline{CH_3}$), 27.10, 29.87, 34.25 (C_4, C_5, C_6), 56.60 (C_7), 123.41, 128.60, 129.92, 132.39 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$, $C_{6'}$), 134.51 (C_β), 136.74 (C_3), 164.86 (C_2); ESI-MS m/z: 249 ($M^{+\cdot}$, 58.3%)/251 ($M^{+\cdot}$+2, 19.6%), 248 ($M^{+\cdot}$-1, 63.4 %)/250 ($M^{+\cdot}$-1, 20.8 %), 221 (65.1%)/223 (21.8%), 214 (37.1%), 150 (26.4%)/152 (8.5%), 149 (70.3%)/151 (23.5%), 125 (5.2%)/127 (1.7%), 115 (100%); *Anal.* Calcd. for $C_{14}H_{16}ClNO$ (249.09): C, 67.33; H, 6.46; N, 5.61. Found: C, 67.56; H, 6.73; N, 5.84.

3. Results and discussion

3.1 Chemistry

The general approach towards the synthesis of lactams (**6**) involves an initial condensation of 2-methylcyclohexanone (**1**) with appropriate 4-substituted benzaldehydes (**2**) by base-catalyzed condensation to furnish the corresponding (*E*)-2-arylidene-6-methylcyclohexanones (**3**) in good yields. The arylidenes (**3**) upon refluxing with $NH_2OH.HCl$ and NaOH in methanol furnished (1*E*,2*E*)-2-arylidene-6-methylcyclohexanone oximes (**4**) which upon subsequent stirring with equimolar quantities of *p*-toluenesulfonyl chloride in the presence of pyridine afforded (1*E*,2*E*)-2-arylidene-6-methylcyclohexanone *O*-tosyl oximes (**5**) in high yields. The *O*-tosyl oximes (**5**) thus obtained were subjected to thionyl chloride mediated Beckmann rearrangement in dry dioxane under stirring at room temperature to furnish the corresponding lactams, *i.e.* (*E*)-3-arylidene-7-methylazepan-2-ones (**6**) in 56-64% yields (Scheme 1).

The (*E*)-2-arylidene-6-methylcyclohexanones (**3a**–**3d**) needed for the purpose were synthesized by base-catalyzed condensation of equimolar

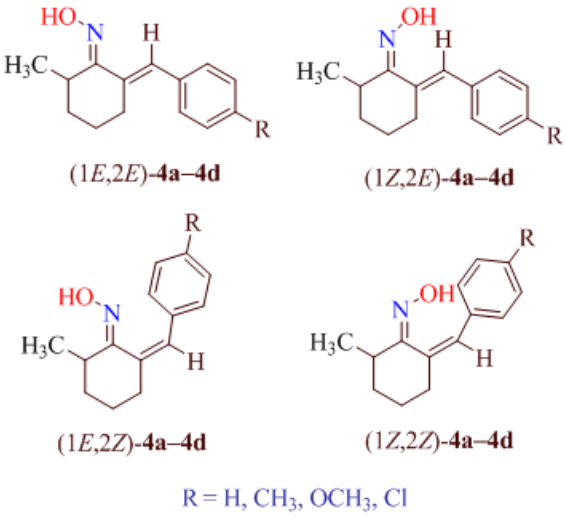


Scheme 1: Synthetic route for the preparation of (*E*)-3-arylidene-7-methylazepan-2-ones (**6**)

quantities of 2-methylcyclohexanone (**1**) with appropriate benzaldehydes (**2**) in fairly good yields (53–62%) according to the procedure as described in the literature [25,26]. The purity of the entire synthesized **3a**–**3d** was checked through TLC and their melting points.

The synthesis of oximes (**4a–4d**) was carried out by refluxing a mixture of appropriate (*E*)-2-arylidene-6-methylcyclohexanones (**3**, 0.09 mole), $NH_2OH.HCl$ (7.0 g, 0.1 mole) and NaOH (4.0 g) in methanol (150 mL) for 2.5–4h. Usual work up of the resulting reaction mixture furnished a solid which upon crystallization from a suitable solvent afforded the corresponding (1*E*,2*E*)-2-arylidene-6-methylcyclohexanone oximes (**4**) in high yields (79.3–86%) (Scheme 1).

The structures of all the oximes thus synthesized were established on the basis of spectral (IR, ^1H NMR and ^{13}C NMR) and elemental analysis results. In principle, the oximes (**4a**–**4d**) can exist in four stereoisomeric forms on the basis of differences in orientation around C=N and C=C bonds, *i.e.* (1*E,*2*E*)-**4a**–**4d**, (1*Z,*2*E*)-**4a**–**4d**, (1*E,*2*Z*)-**4a**–**4d** and (1*Z,*2*Z*)-**4a**–**4d**.

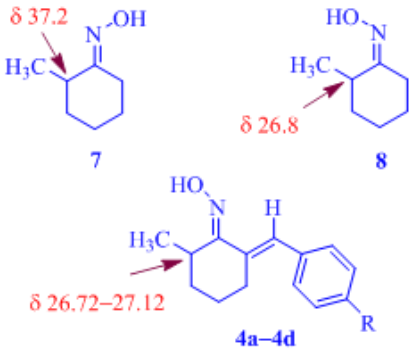


Out of the four possible stereoisomeric forms, the configurations, (1*Z,*2*Z*) and (1*E,*2*Z*) for the oximes (**4a**–**4d**) can easily be discarded on the basis of arguments presented below:

Since the precursor (*E*)-2-arylidene-6-methylcyclohexanones (**3a**–**3d**) possess (*E*)-configuration and it is highly unlikely that under base-catalyzed equilibrium conditions, a thermodynamically more stable ketone with (*E*)-configuration is converted into a thermodynamically less stable ketone with (*Z*)-configuration, therefore, it seems logical to assume that during the formation of oximes (**4**), there is no change in configuration around C=C, hence the configurations (1*Z*,2*Z*) and (1*E*,2*Z*) for the oximes (**4**) stand rejected. In order to distinguish between the remaining two configurations, *i.e.* (1*E,2E*) and (1*Z,*2*E*), the IR, ^{1}H NMR and ^{13}C NMR spectra of oximes (**4**) were critically examined. The IR spectra of oximes (**4a**–**4d**), in each case, exhibited a broad band in the region at 3218–3298 cm^{-1} due to O–H stretching, a band of weak intensity in the region at 1625–1636 cm^{-1} due to C=N stretching and another band of medium intensity in the region at 1590–1605 cm^{-1} due to C=C stretching. The ^{1}H NMR (300/400MHz, $CDCl_3$) spectra of oximes (**4a**–**4d**) displayed the required integral ratio of aromatic to non-aromatic protons. In the aliphatic region, in each case, at the highest field was located a doublet (J = 7.2 Hz) corresponding to three protons in the region at δ 1.09–1.14 which could safely be assigned to the protons of C_6-CH_3 group. Next, towards the lower field was exhibited a four-proton multiplet in the region at δ 1.42–1.93 assigned to C_4 and C_5 protons which was followed by another three-proton multiplet in the region at δ 2.23–2.99 assignable to C_3 and C_6 protons. The singlet displayed, in each case, in the region at δ 6.76–6.82 integrating for one proton was undoubtedly assigned to olefinic proton (C_β-H). A broad singlet (exchangeable with D_2O) observed in the region at δ 8.06–10.05 was safely assigned to the proton of the oxime (=N–OH) group. The signals due to the remaining aliphatic and aromatic protons were observed in the expected regions (*vide experimental*). The ^{13}C NMR spectra of oximes (**4a**–**4d**), in each case, in the highest field, exhibited a signal in the region at δ 14.15–19.20 which was safely assigned to the carbon of methyl group located at C_6. Next, towards the lower field, the signals displayed in the regions at δ 21.60–22.53, δ 26.72–27.12, δ 29.40–30.06 and δ 30.53–30.98 were ascribed to the methylene carbons of the aliphatic ring whereas the signals observed in the regions at δ 133.17–135.03 and δ 136.18–137.91 were easily assigned to C_β and C_2, respectively. The signal exhibited, in the lowest field, in the region at δ 163.16–164.13 could undoubtedly be ascribed due to C_1. The signals due to the remaining aliphatic and aromatic carbons were observed in the expected regions (*vide experimental*).

The (1*E,*2*E*)-configuration of the oximes (**4a**–**4d**) finds rationale from the results reported in the literature in view of steric effect of the arylidene group as supported by the work carried out by Sato *et al.*[20a] on 2-benzylidenecyclohexanone oxime. Further, Kelly and Matthews [27] also found that *anti*-configuration to be the most probable structure in several 2-substituted cyclohexanone oximes. Moreover, the oximes synthesized by Smith *et al.* [28] are known to possess (*E*)-configuration around C=N bond. In view of steric effect of the arylidene group, the 2-arylidenecyclohexanone oximes have been assigned (1*E,2E*) configuration. But for assigning the configuration to oximes (**4a**–**4b**), the steric effect of both the arylidene and α-methyl group is to be taken into consideration. This argument finds rationale from an earlier observation of Hawkes *et al*. [29] for the assignment of configuration to oximes on the basis of chemical shifts of α-methylene carbons in the ^{13}C NMR spectra of 2-methylcyclohexanone oximes (**7**) and (**8**) in which α-methylene carbons (C_2) are found to display signals at δ 37.2 and δ 26.8, respectively.

Hence, on analogy with the chemical shift of similar carbon (C_2) in ^{13}C NMR spectrum of 2-methylcyclohexanone oxime (**8**), the oximes (**4a**–**4d**), have been assigned (*E*)-configuration around C=N bond.



4a, R = H; **4b**, R = CH_3
4c, R = OCH_3; **4d**, R = Cl

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The *O*-tosyl oximes (**5a**–**5d**) needed for the purpose were prepared by stirring solution of appropriate oximes (**4a**–**4d**, 0.01 mole) and *p*-toluenesulphonyl chloride (1.90 g, 0.01 mole) in pyridine at room temperature for 2–3h in excellent yields (85–90.2%) (Scheme 1).

Since during the tosylation of oximes (**4a**–**4d**), the C=C and C=N bonds are not affected, hence it is rational to assume that the configuration of oximes, *i.e.* (1*E*,2*E*) is retained in their *O*-tosyl oximes (**5a**–**5d**).

The structures of all the *O*-tosyl oximes (**5a**–**5d**) have been established on the basis of their spectral (IR, ^1H NMR and ^{13}C NMR) as well as elemental analytical results. IR spectra of *O*-tosyl oximes (**5a**–**5d**) displayed the characteristic absorption due to C=N stretching in the region at 1599–1611 cm^{-1}. The ^1H NMR (300 MHz, $CDCl_3$/DMSO-d_6) spectra of *O*-tosyl oximes (**5a**–**5d**), in each case, displayed the required integral ratio of aromatic to non-aromatic protons. The *O*-tosyl oximes (**5a**–**5d**), in the aliphatic region, at the highest field, in each case, displayed a three-proton doublet (J = 7.2 Hz) in the region at δ 1.11–1.14 which was undoubtedly assigned to the protons of C_6-CH_3 group. The aliphatic region of **5a**–**5d**, in each case, exhibited a multiplet corresponding to four protons in the region at δ 1.47–1.91 which was safely assigned to C_4- and C_5-protons. Next, towards the lower field, was located a multiplet in the region at δ 2.28–2.98 integrating for six protons ascribable to C_3-, C_6- and $C_{4''}$-CH_3 protons. However, in **5b**, the resonance due to $C_{4'}$-CH_3 also got merged with the multiplet due to C_3-, C_6- and $C_{4''}$-CH_3 protons and was appeared in the region at δ 2.33–2.98. To the downfield side, in each case, was observed a signal in the region at δ 6.90–6.94 assignable to vinylic proton (C_β-H). At the lowest field of spectra, in each case, was exhibited a two-proton doublet (J = 8.4 Hz) in the region at δ 7.90–7.94. The most suitable contender for this signal seems to be $C_{2''}$-H and $C_{6''}$-H in accord with the results reported in literature for analogous compound [30]. The signals due to the remaining aliphatic and aromatic protons were observed in the expected regions (*vide experimental*). ^{13}C NMR spectra of *O*-tosyl oximes (**5a**–**5d**), in each case, in the aliphatic region, at the highest field, displayed a signal in the region at δ 14.15–15.12 ascribable to the carbon of methyl group located at C_6, however, the signal due to methyl carbon present at $C_{4''}$ was observed in the region at δ 20.18–20.47. Next, towards the lower field, the signals due to methylene carbons (C_3, C_4, C_5, C_6) were observed in the regions at δ 21.78–22.68, δ 27.75–27.95, δ 29.87–30.86 and δ 31.53–31.95. The compounds **5a**–**5d**, in each case, displayed signals in the regions at δ 133.84–134.94 and δ 136.12–137.73 assignable to C_β and C_2, respectively. The signal due to $C_{1''}$, characteristic of tosyl group, was appeared in the region at δ 143.05–143.73 whereas signal exhibited in the most downfield region at δ 159.96–161.10 was safely assigned to C_1. The remaining aliphatic and aromatic carbons were found to display signals in their characteristic regions (*vide experimental*).

After having established the structures of

O-tosyl oximes (**5**), the next step was the synthesis of lactams (**6**), which were prepared by the Beckmann rearrangement of **5**.

Initially, Beckmann rearrangement of the oxime (**4a**) and *O*-tosyl oxime (**5a**) was carried out using various reagents such as PPA, CNC (cyanuric chloride (2,4,6-trichloro-[1,3,5]triazine))/ DMF, CNC/CH_3CN, CNC and $ZnCl_2$/CH_3CN by employing different reaction conditions. In each case, the product obtained was similar, *i.e.* **6a** but in varying yields as shown in Table 1.

Table 1: Beckmann rearrangement of **4a** and **5a** under different reaction conditions.

Substrate used	Product formed	Reagents used	Reaction conditions applied	Yield (%)
4a	**6a**	PPA	reflux, 6h	12
4a	**6a**	CNC/DMF	stirring, rt, 8–10h	18
4a	**6a**	CNC/CH_3CN	reflux, 4–5h	23
4a	**6a**	CNC, $ZnCl_2$/ CH_3CN	reflux, 4–5h	31
4a	**6a**	$SOCl_2$/dry dioxane	stirring, rt, 9h	51
5a	**6a**	PPA	reflux, 5h	20
5a	**6a**	CNC/DMF	stirring, rt, 7–8h	26
5a	**6a**	CNC/CH_3CN	reflux, 3–5h	30
5a	**6a**	CNC, $ZnCl_2$/ CH_3CN	reflux, 4–5h	38
5a	**6a**	$SOCl_2$/dry dioxane	stirring, rt, 8h	62

Among the reagents employed as mentioned in Table 1, the optimization of reaction conditions established $SOCl_2$/dry dioxane to be a better reagent. Hence, it was thought worthwhile to undertake $SOCl_2$/dry dioxane mediated Beckmann rearrangement of *O*-tosyl oximes (**5a**–**5d**) instead of oximes (**4a**–**4d**) to obtain the better yields of lactams (**6a**–**6d**).

The general approach towards the synthesis of lactams (**6**) by Beckmann rearrangement involves the stirring a solution of (1*E*,2*E*)-2-arylidenecycloalkanone *O*-tosyl oximes (**5**) in dry dioxane with thionyl chloride at room temperature for 10–11h to afford **6** in moderate to good yields (56–64%) (Scheme 1). The TLC analysis of the mother liquor left after filtration of the lactam (**6**) revealed the presence of starting *O*-tosyl oxime (**5**) along with traces of the lactam (**6**) thereby confirming that Beckmann rearrangement of (1*E*,2*E*)-2-arylidene-6-methylcyclohexanone *O*-tosyl oximes (**5**) furnished (*E*)-3-arylidene-7-methylazepan-2-ones (**6**) as a single product.

The structures of all the lactams (**6a**–**6d**) had been elucidated through spectral (IR, ^{1}H NMR, ^{13}C NMR and mass) and elemental analytical results. IR spectra of all the lactams **6a**–**6d**, in each case, exhibited a medium intensity absorption band in the region at 3163–3289 cm^{-1} due to N–H stretching of secondary amide. Another noteworthy feature was the presence of two intensive bands at 1662–1673 cm^{-1} and 1595–1612 cm^{-1} assignable to C=O stretching of *α,β*-unsaturated amide group and C=C stretching, respectively. The ^{1}H NMR spectra of **6a**–**6d**, in each case, displayed the required integral ratio of aromatic to non-aromatic protons. In the aliphatic region at the highest field, was located a doublet (J = 6.6 Hz) in the region at δ 1.12–1.18 corresponding to three protons of methyl group present at C_7. It was followed by a four-proton multiplet due to methylene protons of C_5 and C_6 in the region at δ 1.43–2.05. Next, towards the lower field was located another two-proton multiplet in the region at δ 2.33–2.71 which could safely be assigned to C_4 protons contiguous to exocyclic double bond. A one-proton multiplet observed in the region at δ 3.43–3.49 was undoubtedly assigned to C_7-methylene protons which finds support from the earlier observations reported in the literature for analogous 7-methylazepan-2-one (**9**) [31] in which similar proton, *i.e.*

C_7-H appears at δ 3.50. The signal due to NH proton, however, was appeared as a broad singlet (exchangeable with D_2O) in the region at δ 5.74–6.62. Another distinguishing feature of ^{1}H NMR spectra of **6a**–**6d**, is the chemical shift of vinylic proton (C_β-H), which appeared as a singlet in the lowest field of spectra, in the region at δ 7.45–7.62 due to deshielding by C=O group. The signals due to the remaining aliphatic and aromatic protons were observed in their characteristic regions (*vide experimental*).

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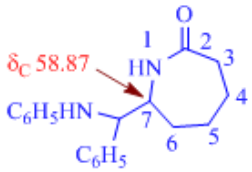

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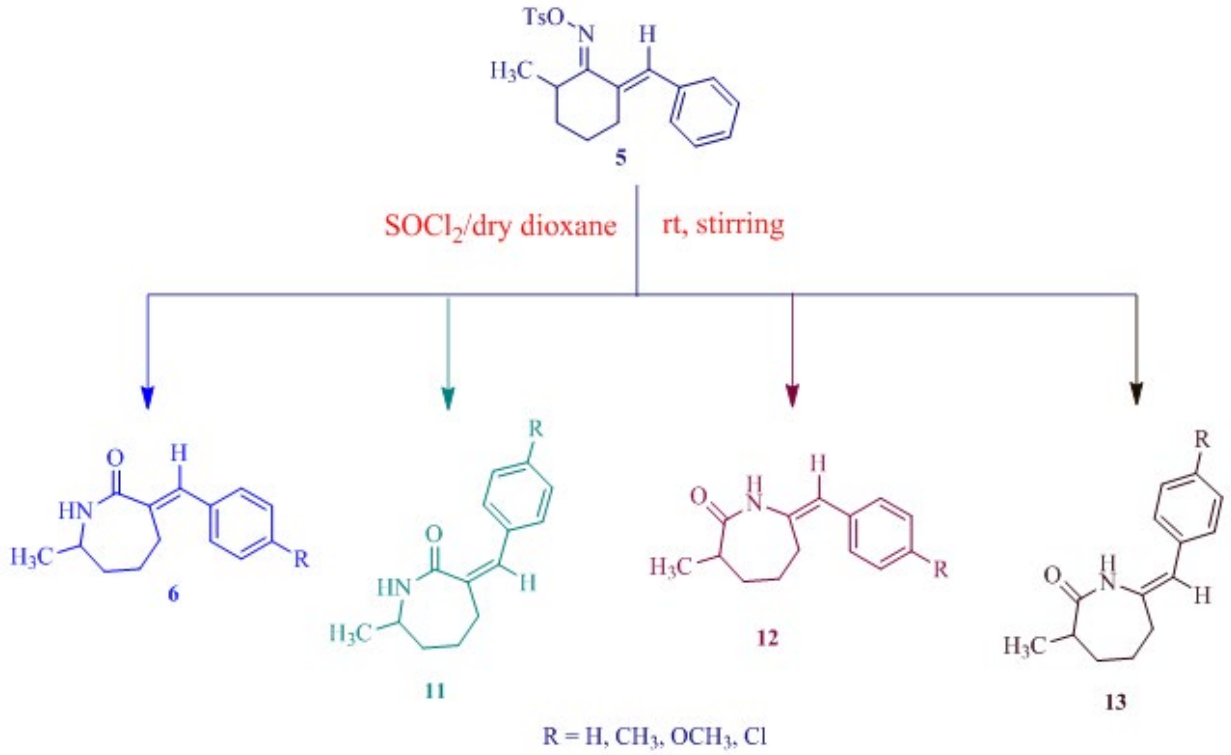
The structures of all the lactams **6a**–**6d** have been further corroborated by their ^{13}C NMR spectra, which in each case, at the highest field displayed a signal in the region at δ 19.65–20.97 that was safely assigned to methyl carbon located at C_7. Their ^{13}C NMR spectra are characterized by the presence of a signal in the aliphatic region at δ 56.32–57.37 ascribable to C_7 in analogy with ^{13}C NMR spectrum of 7-[(*N*-phenylamino) benzyl]azepan-2-one (**10**) [32] in which similar carbon, *i.e.* C_7 resonates at δ 58.87. The signals due to the methylene carbons (C_4, C_5, C_6) were observed in the regions at δ 27.10–27.84, δ 29.32–29.87 and δ 33.22–34.25. The signals displayed in the regions at δ 133.57–135.32 and δ 136.74–137.26 were undoubtedly assigned to the vinylic carbons, *i.e.* C_β and C_3, respectively. The signal displayed in the most downfield region at δ 164.86–165.59 was undoubtedly assigned to C_2 (carbon of C=O group). These assignments also find support from the results reported in literature for analogous compounds, i.e. (*E*)-3-arylideneazepan-2-ones [33]. The signals due to the remaining aliphatic and aromatic carbons were observed in the expected



Scheme 2: Expected products of Beckmann rearrangement of *O*-tosyl oxime (**5**)

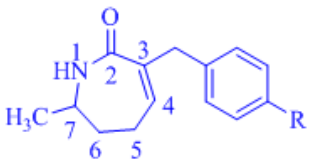
regions (*vide experimental*).

Further, the mass spectra of **6a**–**6d**, in each case, showed the expected fragmentation pattern (*vide experimental*). The base peak, however, was observed at m/z 115 (100%). The characteristic feature of the mass spectra of lactams (**6a**–**6d**) is the sequential elimination of CO, 2-methylazetidine moiety and H from the molecular ion generating ion peaks at $M^{+\cdot}$–28, $M^{+\cdot}$–99 and M^{+}–100, respectively. Moreover, the ion peak at M^{+}–100 may also arise by sequential elision of H-atom and 5-methylpyrrolidin-2-one (99 mass units). The analytical data of all the lactams **6a**–**6d** were also found in good agreement with their molecular formulae (*vide experimental*).

In principle, Beckmann rearrangement of *O*-tosyl oxime (**5**), in each case, is expected to furnish **6** through alkyl migration in which configuration around C=C is (*E*), **11** by alkyl migration in which configuration around C=C is (*Z*), **12** by vinyl migration in which configuration around C=C is (*E*) and **13** by vinyl migration in which configuration around C=C is (*Z*) (Scheme 2).

If the product would have an alternate structure, *i.e.* **11** or **12** or **13** than C_{β}-H must have resonated at a comparatively higher field in their ^{1}H NMR spectra, because this will not lie in the deshielding zone of C=O group in all these cases. Hence, downfield shifting of C_{β}-H unequivocally proves the formation of **6** and formation of lactams **11**, **12** and **13** stands discarded.

One more appealing point which deserves consideration here is that during the Beckmann rearrangement of **5**, there occurs no movement of *α,β*-unsaturated double bond from exocyclic to endocyclic position to furnish lactam (**14**). If this migration had happened, it must have exhibited a two-proton signal due to C_3-benzylic CH_2-group and a resonance characteristic of the C_4-vinylic proton but no such type of resonances were obsereved in ^{1}H NMR spectrum of the product formed.



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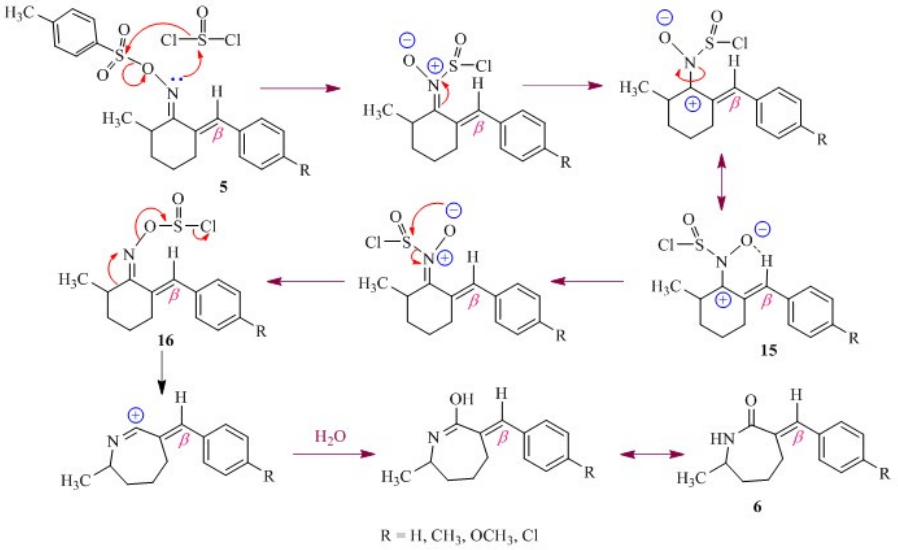
R = H, CH_3, OCH_3, Cl



R = H, CH_3, OCH_3, Cl

Scheme 3: Mechanistic pathway for the formation of (*E*)-3-arylideneazepan-2-ones (**6**) by Beckmann rearrangement of *O*-tosyl oximes (**5**)

Hence, all these arguments support the formation of **6** by alkyl migration in which configuration around C=C bond is retained during the Beckmann rearrangement of **5**.

Mechanistically, the conversion of **5** → **6** is envisaged to occur through an initial thionyl chloride catalyzed isomerization around C=N to afford **16** (Scheme 3). Driving force for this isomerization is presumably the stabilization of the intermediate carbocation (**15**) through *H*-bonding between O^{-} and H-atom of the C_{β}-H. The intermediate **16** thus obtained subsequently underwent *anti* migration of alkyl group to afford the lactam **6**.

Conclusion

From the above disscusion, it is concluded that the thionyl chloride mediated Beckmann rearrangement of *O*-tosyl oximes (**5a**–**5d**) in dry dioxane leads to the formation of the corresponding lactams, *i.e.* (*E*)-3-arylideneazepan-2-ones (**6a**–**6d**) in moderate to good yields by alkyl migration without shifting of double bond from exocyclic to endocylic position.

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References

1. a) G. R. Proctor, I. Redpath, in Monocyclic Azepines, ed. E. C. Taylor, Wiley-VCH, New York, **1996**; b) P. A. Wender, T. M. Pedersen, M. J. C. Scanio, J. Am. Chem. Soc., **2002**, 124, 15154–15155; c) S. Maier, T. Loontjens, B. Scholtens, R. M¨ulhaupt, Angew. Chem. Int. Ed., **2003**, 42, 5094–5097; d) H. Cho, K. Murakami, H. Nakanishi, A. Fujisawa, H. Isoshima, M. Niwa, K. Hayakawa, Y. Hase, I. Uchida, H. Watanabe, K. Wakitani, K. Aisaka, J. Med. Chem., **2004**, 47, 101–109; e) J. S. Carey, D. Laffan, C. Thomson, M. T. Williams, Org. Biomol. Chem., **2006**, 4, 2337–2347; f) G. Liu, Y.-M. Ma, W.-Y. Tai, C.-M. Xie, Y.-L. Li, J. Li, F.-J. Nan, ChemMedChem, **2008**, 3, 74–78; g) S. Tomasi, J. Renault, B. Martin, S. Duhieu, V. Cerec, M. L. Roch, P. Uriac, J.-G. Delcros, J. Med. Chem., **2010**, 53, 7647–7663; h) M. E. Welsch, S. A. Snyder, B. R. Stockwell, Curr. Opin. Chem. Biol., **2010**, 14, 347–361; i) S. Dandapani, L. A. Marcaurelle, Curr. Opin. Chem. Biol., **2010**, 14, 362–370; j) G. L. Thomas, C. W. Johannes, Curr. Opin. Chem. Biol., **2011**, 15, 516–522; k) R. Tohme, N. Darwiche, H. Gali-Muhtasib, Molecules, **2011**, 16, 9665–9696.
2. a) J. Hu, M. J. Miller, Tetrahedron Lett., **1995**, 36, 6379–6382; b) E. Torres-Marquez, J. Sinnett-Smith, S. Guha, R. Kui, R. T. Waldron, O. Rey, E. Rozengurt, Biochem. Biophys. Res. Commun., **2010**, 391, 63–68; c) Y.-F. Song, Y. Qu, X.-P. Cao, W. Zhang, Mar. Biotechnol., **2011**, 13, 868–882.
3. a) M. Shamma, M. J. Hillman, Tetrahedron, **1971**, 27, 1363–1374; b) J. M. Boente, L. Castedo, R. Cuadros, J. M. Sa, R. Suau, A. Perales, M. Martnez-Ripoll, J. Fayos, Tetrahedron Lett., **1983**, 24, 2029–2030; c) J. Miyata, H. Nakashima, H. Nemoto, H.-S. Kim, Y. Wataya, M. Ihara, Heterocycles, **1998**, 49, 101–104; d) A. Padwa, L. Precedo, M. A. Semone, J. Org. Chem., **1999**, 64, 4079–4088; e) R. Suau, J. M. Lpez-Romero, A. Ruiz, R. Rico, Tetrahedron, **2000**, 56, 993–998.
4. J. Jampilek, K. Brychtova, Med. Chem. Res. Rev., **2012**, 32, 907–947.
5. F. Hou, X. Zhang, G. Zhang, D. Xie, P. Chen, W. Zhang, J. Jiang, M. Liang, G. Wang, Z. Liu, R. Geng, N. Engl. J. Med., **2006**, 354, 131–140.
6. P. Lancellotti, Rev Med Liege, **2008**, 63, 220–224.
7. E. A. MacGregor, Clinical Medicine Insights: Therapeutics, **2011**, 3, 301– 314.
8. a) H. Yamaguchi, S. Sato, S. Yoshida, K. Takada, M. Itoh, H. Seto, N. Otake, J. Antibiot., **1986**, 39, 1047–1053; b) T. Dubuisson, E. Bogatcheva, M. Y. Krishnan, M. T. Collins, L. Einck, C. A. Nacy, V. M. Reddy, J. Antimicrob. Chemother., **2010**, 65, 2590–2597; c) E. Bogatcheva, T. Dubuisson, M. Protopopova, L. Einck, C. A. Nacy, V. M. Reddy, J. Antimicrob. Chemother., **2011**, 66, 578–587.
9. B. Schneider, D. Doskočilová, P. Schmidt, J. Štokr and P. Čefelín, J. Mol. Struct., **1976**, 35, 161–174.
10. a) M. Miller, J. Hope, W. J. Porter, J. K. Reel, A. Rubio-Esteban, U.S. Patent Appl. 2010/0197660, **2010**; b) J. A. Robl, R. Sulsky, E. Sieber-McMaster, D. E. Ryono, M. P. Cimarusti, L. M. Simpkins, D. S. Karanewsky, S. Chao, M. M. Asaad, A. A. Seymour, M. Fox, P. L. Smith, N. C. Trippodo, J. Med. Chem., **1999**, 42, 305–311.
11. a) J. Ritz, H. Fuchs, H. Kieczka, W. C. Moran, Caprolactam in Ullmann's Encyclopedia of Industrial Chemistry, Wiley-VCH, Weinheim, **2002**; b) M. M. Green and H. A. Wittcoff, Organic Chemistry Principles and Industrial Practice, Wiley-VCH, Weinheim, **2003**.
12. a) D. A. Wicks, PCT Int. Appl., WO 2010011949 A2

20100128,**2010**; b) D. A. Wicks, PCT Int. Appl., WO 2010011924 A2 20100128, **2010**; c) E. Tarkin-Tas, L. J. Mathias, Macromolecules, **2010**, 43, 968–974.

13. J. Ramos, A. Imaz, J. Forcada, Polymer Chem., **2012**, 3, 852–856.
14. a) F. J. Villani, J. Med. Chem., **1967**, 10, 497–498; b) T. J. V. Bergen, R. M. Kellogg, J. Org. Chem., **1971**, 36, 978–983; c) D. J. Anderson, A. Fiassner, J. Am. Chem. Soc., **1971**, 93, 4339–4340; d) F. R. Atherton, R. W. Lambert, J. Chem. Soc., Perkin Trans. 1, **1973**, 1079–1084; e) N. Finch, L. Blanchard, L. H. Werner, J. Org. Chem., **1977**, 42, 3933–3937; f) M. Masaki, K. Fukui, J. Kita, Bull. Chem. Soc. Jpn., **1977,** 50*,* 2013; g) J. J. Fitt, H.W. Gschwend, A. Hamdan, S. K. Boyer, H. M. Haidert, J. Org. Chem., **1982**, 47, 3658–3660; h) R. A. Mustill, A. H. Rees, J. Org. Chem., **1983**, 48, 5041–5043; i) Y. Endo, K.-i. Kataoko, N. Haga, K. Shudo, Tetrahedron Lett., **1992**, 33, 3339–3342; j) K. Knobloch, W. Eberbach, Org. Lett., **2000**, 2, 1117–1120; k) C. E. Masse, A. J. Morgan, J. S. Panek, Org. Lett., **2000**, 2, 2571–2573; l) A. B. Smith III; Y. S. Cho, L. E. Zawacki, R. Hirschmann, G. R. Pettit, Org. Lett., **2001**, 3, 4063–4066; m) H.-U. Reissig, G. Böttcher, R. Zimmer, Can. J. Chem.**, 2004,** 82, 166–176; n) K. Knobloch, J. Koch, M. Keller, W. Eberbach, Eur. J. Org. Chem., **2005,** 2715–2733; o) N. D. Shapiro, F. D. Toste, J. Am. Chem. Soc., **2008**, 130, 9244–9245; p) L. Cui, G. Zhang, Y. Peng, L. Zhang, Org. Lett., 11, **2009**, 1125–1128; q) H. Cho, Y. Iwama, K. Sugimoto, S. Mori, H. Tokuyama, J. Org. Chem., **2010**, 75, 627–636; r) F. R. Bou-Hamdan, F. Lévesque, A. G. O'Brien, P. H. Seeberger, Beilstein J. Org. Chem., **2011**, 7, 1124–1129; s) S. Cui, Y. Zhang, Q. Wu, Chem. Sci., **2013**, 4, 3421–3426; t) Z. Shi, C. Grohmann, F. Glorius, Angew. Chem. Int. Ed., **2013**, 52, 5393–5397.
15. E. O. Beckmann, Chem. Ber., **1886**, 89, 988–993.
16. a) P. S. Singh, R. Bandyopadhyay, S. G. Hegde, B. S. Rao, Appl. Catal. A, **1996**, 136, 249– 263; b) L. D. Luca, G. Giacomelli, A. Porcheddu, J. Org. Chem., **2002**, 67, 6272–6274; c) S. Guo, Y. Deng, Catal. Commun., **2005**, 6, 225–228; c) A. Zicmanis, S. Katkevica, P. Mekss, Catal. Commun., **2009**, 10, 614–619; d) C. W. Kuo, M. T. Hsieh, S. Gao, Y. M. Shao, C. F. Yao, K. S. Shia, Molecules, **2012**, 17, 13662–13672; e) J. L. Kenwright, W. R. J. D. Galloway, L. Wortmann, D. R. Spring, Synth. Commun., **2013**, 43, 1508–1516; f) G. Quartarone, E. Rancan, L. Ronchin, Appl. Catal. A: Gen., **2014**, 472, 167–177; g) V. Yu. Kuksenok, V. V. Shtrykova, V. D. Filimonov, S. P. Sidel'nikova, Russ. J. Org. Chem., **2016**, 52, 196–199.
17. a) J. S. Reddy, R. Ravishankar, S. Sivanker, P. Ratnasamy, Catal. Lett., **1993**, 17, 139–140; b) J. S. Yadav, B.V. S. Reddy, A. V. Madhavi, Y. S. S. Ganesh*,* J. Chem. Res. (S), **2002**, 2002 (5), 236–238; c) J. K. Lee, D. C. Kim, C. E. Song, S. G. Lee, Synth. Commun., **2003**, 33, 2301–2307; d) B. Thomas, S. Prathapan, S. Sugunan, Microporous and Mesoporous Materials, **2005**, 84, 137–143; e) P. Yan, P. Batamack, G. K. S. Prakash, G. A. Olah, Catal. Lett., **2005**, 103, 165–168; f) K. T. Kang, T. M. Sung, H. C. Jung, J. G. Lee, Bull. Korean Chem. Soc., **2008**, 29, 1669–1670; g) V. Yadav, N. Yadav, M. Agrawal, D. Kishore, Der Pharma Chemica, **2011**, 3, 127–132; h) G. Raju, V. Guguloth, B. Satyanarayana, RSC Adv., **2016**, 6, 45036–45040.
18. a) R. H. Mazur, J. Am. Chem. Soc., **1959**, 81, 1454–1456; b) J. A. Zderic, J. Iriarte, J. Org. Chem., **1962**, 27, 1756–1760; c) C. W. Shoppee, S. K. Roy, J. Chem. Soc., **1963**, 3774–3777; d) P. Catsoulacos, D. Catsoulacos, J. Hetreocycl. Chem., **1993**, 30, 1–10.
19. a) A. H. Blatt, Chem. Rev., **1933**, 12, 215–260; b) B. Jones, Chem. Rev., **1944**, 35, 335–350; c) L. G. Donaruma, W. Z. Heldt*,* Org. React., **1960**, 11, 1–156; d) R. E. Gawley, Org. React., **1988**, 35, 14–24; e) T. Tatsumi, In: R. A. Sheldon, H. Bekkum (Ed.), Beckmann Rearrangement, Weinheim: Wiley-VCH, New York, **2001**, 185–204; f) N. Kaur, P. Sharma, D. Kishore, J. Chem. Pharm. Res., **2012**, 4, 1938–1946.
20. a) T. Sato, H. Wakatsuka, K. Amano, Tetrahedron, **1971**, 27, 5381–5390; b) I. Flemming, R. B. Woodword, J. Chem, Soc. Perkin I, **1973**, 1653–1657; c) K. Oka, S. Hara, J. Org. Chem., **1978**, 43, 3790–3791; d) J. W. Lyga, J. Heterocycl. Chem., **1996**, 33, 1631–1635; e) D. Shouro, Y. Moriya, T. Nakajima, S. Mishima, Appl. Catal. A, **2000**, 198, 275–282; f) N. Krstic, M. S. Bjelakovic, M. M. Dabovic, L. B. Lorenc, V. D. Pavlovic, J. Serb. Chem. Soc., **2004**, 69, 413–420; g) C. Ramalingan, Y. T. Park, J. Org. Chem., **2007**, 72, 4536–4538; h) A. R. Sardarian, Z. Shahsavari-Fard, H. R. Shahsavari, Z. Ebrahimi, Tetrahedron Lett., **2007**, 48, 2639–2643.
21. a) S. Mor, P. Pahal, Der Pharma Chemica, **2015**, 7, 118–129; b) S. Mor, P. Pahal, Chemistry & Biology Interface, **2016**, 6, 198–209; c) N. Devi, D. Singh, Honey, S. Mor, S. Chaudhary, R. K. Rawal, V. Kumar, A. K. Chowdhury, V. Singh, RSC Adv., **2016**, 6, 43881–43891.
22. W. S. Johnson, J. Am. Chem. Soc., **1943**, 65, 1317–1324.
23. B. M. Trost, G. M. Schroeder, J. Am. Chem. Soc., **1999**, 121, 6759–6760.
24. A. Hassner, T. C. Mead, Tetrahedron Lett., **1962**, 1223–1224.
25. H. Chen, Z. Ji, L. K. Wong, J. F. Siuda, V. L. Narayanan, Pharma. Res., **1996**, 12, 1482–1487.
26. S. V. Popkov, L. V. Kovalenko, V. P. Tashchi, L. Ya. Bogel'fer, Russian Chemical Bulletin, **1994**, 43, 1363–1367.
27. K. K. Kelly, J. S. Matthews, Tetrahedron, **1970**, 26, 1555–1559.
28. P. J. Smith, J. R. Dimmock, W. A. Turner, Can. J. Chem., **1973**, 51, 1471–1475.
29. G. E. Hawkes, K. Herwing, J. D. Roberts, J. Org. Chem., **1974**, 39, 1017–1028.
30. B. S. Lee, D. Y. Chi, Bull. Korean Chem. Soc., **1998**, 19, 1373–1375.

31. D. Christopher, E. Mark, D. John, WO, 048017 A1, **2010**.
32. E. M. Afsah, E. Abdel-Galil, M. Hammouda, I. A. Youssef, Res. J. Pharm. Biol. Chem. Sci., **2011**, 2, 1066–1078.
33. X. Liu, Z. Han, Z. Wang, K. Ding, Angew. Chem. Int. Ed., **2014**, 53, 1978–1982.