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Synthesis of some (*E*)-3-arylidene-6-methylpiperidin-2-ones *via* Beckmann rearrangement

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

Keywords: Beckmann rearrangement; (*E*)-2-arylidenecyclopentanones; (*E*)-3-arylidene-6-methylpiperidin-2-ones; 2-methylcyclopentanone; oximes; thionyl chloride.

1. Introduction

The rearrangement of a ketoxime to the corresponding amide was discovered by E. O. Beckmann [1] in 1886 and is known as Beckmann rearrangement. It accomplishes both the cleavage of a carbon–carbon bond and formation of a carbon–nitrogen bond. With the test of time, the Beckmann rearrangement has arisen as one of the most widely employed method for the transformation of oximes into *N*-substituted amides and lactams [2–8]. It also finds numerous applications in the synthesis of a variety of heterocyclic compounds [9–15] and aza steroids [16–19]. Literature survey reveals that many reagents are used to carry out the Beckmann rearrangement [20]. Ever since the discovery of the reaction, a number of reviews [21–26] are available which deal with the mechanism of reaction, the determination of stereochemical configuration of oximes employed and synthetic applications of the reaction. Despite wide interest in the Beckmann rearrangement of a variety of oximes, chemists in the past have exhibited only intermittent attention towards the Beckmann rearrangement of alicylic and cyclic *α,β*-unsaturated ketones [27–34]. Keeping in view of this and in continuation of our previous studies [35], herein, we during the present investigation have reported the synthesis of some (*E*)-3-arylidene-6-methylpiperidin-2-ones (**6**) derived

from 2-methylcyclopentanone (**1**) *via* thionyl chloride/dry dioxane mediated Beckmann rearrangement in moderate yields with an aim to examine whether (i) *O*-tosyl oximes (**5**) undergo alkyl or vinyl migration, and (ii) the rearrangement is accompanied by the movement 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 purchased from Sigma-Aldrich, Qualigens, CDH, Himedia and Spectrochem. All the chemicals were used as such or after necessary purification as per literature procedures. Melting & boiling points (°C) of the synthesized compounds were determined on an electrothermal apparatus in open head capillaries and are uncorrected. Purity and progress of the reactions of the synthesized compounds were monitored by thin layer chromatography (TLC) using commercially available precoated silica gel (HF_{254}, 200 mesh) plates as stationary phase and various combinations of solvents as mobile phase, and developed 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 on a water bath. The structures of the synthesized compounds were corroborated by employing different spectral (IR, NMR, Mass) and elemental analytical techniques. The 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. The ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Advance 300/400 MHz spectrometer at 300/400 MHz and 75/100 MHz, respectively in $CDCl_3$/DMSO-d_6 and chemical shift values (δ) are reported in parts per million (ppm) using tetramethylsilane (TMS) 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 reported 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-5-methylcyclopentanones (3): To a solution of 2-methylcyclopentanone (**1**, 3.13 g, 0.032 mole) and an appropriate benzaldehyde (**2**, 0.048 mole) in methanol (20 mL) was added 5% aqueous NaOH (12 mL) drop wise while stirring with the aid of a magnetic stirrer. The reaction mixture was further stirred for 9–13h at room temperature. Thereafter, the reaction mixture was poured in cold water and extracted with chloroform (3×20 mL). The organic layer was washed with dil. HCl and water and dried over anhydrous $MgSO_4$, and chloroform was removed under reduced pressure. The resulting residue upon further purification, *i.e.* distillation or crystallization afforded the corresponding (*E*)-2-arylidene-5-methylcyclopentanones (**3**) in moderate to good yields [36]. Their physical data are given as follows:

(*E*)-2-benzylidene-5-methylcyclopentanone (3a): Obtained by stirring for 13h; yield 71%; bp135–139 °C/ 0.1 torr (Lit. [37] bp 140–145 °C/ 0.1 torr, 181–181.5 °C/ 19 torr).

(*E*)-2-(4-methylbenzylidene)-5-methylcyclopentanone (3b): Obtained by stirring for 10h; yield 53%; mp 120 °C.

(*E*)-2-(4-methoxybenzylidene)-5-methylcyclopentanone oxime (3c): Obtained by stirring for 9h; yield 74.3%; mp 88–91 °C (Lit. [36] mp 92–94 °C).

(*E*)-2-(4-chlorobenzylidene)-5-methylcyclopentanone oxime (3d): Obtained by stirring for 11h; yield 69%; mp 85–86 °C (Lit. [36] mp 80–87 °C).

2.3 General procedure for the synthesis of (1*E*,2*E*)-2-arylidene-5-methylcyclopentanone oximes (4): A mixture of an appropriate (*E*)-2-arylidene-5-methylcyclopentanone (**4**, 0.009 mole), NH_2OH. HCl (0.70 g, 0.01 mole) and NaOH (4.0 g) in methanol (150 mL) was refluxed on a water bath for 2–5h. Thereafter, the hot mixture was filtered and 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-5-methylcyclopentanone oximes (**4**) in good yields (70.3–76%). Their spectral parameters and other characteristics are given below:

(1*E*,2*E*)-2-benzylidene-5-methylcyclopentanone oxime (4a): Obtained by refluxing for 3h as yellowish-white crystals (ethanol), yield 72%; mp 112–113 °C; IR (KBr, cm^{-1}): 3266 (O–H, stretching), 1630 (C=N, stretching), 1602 (C=C, stretching); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.18 (*d*, *J* = 6.9 Hz, 3H, CH_3-5), 1.57–1.90 (*m*, 2H, H-4), 2.20–2.68 (*m*, 3H, H-3, H-5), 6.85 (*s*, 1H, H_β), 7.25–7.46 (*m*, 5H, H-2′, H-3′, H-4′, H-5′, H-6′), 9.01 (*br s*, 1H, OH, exchangeable with D_2O); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.92 (C_5-$\underline{CH_3}$), 29.20 (C_4), 32.12 (C_3), 39.30 (C_5), 127.60 ($C_{3'}$ & $C_{5'}$), 127.96 ($C_{2'}$ & $C_{6'}$), 128.23 ($C_{1'}$), 129.11 ($C_{4'}$), 136.53 (C_β), 138.02 (C_2), 163.01 (C_1); *Anal.* Calcd. for $C_{13}H_{15}NO$ (201.26): C, 77.58; H, 7.51; N, 6.96. Found: C, 77.80; H, 6.63; N, 7.11.

(1*E*,2*E*)-2-(4-methylbenzylidene)-5-methylcyclopentanone oxime (4b): Obtained by refluxing for 2h as yellow crystals (benzene), yield 76%; mp 130–132 °C; IR (KBr, cm^{-1}): 3290 (O–H, stretching), 1625 (C=N, stretching), 1587 (C=C, stretching); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28 (*d*, *J* = 6.9 Hz, 3H, CH_3-5), 1.59–1.87 (*m*, 2H, H-4), 2.16–2.72 (*m,* 6H, H-3, H-5, CH_3-4′), 6.92 (*s*, 1H, H_β), 7.20 (*d*, *J* = 7.5 Hz, 2H, H-3′ & H-5′), 7.43 (*d*, *J* = 7.5 Hz, 2H, H-2′ & H-6′), 8.02 (*br s*, 1H, OH, exchangeable with D_2O); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.01 (C_5-$\underline{CH_3}$), 20.13 ($C_{4'}$-$\underline{CH_3}$), 30.12 (C_4), 32.73 (C_3), 39.51 (C_5), 125.28 ($C_{3'}$ & $C_{5'}$), 129.64 ($C_{2'}$ & $C_{6'}$), 130.12 ($C_{1'}$), 133.74 ($C_{4'}$), 135.12 (C_β), 136.71 (C_2), 163.44 (C_1); *Anal.* Calcd. for $C_{14}H_{17}NO$ (215.29): C, 78.10; H, 7.96; N, 6.51. Found: C, 78.36; H, 7.74; N, 6.23.

(1*E*,2*E*)-2-(4-methoxybenzylidene)-5-methylcyclopentanone oxime (4c): Obtained by refluxing for 5h as white crystals (methanol), yield 72.6%; mp 108–109 °C; IR (KBr, cm^{-1}): 3280 (O–H, stretching), 1628 (C=N, stretching), 1599 (C=C, stretching); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21 (*d*, *J* = 6.9 Hz, 3H, CH_3-5), 1.61–1.99 (*m*, 2H, H-4), 2.23–2.82 (*m*, 3H, H-3, H-5), 3.82 (*s*, 3H, OCH_3-4′), 6.82 (*s*, 1H, H_β), 6.98 (*d, J* = 8.1 Hz, 2H, H-3′ & H-5′), 7.37 (*d*, *J* = 8.1 Hz, 2H, H-2′ & H-6′), 8.50 (*br s*, 1H, OH, exchangeable with D_2O); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.05 (C_5-$\underline{CH_3}$) 29.55 (C_4), 31.98 (C_3), 39.07 (C_5), 55.26 ($C_{4'}$-O$\underline{CH_3}$), 112.96 ($C_{3'}$ & $C_{5'}$), 123.74 ($C_{2'}$ & $C_{6'}$), 129.12 ($C_{1'}$), 134.80 (C_β), 136.83 (C_2), 158.62 ($C_{4'}$), 164.11 (C_1); *Anal.* Calcd. for $C_{14}H_{17}NO_2$ (231.29): C, 72.70; H, 7.41; N, 6.06. Found: C, 72.95; H, 7.13; N, 6.03.

(1*E*,2*E*)-2-(4-chlorobenzylidene)-5-methylcyclopentanone oxime (4d): Obtained by refluxing for 3.5h as yellow crystals (methanol), yield 70.3%; mp 110–112 °C; IR (KBr, cm^{-1}): 3296 (O–H, stretching), 1635 (C=N, stretching), 1611 (C=C, stretching); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.23 (*d*, *J* = 6.9 Hz, 3H, CH_3-5), 1.63–1.87 (*m*, 2H, H-4), 2.15–2.79 (m, 3H, H-3, H-5), 6.86 (*s*, 1H, H_β), 7.31 (*d*, *J* = 8.1 Hz, 2H, H-3′ & H-5′), 7.42 (*d*, *J* = 8.1 Hz, 2H, H-2′ & H-6′), 8.10 (*br s*, 1H, OH,

exchangeable with D_2O); ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.11 (C_5-$\underline{CH_3}$), 30.23 (C_4), 32.41 (C_3), 38.72 (C_5), 122.61 ($C_{3'}$ & $C_{5'}$), 129.09 ($C_{2'}$ & $C_{6'}$),130.46 ($C_{1'}$), 132.62 ($C_{4'}$), 135.22 (C_β), 137.53 (C_2), 163.73 (C_1); *Anal.* Calcd. for $C_{13}H_{14}ClNO$ (235.71): C, 66.24; H, 5.99; N, 5.94. Found: C, 66.39; H, 5.73; N, 6.17.

2.4 General procedure for the synthesis of (1*E*,2*E*)-2-arylidene-5-methylcyclopentanone *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-5-methylcyclopentanone oxime (0.01 mole) in pyridine (7 mL) at 0 °C and the reaction mixture was stirred for 2–3h at 0 °C . Then reaction mixture was further stirred for 45 min at room temperature, and poured onto crushed ice containing 5 mL of dil. H_2SO_4. The solid thus obtained was collected by filteration and recrystallized from a suitable solvent to afford the corresponding (1*E*,2*E*)-2-arylidene-5-methylcyclopentanone *O*-tosyl oximes (**5**) in high yields (82.6–89.1%). Their spectral parameters and other characteristics are given below:

(1*E*,2*E*)-2-benzylidene-5-methylcyclopentanone *O*-tosyl oxime (5a): Obtained by stirring for 2h as white crystals (ethanol), yield 89%; mp 110–113 °C; IR (KBr, cm^{-1}): 1610 (C=N, stretching); ^1H NMR (300 MHz, $CDCl_3$): δ 1.20 (*d*, *J* = 6.9 Hz, 3H, CH_3-5), 1.63–1.86 (*m*, 2H, H-4), 2.09–2.73 (*m*, 6H, H-3, H-5, CH_3-4″), 6.81 (*s*, 1H, H_β), 7.20–7.53 (*m*, 7H, H-2′, H-3′, H-4′, H-5′, H-6′, H-3″, H-5″), 7.88 (*d*, *J* = 8.4 Hz, 2H, H-2″ & H-6″); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.23 (C_5-$\underline{CH_3}$), 21.30 ($C_{4''}$-$\underline{CH_3}$), 28.12, 31.72, 37.22 (C_3, C_4, C_5), 127.10, 127.71, 128.11, 128.87, 129.10, 129.71, 131.11 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$, $C_{6'}$, $C_{2''}$, $C_{3''}$, $C_{4''}$, $C_{5''}$, $C_{6''}$), 136.22 (C_β), 137.74 (C_2), 143.12 ($C_{1''}$), 159.90 (C_1); *Anal.* Calcd. for $C_{20}H_{21}NO_3S$ (355.45): C, 67.58; H, 5.95; N, 3.94. Found: C, 67.76; H, 5.84; N, 3.86.

(1*E*,2*E*)-2-(4-methylbenzylidene)-5-methylcyclopentanone *O*-tosyl oxime (5b): Obtained by stirring for 2.5h as yellowish white crystals (benzene–pet-ether), yield 85.7%; mp 170–172 °C ; IR (KBr, cm^{-1}): 1606 (C=N, stretching); ^1H NMR (300 MHz, $CDCl_3$): δ 1.23 (*d*, *J* = 6.9 Hz, 3H, CH_3-5), 1.53–1.90 (*m*, 2H, H-4), 2.11–2.86 (*m*, 9H, H-3, H-5, CH_3-4′, CH_3-4″), 6.91 (*s*, 1H, H_β), 7.15 (*d*, *J* = 7.5 Hz, 2H, H-3′ & H-5′), 7.25 (*d*, *J* = 7.5 Hz, 2H, H-2′ & H-6′), 7.43 (*d*, *J* = 8.4 Hz, 2H, H-3″ & H-5″), 7.85 (*d*, *J* = 8.4 Hz, 2H, H-2″ & H-6″); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.11 (C_5-$\underline{CH_3}$), 20.54 ($C_{4'}$-$\underline{CH_3}$), 21.35 ($C_{4''}$-$\underline{CH_3}$), 28.63, 30.85, 38.11 (C_3, C_4, C_5), 127.42, 128.55, 128.90, 129.45, 130.58, 131.23, 134.15 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$, $C_{6'}$, $C_{2''}$, $C_{3''}$, $C_{4''}$, $C_{5''}$, $C_{6''}$), 137.05 (C_β), 138.17 (C_2), 142.56 ($C_{1''}$), 160.87 (C_1); *Anal.* Calcd. for $C_{21}H_{23}NO_3S$ (369.48): C, 68.27; H, 6.27; N, 3.79. Found: C, 68.56; H, 6.09; N, 3.75.

(1*E*,2*E*)-2-(4-methoxybenzylidene)-5-methylcyclopentanone *O*-tosyl oxime (5c): Obtained by stirring for 2h as white crystals (methanol), yield 89.1%; mp 208–210 °C; IR (KBr, cm^{-1}): 1598 (C=N, stretching); ^1H NMR (300 MHz, $CDCl_3$): δ 1.18 (*d*, *J* = 6.9 Hz, 3H, CH_3-5), 1.57–1.92 (*m*, 2H, H-4), 2.20–2.93 (*m*, 6H, H-3, H-5, CH_3-4″), 3.80 (*s*, 3H, OCH_3-4′) 6.85 (*s*, 1H, H_β), 6.96 (*d*, *J* = 8.1 Hz, 2H, H-3′ & H-5′), 7.31–7.44 (*m*, 4H, H-2′, H-6′, H-3″, H-5″), 7.92 (*d*, *J* = 8.4 Hz, 2H, H-2″ & H-6″); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.09 (C_5-$\underline{CH_3}$), 20.65 ($C_{4''}$-$\underline{CH_3}$), 27.92, 30.12, 37.41 (C_3, C_4, C_5), 55.12 ($C_{4'}$-O$\underline{CH_3}$), 113.20 ($C_{3'}$ & $C_{5'}$), 127.05, 128.17, 129.03, 130.74, 131.57 ($C_{1'}$, $C_{2'}$, $C_{4'}$, $C_{6'}$, $C_{2''}$, $C_{3''}$, $C_{4''}$, $C_{5''}$, $C_{6''}$), 134.47 (C_β), 136.68 (C_2), 143.68 ($C_{1''}$), 160.03 ($C_{4'}$), 161.68 (C_1); *Anal.* Calcd. for $C_{21}H_{23}NO_4S$ (385.48): C, 65.43; H, 6.01; N, 3.63. Found: C, 65.51; H, 5.84; N, 3.75.

(1*E*,2*E*)-2-(4-chlorobenzylidene)-5-methylcyclopentanone *O*-tosyl oxime (5d): Obtained by stirring for 3h as yellow crystals

(ethanol), 82.6% yield; mp 160–162 °C; IR (KBr, cm^{-1}): 1621 (C=N, stretching); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20 (*d*, *J* = 6.9 Hz, 3H, CH_3-5), 1.50–1.91 (*m*, 2H, H-4), 2.07–2.69 (*m*, 6H, H-3, H-5, CH_3-4″), 6.90 (*s*, 1H, H_β), 7.29–7.47 (*m*, 6H, H-2′, H-3′, H-5′, H-6′, H-3″, H-5″), 7.90 (*d*, *J* = 8.4 Hz, 2H, H-2″ & H-6″); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.03 (C_5-$\underline{CH_3}$), 20.74 ($C_{4''}$-$\underline{CH_3}$), 28.45, 30.53, 37.02 (C_3, C_4, C_5), 123.56, 127.21, 128.75, 129.74, 130.83, 131.72, 134.58 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$, $C_{6'}$, $C_{2''}$, $C_{3''}$, $C_{4''}$, $C_{5''}$, $C_{6''}$), 135.53 (C_β), 137.17 (C_2), 143.95 ($C_{1''}$), 162.04 (C_1); *Anal.* Calcd. for $C_{20}H_{20}ClNO_3S$ (389.90): C, 61.61; H, 5.17; N, 3.59. Found: C, 61.69; H, 4.94; N, 3.66.

2.5 General procedure for the synthesis of (*E*)-3-arylidene-6-methylpiperidin-2-ones (6): A solution of an appropriate (1*E*,2*E*)-2-arylidene-5-methylcyclopentanone *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 11–12h. Thereafter, water was added to the reaction mixture and extracted with diethyl ether (3×20 mL). The combined extracts were washed with water, $NaHCO_3$, and water and dried over anhydrous Na_2SO_4. Rotaevaporation of the solvent furnished a solid which upon crystallization from a suitable solvent furnished the corresponding (*E*)-3-arylidene-6-methylpiperidin-2-ones **(6)** in moderate yields (42–46%). Their spectral parameters and other characteristics are given below:

(*E*)-3-benzylidene-6-methylpiperidin-2-one (6a): Obtained by stirring for 12h as white crystals (methanol), yield 42%; mp 217–219 °C; IR (KBr, cm^{-1}): 3252 (N–H, stretching), 1652 (C=O, stretching), 1604 (C=C, stretching); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20 (*d*, *J* = 6.3 Hz, 3H, CH_3-6), 1.70–1.98 (*m*, 2H, H-5), 2.31–2.46 (*m*, 2H, H-4), 3.26–3.49 (*m*, 1H, H-6), 6.60 (*br s*, 1H, N-H, exchangeable with D_2O), 7.20–7.38 (*m*, 5H, H-2′, H-3′, H-4′, H-5′, H-6′), 7.78 (*s*, 1H, H_β); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.13 (C_6-$\underline{CH_3}$), 22.72 (C_5), 31.12 (C_4), 51.60 (C_6), 128.32, 129.12, 130.35, 131.60 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$, $C_{6'}$), 134.36 (C_β), 137.11 (C_3), 166.06 (C_2); ESI-MS: m/z 201 ($M^{+\cdot}$, 53), 200 (100), 173 (8.6), 130 (7.5), 129 (16.3), 116 (5.8), 115 (19.2), 102 (6.6), 91 (8.6), 77 (5.1); *Anal.* Calcd. for $C_{13}H_{15}NO$ (201.12): C, 77.58; H, 7.51; N, 6.96. Found: C, 77.76; H, 7.84; N, 7.21.

(*E*)-6-methyl-3-(4-methylbenzylidene) piperidin-2-one (6b): Obtained by stirring for 11h as light brown crystals (benzene), yield 45.3%; mp 78–81 °C; IR (KBr, cm^{-1}): 3270 (N–H, stretching), 1667 (C=O, stretching), 1603 (C=C, stretching); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21 (*d*, *J* = 6.3 Hz, 3H, CH_3-6), 1.67–2.09 (*m*, 2H, H-5), 2.27–2.51 (*m*, 5H, H-4, CH_3-4′), 3.30–3.48 (*m*, 1H, H-6), 6.58 (*br s*, 1H, N-H, exchangeable with D_2O), 7.24 (*d*, *J* = 7.5 Hz, 2H, H-3′ & H-5′), 7.35 (*d*, *J* = 7.5 Hz, 2H, H-2′ & H-6′), 7.89 (*s*, 1H, H_β); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.02 (C_6-$\underline{CH_3}$), 21.15 ($C_{4'}$-$\underline{CH_3}$), 23.01 (C_5), 31.74 (C_4), 51.17 (C_6), 128.87, 129.93, 130.71, 133.14 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$, $C_{6'}$), 135.57 (C_β), 138.20 (C_3), 165.89 (C_2); ESI-MS: m/z 215 ($M^{+\cdot}$, 52.4), 214 (100), 200 (6.5), 187 (7.3), 186 (5.7), 130 (4), 129 (19.2), 128 (13.2), 116 (6.3), 115 (20.5), 105 (5), 91 (2.3), 77 (1.2); *Anal.* Calcd. for $C_{14}H_{17}NO$ (215.13): C, 78.10; H, 7.96; N, 6.51. Found: C, 78.32; H, 7.66; N, 6.74.

(*E*)-3-(4-methoxybenzylidene)-6-methylpiperidin-2-one (6c): Obtained by stirring for 11.5h as white crystals (methanol), yield 43%; mp 212–214 °C; IR (KBr, cm^{-1}): 3285 (N–H, stretching), 1662 (C=O, stretching), 1589 (C=C, stretching); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20 (*d*, *J* = 6.3 Hz, 3H, CH_3-6), 1.55–2.04 (*m*, 2H, H-5), 2.30–2.62 (*m*, 2H, H-4), 3.22–3.41 (*m*, 1H, H-6), 3.80 (*s*, 3H, OCH_3-4′), 6.68 (*br s*, 1H, N-H, exchangeable with D_2O), 6.92 (*d*, *J* = 7.5 Hz, 2H, H-3′ & H-5′), 7.42 (*d*, *J* = 7.5 Hz, 2H, H-2′ & H-6′), 7.73 (*s*, 1H, H_β);

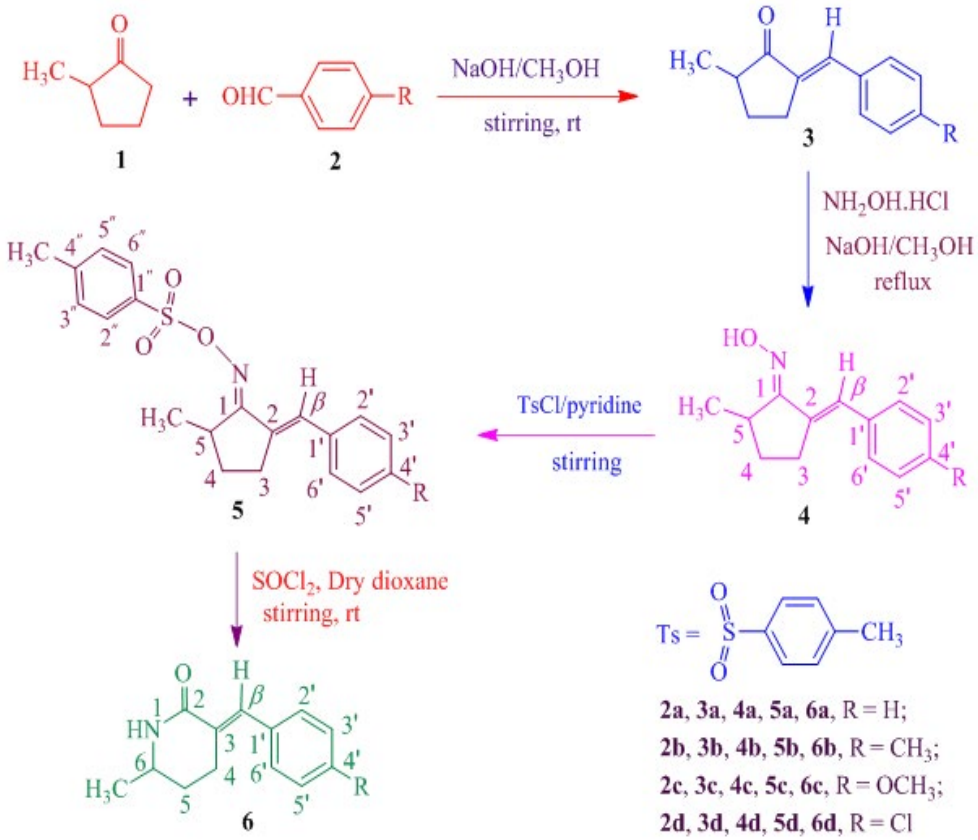
^{13}C NMR (75 MHz, $CDCl_3$): δ 19.67 (C_6-$\underline{CH_3}$), 22.38 (C_5), 31.66 (C_4), 51.02 (C_6), 55.02 ($C_{4'}$-$O\underline{CH_3}$), 113.92 ($C_{3'}$ & $C_{5'}$), 129.25, 130.25 ($C_{1'}$, $C_{2'}$ & $C_{6'}$), 133.45 (C_β), 136.41 (C_3), 160.13 ($C_{4'}$), 166.78 (C_2); ESI-MS: m/z 231 ($M^{+\cdot}$, 56), 230 (100), 216 (4.7), 203 (7.5), 188 (21), 172 (2.9), 160 (4), 159 (8.4), 145 (7.5), 121 (6.5), 115 (13), 91 (5.8); *Anal.* Calcd. for $C_{14}H_{17}NO_2$ (231.13): C, 72.70; H, 7.41; N, 6.06. Found: C, 72.96; H, 7.11; N, 6.32.

(*E*)-3-(4-chlorobenzylidene)-6-methylpiperidin-2-one (6d): Obtained by stirring for 11h as dark brown crystals (benzene–pet-ether), yield 46%; mp 125–129 °C; IR (KBr, cm^{-1}): 3260 (N–H, stretching), 1670 (C=O, stretching), 1610 (s, C=C, stretching); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (*d*, *J* = 6.3 Hz, 3H, CH_3-6), 1.53–1.98 (*m*, 2H, H-5), 2.44–2.68 (*m*, 2H, H-4), 3.17–3.45 (*m*, 1H, H-6) 6.65 (*br s*, 1H, N-H, exchangeable with D_2O), 7.29–7.55 (*m*, 4H, H-2′, H-3′, H-5′, H-6′), 7.85 (*s*, 1H, H_β); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.78 (C_6-$\underline{CH_3}$), 22.75 (C_5), 32.63 (C_4), 50.84 (C_6), 122.89, 129.34, 132.25, 134.32 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$, $C_{6'}$), 135.73 (C_β), 137.25 (C_3), 164.55 (C_2); ESI-MS: m/z 235 ($M^{+\cdot}$, 51.3)/237 ($M^{+\cdot}$+2, 15.6), 234 ($M^{+\cdot}$-1, 100)/236 ($M^{+\cdot}$-1, 35.9), 207 (12.5)/209 (4.5), 200 (3.5)/202 (35), 172 (1.9), 125 (5.1)/127 (1.5), 115 (14.5); *Anal.* Calcd. for $C_{13}H_{14}ClNO$ (235.08): C, 66.24; H, 5.99; N, 5.94. Found: C, 66.41; H, 5.71; N, 5.73.

3. Results and discussion

3.1 Chemistry

General approach toward the synthesis



Scheme 1. Synthetic route for the preparation of (*E*)-3-arylidene-6-methylpiperidin-2-ones (**6**).

of (*E*)-3-arylidene-6-methylpiperidin-2-ones (**6**) involves an initial condensation of 2-methylcyclopentanone (**1**) with appropriate 4-substituted benzaldehydes (**2**) under base-catalyzed conditions [36] to furnish (*E*)-2-arylidene-5-methylcyclopentanones (**3**) in good yields. The arylidenes (**3**) upon refluxing with $NH_2OH.HCl$ in NaOH/methanol furnished (1*E*,2*E*)-2-arylidene-5-methylcyclopentanone oximes (**4**) which upon subsequent stirring with *p*-toluenesulphonyl chloride in equimolar quantities in presence of pyridine afforded (1*E*,2*E*)-2-arylidene-5-methylcyclopentanone *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 (*E*)-3-arylidene-6-methylpiperidin-2-ones (**6**) in moderate yields (Scheme 1).

The purity of the entire synthesized (*E*)-2-arylidene-5-methylcyclopentanones (**3**) was checked through TLC and their melting points.

The structures of all the oximes (**4**) were well established by satisfactory spectral (IR, ^{1}H NMR and ^{13}C NMR) and analytical data. The oximes (**4a**–**4d**), in principle, 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**. The configurations (1*Z,*2*Z*) and (1*E,*2*Z*) can easily be discarded on the basis of argument that under base-catalyzed equilibrium conditions, a thermodynamically more stable ketone with (*E*)-configuration is highly unlikely to be converted into a thermodynamically less stable ketone with (*Z*)-configuration. Therefore, it seems logical to assume that during the formation of oximes (**4**), configuration around C=C is retained. 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.

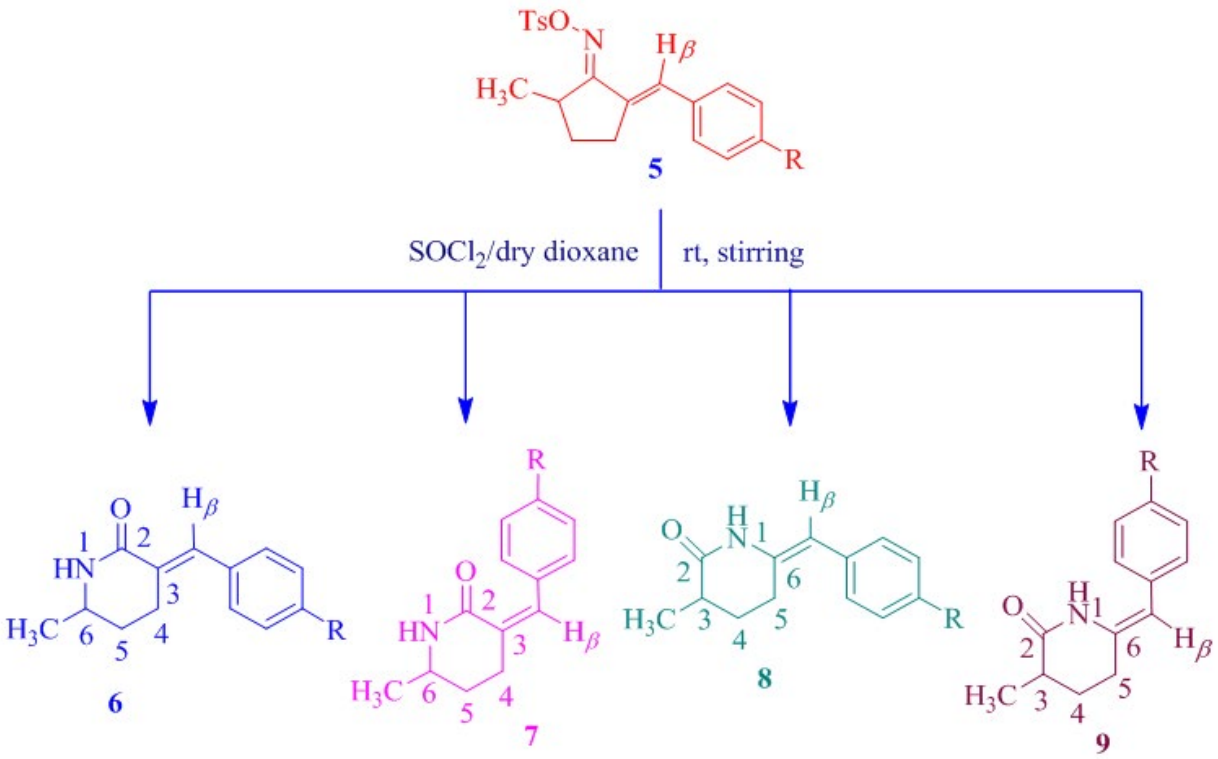
The IR spectra of oximes (**4a**–**4d**), in each case, exhibited a broad absorption band in the region at 3266–3296 cm^{-1} due to O–H stretching, a band of medium intensity in the region at 1625–1635 cm^{-1} due to C=N stretching and another band of medium intensity at 1587–1611 cm^{-1} due to C=C stretching. ^{1}H NMR spectra of oximes (**4a**–**4d**), in the aliphatic region, displayed a doublet integrating for three protons in the region at δ 1.18–1.28 assignable to CH_3-5 protons. It was followed by a two-proton multiplet in the region at δ 1.57–1.99 which could safely be assigned to H-4 protons. Next, towards the lower field was located a multiplet corresponding to three protons in the region at δ 2.15–2.82 ascribable to H-3 and H-5 protons. The singlet appeared in the region at δ 6.82–6.92 could safely be assigned to vinylic proton (H_β). However, the proton of oxime (=N–OH) group was appeared as a broad singlet (exchangeable with D_2O) in the region at δ 8.02–9.01. The signals due to the remaining aliphatic and aromatic protons were observed in the expected regions (*vide experimental*). To make the certainty whether the exact configuration of the oximes (**4a**–**4d**) is (1*E,*2*E*) or (1*Z,*2*E*), their ^{13}C NMR spectra were analyzed. The ^{13}C NMR spectra of oximes

(**4a**–**4d**), in each case, exhibited a signal in the region at δ 13.92–14.11 which could safely be assigned to the carbon of methyl group located at C_5 which was followed by signals due to methylene carbons appeared in the regions at δ 29.20–30.23, δ 31.98–32.73 and δ 38.72–39.51 due respectively to C_4, C_3 and C_5. All these assignments find support from the results reported in the literature [38–40] for ^{13}C NMR spectra of analogous compounds. For example, 2-allylcyclopentanone oxime, exhibited signals due to C_2 in *syn* and *anti* configurations at δ 39.1 and δ 43.1, respectively. Hence, on comparison with the chemical shift value of C_2 in ^{13}C NMR spectrum of the analogous 2-allylcyclopentanone oxime with *syn* configuration, the oximes (**4a**–**4d**) have been assigned (*E*)-configuration around C=N bond. The signals due to the vinylic carbon atoms, *i.e.* C_β and C_2 were observed in the regions at δ 134.80–136.53 and δ 136.71–138.02, respectively. The signal exhibited in the most downfield region at δ 163.01–164.11 could undoubtedly be assigned to C_1. The signals due to the remaining aliphatic and aromatic carbons were observed in the expected regions (*vide experimental*).

Since during the tosylation of oximes (**4a**–**4d**), C=C and C=N bonds are not affected, hence it is reasonable to assume that 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 analytical results. IR spectra of (1*E*,2*E*)-2-arylidene-5-methylcyclopentanone *O*-tosyl oximes (**5a**–**5d**), in each case, displayed characteristic absorptions due to C=N stretching in the region at 1598–1621 cm^{-1}. The ^1H NMR spectra of **5a**–**5d**, in each case, in the aliphatic region, at the highest field, exhibited a three-proton doublet (J = 6.9 Hz) in the region at δ 1.18–1.23 which was *undoubtedly* assigned to CH_3-5 protons. Downward to this was appeared a two-proton multiplet, in each case, in the region at δ 1.50–1.92 ascribable to C_4-protons whereas the resonances due to H-3, H-5, and CH_3-4″ protons got merged and observed as a six-proton multiplet in the region at δ 2.07–2.93. The salient feature of ^1H NMR spectra of **5a**–**5d**, in each case, is the appearance of a signal due to vinylic proton (H_β) in the region at δ 6.81–6.91. At the lowest field of spectra, in each case, was exhibited a two-proton doublet (J = 8.4 Hz) in the region at δ 7.85–7.92, easily assigned to $C_{2''}$-H and $C_{6''}$-H in accord with the results reported in literature [41]. The signals due to 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, exhibited a signal in the aliphatic region at δ 14.03–14.23 due to carbon of methyl group located at C_5. The signal displayed in the region at δ 20.65–21.35 was assigned to the methyl carbon present at $C_{4''}$. Next, towards the lower field, were observed signals in the regions at δ 27.92–28.63, δ 30.12–31.72 and δ 37.02–38.11 ascribable to the methylene carbons (C_3, C_4, C_5) while signals displayed in the regions at δ 134.47–137.05 and δ 136.68–138.17 were assigned to C_β and C_2, respectively. The signal due to $C_{1''}$, characteristic of tosyl group, was appeared in the region at δ 142.56–143.95 whereas signal exhibited in the most downfield region at δ 159.90–162.04 was safely assigned to C_1. The remaining aliphatic and aromatic carbons were found to show signals in their characteristic regions (*vide experimental*).

IR spectra of **6a**–**6d**, in each case, exhibited a characteristic medium intensity absorption band in the region at 3252–3285 cm^{-1} due to N–H stretching of secondary amide whereas two strong absorption bands due respectively to C=O stretching and C=C stretching were observed in the regions at 1652–1670 cm^{-1} and 1589–1610 cm^{-1}. ^1H NMR spectra of **6a**–**6d**, in each case, exhibited a three-proton doublet at the highest field in the region at δ

1.20–1.23 which could safely be assigned to the protons of methyl group located at C_6. The two multiplets due to methylene protons of C_5 and C_4 were observed in the regions at δ 1.53–2.09 and 2.27–2.68, respectively. Next, towards the lower field was displayed a two-proton multiplet in the region at δ 3.17–3.49 assigned to H-6 in accord with the results reported in literature for analogous compound, *i.e.* 6-pentylpiperidin-2-one [42] in which H-6 proton contiguous to NH group has been found to resonate at δ 3.35. The N-H proton (exchangeable with D_2O), however, appeared as a broad singlet in the region at δ 6.58–6.68. At the lowest field of the spectra, in each case, was located a singlet in the region at δ 7.73–7.89 which was assigned to vinylic proton (H_β). The signals due to the remaining aliphatic and aromatic protons were observed in the expected regions. In ^{13}C NMR spectra of **6a**–**6d**, in each case, was observed a signal in the region at δ 19.67–20.13 which was safely assigned to carbon of methyl group located at C_6. The signals due to the aliphatic ring carbons (C_5, C_4 and C_6) were displayed in the regions at δ 22.38–23.01, δ 31.12–32.63 and δ 50.84–51.60, respectively [42], and signals exhibited in the regions at δ 133.45–135.73 and δ 136.41–138.20 were undoubtedly assigned to vinylic carbons, *i.e.* C_β and C_3, respectively. The signal appeared in the lowest field of spectra, in each case, in the region at δ 164.55–166.78 was easily assigned to C_2. The signals due to the remaining aliphatic and aromatic carbons were observed in the expected regions. Further, the mass spectra of **6a**–**6d** showed the expected fragmentation pattern. The base peak, however, formed by the loss of H-atom from the molecular ion. The main characteristic feature of the mass spectra of lactams (**6a**–**6d**) is the sequential loss of CO, 2-methylaziridine moiety and H-atom from the molecular ion to give ion peaks at $M^{+\cdot}$–28, $M^{+\cdot}$–85 and M^{+}–86. Moreover, the ion peak at

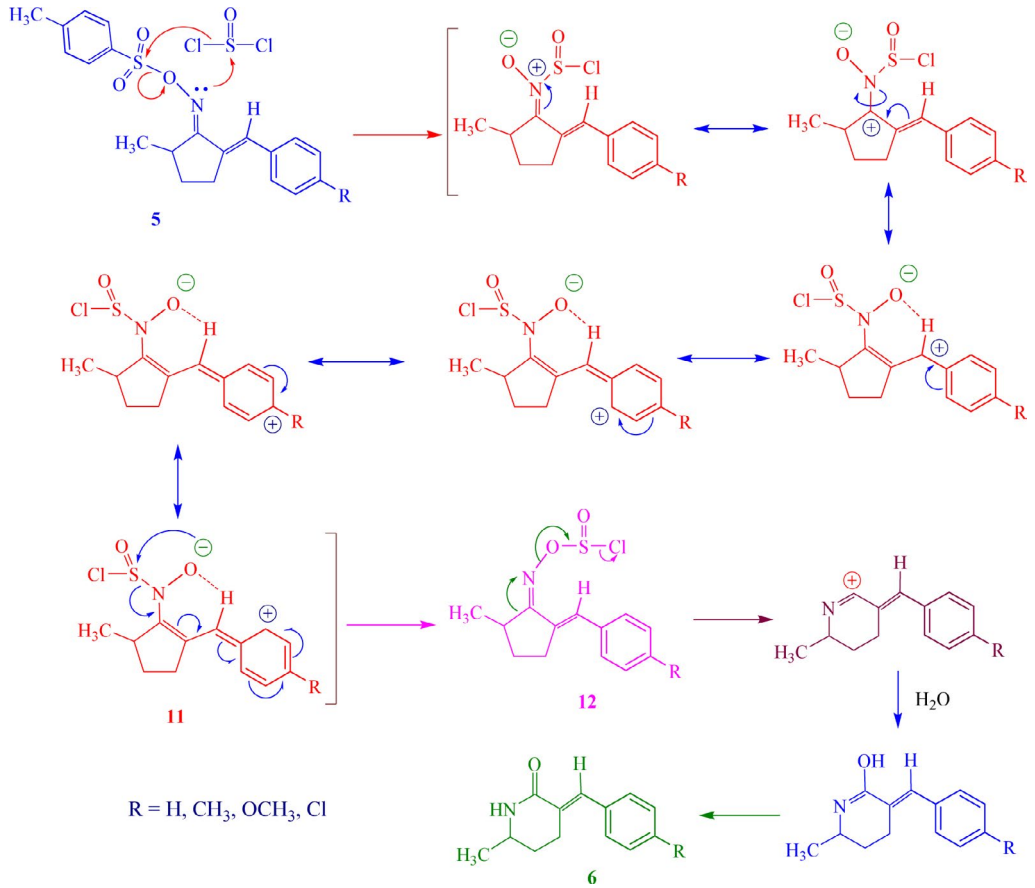


Scheme 2. Expected products of Beckmann rearrangement of (1*E*,2*E*)-2-arylidene-5-methylcyclopentanone *O*-tosyl oximes (**5**).

M^+–86 may also arise by the sequential elision of H-atom and 4-methylazetidin-2-one (mass unit 85) moiety from the molecular ion.

Beckmann rearrangement of *O*-tosyl oximes (**5**), in principle, are expected to furnish **6** and **7** by alkyl migration in which configuration around C=C is (*E*) and (*Z*), respectively and **8** and **9** by vinyl migration in which configuration around C=C is (*E*) and (*Z*), respectively (Scheme 2). The vinylic proton (H_β) in the product obtained, *i.e.* **6** resonates in the lower field in the region at δ 7.78–7.90. If the products would have alternate structures, *i.e.* **7** or **8** or **9**, than this must have resonated comparatively at a higher field, because it will not lie in the deshielding zone of C=O group in these cases. This argument along with the earlier results reported in the literature [43–49] supports the formation of **6** and the formation of lactams **7**, **8** and **9** stands rejected.

One more appealing point which warrants attention here is that during the Beckmann rearrangement of *O*-tosyl oximes (**5**), there occurs no movement of *α,β*-unsaturated double bond from exocyclic to endocyclic position to provide the lactam, *i.e.* 3-benzyl/4-substituted benzyl-6-methyl-5,6-dihydropyridin-2(1*H*)-one (**10**). If this migration had occurred, it must have exhibited a signal integrating for two protons 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 observed in ^{1}H NMR spectra of the products formed. Hence, all these arguments favour the formation of **6** by alkyl migration in which configuration around C=C bond is retained without movement of *α,β*-unsaturated double bond from exocyclic to endocyclic position during the Beckmann rearrangement of **5**.



Scheme 3. Mechanistic pathway for the synthesis of (*E*)-3-arylidene-6-methylpiperidin-2-ones (**6**).

Mechanistic details of the transformation, **5** → **6** have not been unraveled in the present investigation. However, a plausible mechanism is sketched in Scheme 3. The conversion may be envisaged to occur through an initial thionyl chloride catalyzed isomerization around C=N to give **12**. Driving force for this isomerization is most probably the stabilization of the intermediate carbocation **11** through H-bonding between O^{-} and H-atom of the C_{β}-H. The intermediate **12** thus obtained upon subsequent *anti* migration of alkyl group affords the lactam **6**.

Conclusion

In conclusion, thionyl chloride/dry dioxane mediated Beckmann rearrangement of (1*E*,2*E*)-2-arylidene-5-methylcyclopentanone *O*-tosyl oximes (**5**) leads to exclusive formation of the corresponding (*E*)-3-arylidene-6-methylpiperidin-2-ones (**6**) in moderate yields by alkyl migration without shifting of double bond from exocyclic to endocyclic position.

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