Expeditious Synthesis of Functionalized Piperidines by Regioselective Ring Opening of Aziridines by Enals Catalyzed by an N-Heterocyclic Carbene

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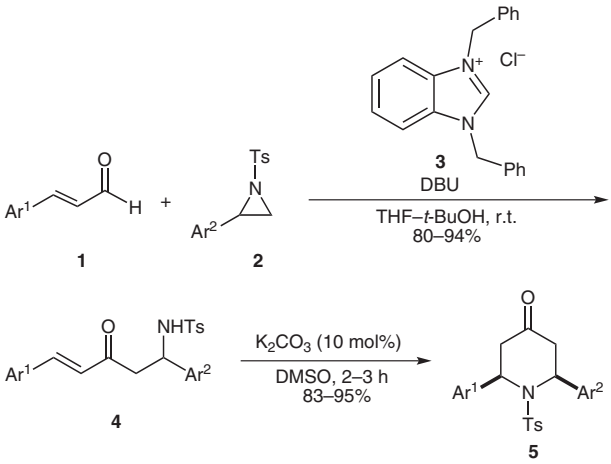
Abstract: A novel, expeditious, and diastereoselective synthesis of 2,6-disubstituted piperidin-4-ones is reported. Regioselective ring opening catalyzed by an N-heterocyclic carbene (NHC) of terminal aziridines by enals affords β′-amino α,β-unsaturated ketones, which on intramolecular aza-Michael addition in the presence of potassium carbonate furnish 2,6-disubstituted piperidin-4-ones *cis*-selectively, in excellent yields (83–95%). The protocol involves carbonyl umpolung reactivity of enals, in which the carbonyl carbon nucleophilically attacks the electrophilic terminal aziridines. The absence of byproduct formation, operational simplicity, the use of ambient temperature, high yields, and regio- and diastereoselectivity are the salient features of this procedure.

Key words: N-heterocyclic carbenes, aziridines, umpolung, enals, aza-Michael addition, piperidines

The piperidine ring is an essential building block for numerous bioactive alkaloids, natural products, and synthetic pharmaceuticals.[1] Several 2,6-disubstituted piperidine derivatives have been found to possess useful biological activities.[2] The biological activities of piperidones were found to be excellent if 2- and/or 6-positions are occupied by aryl groups.[2a,b,3] Accordingly, antibacterial and antifungal activities of 2,6-diarylpiperidin-4-ones and their derivatives have been well explored.[2b,4] Modular constructions of functionalized piperidines such as substituted piperidin-4-ones are important synthetic targets because these are intermediates for the preparation of various alkaloids and pharmaceuticals. Especially 2,6-disubstituted piperidin-4-ones are regarded as important frameworks, and serve as precursors for chiral biologically active natural alkaloids.[1h,5] As a consequence, the development of general methods for the synthesis of piperidine derivatives has been the subject of considerable synthetic effort and still requires attention.[6] Moreover, β-amino carbonyl compounds are ubiquitous in the natural product arena and have been used as building blocks for many N-containing biologically important compounds[7] such as 1,2-diamines and β-lactams.[8,9] We envisioned that intramolecular aza-Michael addition of β′-amino α,β-unsaturated ketones would be an expeditious method for direct access to the 2,6-disubstituted piperidine framework.

The inversion of standard functional group polarity, or umpolung, is a powerful strategy in chemistry, and facilitates the construction of organic molecules in unusual ways.[10,11] Over the last decade, there has been a continuously growing number of successful and novel applications of N-heterocyclic carbenes (NHCs) as organocatalysts and reagents for an expanding set of reactions.[11] NHC-catalyzed umpolung reactivity of α,β-unsaturated aldehydes (enals) via the Breslow or homoenolate intermediate and its synthetic utilization has been well documented,[12–14] where addition of an appropriate NHC to an enal renders it a d^3 nucleophile. Stetter and coworkers published as early as 1979 a few examples of the Michael addition of enals as acyl anions.[15] Since then, there have been only two reports on NHC-catalyzed umpolung reactivity of enals rendering them acyl anion equivalents (d^1 nucleophiles), although it would be of considerable synthetic utility.[16a,b]

In view of filling this remarkable gap in the literature on the synthetic utility of NHC-catalyzed acyl anion equivalent reactivity of enals, and in continuation of our ongoing efforts to develop synthetically useful processes,[16] we report herein a novel methodology developed for an efficient construction of chemically and pharmaceutically potent 2,6-disubstituted piperidin-4-ones **5**. The protocol involves intramolecular aza-Michael addition of β′-amino α,β-unsaturated ketones **4** generated by NHC-catalyzed regioselective ring opening of terminal aziridines **2** by enals **1** (Scheme 1). Recently, various NHC-catalyzed re-



Scheme 1 Synthesis of 2,6-disubstituted piperidin-4-ones **5**

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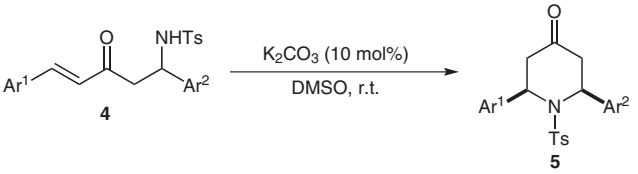
gioselective ring-opening reactions of aziridines with aldehydes, acid anhydrides, and silylated nucleophiles have been reported.[17] Several examples of intramolecular cyclization by the aza-Michael reaction have also been reported for the synthesis of substituted piperidines.[18] Interestingly, in the present study the key intermediates β′-amino ketones **4** are obtained by the carbonyl umpolung reaction of enals with terminal aziridines,[16b] which on further treatment with potassium carbonate afford 2,6-disubstituted piperidin-4-ones **5**.

To begin with, the requisite β′-amino ketones were conveniently prepared by recently reported NHC-catalyzed ring opening of aziridines[16b] (Scheme 1). Then we optimized the catalyst for the intramolecular aza-Michael addition, and found that potassium carbonate was the best among 1,8-diazabicyclo[5.4.0]undec-7-ene, 1,4-diazabicyclo[2.2.2]octane, potassium carbonate, triethylamine, and basic alumina. The effect of the solvent on the formation of **5a** ($Ar^1 = Ar^2 = Ph$; Table 1) was also examined and it was noted that dimethyl sulfoxide was the best solvent in terms of yield among the tested solvents tetrahydrofuran, dichloromethane, methanol, and dimethyl sulfoxide. The reaction was performed at room temperature. On stirring ketone **4a** ($Ar^1 = Ar^2 = Ph$) in dimethyl sulfoxide with five mol% of potassium carbonate at room temperature for 15 hours, the corresponding piperidin-4-one **5a** was obtained only in moderate yield (51%). When the catalyst loading was increased to ten mol%, we found that the reaction conversion was completed within three hours to give an excellent yield (91%) of **5a**. However, on further increasing the catalyst loading to 15 mol%, no improvement in the yield was noticed. Therefore, ten mol% of potassium carbonate in dimethyl sulfoxide was used for the intramolecular aza-Michael addition step.

Table 1 Intramolecular Aza-Michael Addition of β′-Amino Ketones **4** Leading to 2,6-Disubstituted Piperidin-4-ones **5**



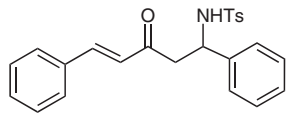
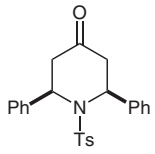
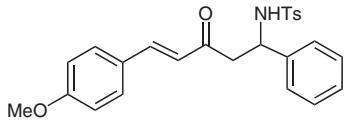
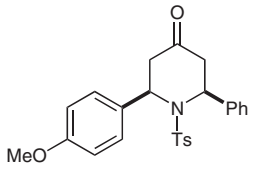
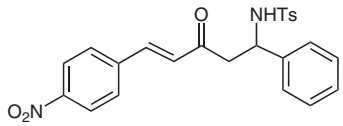
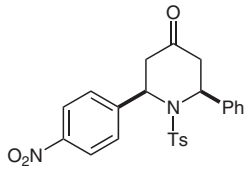
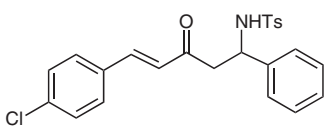
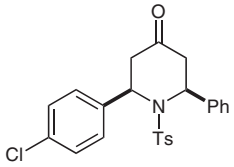
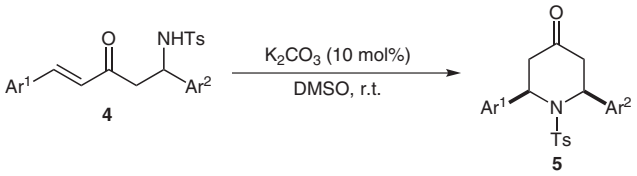
Entry	β′-Amino ketone **4**	Time[a] (h)	Piperidin-4-one **5**	Yield[b,c] (%)
1	 **4a**	3	 **5a**	91
2	 **4b**	2	 **5b**	91
3	 **4c**	2	 **5c**	88
4	 **4d**	3	 **5d**	90

Table 1 Intramolecular Aza-Michael Addition of β′-Amino Ketones **4** Leading to 2,6-Disubstituted Piperidin-4-ones **5** (continued)



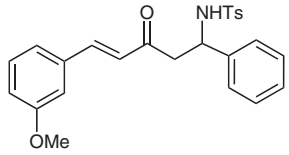
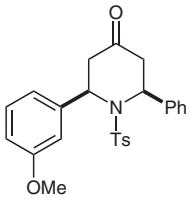
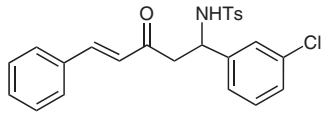
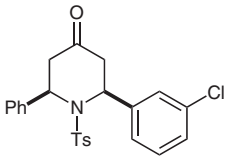
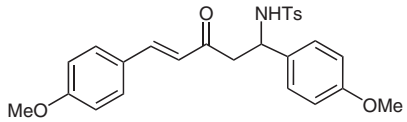
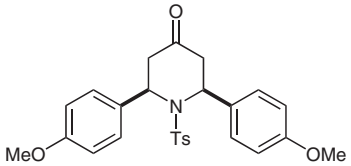
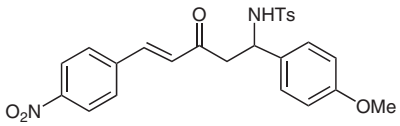
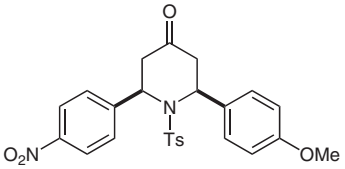
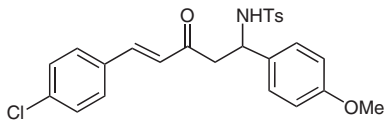
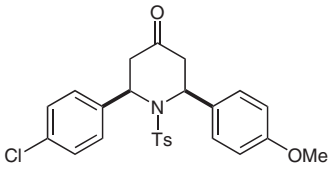
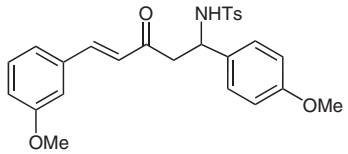
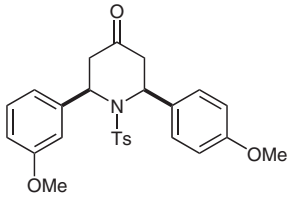
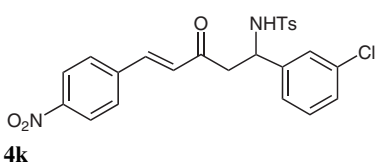
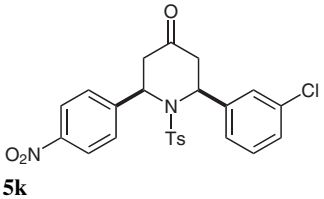
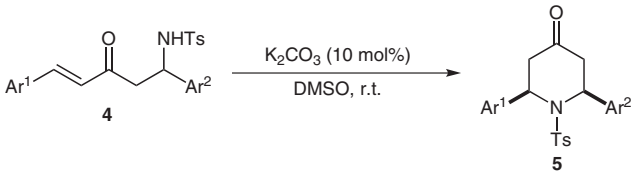
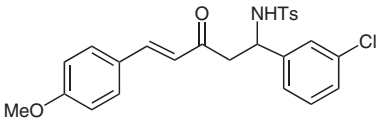
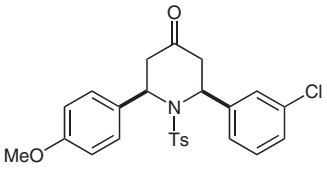
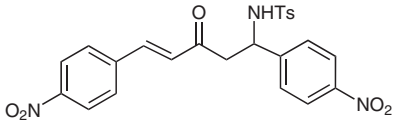
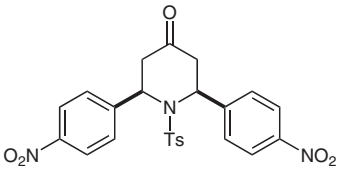
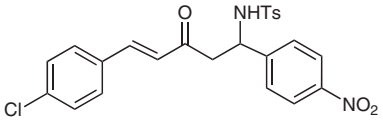
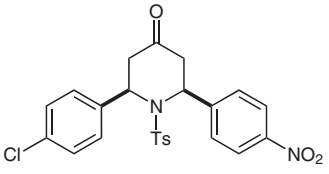
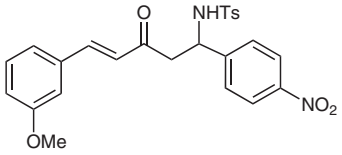
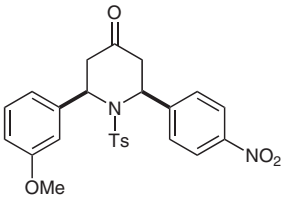
Entry	β′-Amino ketone **4**	Time[a] (h)	Piperidin-4-one **5**	Yield[b,c] (%)
5	 **4e**	2	 **5e**	83
6	 **4f**	3	 **5f**	92
7	 **4g**	3	 **5g**	88
8	 **4h**	2	 **5h**	95
9	 **4i**	2	 **5i**	94
10	 **4j**	2	 **5j**	90
11	 **4k**	3	 **5k**	93

Table 1 Intramolecular Aza-Michael Addition of β′-Amino Ketones **4** Leading to 2,6-Disubstituted Piperidin-4-ones **5** (continued)



Entry	β′-Amino ketone **4**	Time[a] (h)	Piperidin-4-one **5**	Yield[b,c] (%)
12	 **4l**	2	 **5l**	93
13	 **4m**	2	 **5m**	92
14	 **4n**	2	 **5n**	90
15	 **4o**	3	 **5o**	89

[a] Stirring time at r.t.
[b] Yield of isolated and purified product.
[c] All compounds gave satisfactory elemental analysis (C, H, and N; ±0.38%) and spectral (IR, ^{1}H NMR, ^{13}C NMR, and EIMS) data.

Next, we probed the scope of this reaction by using the optimized reaction conditions with a variety of intermediate ketones **4** (Table 1). We were successful at preparing a library of 15 piperidin-4-ones in excellent yields (83–95%), with **5h** obtained in the highest yield of 95% (Table 1, entry 8). It was gratifying to find that the formation of the 2,6-disubstituted piperidin-4-ones **5** was entirely diastereoselective in favor of the *cis* isomer. The relative stereochemistry of **5** was established by NOE experiments (Figure 1). Strong NOE (5.6–6.1%) was observed between H-2 and H-6 of products **5**, which conclusively demonstrates their *cis* stereochemistry.

In summary, we have developed a convenient and efficient synthetic route to piperidin-4-ones from aziridines. The protocol also fills a remarkable gap in the literature on the synthetic utility of NHC-catalyzed acyl anion equivalent reactivity of enals. The present atom-economic and workable methodology would be a practical alternative to the existing procedures for the synthesis of this kind of fine chemicals.

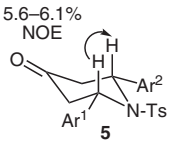


Figure 1

Melting points were determined by the open glass capillary method and are uncorrected. IR spectra of samples prepared in KBr were recorded on a Perkin-Elmer 993 IR spectrophotometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker WM-40 C FT spectrometer, with TMS as internal reference. Mass spectra were recorded on a JEOL D-300 mass spectrometer. Elemental analyses were carried out in a Coleman automatic carbon, hydrogen, and nitrogen analyzer. All chemicals used were reagent

grade and were used as received without further purification. Silica gel-G was used for TLC.

2,6-Disubstituted Piperidin-4-ones 5; General Procedure

A mixture of β′-amino-α,β-unsaturated ketone **4** (0.5 mmol) and K_2CO_3 (0.05 mmol) in DMSO (1 mL) was stirred at r.t. for 2–3 h. After completion of the reaction as indicated by TLC, the reaction mixture was diluted with EtOAc (3 mL) and washed with H_2O (3 × 5 mL). The volatiles were evaporated under reduced pressure to leave a crude product, which was purified by flash column chromatography (silica gel, hexane–EtOAc, 10:1); this afforded analytically pure piperidinones **5**.

2,6-Diphenyl-1-tosylpiperidin-4-one (5a)

Colorless solid; yield: 0.184 g (91%); mp 109–110 °C.

IR (KBr): 3021 (C–H_{arom}), 2920 (C–$H_{aliphatic}$), 1705 (C=O), 1605, 1581, 1455 (C=C_{arom}), 1321, 1155 (SO_2) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.38 (s, 3 H, Me), 2.85–2.91 (m, 4 H, 2 × CH_2), 4.24 (dd, *J* = 11.6, 3.8 Hz, 2 H, H-2, H-6), 7.07–7.27 (m, 10 H, ArH), 7.33 (d, *J* = 8.5 Hz, 2 H, ArH, 4-MeC_6H_4), 7.69 (d, *J* = 8.5 Hz, 2 H, ArH, 4-MeC_6H_4).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.8 (Me), 44.2 (C-5), 45.1 (C-3), 51.8 (C-6), 52.5 (C-2), 126.5, 127.2, 127.9, 128.6, 129.1, 129.7, 130.5, 131.2, 135.7, 136.5, 137.2, 139.3 (2 × Ph, 4-MeC_6H_4), 205.5 (C=O).

MS (EI): *m*/*z* = 405 [M^+].

Anal. Calcd for $C_{24}H_{23}NO_3S$: C, 71.09; H, 5.72; N, 3.45. Found: C, 71.31; H, 5.91; N, 3.28.

2-(4-Methoxyphenyl)-6-phenyl-1-tosylpiperidin-4-one (5b)

Colorless solid; yield: 0.197 g (91%); mp 147–149 °C.

IR (KBr): 3027 (C–H_{arom}), 2928 (C–$H_{aliphatic}$), 1695 (C=O), 1608, 1585, 1451 (C=C_{arom}), 1325, 1159 (SO_2) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.41 (s, 3 H, Me), 2.81–2.92 (m, 4 H, 2 × CH_2), 3.81 (s, 3 H, OMe), 3.98 (dd, *J* = 12.5, 2.8 Hz, 1 H, H-6), 4.15 (dd, *J* = 11.5, 3.4 Hz, 1 H, H-2), 6.98 (d, *J* = 8.7 Hz, 2 H, ArH, 4-$MeOC_6H_4$), 7.06–7.22 (m, 5 H, ArH, Ph), 7.26 (d, *J* = 8.7 Hz, 2 H, ArH, 4-$MeOC_6H_4$), 7.34 (d, *J* = 8.4 Hz, 2 H, ArH, 4-MeC_6H_4), 7.71 (d, *J* = 8.4 Hz, 2 H, ArH, 4-MeC_6H_4).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.5 (Me), 44.7 (C-5), 46.5 (C-3), 51.2 (C-6), 53.9 (OMe), 58.7 (C-2), 121.2, 126.6, 127.3, 127.9, 128.5, 129.3, 130.0, 130.8, 135.5, 139.1, 140.1, 156.5 (Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$), 205.5 (C=O).

MS (EI): *m*/*z* = 435 [M^+].

Anal. Calcd for $C_{25}H_{25}NO_4S$: C, 68.94; H, 5.79; N, 3.22. Found: C, 68.59; H, 5.58; N, 3.13.

2-(4-Nitrophenyl)-6-phenyl-1-tosylpiperidin-4-one (5c)

Colorless solid; yield: 0.198 g (88%); mp 160–162 °C.

IR (KBr): 3022 (C–H_{arom}), 2921 (C–$H_{aliphatic}$), 1706 (C=O), 1603, 1579, 1458 (C=C_{arom}), 1320, 1153 (SO_2) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.40 (s, 3 H, Me), 2.88–2.91 (m, 4 H, 2 × CH_2), 4.02 (dd, *J* = 12.0, 2.6 Hz, 1 H, H-6), 4.19 (dd, *J* = 11.3, 3.9 Hz, 1 H, H-2), 7.03–7.27 (m, 5 H, ArH, Ph), 7.35 (d, *J* = 8.5 Hz, 2 H, ArH, 4-MeC_6H_4), 7.61 (d, *J* = 8.7 Hz, 2 H, ArH, 4-$O_2NC_6H_4$), 7.71 (d, *J* = 8.5 Hz, 2 H, ArH, 4-MeC_6H_4), 8.19 (d, *J* = 8.7 Hz, 2 H, ArH, 4-$O_2NC_6H_4$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.3 (Me), 44.5 (C-5), 48.3 (C-3), 51.5 (C-6), 58.9 (C-2), 126.2, 126.8, 127.4, 128.1, 128.8, 129.4, 130.5, 131.2, 135.5, 139.1, 140.8, 145.2 (Ph, 4-MeC_6H_4, 4-$O_2NC_6H_4$), 205.9 (C=O).

MS (EI): *m*/*z* = 450 [M^+].

Anal. Calcd for $C_{24}H_{22}N_2O_5S$: C, 63.98; H, 4.92; N, 6.22. Found: C, 64.33; H, 4.79; N, 6.39.

2-(4-Chlorophenyl)-6-phenyl-1-tosylpiperidin-4-one (5d)

Colorless solid; yield: 0.197 g (90%); mp 139–141 °C.

IR (KBr): 3017 (C–H_{arom}), 2923 (C–$H_{aliphatic}$), 1708 (C=O), 1599, 1585, 1457 (C=C_{arom}), 1322, 1156 (SO_2) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.37 (s, 3 H, Me), 2.09–2.95 (m, 4 H, 2 × CH_2), 3.95 (dd, *J* = 12.5, 2.8 Hz, 1 H, H-6), 4.11 (dd, *J* = 11.5, 3.9 Hz, 1 H, H-2), 6.96 (d, *J* = 8.5 Hz, 2 H, ArH, 4-ClC_6H_4), 7.05–7.21 (m, 5 H, ArH, Ph), 7.25 (d, *J* = 8.5 Hz, 2 H, ArH, 4-ClC_6H_4), 7.32 (d, *J* = 8.7 Hz, 2 H, ArH, 4-MeC_6H_4), 7.70 (d, *J* = 8.7 Hz, 2 H, ArH, 4-MeC_6H_4).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.9 (Me), 44.8 (C-5), 46.9 (C-3), 51.5 (C-6), 60.4 (C-2), 125.8, 126.5, 127.1, 127.7, 128.5, 129.2, 130.6, 132.1, 134.8, 135.7, 139.1, 139.9 (Ph, 4-MeC_6H_4, 4-ClC_6H_4), 205.5 (C=O).

MS (EI): *m*/*z* = 439 [M^+], 441 [M^+ + 2].

Anal. Calcd for $C_{24}H_{22}ClNO_3S$: C, 65.52; H, 5.04; N, 3.18. Found: C, 65.39; H, 5.31; N, 3.01.

2-(3-Methoxyphenyl)-6-phenyl-1-tosylpiperidin-4-one (5e)

Colorless solid; yield: 0.180 g (83%); mp 151–153 °C.

IR (KBr): 3025 (C–H_{arom}), 2931 (C–$H_{aliphatic}$), 1703 (C=O), 1605, 1585, 1449 (C=C_{arom}), 1321, 1151 (SO_2) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.39 (s, 3 H, Me), 2.80–2.89 (m, 4 H, 2 × CH_2), 3.79 (s, 3 H, OMe), 3.99 (dd, 1 H, *J* = 12.5, 2.6 Hz, H-6), 4.11 (dd, *J* = 11.5, 3.2 Hz, 1 H, H-2), 6.98–7.31 (m, 9 H, ArH, Ph, 3-$MeOC_6H_4$), 7.31 (d, *J* = 8.5 Hz, 2 H, ArH, 4-MeC_6H_4), 7.72 (d, *J* = 8.5 Hz, 2 H, ArH, 4-MeC_6H_4).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.5 (Me), 45.1 (C-5), 47.2 (C-3), 52.0 (C-6), 55.3 (OMe), 59.3 (C-2), 117.3, 126.2, 126.9, 127.5, 128.4, 129.2, 129.9, 130.5, 131.2, 135.9, 137.5, 139.1, 140.4, 157.1 (Ph, 4-MeC_6H_4, 3-$MeOC_6H_4$), 206.2 (C=O).

MS (EI): *m*/*z* = 435 [M^+].

Anal. Calcd for $C_{25}H_{25}NO_4S$: C, 68.94; H, 5.79; N, 3.22. Found: C, 69.13; H, 5.65; N, 3.57.

2-(3-Chlorophenyl)-6-phenyl-1-tosylpiperidin-4-one (5f)

Colorless solid; yield: 0.201 g (92%); mp 103–105 °C.

IR (KBr): 3019 (C–H_{arom}), 2928 (C–$H_{aliphatic}$), 1702 (C=O), 1608, 1581, 1455 (C=C_{arom}), 1320, 1155 (SO_2) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.43 (s, 3 H, Me), 2.81–2.94 (m, 4 H, 2 × CH_2), 4.01 (dd, *J* = 12.4, 2.8 Hz, 1 H, H-6), 4.23 (dd, *J* = 11.9, 3.5 Hz, 1 H, H-2), 7.01–7.31 (m, 9 H, ArH, Ph, 3-ClC_6H_4), 7.34 (d, *J* = 8.4 Hz, 2 H, ArH, 4-MeC_6H_4), 7.74 (d, *J* = 8.4 Hz, 2 H, ArH, 4-MeC_6H_4).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.3 (Me), 44.5 (C-5), 46.5 (C-3), 51.6 (C-6), 58.8 (C-2), 121.2, 124.8, 125.9, 126.5, 127.1, 128.5, 129.4, 130.2, 131.3, 135.7, 136.4, 138.1, 139.2, 140.4 (Ph, 4-MeC_6H_4, 3-ClC_6H_4), 206.8 (C=O).

MS (EI): *m*/*z* = 439 [M^+].

Anal. Calcd for $C_{24}H_{22}ClNO_3S$: C, 65.52; H, 5.04; N, 3.18. Found: C, 65.19; H, 5.28; N, 3.39.

2,6-Bis(4-methoxyphenyl)-1-tosylpiperidin-4-one (5g)

Colorless solid; yield: 0.204 g (88%); mp 119–121 °C.

IR (KBr): 3011 (C–H_{arom}), 2925 (C–$H_{aliphatic}$), 1699 (C=O), 1603, 1585, 1459 (C=C_{arom}), 1326, 1154 (SO_2) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.40 (s, 3 H, Me), 2.79–2.90 (m, 4 H, 2 × CH_2), 3.81 (s, 3 H, OMe), 3.85 (s, 3 H, OMe), 4.19 (dd,

J = 11.2, 3.5 Hz, 2 H, H-2, H-6), 7.02 (d, J = 8.6 Hz, 4 H, ArH, 2 × 4-MeOC_6H_4), 7.21 (d, J = 8.6 Hz, 4 H, ArH, 2 × 4-MeOC_6H_4), 7.33 (d, J = 8.5 Hz, 2 H, ArH, 4-MeC_6H_4), 7.72 (d, J = 8.5 Hz, 2 H, ArH, 4-MeC_6H_4).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.1 (Me), 44.7 (C-5), 45.5 (C-6), 46.6 (C-3), 54.2 (OMe), 55.0 (OMe), 58.9 (C-2), 117.3, 118.5, 126.2, 127.1, 128.6, 129.4, 131.2, 135.6, 140.3, 130.5, 156.3, 157.1 (4-MeC_6H_4, 2 × 4-MeOC_6H_4), 207.7 (C=O).

MS (EI): m/z = 465 [M$^+$].

Anal. Calcd for $C_{26}H_{27}NO_5S$: C, 67.08; H, 5.85; N, 3.01. Found: C, 66.79; H, 5.96; N, 2.88.

2-(4-Methoxyphenyl)-6-(4-nitrophenyl)-1-tosylpiperidin-4-one (5h)

Colorless solid; yield: 0.228 g (95%); mp 143–145 °C.

IR (KBr): 3021 (C–H_{arom}), 2920 (C–$H_{aliphatic}$), 1705 (C=O), 1608, 1587, 1456 (C=C_{arom}), 1319, 1152 (SO_2) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.38 (s, 3 H, Me), 2.68–2.92 (m, 4 H, 2 × CH_2), 3.78 (s, 3 H, OMe), 3.93 (dd, J = 12.3, 2.9 Hz, 1 H, H-6), 4.21 (dd, J = 11.4, 3.8 Hz, 1 H, H-2), 7.04 (d, J = 8.7 Hz, 2 H, ArH, 4-MeOC_6H_4), 7.23 (d, J = 8.7 Hz, 2 H, ArH, 4-MeOC_6H_4), 7.32 (d, J = 8.6 Hz, 2 H, ArH, 4-MeC_6H_4), 7.59 (d, J = 8.9 Hz, 2 H, ArH, 4-$O_2NC_6H_4$), 7.74 (d, J = 8.6 Hz, 2 H, ArH, 4-MeC_6H_4), 8.20 (d, J = 8.9 Hz, 2 H, ArH, 4-$O_2NC_6H_4$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.8 (Me), 45.5 (C-5), 46.9 (C-3), 52.8 (C-6), 54.9 (OMe), 60.3 (C-2), 118.2, 125.6, 126.4, 127.1, 128.7, 129.4, 130.3, 135.7, 140.5, 143.6, 145.5, 155.5 (4-MeC_6H_4, 4-MeOC_6H_4, 4-$O_2NC_6H_4$), 207.1 (C=O).

MS (EI): m/z = 480 [M$^+$].

Anal. Calcd for $C_{25}H_{24}N_2O_6S$: C, 62.49; H, 5.03; N, 5.83. Found: C, 62.31; H, 4.31; N, 5.59.

2-(4-Chlorophenyl)-6-(4-methoxyphenyl)-1-tosylpiperidin-4-one (5i)

Colorless solid; yield: 0.220 g (94%); mp 136–138 °C.

IR (KBr): 3023 (C–H_{arom}), 2919 (C–$H_{aliphatic}$), 1705 (C=O), 1605, 1585, 1455 (C=C_{arom}), 1322, 1157 (SO_2) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.42 (s, 3 H, Me), 2.79–2.90 (m, 4 H, 2 × CH_2), 3.80 (s, 3 H, OMe), 3.96 (dd, J = 12.5, 2.6 Hz, 1 H, H-6), 4.18 (dd, J = 11.7, 3.9 Hz, 1 H, H-2), 6.95 (d, J = 8.8 Hz, 2 H, ArH, 4-ClC_6H_4), 7.02 (d, J = 8.7 Hz, 2 H, ArH, 4-MeOC_6H_4), 7.21 (d, J = 8.7 Hz, 2 H, ArH, 4-MeOC_6H_4), 7.25 (d, J = 8.8 Hz, 2 H, ArH, 4-ClC_6H_4), 7.36 (d, J = 8.5 Hz, 2 H, ArH, 4-MeC_6H_4), 7.71 (d, J = 8.5 Hz, 2 H, ArH, 4-MeC_6H_4).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.0 (Me), 45.3 (C-5), 47.8 (C-3), 51.3 (C-6), 54.5 (OMe), 59.1 (C-2), 117.8, 126.5, 127.2, 127.9, 130.5, 131.1, 131.9, 132.9, 135.1, 136.4, 139.7, 156.2 (4-MeC_6H_4, 4-MeOC_6H_4, 4-ClC_6H_4), 205.9 (C=O).

MS (EI): m/z = 469 [M$^+$], 471 [M$^+$ + 2].

Anal. Calcd for $C_{25}H_{24}ClNO_4S$: C, 63.89; H, 5.15; N, 2.98. Found: C, 63.61; H, 5.01; N, 3.36.

2-(3-Methoxyphenyl)-6-(4-methoxyphenyl)-1-tosylpiperidin-4-one (5j)

Colorless solid; yield: 0.209 g (90%); mp 149–151 °C.

IR (KBr): 3025 (C–H_{arom}), 2923 (C–$H_{aliphatic}$), 1707 (C=O), 1603, 1588, 1452 (C=C_{arom}), 1321, 1155 (SO_2) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.41 (s, 3 H, Me), 2.81–2.95 (m, 4 H, 2 × CH_2), 3.79 (s, 3 H, OMe), 3.91 (s, 3 H, OMe), 4.03 (dd, J = 12.5, 2.3 Hz, 1 H, H-6), 4.27 (dd, J = 11.5, 3.4 Hz, 1 H, H-2), 6.97 (d, J = 8.7 Hz, 2 H, ArH, 4-MeOC_6H_4), 7.02–7.21 (m, 4 H, ArH, 3-MeOC_6H_4), 7.24 (d, J = 8.7 Hz, 2 H, ArH, 4-MeOC_6H_4), 7.31 (d, J = 8.5 Hz, 2 H, ArH, 4-MeC_6H_4), 7.69 (d, J = 8.5 Hz, 2 H, ArH, 4-MeC_6H_4).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.7 (Me), 45.0 (C-5), 46.6 (C-3), 51.7 (C-6), 54.1 (OMe), 54.9 (OMe), 60.3 (C-2), 115.8, 117.7, 118.9, 126.5, 127.3, 127.9, 128.6, 129.7, 130.4, 135.9, 138.3, 140.5, 155.1, 156.8 (4-MeOC_6H_4, 3-MeOC_6H_4, 4-MeC_6H_4), 207.5 (C=O).

MS (EI): m/z = 465 [M$^+$].

Anal. Calcd for $C_{26}H_{27}NO_5S$: C, 67.08; H, 5.85; N, 3.01. Found: C, 66.91; H, 5.63; N, 3.36.

2-(3-Chlorophenyl)-6-(4-nitrophenyl)-1-tosylpiperidin-4-one (5k)

Colorless solid; yield: 0.225 g (93%); mp 125–127 °C.

IR (KBr): 3021 (C–H_{arom}), 2928 (C–$H_{aliphatic}$), 1703 (C=O), 1598, 1581, 1451 (C=C_{arom}), 1325, 1151 (SO_2) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 2.35 (s, 3 H, Me), 2.80–2.97 (m, 4 H, 2 × CH_2), 4.07 (dd, J = 12.4, 2.5 Hz, 1 H, H-6), 4.25 (dd, J = 11.6, 3.8 Hz, 1 H, H-2), 7.03–7.26 (m, 4 H, ArH, 3-ClC_6H_4), 7.33 (d, J = 8.5 Hz, 2 H, ArH, 4-MeC_6H_4), 7.58 (d, J = 8.8 Hz, 2 H, ArH, 4-$O_2NC_6H_4$), 7.72 (d, J = 8.5 Hz, 2 H, ArH, 4-MeC_6H_4), 8.18 (d, J = 8.8 Hz, 2 H, ArH, 4-$O_2NC_6H_4$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.5 (Me), 45.8 (C-5), 47.5 (C-3), 52.5 (C-6), 60.1 (C-2), 122.5, 126.2, 127.5 128.1, 128.8, 129.7, 130.6, 131.4 133.6, 135.6, 136.4, 140.9, 143.5, 145.2 (3-ClC_6H_4, 4-$O_2NC_6H_4$, 4-MeC_6H_4), 205.4 (C=O).

MS (EI): m/z = 484 [M$^+$].

Anal. Calcd for $C_{24}H_{21}ClN_2O_5S$: C, 59.44; H, 4.36; N, 5.78. Found: C, 59.78; H, 4.53; N, 5.59.

2-(3-Chlorophenyl)-6-(4-methoxyphenyl)-1-tosylpiperidin-4-one (5l)

Colorless solid; yield: 0.218 g (93%); mp 122–124 °C.

IR (KBr): 3019 (C–H_{arom}), 2921 (C–$H_{aliphatic}$), 1702 (C=O), 1601, 1589, 1455 (C=C_{arom}), 1324, 1151 (SO_2) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.39 (s, 3 H, Me), 2.79–2.94 (m, 4 H, 2 × CH_2), 3.85 (s, 3 H, OMe), 3.95 (dd, J = 12.8, 2.9 Hz, 1 H, H-6), 4.19 (dd, J = 11.5, 3.6 Hz, 1 H, H-2), 6.98 (d, J = 8.7 Hz, 2 H, ArH, 4-MeOC_6H_4), 7.02–7.21 (m, 4 H, ArH, 3-ClC_6H_4), 7.25 (d, J = 8.7 Hz, 2 H, ArH, 4-MeOC_6H_4), 7.32 (d, J = 8.5 Hz, 2 H, ArH, 4-MeC_6H_4), 7.68 (d, J = 8.5 Hz, 2 H, ArH, 4-MeC_6H_4).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.4 (Me), 44.5 (C-5), 47.2 (C-3), 51.2 (C-6), 54.3 (OMe), 60.8 (C-2), 117.2, 124.9, 125.6, 126.4, 127.2, 127.9, 128.8, 129.9, 130.7, 131.5, 135.5, 138.7, 140.2, 155.4 (4-MeOC_6H_4, 3-ClC_6H_4, 4-MeC_6H_4), 207.1 (C=O).

MS (EI): m/z = 469 [M$^+$].

Anal. Calcd for $C_{25}H_{24}ClNO_4S$: C, 63.89; H, 5.51; N, 2.98. Found: C, 63.13; H, 5.21; N, 3.19.

2,6-Bis(4-nitrophenyl)-1-tosylpiperidin-4-one (5m)

Colorless solid; yield: 0.227 g (92%); mp 123–125 °C.

IR (KBr): 3021 (C–H_{arom}), 2925 (C–$H_{aliphatic}$), 1706 (C=O), 1605, 1585, 1459 (C=C_{arom}), 1322, 1157 (SO_2) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.44 (s, 3 H, Me), 2.82–2.93 (m, 4 H, 2 × CH_2), 4.27 (dd, J = 11.5, 3.8 Hz, 2 H, H-2, H-6), 7.32 (d, J = 8.7 Hz, 2 H, ArH, 4-MeC_6H_4), 7.56 (d, J = 8.8 Hz, 4 H, ArH, 2 × 4-$O_2NC_6H_4$), 7.71 (d, J = 8.7 Hz, 2 H, ArH, 4-MeC_6H_4), 8.21 (d, J = 8.8 Hz, 4 H, ArH, 2 × 4-$O_2NC_6H_4$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.2 (Me), 44.3 (C-5), 45.0 (C-6), 47.3 (C-3), 58.7 (C-2), 121.7, 122.3, 127.9, 128.6, 129.3, 130.5, 135.7, 139.8, 143.1, 143.9, 144.7, 145.8 (2 × 4-$O_2NC_6H_4$, 4-MeC_6H_4), 206.2 (C=O).

MS (EI): *m*/*z* = 495 [M$^+$].

Anal. Calcd for $C_{24}H_{21}N_3O_7S$: C, 58.17; H, 4.27; N, 8.48. Found: C, 57.79; H, 4.11; N, 8.72.

2-(4-Chlorophenyl)-6-(4-nitrophenyl)-1-tosylpiperidin-4-one (5n)

Colorless solid; yield: 0.217 g (90%); mp 155–157 °C.

IR (KBr): 3025 (C–H_{arom}), 2932 (C–$H_{aliphatic}$), 1706 (C=O), 1608, 1588, 1450 (C=C_{arom}), 1321, 1152 (SO_2) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.41 (s, 3 H, Me), 2.70–2.88 (m, 4 H, 2 × CH_2), 3.99 (dd, *J* = 12.5, 2.6 Hz, 1 H, H-6), 4.25 (dd, *J* = 11.7, 3.5 Hz, 1 H, H-2), 7.03 (d, *J* = 8.7 Hz, 2 H, ArH, 4-ClC_6H_4), 7.23 (d, *J* = 8.7 Hz, 2 H, ArH, 4-ClC_6H_4), 7.34 (d, *J* = 8.5 Hz, 2 H, ArH, 4-MeC_6H_4), 7.58 (d, *J* = 8.8 Hz, 2 H, ArH, 4-$O_2NC_6H_4$), 7.68 (d, *J* = 8.5 Hz, 2 H, ArH, 4-MeC_6H_4), 8.18 (d *J* = 8.8 Hz, 2 H, ArH, 4-$O_2NC_6H_4$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.1 (Me), 45.2 (C-5), 46.8 (C-3), 52.5 (C-6), 60.4 (C-2), 122.2, 126.8, 128.5, 129.1, 130.8, 131.5, 133.5, 135.8, 136.5, 140.1, 143.4, 146.2 (4-ClC_6H_4, 4-$O_2NC_6H_4$, 4-MeC_6H_4), 205.9 (C=O).

MS (EI): *m*/*z* = 484 [M$^+$], 486 [M$^+$ + 2].

Anal. Calcd for $C_{24}H_{21}ClN_2O_3S$: C, 59.44; H, 4.36; N, 5.78. Found: C, 59.71; H, 4.22; N, 5.56.

2-(3-Methoxyphenyl)-6-(4-nitrophenyl)-1-tosylpiperidin-4-one (5o)

Colorless solid; yield: 0.213 g (89%); mp 131–133 °C.

IR (KBr): 3022 (C–H_{arom}), 2941 (C–$H_{aliphatic}$), 1705 (C=O), 1603, 1585, 1455 (C=C_{arom}), 1323, 1155 (SO_2) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.39 (s, 3 H, Me), 2.81–2.90 (m, 4 H, 2 × CH_2), 3.81 (s, 3 H, OMe), 4.01 (dd, *J* = 12.3, 2.8 Hz, 1 H, H-6), 4.22 (dd, *J* = 11.5, 3.9 Hz, 1 H, H-2), 6.98–7.26 (m, 4 H, ArH, 3-$MeOC_6H_4$), 7.31 (d, *J* = 8.5 Hz, 2 H, ArH, 4-MeC_6H_4), 7.56 (d, *J* = 8.8 Hz, 2 H, ArH, 4-$O_2NC_6H_4$), 7.71 (d, *J* = 8.5 Hz, 2 H, ArH, 4-MeC_6H_4), 8.17 (d, *J* = 8.8 Hz, 2 H, ArH, 4-$O_2NC_6H_4$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.9 (Me), 45.8 (C-5), 47.1 (C-3), 51.9 (C-6), 55.2 (OMe), 59.8 (C-2), 118.5, 122.2, 125.9, 126.5, 127.3, 128.7, 129.6, 130.8, 135.1, 149.8, 140.7, 143.9, 145.5, 156.8 (3-$MeOC_6H_4$, 4-$O_2NC_6H_4$, 4-MeC_6H_4), 207.3 (C=O).

MS (EI): *m*/*z* = 480 [M$^+$].

Anal. Calcd for $C_{25}H_{24}N_2O_6S$: C, 62.49; H, 5.03; N, 5.83. Found: C, 62.71; H, 4.88; N, 5.69.

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