An Efficient and Versatile One-Pot Beckmann Rearrangement of Ketoximes Using Mesitylenesulfonyl Chloride

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Abstract: A variety of oxime mesitylenesulfonates, generated in situ from their heterocyclic, carbocyclic, and acyclic ketoximes in the presence of lithium hydroxide in tetrahydrofuran, efficiently rearrange into their corresponding lactams and amides. The stereochemistry of diazepan-5-one lactams resulting from the rearrangement of heterocyclic ketoximes (piperidin-4-one oximes), has been deduced based on one- and two-dimensional NMR analyses. The seven-membered heterocyclic ring of the product lactams adopts chair conformations with equatorial configurations of all the alkyl and aryl substituents except one of the methyl groups at C-3 on a 3,3-disubstituted product, which possess an axial configuration.

Key words: piperidin-4-one oximes, ketoximes, mesitylenesulfonyl chloride, Beckmann rearrangement, diazepan-5-ones, lactams, amides

Beckmann rearrangement has become a powerful tool in the syntheses of amides and lactams from their corresponding oximes since its discovery in 1886.[1] This rearrangement usually takes place in strongly acidic and dehydrating media such as sulfuric acid at high reaction temperature. To avoid these requisite harsh conditions, several methodologies in liquid-phase,[2–4] in supercritical water,[5] in ionic liquids,[6] and in the vapor-phase[7] have been developed. Of the liquid-phase rearrangements, the use of rhodium complex[2] and cyanuric chloride,[3] are elegant and recent approaches. We recently reported another, milder methodology for the rearrangement of ketoximes into amides/lactams using mercury chloride in acetonitrile.[8] Since some 1,4-diazepanone cores exhibit diverse biological activities,[9] we have directed our recent research towards the syntheses of 1,4-diazepanones as biological agents. Thus, the methodologies using the rhodium complex and cyanuric chloride[2,3] were applied to the piperidin-4-one oxime **1a** in order to form the diazepanone lactam **2a**. These methods, however, resulted only in exclusive recovery of the starting oxime, despite the reported high efficiency on other systems. Application of the mercury-catalysis method to the piperidin-4-one oxime **1a** also failed to provide the lactam **2a**. During further efforts at converting **1a**, we found a mild and efficient 'one-pot' rearrangement method using lithium hydroxide and mesitylenesulfonyl chloride in tetrahydrofuran (THF). Several other ketoximes were also examined in order to generalize the new method.

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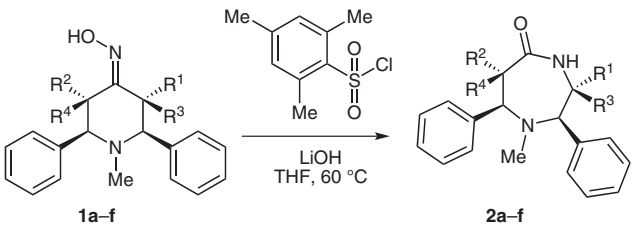


Scheme 1 Synthesis of diazepan-5-one lactams **2a–f** from piperidin-4-one oximes **1a–f**

When mesitylenesulfonyl chloride was added to a stirring THF solution of the *E*-isomer of oxime **1a** (OH *anti* to C-3),[10,11,12] in the presence of lithium hydroxide at ambient temperature, and the mixture was further stirred at the same temperature for one hour then at 60 °C for 10 hours, diazepan-5-one lactam **2a** was formed in 75% yield (Scheme 1; R^1 = Me, $R^2 = R^3 = R^4$ = H). Thus, insertion of an NH group into the bond between the imino carbon and the α-carbon bearing the methyl group, occurred during the rearrangement.

The structure of the diazepanone lactam **2a** was unequivocally established on the basis of IR, NMR, GC/MS, and elemental analysis. Representative ^{1}H NMR (**A**) and ^{13}C NMR (**B**) spectra, including the specific assignments of the lactam **2a** are shown in Figure 1.

In the ^{1}H NMR spectrum, the observed vicinal coupling constants for the hydrogens on C-7 (d, 11.0 Hz) and C-2 (d, 8.5 Hz), vicinal and geminal coupling constants for one of the hydrogens on C-6 (dd, 10.9 Hz and 14.6 Hz, respectively) and a geminal coupling constant for the second C-6 hydrogen (d, 14.6 Hz), imply that the seven-membered heterocyclic ring adopts a chair conformation with equatorial orientations of both the phenyl groups on C-7 and C-2, and the methyl group on C-3.[13] In other words, the plausible conformation of the seven-membered heterocyclic ring is a chair in which the hydrogens on C-7, C-3 and C-2 occupy axial positions. Of the hydrogens on C-6, the proton resonating as a doublet (δ = 2.49 ppm) with geminal coupling takes an equatorial orientation, while the second, which exhibits a doublet of doublet (δ = 3.29 ppm) takes an axial orientation. The axial orientation of the hydrogens on C-7, C-3, C-2, and one of the two hydrogens on C-6, has further been confirmed by NOESY experiments. In addition, the absence of any coupling for the axial hydrogen on C-7 with the equatorial hy-

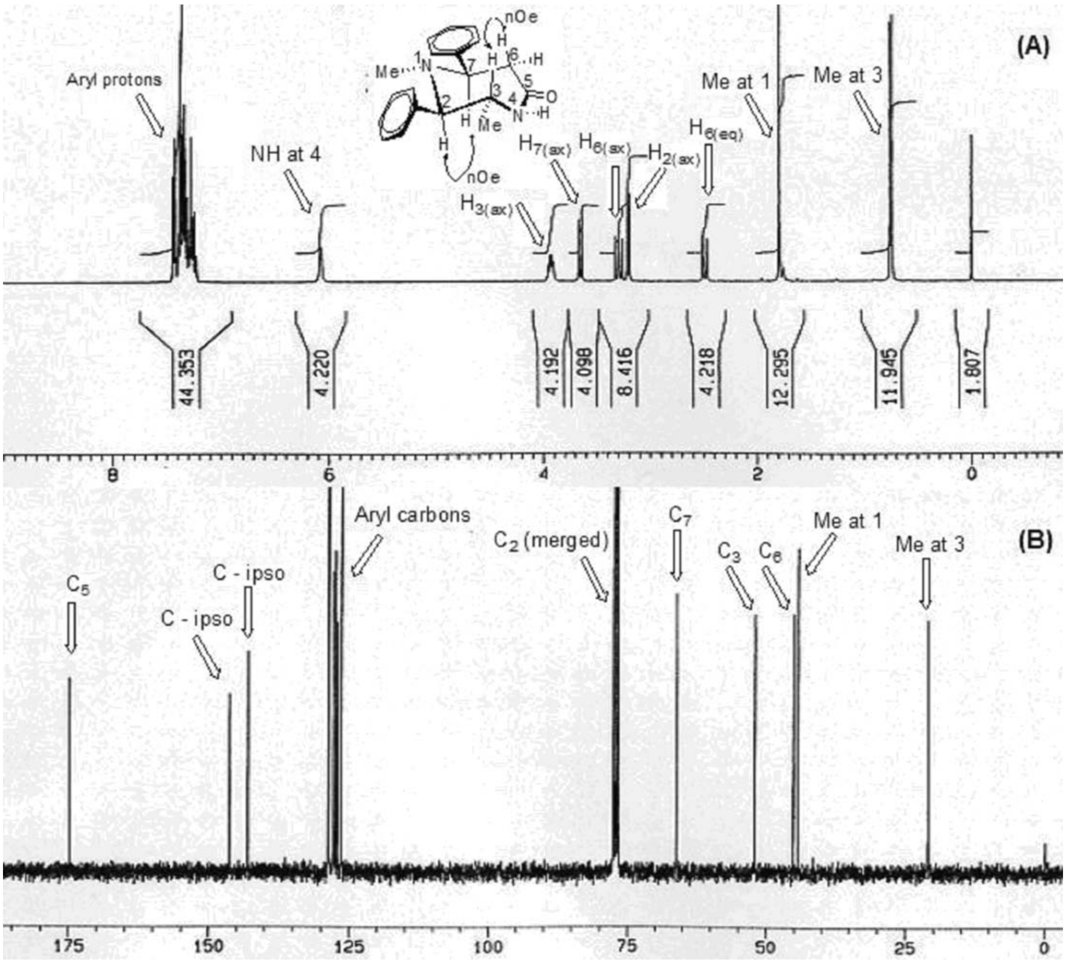


Figure 1 400 MHz ^{1}H NMR (**A**) and ^{13}C NMR (**B**) spectra of **2a** in $CDCl_3$

drogen on C-6 suggests a dihedral angle of ~90°.[13] The relative stereochemistry of **2a** is thus 2*RS*, 3*SR*, and 7*SR*.

In the ^{13}C NMR spectrum, the deshielded absorption of C-2 ($\Delta\delta$ = ~11.4 ppm) compared to that of C-7 is due to the combined effect of the equatorial methyl group at C-3 and the NH group beta to C-2, while the deshielded absorption of C-3 ($\Delta\delta$ = ~6.9 ppm) compared to that of C-6 is largely due to the α-effects of both the equatorial methyl group at C-3 and the NH group.

The assignment for the carbons C-2, C-3, C-6 and C-7 of the seven-membered heterocyclic ring of **2a** was further accomplished by their one-bond hetero-correlation (^{1}H–^{13}C COSY/HETCOR) with the associated hydrogens. The deshielding absorption of the methyl carbon on N-1, compared to the methyl carbon on C-3 is obviously due to the presence of the electronegative nitrogen and equatorial phenyl groups on both the carbons beta to the methyl group.

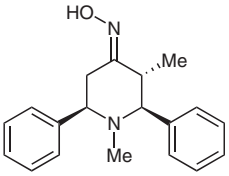
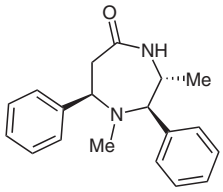
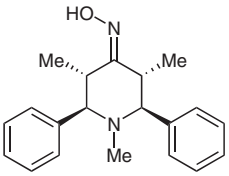
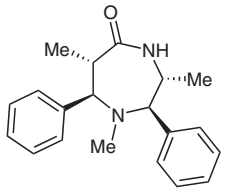
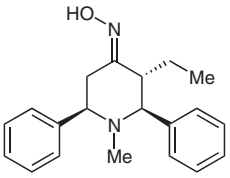
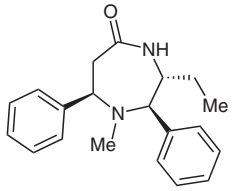
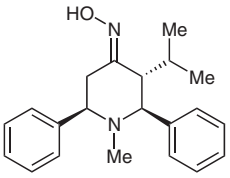
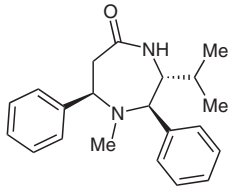
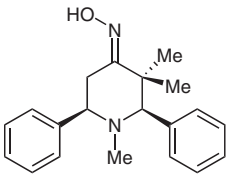
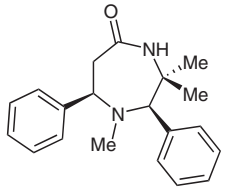
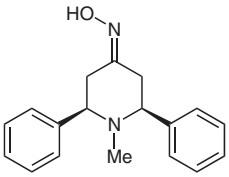
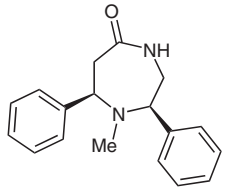
Furthermore, it is known from IR that the Bohlmann bands arise due to the interaction of the lone-pair electrons of nitrogen in its axial orientation with at least two antiperiplanar α-hydrogens.[14] Hence, in the IR spectrum of **2a**, the weak Bohlmann bands observed in the region between 2800 and 2700 cm^{-1} indicate that both the hydrogens on C-7 and C-2 are axial but that one of them is not exactly antiperiplanar to the lone-pair electrons on N-1.

The effect of various bases/reagents on the rearrangement of **1a** has also been examined. The use of tosyl chloride or

Table 1 Effect of Solvents on the Yield of the Beckmann Rearrangement of Oxime **1a**

Entry	Solvent	Temp (°C)	Time (h)	Yield (%)
1	THF	60	11.5	75
2	MeCN	60	11.5	69
3	DCE	60	11.5	57
4	DMF	60	11.5	54
5	toluene	60	11.5	52
6	acetone	reflux	11.5	48
7	*n*-hexane	60	11.5	45
8	DMA	60	11.5	31
9	1,4-dioxane	60	11.5	30
10	DMSO	60	11.5	6

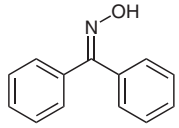
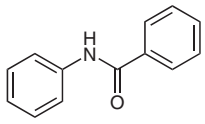
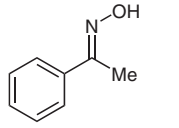
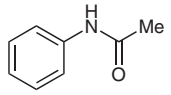
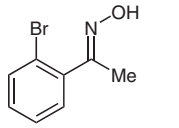
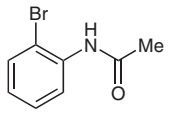
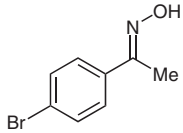
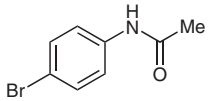
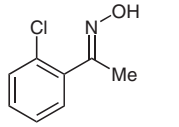
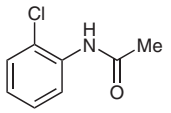
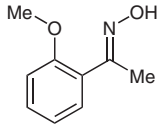
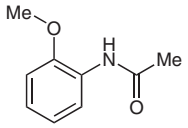
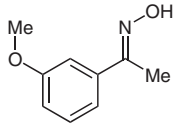
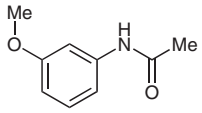
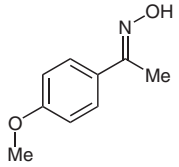
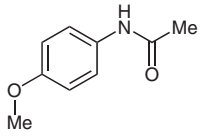
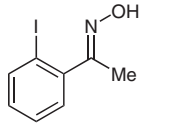
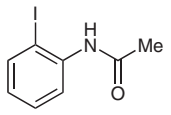
Table 2 The Yields of Diazepan-5-one Lactams **2a–f** from Piperidin-4-one Oximes **1a–f**

Entry	Oxime	Time (h)	Lactam	Yield (%)
1	 **1a** *E*-isomer	11.5	 **2a**	75
2	 **1b**	11.5	 **2b**	70
3	 **1c** *E*-isomer	13.0	 **2c**	76
4	 **1d** *E*-isomer	13.0	 **2d**	63
5	 **1e** *E*-isomer	13.0	 **2e**	59
6	 **1f**	9.5	 **2f**	83

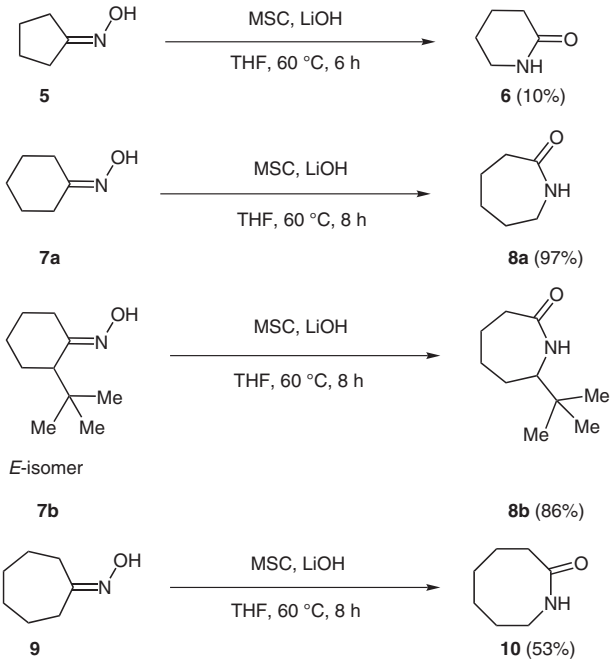
benzenesulfonyl chloride in place of mesitylenesulfonyl chloride reduced the yield of lactam formation (50 and 35%, respectively). Probably, the greater bulk of the mesitylenesulfonate of the reactant oxime has a higher propensity for leaving than tosylate and benzenesulfonate, and thus produces the lactam in better yield. Common bases such as potassium hydroxide and sodium hydroxide in place of lithium hydroxide afforded the lactam **2a** in lower yield (45 and 60%, respectively). The superiority of lithium hydroxide over sodium hydroxide and potassium hydroxide is presumably due to its facile solubility in THF; the use of a basic solvent, pyridine without lithium hydroxide provided the lactam **2a** in only 6% yield.

The effect of various solvents on the rearrangement of **1a** in the presence of lithium hydroxide was examined. Among solvents such as THF, acetonitrile, 1,2-dichloroethane (DCE), *N*,*N*-dimethylformamide (DMF), toluene, acetone, *n*-hexane, dimethylacetamide (DMA), 1,4-dioxane, and dimethylsulfoxide (DMSO), THF proved to be the most preferable (Table 1). Thus, the above reaction conditions with mesitylenesulfonyl chloride and LiOH in

Table 3 Synthesis of Amides **4a–i** from Acyclic Ketoximes **3a–i**

Entry	Oxime	Time (h)	Amide	Yield (%)
1	 **3a**	7.0	 **4a**	98
2	 **3b** *E*-isomer	7.0	 **4b**	98
3	 **3c** *E*-isomer	8.5	 **4c**	83
4	 **3d** *E*/*Z*-isomer (9.7:0.3)	8.5	 **4d**	92
5	 **3e** *E*-isomer	14.0	 **4e**	85
6	 **3f** *E*-isomer	12.0	 **4f**	89
7	 **3g** *E*/*Z*-isomer (9.8:0.2)	7.5	 **4g**	85
8	 **3h** *E*-isomer	10.0	 **4h**	98
9	 **3i** *E*-isomer	10.0	 **4i**	76

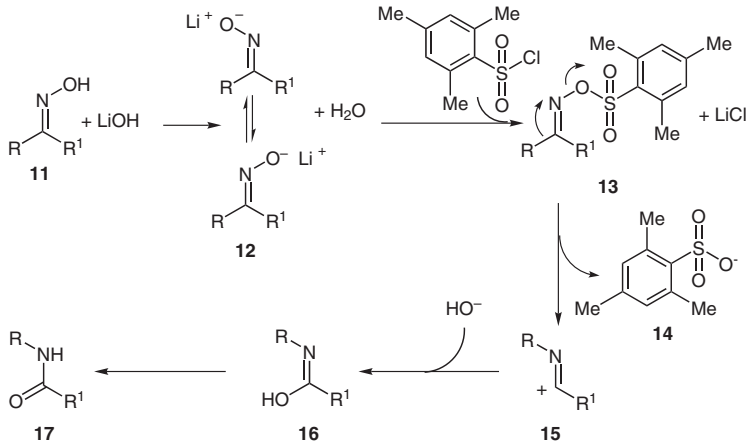
THF proved optimal for the conversion of piperidin-4-one oxime **1a** into its corresponding lactam **2a**.



Scheme 2 Synthesis of lactams from five-, six- and seven-membered carbocyclic ketoximes

Similarly, a series of piperidin-4-one oximes (**1b–f**) was smoothly transformed into their corresponding diazepanone lactams (**2b–f**) in good yields (Table 2). The NMR analyses confirmed that the diazepanone lactams **2b–f** adopt chair conformations akin to **2a** with the equatorial dispositions of all the alkyl and aryl substituents except for **2e**, in which one of the methyl groups on C-3 occupies the axial position (see the experimental section for complete characterization). The effects of substituents alpha to the oximino carbon of piperidin-4-one oxime on the rearrangement were pronounced. For example, piperidin-4-one oximes with bulky groups such as isopropyl and *gem*-dimethyl groups at the 3-position of the piperidine ring provided the corresponding lactams in lower yields (63% and 59% respectively; entries 4 and 5), while piperidin-4-one oxime without any substituent at the 3-position of the piperidine ring afforded the corresponding lactam in higher yield (83%; entry 6). Furthermore, the more substituted, electron-rich carbon exclusively migrated; an observation that is consistent with the migration to an electron-deficient species in analogy to the classical Beckmann rearrangement.

The compatibility of this method with various types of oximes, such as acyclic ketoximes and carbocyclic ketoximes, which include five-, six- and seven-membered rings, has been investigated under the optimal conditions (Scheme 2 and Table 3). All the unsymmetrical ketoximes used in this investigation possess *E*-geometric configuration except **3d** and **3g**, which possessed mainly *E*-isomers with a small amount of their *Z*-isomers (3% and 2%, respectively) as minor components. Acyclic ketoximes without substituents on the aryl moieties cleanly underwent the Beckmann rearrangement with yields of



Scheme 3 Mechanism for the Beckmann rearrangement

~98% (entries 1 and 2). However, acyclic ketoximes with *ortho* substituents on the aryl moieties provided the amides in yields of around 10–22% lower than that of the unsubstituted analogue (entries 3, 5, 6 and 9). Among the *para*-substituted aryl oximes, the one with an electron-withdrawing group afforded the amide in a yield 6% lower than that of the unsubstituted counterpart (entry 4), whereas the oxime with an electron-donating group gave the amide in a yield akin to that of the unsubstituted aryl oxime (entry 8). In the case of unsymmetrical acyclic ketoximes, exclusive migrations of electron-rich phenyl groups over alkyl groups occurred (Table 3).

Although the conversions of cyclohexanone oxime (**7a**), 2-*tert*-butylcyclohexanone oxime (**7b**), and cycloheptanone oxime (**9**) furnished their corresponding lactams in good to excellent yields under the optimal conditions, the conversion of cyclopentanone oxime (**5**) into its corresponding lactam was not as efficient (Scheme 2). For this rearrangement, neither changing to solvents such as DMF or acetonitrile nor changing the LiOH concentration gave significantly improved yields. Other reactions of the strained cyclopentanone oxime **5** probably competed with the rearrangement since, although the rearrangement yield was low, the reactant disappeared completely. The recent liquid-phase methodologies that have been developed, such as the use of rhodium complex[2] and cyanuric chloride,[3a,b] were examined for the rearrangement of cyclopentanone oxime, however, neither approaches provided the corresponding lactam. The use of an equimolar amount of cyanuric chloride in DMF (cyanuric chloride–DMF complex)[3a] afforded only trace amounts of the piperidin-2-one lactam (<5% yield). Tamura et al.[15] achieved the synthesis of piperidin-2-one lactam (**6**) in good yield (81%) directly from cyclopentanone via its oxime mesitylenesulfonate by condensing *o*-mesitylenesulfonyl hydroxylamine with cyclopentanone, followed by Beckmann rearrangement. In the case of the unsymmetrical cyclic system **7b**, the bulky and electron-rich group exclusively migrated to the nitrogen terminus of the oxime.

A general schematic representation for a plausible mechanism of Beckmann rearrangement is depicted in Scheme 3.

The intermediate, *E*-(2*RS*,3*SR*,6*SR*)-1,3-dimethyl-2,6-diphenylpiperidin-4-one oxime mesitylenesulfonate (**13a**) was isolated at lower temperature (2 °C) because of its instability at the optimized reaction temperature (see the experimental section for the detailed procedure). In the ^{1}H NMR spectrum of this intermediate, the signal for the equatorial proton on C-5 was observed at an unusual downfield region compared to the protons on C-2 and C-6, as in the case of its corresponding oxime **1a**, due to the 1,3-spatial proximity effect. This would imply that **13a** also possess *E* (*anti*) geometric configuration akin to that of its corresponding oxime **1a**. The presence of one of the intermediates in the reaction, (2*RS*,3*SR*,6*SR*)-1,3-dimethyl-2,6-diphenylpiperidin-4-one oxime mesitylenesulfonate, with *E*-geometry, supports the proposed mechanism.

In conclusion, the synthesis of diazepan-5-ones from their corresponding piperidin-4-one oximes through in situ generation of oxime mesitylenesulfonates has efficiently been accomplished. The one- and two-dimensional NMR analyses show that the conformation of all the diazepan-5-ones **2a–f** is chair, in which all the alkyl and aryl substituents occupy equatorial positions, except diazepanone **2e**, in which one of the methyl groups at C-3 occupies the axial position. This method has led to the syntheses of various amides and lactams from both acyclic and cyclic oximes, reflecting its versatility.

All reagents were purchased as reagent grade and were used without further purification. All solvents were distilled prior to use. Thin-layer chromatography (TLC) was performed on Silica gel 60 F plates eluted with the solvents indicated. Flash column chromatography was performed on Silica gel 230–400 mesh slurry packed in glass columns with the eluent systems indicated. All the reported melting points were measured in open capillaries and are uncorrected. ^{1}H NMR spectra were acquired at 400 MHz or 300 MHz, and ^{13}C NMR spectra were acquired at 100 MHz and 75 MHz using $CDCl_3$ or DMSO-d_6 as solvents (25 °C), on Bruker Avance 400 and

Varian 300 instruments. GC-MS were performed on an HP6890 and Agilent 5973N MSD instrument. IR spectra were recorded on a Mattson Galaxy 7020A FTIR spectrometer. Elemental analyses were obtained using a FISONE EA1106 instrument.

Rearrangement of Ketoximes into Lactams/Amides; General Procedure

To a solution of oxime (1.5 mmol) in THF (4 mL) in a two-necked flask equipped with reflux condenser and addition funnel under nitrogen atmosphere, was added LiOH (1.8 mmol). After being stirred for 30 min at r.t., a solution of mesitylenesulfonyl chloride (1.5 mmol) in THF (4 mL) was added and stirring was continued for 1 h at ambient temperature followed by 60 °C until the reaction was complete (monitored by TLC). The reaction was allowed to cool and quenched by addition of H_2O (10 mL). The solvents were removed under reduced pressure and then H_2O (15 mL) and Et_2O (15 mL) were added. The organic phase was separated and the aqueous phase was extracted with Et_2O (2 × 15 mL). The combined organic phases were washed with brine (2 × 10 mL), dried over Na_2SO_4 and filtered. The crude product obtained after evaporation of the filtrate was purified by flash column chromatography (CH_2Cl_2–MeOH, 100:2) to provide the lactam/amide.

(2*RS*,3*SR*,7*SR*)-1,3-Dimethyl-2,7-diphenyl[1,4]diazepan-5-one (2a, Table 2, Entry 1)

Mp 190–191 °C.

IR (KBr): 3203, 3083, 3027, 2976, 2910, 2844, 2810, 2793, 2779, 1672, 1601, 1492, 1442, 1421, 1356, 1327, 1275, 1227, 1173, 1138, 1116, 1083 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.61–7.23 (m, 10 H, ArH), 6.07 [br s, 1 H, N(4)H], 3.95–3.90 (m, 1 H, H-3_{ax}), 3.65 (d, *J* = 11.0 Hz, 1 H, H-7_{ax}), 3.29 (dd, *J* = 10.9, 14.6 Hz, 1 H, H-6_{ax}), 3.20 (d, *J* = 8.5 Hz, 1 H, H-2_{ax}), 2.49 (d, *J* = 14.6 Hz, 1 H, H-6_{eq}), 1.79 [s, 3 H, N(1)CH_3], 0.75 [d, *J* = 6.8 Hz, 3 H, C(3)CH_3].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.9 (C-5), 146.3, 143.1 (2 × C_{ipso}), 128.8, 128.6, 127.8, 127.5, 127.1, 126.4 (Ar), 77.6 (C-2), 66.2 (C-7), 52.1 (C-3), 45.2 (C-6), 44.4 [C(1)*C*H$_3$], 21.0 [C(3)*C*H$_3$].

GC-MS: *m*/*z* (%) = 294 [M^+], 281, 222, 207, 191, 176, 165, 146, 131, 120 (100), 104, 91, 77, 65, 56, 44, 32.

Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.51; H, 7.53; N, 9.52. Found: C, 77.28; H, 7.84; N, 9.52.

(2*RS*,3*SR*,6*RS*,7*SR*)-1,3,6-Trimethyl-2,7-diphenyl[1,4]diazepan-5-one (2b, Table 2, Entry 2)

Mp 197–198 °C.

IR (KBr): 3223, 3094, 3023, 2997, 2985, 2937, 2916, 2851, 2792, 2784, 1673, 1453, 1409, 1381, 1355, 1318, 1293, 1180, 1111, 1085, 1067 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.20 (m, 10 H, ArH), 5.84 [br d, 1 H, N(4)H], 4.10–3.98 (m, 1 H, H-3_{ax}), 3.40 (d, *J* = 9.6 Hz, 1 H, H-7_{ax}), 3.35–3.28 (m, 1 H, H-6_{ax}), 3.22 (d, *J* = 9.0 Hz, 1 H, H-2_{ax}), 1.80 [s, 3 H, N(1)CH_3], 0.77 [d, *J* = 6.6 Hz, 3 H, C(3)CH_3], 0.64 [d, *J* = 6.6 Hz, 3 H, C(6)CH_3].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.3 (C-5), 143.9, 143.4 (2 × C_{ipso}), 128.5, 128.3, 128.1, 127.8, 127.4, 127.1 (6 × Ar), 77.6 (C-2), 71.5 (C-7), 51.0 (C-3), 44.8 [C(1)*C*H$_3$], 41.6 (C-6), 20.7 [C(3)*C*H$_3$], 15.4 [C(6)*C*H$_3$].

GC-MS: *m*/*z* (%) = 308 [M^+], 291, 279, 265, 250, 236, 220, 208, 194, 186, 175, 165, 153, 145, 134, 120 (100), 112, 103, 91, 77, 65, 51.

Anal. Calcd for $C_{20}H_{24}N_2O$: C, 77.89; H, 7.84; N, 9.08. Found: C, 77.78; H, 8.04; N, 9.17.

(2*RS*,3*SR*,7*SR*)-3-Ethyl-1-methyl-2,7-diphenyl[1,4]diazepan-5-one (2c, Table 2, Entry 3)

Mp 183–184 °C.

IR (KBr): 3203, 3082, 3030, 2982, 2795, 2787, 1664, 1492, 1453, 1427, 1365, 1303, 1173, 1117, 1027 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.24 (m, 10 H, ArH), 6.24 [br d, 1 H, N(4)H], 3.73–3.68 (m, 1 H, H-3_{ax}), 3.65 (d, *J* = 11.0 Hz, 1 H, H-7_{ax}), 3.24 (d, *J* = 6.5 Hz, 1 H, H-2_{ax}), 3.28 (dd, *J* = 10.9, 14.7 Hz, 1 H, H-6_{ax}), 2.46 (d, *J* = 14.6 Hz, 1 H, H-6_{eq}), 1.77 [s, 3 H, C(1)CH_3], 1.07–0.96 (m, 2 H, C*H*$_2$CH$_3$), 0.80 (t, *J* = 7.3 Hz, 3 H, CH$_2$C*H*$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.3 (C-5), 146.4, 142.9 (2 × C_{ipso}), 128.8, 128.6, 128.0, 127.5, 127.1, 126.4 (6 × Ar), 76.6 (C-2), 66.5 (C-7), 58.1 (C-3), 45.2 (C-6), 44.4 [C(1)*C*H$_3$], 26.4 (*C*H$_2$CH$_3$), 10.5 (CH$_2$*C*H$_3$).

GC-MS: *m*/*z* (%) = 308 [M^+], 293, 279, 251, 222, 208, 190, 160, 131, 120 (100), 104, 91, 77, 68, 58, 42, 30.

Anal. Calcd for $C_{20}H_{24}N_2O$: C, 77.89; H, 7.84; N, 9.08. Found: C, 77.78; H, 8.02; N, 9.16.

(2*RS*,3*SR*,7*SR*)-3-Isopropyl-1-methyl-2,7-diphenyl[1,4]diazepan-5-one (2d, Table 2, Entry 4)

Mp 178–179 °C.

IR (KBr): 3222, 3086, 3029, 2969, 2884, 2798, 2782, 1670, 1490, 1454, 1418, 1360, 1297, 1262, 1132, 1076, 1013 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.26 (m, 10 H, ArH), 5.76 [br d, 1 H, N(4)H], 3.78–3.74 (m, 1 H, H-3_{ax}), 3.66 (d, *J* = 10.5 Hz, 1 H, H-7_{ax}), 3.36 (d, *J* = 9.0 Hz, 1 H, H-2_{ax}), 3.27 (dd, *J* = 11.1, 18.4 Hz, 1 H, H-6_{ax}), 2.49 (d, *J* = 18.6 Hz, 1 H, H-6_{eq}), 1.77 [s, 3 H, C(1)CH_3], 1.39–1.32 [m, 1 H, C*H*(CH$_3$)$_2$], 0.86 [d, *J* = 7.0 Hz, 3 H, CH(C*H*$_3$)$_2$], 0.80 (d, *J* = 6.5 Hz, 3 H, CH(C*H*$_3$)$_2$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.3 (C-5), 146.4, 142.7 (2 × C_{ipso}), 128.8, 128.6, 128.0, 127.5, 127.1, 126.4 (6 × Ar), 74.6 (C-2), 66.4 (C-7), 60.9 (C-3), 45.2 (C-6), 44.3 [C(1)*C*H$_3$], 28.8 [*C*H(CH$_3$)$_2$], 21.2, 14.2 [2 × CH(*C*H$_3$)$_2$].

GC-MS: *m*/*z* (%) = 322 [M^+], 307, 279, 261, 251, 231, 222, 208, 194, 175, 160, 146, 131, 120 (100), 104, 91, 77, 65, 55, 42, 30.

Anal. Calcd for $C_{21}H_{26}N_2O$: C, 78.22; H, 8.14; N, 8.69. Found: C, 78.02; H, 8.28; N, 8.78.

(2*RS*,7*SR*)-1,3,3-Trimethyl-2,7-diphenyl[1,4]diazepan-5-one (2e, Table 2, Entry 5)

Mp 198–199 °C.

IR (KBr): 3207, 3082, 3028, 2982, 2883, 2798, 2780, 1675, 1490, 1418, 1327, 1302, 1223, 1114, 1027 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.22 (m, 10 H, ArH), 6.18 [br s, 1 H, N(4)H], 3.56 (d, *J* = 12.0 Hz, 1 H, H-7_{ax}), 3.40 (s, 1 H, H-2_{ax}), 3.39–3.32 (m, 1 H, H-6_{ax}), 2.53–2.45 (m, 1 H, H-6_{eq}), 1.75 [s, 3 H, C(1)CH_3], 1.74 [s, 3 H, C(3)$CH_{3(ax)}$], 0.88 [s, 3 H, C(3)$CH_{3(eq)}$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.4 (C-5), 146.6, 142.3 (2 × C_{ipso}), 128.8, 128.7, 128.2, 127.4, 127.1, 126.4 (6 × Ar), 80.8 (C-2), 67.8 (C-7), 54.5 (C-3), 45.8 (C-6), 45.7 [C(1)*C*H$_3$], 32.9 [C(3)*C*H$_{3(ax)}$], 22.6 [C(3)*C*H$_{3(eq)}$].

GC-MS: *m*/*z* (%) = 308 [M^+], 294, 275, 265, 251, 235, 222, 208, 194, 174, 165, 152, 141, 131, 120, 106 (100), 91, 77, 68, 58, 42, 30.

Anal. Calcd for $C_{20}H_{24}N_2O$: C, 77.88; H, 7.86; N, 9.09. Found: C, 77.69; H, 8.00; N, 9.13.

(2*RS*,7*SR*)-1-Methyl-2,7-diphenyl[1,4]diazepan-5-one (2f, Table 2, Entry 6)

Mp 163–164 °C.

IR (KBr): 3230, 3086, 3032, 2846, 2796, 2788, 1705, 1490, 1453, 1422, 1354, 1330, 1261, 1141, 1114, 1075 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.23 (m, 10 H, ArH), 6.34 [br s, 1 H, N(4)H], 3.74–3.70 (m, 1 H, H-3_{ax}), 3.60 (d, *J* = 10.8 Hz, 1 H, H-7_{ax}), 3.46 (d, *J* = 9.0 Hz, 1 H, H-2_{ax}), 3.27 (dd, *J* = 10.8, 14.5 Hz, 1 H, H-6_{ax}), 3.12–3.06 (m, 1 H, H-3_{eq}), 2.51 (d, *J* = 14.6 Hz, 1 H, H-6_{eq}), 1.82 [s, 3 H, C(1)CH_3].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.8 (C-5), 145.8, 143.2 (2 × C_{ipso}), 128.9, 128.8, 127.6, 127.2, 126.8, 126.6 (6 × Ar), 72.4 (C-2), 66.1 (C-7), 49.2 (C-3), 45.3 (C-6), 43.8 [C(1)*C*H_3].

GC-MS: *m*/*z* (%) = 280 [M^+], 252, 222, 207, 177, 162, 133, 120 (100), 104, 91, 77, 65, 44, 32.

Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.29; N, 9.99. Found: C, 76.90; H, 7.43; N, 9.92.

N-Phenylbenzamide (4a, Table 3, Entry 1)[16]
^1H NMR (400 MHz, $CDCl_3$): δ = 7.91 (br s, 1 H), 7.85–7.83 (m, 2 H), 7.62 (d, *J* = 8.0 Hz, 2 H), 7.54–7.49 (m, 1 H), 7.46–7.43 (m, 2 H), 7.36–7.32 (m, 2 H), 7.14–7.11 (m, 1 H).

N-Phenylacetamide (4b, Table 3, Entry 2)[3b]
^1H NMR (400 MHz, $CDCl_3$): δ = 8.44 (br s, 1 H), 7.50 (d, *J* = 8.5 Hz, 2 H), 7.25 (t, *J* = 7.8 Hz, 2 H), 7.05 (t, *J* = 7.2 Hz, 1 H), 2.09 (s, 3 H).

N-(2-Bromophenyl)acetamide (4c, Table 3, Entry 3)[17]
^1H NMR (400 MHz, $CDCl_3$): δ = 8.31 (d, *J* = 8.5 Hz, 1 H), 7.68 (br s, 1 H), 7.54 (dd, *J* = 8.0, 1.5 Hz, 1 H), 7.31 (dt, *J* = 1.3, 8.0 Hz, 1 H), 6.99 (t, *J* = 7.3 Hz, 1 H), 2.25 (s, 3 H).

N-(4-Bromophenyl)acetamide (4d, Table 3, Entry 4)[18]
^1H NMR (400 MHz, DMSO-d_6): δ = 10.04 (br s, 1 H), 7.55 (d, *J* = 8.5 Hz, 2 H), 7.46 (d, *J* = 9.0 Hz, 2 H), 2.03 (s, 3 H).

N-(2-Chlorophenyl)acetamide (4e, Table 3, Entry 5)[19]
^1H NMR (400 MHz, $CDCl_3$): δ = 8.34 (d, *J* = 8.0 Hz, 1 H), 7.65 (br s, 1 H), 7.35 (dd, *J* = 8.0, 1.5 Hz, 1 H), 7.28–7.24 (m, 1 H), 7.03 (t, *J* = 7.3 Hz, 1 H), 2.23 (s, 3 H).

N-(2-Methoxyphenyl)acetamide (4f, Table 3, Entry 6)[3b]
^1H NMR (400 MHz, $CDCl_3$): δ = 8.36 (dd, *J* = 1.8, 7.8 Hz, 1 H), 7.77 (br s, 1 H), 7.08–6.93 (m, 2 H), 6.87 (dd, *J* = 1.8, 8.1 Hz, 1 H), 3.87 (s, 3 H), 2.21 (s, 3 H).

N-(3-Methoxyphenyl)acetamide (4g, Table 3, Entry 7)[3b]
^1H NMR (400 MHz, $CDCl_3$): δ = 7.75 (br s, 1 H), 7.29–7.17 (m, 2 H), 6.94 (d, *J* = 8.1 Hz, 1 H), 6.63 (dd, *J* = 2.1, 8.0 Hz, 1 H), 3.80 (s, 3 H), 2.17 (s, 3 H).

N-(4-Methoxyphenyl)acetamide (4h, Table 3, Entry 8)[3b]
^1H NMR (400 MHz, $CDCl_3$): δ = 7.38 (d, *J* = 9.0 Hz, 2 H), 7.06 (br s, 1 H), 6.84 (d, *J* = 9.0 Hz, 2 H), 3.80 (s, 3 H), 2.15 (s, 3 H).

N-(2-Iodophenyl)acetamide (4i, Table 3, Entry 9)[20]
^1H NMR (400 MHz, $CDCl_3$): δ = 8.19 (d, *J* = 8.0 Hz, 1 H), 7.78 (d, *J* = 8.0 Hz, 1 H), 7.46 (br s, 1 H), 7.34 (dt, *J* = 1.0, 7.8 Hz, 1 H), 6.85 (t, *J* = 7.5 Hz, 1 H), 2.24 (s, 3 H).

Piperidin-2-one (6, Scheme 2)[21]
^1H NMR (400 MHz, $CDCl_3$): δ = 7.44 (br s, 1 H), 3.34–3.29 (m, 2 H), 2.36–2.32 (m, 2 H), 2.00–1.54 (m, 4 H).

Azepan-2-one (8a, Scheme 2)[21]
^1H NMR (400 MHz, $CDCl_3$): δ = 7.46 (br s, 1 H), 3.21–3.16 (m, 2 H), 2.45–2.40 (m, 2 H), 1.75–1.71 (m, 2 H), 1.68–1.62 (m, 4 H).

7-*tert*-Butylazepan-2-one (8b, Scheme 2)[22]
^1H NMR (400 MHz, $CDCl_3$): δ = 5.68 (br s, 1 H), 3.03 (dd, *J* = 9.5, 6.0 Hz, 1 H), 2.52 (dt, *J* = 2.2, 12.8 Hz, 1 H), 2.45–2.40 (m, 1 H), 2.04–2.00 (m, 1 H), 1.97–1.92 (m, 1 H), 1.90–1.85 (m, 1 H), 1.60–1.45 (m, 2 H), 1.27–1.18 (m, 1 H), 0.96 (s, 9 H).

Azocan-2-one (10, Scheme 2)[21]
^1H NMR (400 MHz, $CDCl_3$): δ = 7.28 (br s, 1 H), 3.36–3.34 (m, 2 H), 2.44 (t, *J* = 6.5 Hz, 2 H), 1.93–1.86 (m, 2 H), 1.82–1.79 (m, 2 H), 1.63–1.58 (m, 2 H), 1.55–1.49 (m, 2 H).

***E*-(2*RS*,3*SR*,6*SR*)-1,3-Dimethyl-2,6-diphenylpiperidin-4-one Oxime Mesitylenesulfonate (13a)**
To a stirred mixture of piperidin-4-one oxime **1a** (440 mg, 1.50 mmol) and LiOH (72 mg, 3.00 mmol) in THF (6 mL) cooled to about –35 °C for 30 min, was added a solution of mesitylenesulfonyl chloride (492 mg, 2.25 mmol) in THF (6 mL). The solution was stirred at –35 °C for 1 h and then at ~2 °C for 6 h. The mixture was allowed to reach r.t. and then poured into ice-cold water. After stirring the mixture for a few minutes, a white solid was produced. Crystallization (MeOH) yielded pure **13a**.

Yield: 680 mg (95%); mp 149–150 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.28 (m, 10 H, ArH), 7.00 (s, 2 H, ArH), 3.47 (t, *J* = 12.6 Hz, 1 H, H-5_{eq}), 3.20 (d, *J* = 8.0 Hz, 1 H, H-6_{ax}), 2.86–2.83 (m, 1 H, H-2_{ax}), 2.71 (s, 1 H, H-3_{ax}), 2.67 (s, 6 H, 2 × *o*-CH_3), 2.34 (s, 3 H, *p*-CH_3), 2.30 (s, 1 H, H-5_{ax}), 1.70 [s, 3 H, C(1)CH_3], 0.69 [d, *J* = 6.0 Hz, 3 H, C(3)CH_3].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.8 (C-4), 143.7, 142.3, 141.1, 140.1, 139.2, 137.5, 131.9, 131.3, 131.1, 129.2, 129.0, 128.4, 128.1, 127.8, 127.5 (Ar), 69.6 (C-2), 68.4 (C-6), 44.1 (C-3), 41.6 [C(1)*C*H_3], 36.6 (C-5), 23.3 (2 × *o*-CH_3), 21.5 (*p*-CH_3), 12.5 [C(3)*C*H_3].

GC-MS: *m*/*z* (%) = 357 [M^+ – mesityl], 341 [sulfoxy oxime], 275 (100) [iminopiperidine], 184 [M^+ – mesitylsulfonyl], 325, 311, 261, 234, 217, 199, 185, 171, 156, 142, 129, 115, 91, 77, 63, 42.

Anal. Calcd for $C_{28}H_{32}N_2O_3S$: C, 70.56; H, 6.77; N, 5.88. Found: C, 70.65; H, 6.70; N, 5.93.

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