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Stereoselective Synthesis of β-Amino Ketones via Direct Mannich-Type Reaction Catalyzed with SO_4^{2-}/TiO_2 and SO_4^{2-}/Nano TiO_2

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Abstract: At room temperature, SO_4^{2-}/TiO_2 and SO_4^{2-}/nano-TiO_2 efficiently catalyze the direct Mannich-type reaction of varieties of in situ–generated aldimines using aldehydes and anilines with ketones in a three-component reaction under solvent-free conditions. The reaction proceeds rapidly and affords the corresponding β-amino ketones in good to high yields with good to excellent stereoselectivity. The catalyst can be recycled for subsequent reactions without any appreciable loss of efficiency.

Keywords: β-Amino ketones, Mannich reaction, nano-TiO_2, SO_4^{2-}/TiO_2

INTRODUCTION

β-Amino carbonyl compounds are attractive targets for chemical synthesis because of their prevalence and wide utility. One of their earliest applications was in the preparation of important β-amino alcohols, versatile synthetic intermediates for a large number of natural products,[1] antibiotics,[2] and chiral auxiliaries.[3] Further, the β-amino carbonyl

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moiety is common in a large variety of biologically active compounds[4] and finds use as an important intermediate for fine chemicals[5] and pharmaceuticals.[6] Therefore, the development of new catalytic methods for its preparation is of prime importance in organic synthesis. Catalytic Mannich-type reactions have been reported by several groups as an efficient method to prepare β-amino carbonyl compounds.[7]

Solid acids such as zeolites, oxides, and aluminophosphates and their modified forms such as sulfated oxides have been extensively studied as possible alternatives to conventional Lewis/Brønsted acid catalysts.[8] Acidity of oxides increases on sulfate ion treatment,[9] and that of zeolites increases by protonation.[10] The increase in acidity is due to an increase in the number and the strength of acid sites. In several reactions the yield and selectivity of a product depend not only on the concentration but also on the strength of the acid sites. The solid superacids such as SO_4^{2-}/TiO_2 ($H_0 < -11.93$), which can be easily prepared, are sufficiently stable at the elevated reaction temperature and regenerated conveniently. Different kinds of solid superacids and the fields in which they are used have been developed. They have been used in isomerization, alkylation, acylation, polymerization, oligomerization, esterification, and oxidation processes.[11]

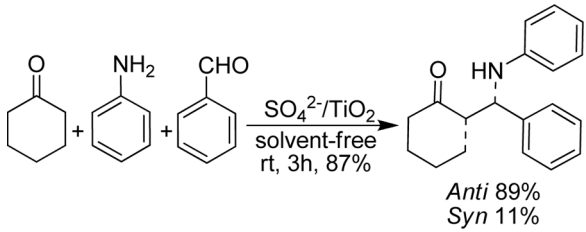
As part of our research on chemical transformations,[12] herein we report a simple and environmentally benign methodology for stereoselective synthesis of β-amino ketones via direct Mannich-type reaction of aldehydes, anilines, and ketones under solvent-free conditions at room temperature using SO_4^{2-}/TiO_2 as catalyst.

RESULTS AND DISCUSSION

SO_4^{2-}/TiO_2 was prepared, according to the literature,[13] by immersing TiO_2 in 1 N H_2SO_4 solution for 30 min, which was then decanted and dried from 80 to 150°C. The resulting solid was calcinated at 200 to 500°C and powdered.

The SO_4^{2-}/TiO_2-catalyzed direct Mannich-type reaction was first studied with performed aniline, benzaldehyde, and cyclohexanone under solvent-free conditions for 3 h at room temperature. 2-[Phenyl(phenylamino)methyl]cyclohexanone was isolated in good yield (87%), with 89% *anti*-selectivity. The overall reaction is shown in Scheme 1.

To examine the optimal conditions for SO_4^{2-}/TiO_2-catalyzed direct Mannich-type reaction of benzaldehyde, aniline, and cyclohexanone, we carried out different experiments (entries 1–12, Table 1). The reaction was carried out with aniline (1 mmol), benzaldehyde (1 mmol), and cyclohexanone (3 mmol) for 3 h under different conditions. Entries 1–7 show



Scheme 1. Direct Mannich-type reaction of aniline, benzaldehyde, and cyclohexanone catalyzed with SO_4^{2-}/TiO_2.

the effect of various solvents and solvent-free conditions on the yield and stereoselectivity of the reaction. Good to excellent *anti*-selectivity was observed in ethanol (EtOH) and CH_2Cl_2 and under solvent-free conditions, whereas the reaction in organic solvent showed poor yield. N-Benzylideneaniline was the only isolated product in H_2O and n-hexane, so we chose solvent-free conditions for good yield and good *anti*-selectivity of the reaction and environmental acceptability. The optimum amount of catalyst (0.03 g of SO_4^{2-}/TiO_2) was determined from experiments corresponding to entries 1 and 8–12. Entry 8 shows the catalytic effect of SO_4^{2-}/TiO_2 on the reaction. Entry 10 describes the yields of three consecutive additions leading to corresponding β-amino ketone. In these experiments, the product was isolated by filtration, the solid

Table 1. Mannich reaction of aniline, benzaldehyde, and cyclohexanone in different conditions

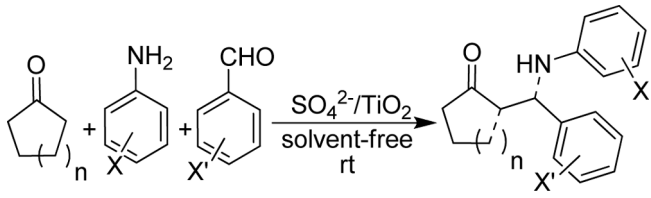
Entry	Solvent	Catalyst (g)	Yield (%)	*Anti*/*syn*
1	Solvent-free	0.05	87	89/11
2	H_2O	0.05	—[a]	—
3	EtOH	0.05	35	94/6
4	CH_2Cl_2	0.05	20	96/4
5	n-Hexane	0.05	—	—
6	Et_2O	0.05	50	—
7	CH_3CN	0.05	30	—
8	Solvent-free	0	0	—
9	Solvent-free	0.01	73	79/21
10	Solvent-free	0.03	92,90,89[b]	88/12
11	Solvent-free	0.07	73	78/22
12	Solvent-free	0.1	67	—

[a]Main product was imine.
[b]Catalyst was used over three runs.

residues were washed with dichloromethane and dried in air, and the remaining catalyst was reloaded with fresh reagents for further runs. No considerable decrease in the yield was observed, demonstrating that SO_4^{2-}/TiO_2 can be reused as a catalyst in direct Mannich-type reactions.

Eleven examples of the direct Mannich-type reaction of anilines, aromatic and heteroaromatic aldehydes, and cyclic ketones are listed in Table 2. The reactions were performed by adding cyclic ketones (3 mmol) to the mixture of anilines (1 mmol) and benzaldehydes (1 mmol) under solvent-free conditions in the presence of SO_4^{2-}/TiO_2 (0.03 g) at room temperature. The data in Table 2 clearly show that the reaction gave the corresponding β-amino ketones in good to excellent yield with good to excellent *anti*-selectivity for cyclohexanone at room temperature. Interestingly, in the case of cycloheptanone the reaction show reverse stereoselectivity, and the *syn* isomer was formed in good yield (entries 9 and 10).

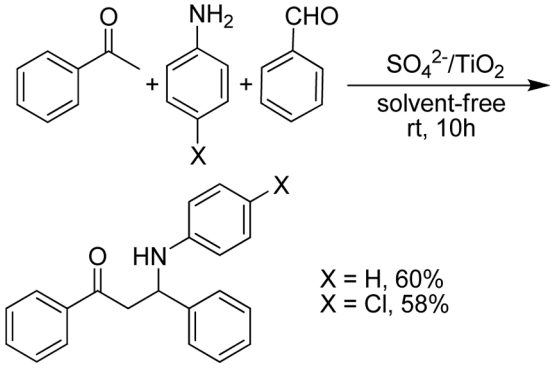
Table 2. Mannich reaction of anilines, aldehydes, and cyclic ketones catalyzed with SO_4^{2-}/TiO_2



Entry	Ketone (n)	Aniline (X)	Aldehyde (X′)	Time (h)	Yield (%)[a]	*Anti*/*syn*[b]
1	1	H	4-Me	1	75	66/33
2	2	H	H	3	92	88/12
3	2	H	4-Cl	2.5	85	61/39
4	2	H	4-NO_2	3.5	89	65/35
5	2	H	Furfural	1.5	80	59/41
6	2	3-Me	H	2.5	81	60/40
7	2	3-Me	4-Cl	2.5	75	100/0
8	2	3-Me	4-NO_2	3	95	75/25
9	3	H	H	5.5	60	16/84
10	3	4-Cl	H	5	70	34/66

[a]Yields refer to isolated products.

[b]Diastereomeric ratio measured by ^{1}HNMR spectroscopy analysis of the crude reaction mixture.



Scheme 2. Mannich reaction of anilines, benzaldehyde, and acetophenone.

Similarly, the Mannich reaction of benzaldehydes and anilines with acetophenone was investigated; the overall reaction is best formulated in Scheme 2.

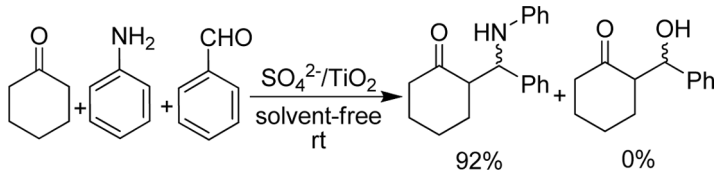
Also, SO_4^{2-} supported on the TiO_2 nanoparticles was investigated as catalyst in the Mannich reaction of aromatic aldehydes and anilines with cyclohexanone (Table 3). Interestingly, it was shown that in the case of aldehyde with an electron-withdrawing group such as 4-nitro benzaldehyde, the *anti*/*syn* ratio decreased from 65/35 and 75/25 (Table 2, entries 4 and 8) when SO_4^{2-}/TiO_2 was used to 58/42 and 53/47 (Table 3, entries 3n and 6n) in the presence of SO_4^{2-}/nano-TiO_2. In contrast, in the case of benzaldehyde, this ratio was increased from 88/12 and 60/40 (Table 2, entries 2 and 6) in the presence of SO_4^{2-}/TiO_2 to 95/5 and 100/0

Table 3. Mannich reaction of anilines, aldehydes, and cyclic ketones catalyzed with SO_4^{2-}/nano-TiO_2

Entry	Ketone (n)	Aniline (X)	Aldehyde (X′)	Time (h)	Yield (%)[a]	*Anti*/*syn*[b]
1n	2	H	H	3	90	95/5
2n	2	H	4-Cl	2.5	83	61/39
3n	2	H	4-NO_2	3.5	89	58/42
4n	2	3-Me	H	2.5	80	100/0
5n	2	3-Me	4-Cl	2.5	70	100/0
6n	2	3-Me	4-NO_2	3	93	53/47

[a]Yields refer to isolated products.

[b]Diastereomeric ratio measured by ^{1}H-NMR spectroscopy analysis of the crude reaction mixture.



Scheme 3. Chemoselectivity of cyclohexanone toward aldimine in preference to aldehydes.

(Table 3, entries 1n and 4n) when SO_4^{2-}/nano-TiO_2 was used as catalyst. No considerable changes were shown in the yield or time of reaction.

Another characteristic feature of the present protocol is the strong chemoselectivity of cyclohexanone toward aldimines, prepared in situ from the reaction of aldehydes and amines, in preference to aldehydes as shown in Scheme 3.

CONCLUSION

In summary, three-component Mannich reactions of aldehydes, anilines, and ketones are efficiently catalyzed by SO_4^{2-}/TiO_2 under solvent-free conditions. Aromatic and heteroaromatic aldehydes can be successfully used as the aldehyde component. Also, we have found that good to excellent *anti*-selectivity was observed in the SO_4^{2-}/TiO_2-catalyzed Mannich reaction of cyclic ketones and aromatic aldimines in very short times at room temperature under solvent-free conditions. When SO_4^{2-}/nano-TiO_2 was used as the catalyst, *anti*-selectivity decreased in the case of aldehyde with electron-withdrawing groups and increased in the case of benzaldehyde.

EXPERIMENTAL

General Reaction Procedure

Benzaldehyde (1 mmol), cyclohexanone (3 equiv.), and SO_4^{2-}/TiO_2 (0.03 g), were added successively to aniline (1 mmol) at room temperature (20–25°C) and stirred at the same temperature for the appropriate time. After completion of the reaction, CH_2Cl_2 (15 ml) was added, and the catalyst was removed by filtration. Filtrates were concentrated to dryness. The crude mixture was washed with hexane to afford 2-(phenyl-phenylamino-methyl)-cyclohexanone in 92% yield as an 88/12 *anti*/*syn* mixture. Products were obtained almost in pure form. In some

cases, further purification was carried out by column chromatography on silica gel using petroleum ether/ethyl acetate. All products were known and characterized by their spectroscopic data (IR and NMR) by comparison with those reported in the litrature.[12a] *Anti*/*syn* ratio was determined by ^{1}HNMR according to the literature.[12a]

Data

2-[(Phenylamino)(*p*-tolyl)methyl]cyclopantanone (**1**)

IR (KBr): $\nu = 3393$ (NH), 3039, 2955, 2871 (CH), 1724 (CO), 1603, 1510 (C=C), 1313 (NH) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.70$–1.79 (m, 2H, CH_2), 1.91–1.94 (m, 2H, CH_2), 2.05–2.15 (m, 1H, CH_2), 2.31–2.35 (m, 1H, CH_2), 2.39 (s, 3H, CH_3), 2.43–2.48 (m, 1H, CH), 4.1 (d, $^3J_{H,H} = 7.44$ Hz, 0.66 H, CH, *anti* isomer), 4.18 (d, $^3J_{H,H} = 6.14$ Hz, 0.34 H, CH, *syn isomer*), 5.11 (s, 1H, NH), 6.55 (d, 3*J*H, H = 7.69 Hz, 2H, CH^{Ar}), 6.65 (t, $^3J_{H,H} = 7.31$Hz, 1H, CH^{Ar}), 7.07 (t, $^3J_{H,H} = 7.43$Hz, 2H, CH^{Ar}), 7.14 (d, $^3J_{H,H} = 7.89$ Hz, 2H, CH^{Ar}), 7.29 (d, $^3J_{H,H} = 7.98$ Hz, 2H, CH^{Ar}) ppm.

2-[Phenyl(phenylamino)methyl]cyclohexanone (**2**)

^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.73$–1.76 (m, 2H, CH_2), 1.89–1.98 (m, 4 H, CH_2), 2.38–2.48 (m, 2H, CH_2), 2.79–2.80 (m, 1H, CH), 4.66 (d, $^3J_{H,H} = 4.99$ Hz, 0.88 H, CH, *anti isomer*), 4.75 (s, 1H, NH), 4.84 (d, $^3J_{H,H} = 3.98$ Hz, 0.12H, CH, *syn* isomer), 6.57 (d, $^3J_{H,H} = 8.50$ Hz, 2H, CH^{Ar}), 6.66 (t, $^3J_{H,H} = 7.50$ Hz, 1H, CH^{Ar}), 7.09–7.12 (m, 2H, CH^{Ar}), 7.26 (d, $^3J_{H,H} = 7.00$ Hz, 1H, CH^{Ar}), 7.34 (t, $^3J_{H,H} = 7.50$ Hz, 2H, CH^{Ar}), 7.41 (t, $^3J_{H,H} = 8.75$ Hz, 2H, CH^{Ar}) ppm.

2-[(4-Chlorophenyl)(phenylamino)methyl]cyclohexanone (**3**)

^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.73$–1.81 (m, 1H, CH_2), 1.85–1.91 (m, 2H, CH_2), 1.94–2.02 (m, 1H, CH_2), 2.05–2.10 (m, 2H, CH_2), 2.20–2.29 (m, 1H, CH), 2.35–2.48 (m, 1H, CH_2), 2.74–2.82 (m, 1H, CH), 4.78 (d, $^3J_{H,H} = 4.90$ Hz, 0.61H, CH, *anti isomer*), 4.94 (d, $^3J_{H,H} = 3.65$ Hz, 0.39 H, CH, *syn isomer*), 5.04 (s, 1H, NH), 6.51 (d, $^3J_{H,H} = 7.79$ Hz, 2H, CH^{Ar}), 6.70 (d, $^3J_{H,H} = 7.40$ Hz, 1H, CH^{Ar}), 7.11 (t, $^3J_{H,H} = 8.11$Hz, 2H, CH^{Ar}), 7.60 (t, $^3J_{H,H} = 8.50$ Hz, 2H, CH^{Ar}), 8.20 (d, $^3J_{H,H} = 8.67$ Hz, 2H, CH^{Ar}) ppm.

2-[(*p*-Nitrophenyl)(phenylamino)methyl]cyclohexanone (**4**)

IR (KBr): $\nu = 3373$ (NH), 3032, 2948, 2858 (CH), 1699 (CO), 1601 (C=C), 1515, 1346 (NO_2), 1287 (NH) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): $\delta = 1.69$–1.78 (m, 1H, CH_2), 1.82–1.88 (m, 2H, CH_2), 1.91–1.99 (m, 1H, CH_2), 2.01–2.08 (m, 2H, CH_2), 2.18–2.28 (m, 1H, CH), 2.33–2.45 (m, 1H, CH_2), 2.71–2.79 (m, 1H, CH), 4.75 (d, $^3J_{H,H} = 4.84$ Hz, 0.65 H, CH, *anti isomer*), 4.90 (d, $^3J_{H,H} = 3.42$Hz, 0.35 H, CH, *syn isomer*), 4.93 (s, 1H, NH), 6.48 (d, $^3J_{H,H} = 7.77$ Hz, 2H, CH^{Ar}), 6.67 (d, $^3J_{H,H} = 7.37$ Hz, 1H, CH^{Ar}), 7.07 (t, $^3J_{H,H} = 8.09$ Hz, 2H, CH^{Ar}), 7.58 (t, $^3J_{H,H} = 8.49$ Hz, 2H, CH^{Ar}), 8.17 (d, $^3J_{H,H} = 8.64$ Hz, 2H, CH^{Ar}) ppm.

2-[Furan-2-yl(phenylamino)methyl]cyclohexanone (**5**)

^1H NMR (500 MHz, $CDCl_3$): $\delta = 1.69$–1.76 (m, 3H, CH_2), 1.91–1.95 (m, 3H, CH_2), 2.31–2.47 (m, 2H, CH_2), 2.91–3.15 (m, 1H, CH), 4.61 (s, 1H, NH), 4.85 (d, $^3J_{H,H} = 5.36$ Hz, 0.59 H, CH, *anti isomer*), 4.92 (d,$^3J_{H,H} = 4.90$ Hz, 0.41H, CH, *syn isomer*), 6.23 (d, 1H, CH^{Ar}), 6.30 (d, 1H, CH^{Ar}), 6.69–6.73 (m, 3H, CH^{Ar}), 7.16–7.20 (m, 2H, CH^{Ar}), 7.34 (t, 1H, CH^{Ar}) ppm.

2-[Phenyl(*m*-tolylamino)methyl]cyclohexanone (**6**)

IR (KBr): $\nu = 3351$ (NH), 3038, 2944 (CH), 1702 (CO), 1602, 1538 (C=C), 1306 (NH) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): $\delta = 1.69$–1.79 (m, 2H, CH_2), 1.82–1.98 (m, 4 H, CH_2), 2.20 (s, 3H, CH_3), 2.33–2.37 (m, 1H, CH_2), 2.44–2.46 (m, 1H, CH_2), 2.70–2.75 (m, 1H, CH), 4.63 (d, $^3J_{H,H} = 6.96$ Hz, 0.60 H, CH, *anti isomer*), 4.72 (br. s, 1H, NH), 4.84 (d, $^3J_{H,H} = 3.47$ Hz, 0.40 H, CH, *syn isomer*), 6.28 (d, $^3J_{H,H} = 6.35$ Hz, 1H, CH^{Ar}), 6.36 (s, 1H, CH^{Ar}), 6.45 (d, $^3J_{H,H} = 7.32$Hz, 1H, CH^{Ar}), 6.93 (t, $^3J_{H,H} = 7.65$ Hz, 1H, CH^{Ar}), 7.23 (t, $^3J_{H,H} = 7.13$Hz, 1H, CH^{Ar}), 7.32 (t, $^3J_{H,H} = 7.41$Hz, 2H, CH^{Ar}), 7.41 (d, $^3J_{H,H} = 7.69$ Hz, 2H, CH^{Ar}) ppm.

2-[(4-Chlorophenyl)(*m*-tolylamino)methyl]cyclohexanone (**7**)

IR (KBr): $\nu = 3349$ (NH), 3045, 2939, 2865 (CH), 1703 (CO), 1603, 1531 (C=C), 1487, 1300 (NH), 710 (C–Cl) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): $\delta = 1.70$–1.77 (m, 1H, CH_2), 1.88–1.94 (m, 2H, CH_2), 2.12–2.14 (m, 1H, CH_2), 2.21–2.29 (m, 2H, CH_2), 2.37 (s, 3H, CH_3), 2.43–2.48 (m, 1H,

CH_2), 2.53–2.57 (m, 1H, CH_2), 2.87–2.92 (m, 1H, CH), 4.78 (d, $^3J_{H,H}$ = 5.03Hz, 1H, CH, *anti isomer*), 4.96 (s, 1H, NH), 6.29 (t, $^3J_{H,H}$ = 7.76 Hz, 1H, CH^{Ar}), 6.38 (s, 1H, CH^{Ar}), 6.56 (t, $^3J_{H,H}$ = 7.74 Hz, 1H, CH^{Ar}), 6.99 (t, $^3J_{H,H}$ = 7.77 Hz, 1H, CH^{Ar}), 7.63 (d, $^3J_{H,H}$ = 8.55 Hz, 2H, CH^{Ar}), 8.22 (d, $^3J_{H,H}$ = 8.57 Hz, 2H, CH^{Ar}) ppm.

2-[(*p*-Nitrophenyl)(*m*-tolylamino)methyl]cyclohexanone (**8**)

IR (KBr): ν = 3373 (NH), 2948, 2858 (CH), 1699 (CO), 1601 (C=C), 1516, 1345 (NO_2), 1300, 1100 (NH) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.61–1.69 (m, 1H, CH_2), 1.81–1.90 (m, 2H, CH_2), 2.02–2.04 (m, 1H, CH_2), 2.10–2.14 (m, 2H, CH_2), 2.27 (s, 3H, CH_3), 2.35–2.40 (m, 1H, CH_2), 2.44–2.48 (m, 1H, CH_2), 2.85–2.90 (m, 1H, CH), 4.74 (d, $^3J_{H,H}$ = 5.00 Hz, 0.75 H, CH, *anti isomer*), 4.89 (d, $^3J_{H,H}$ = 4.00 Hz, 0.25 H, CH, *syn isomer*), 4.91 (br. s, 1H, NH), 6.27 (t, $^3J_{H,H}$ = 7.78 Hz, 1H, CH^{Ar}), 6.36 (s, 1H, CH^{Ar}), 6.50 (t, $^3J_{H,H}$ = 7.71Hz, 1H, CH^{Ar}), 6.96 (t, $^3J_{H,H}$ = 7.76 Hz, 1H, CH^{Ar}), 7.61 (d, $^3J_{H,H}$ = 8.53Hz, 2H, CH^{Ar}), 8.20 (d, $^3J_{H,H}$ = 8.56 Hz, 2H, CH^{Ar}) ppm.

2-[Phenyl(phenylamino)methyl]cycloheptanone (**9**)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.28–1.38 (m, 2H, CH_2), 1.45–1.64 (m, 2H, CH_2), 1.73–176 (m, 1H, CH_2), 1.94 (m, 3H, CH_2), 2.33–2.38 (m, 1H, CH_2), 2.48–2.54 (m, 1H, CH_2), 2.88–2.92 (m, 1H, CH), 4.47 (d, ^3J = 7.50, 0.16 H, CH, *anti isomer*), 4.58 (d, ^3J = 5.00, 0.84 H, CH, *syn isomer*), 4.99 (s, 1H, NH), 6.49 (t, ^3J = 9.98, 2H, CH^{Ar}), 6.61 (t, ^3J = 10.00, 1H, CH^{Ar}), 7.05 (t, ^3J = 8.50, 2H, CH^{Ar}), 7.22–7.28 (m, 1H, CH^{Ar}), 7.3–7.39 (m, 4 H, CH^{Ar}).

2-[(4-Chlorophenylamino)(phenyl)methyl]cycloheptanone (**10**)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.30–1.37 (m, 2H, CH_2), 1.48–1.65 (m, 2H, CH_2), 1.75–1.77 (m, 1H, CH_2), 1.97–2.03 (m, 3H, CH_2), 2.34–2.40 (m, 1H, CH_2), 2.51–2.56 (m, 1H, CH_2), 2.91–2.94 (m, 1H, CH), 4.51 (d, $^3J_{H,H}$ = 7.48, 0.34 H, CH, *anti isomer*), 4.63 (d, $^3J_{H,H}$ = 5.03, 0.66 H, CH, *syn isomer*), 5.01 (s, 1H, NH), 6.53 (d, 2H, CH^{Ar}), 7.11–7.17 (m, 5 H, CH^{Ar}), 7.21–7.28 (m, 2H, CH^{Ar}).

2-[Phenyl(phenylamino)methyl]cyclohexanone (**1n**)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.73–1.78 (m, 2H, CH_2), 1.88–1.97 (m, 4 H, CH_2), 2.38–2.47 (m, 2H, CH_2), 2.79–2.81 (m, 1H, CH), 4.67

(d, $^3J_{H,H} = 4.99$ Hz, 0.95 H, CH, *anti isomer*), 4.75 (s, 1H, NH), 4.84 (d, $^3J_{H,H} = 3.98$ Hz, 0.12H, CH, *syn isomer*), 6.57 (d, $^3J_{H,H} = 8.50$ Hz, 2H, CH^{Ar}), 6.66 (t, $^3J_{H,H} = 7.50$ Hz, 1H, CH^{Ar}), 7.09–7.12 (m, 2H, CH^{Ar}), 7.26 (d, $^3J_{H,H} = 7.00$ Hz, 1H, CH^{Ar}), 7.34 (t, $^3J_{H,H} = 7.50$ Hz, 2H, CH^{Ar}), 7.41 (t, $^3J_{H,H} = 8.75$ Hz, 2H, CH^{Ar}) ppm.

2-[(4-Chlorophenyl)phenylamino)methyl]cyclohexanone (**2n**)

^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.75$–1.82 (m, 1H, CH_2), 1.89–1.93 (m, 2H, CH_2), 1.96–2.08 (m, 1H, CH_2), 2.10–2.12 (m, 2H, CH_2), 2.23–2.28 (m, 1H, CH), 2.37–2.49 (m, 1H, CH_2), 2.75–2.84 (m, 1H, CH), 4.75 (s, 1H, NH), 4.84 (d, $^3J_{H,H} = 5.10$ Hz, 0.61H, CH, *anti isomer*), 4.89 (d, $^3J_{H,H} = 4.05$, 0.39 H, CH, *syn isomer*), 6.55 (d, $^3J_{H,H} = 7.79$ Hz, 2H, CH^{Ar}), 6.79 (d, $^3J_{H,H} = 7.42$Hz, 1H, CH^{Ar}), 7.16 (t, $^3J_{H,H} = 8.11$Hz, 2H, CH^{Ar}), 7.66 (t, $^3J_{H,H} = 8.50$ Hz, 2H, CH^{Ar}), 8.23 (d, $^3J_{H,H} = 8.64$ Hz, 2H, CH^{Ar}) ppm.

2-[(*p*-Nitrophenyl)(phenylamino)methyl]cyclohexanone (**3n**)

^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.67$–1.76 (m, 1H, CH_2), 1.80–1.86 (m, 2H, CH_2), 1.89–1.97 (m, 1H, CH_2), 1.99–2.06 (m, 2H, CH_2), 2.16–2.26 (m, 1H, CH), 2.31–2.43 (m, 1H, CH_2), 2.69–2.77 (m, 1H, CH), 4.73 (d, $^3J_{H,H} = 4.86$ Hz, 0.58 H, CH, *anti isomer*), 4.88 (d, $^3J_{H,H} = 3.44$ Hz, 0.42H, CH, *syn isomer*), 4.91 (s, 1H, NH), 6.46 (d, $^3J_{H,H} = 7.74$ Hz, 2H, CH^{Ar}), 6.65 (d, $^3J_{H,H} = 7.34$ Hz, 1H, CH^{Ar}), 7.04 (t, $^3J_{H,H} = 8.05$ Hz, 2H, CH^{Ar}), 7.50 (t, $^3J_{H,H} = 8.47$ Hz, 2H, CH^{Ar}), 8.15 (d, $^3J_{H,H} = 8.61$ Hz, 2H, CH^{Ar}) ppm.

2-[Phenyl(*m*-tolylamino)methyl]cyclohexanone (**4n**)

^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.74$–1.82 (m, 2H, CH_2), 1.92–2.01 (m, 4 H, CH_2), 2.25 (s, 3H, CH_3), 2.37–2.39 (m, 1H, CH_2), 2.46–2.49 (m, 1H, CH_2), 2.74–2.78 (m, 1H, CH), 4.63 (d, $^3J_{H,H} = 6.96$ Hz, 1H, CH, *anti isomer*), 4.70 (s, 1H, NH), 6.31 (d, $^3J_{H,H} = 6.37$ Hz, 1H, CH^{Ar}), 6.38 (s, 1H, CH^{Ar}), 6.46 (d, $^3J_{H,H} = 7.34$ Hz, 1H, CH^{Ar}), 6.95 (t, $^3J_{H,H} = 7.66$ Hz, 1H, CH^{Ar}), 7.25 (t, $^3J_{H,H} = 7.15$ Hz, 1H, CH^{Ar}), 7.34 (t, $^3J_{H,H} = 7.42$Hz, 2H, CH^{Ar}), 7.40 (d, $^3J_{H,H} = 7.70$ Hz, 2H, CH^{Ar}) ppm.

2-[(4-Chlorophenyl)(*m*-tolylamino)methyl]cyclohexanone (**5n**)

^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.72$–1.85 (m, 3H, CH_2), 1.96–2.01 (m, 3H, CH_2), 2.64 (s, 3H, CH_3), 2.35–2.36 (m, 1H, CH_2), 2.43–2.47

(m, 1H, CH_2), 2.72–2.75 (m, 1H, CH), 4.60 (d, $^3J_{H,H} = 6.18$ Hz, 1H, CH, *anti isomer*), 4.74 (s, 1H, NH), 6.29 (d, $^3J_{H,H} = 7.98$ Hz, 1H, CH^{Ar}), 6.35 (s, 1H, CH^{Ar}), 6.48 (d, $^3J_{H,H} = 7.43$Hz, 1H, CH^{Ar}), 6.96 (t, $^3J_{H,H} =$ 7.72Hz, 1H, CH^{Ar}), 7.31 (d, $^3J_{H,H} = 8.35$ Hz, 2H, CH^{Ar}), 7.35 (d, $^3J_{H,H} = 8.46$ Hz, 2H, CH^{Ar}) ppm.

2-[(*p*-Nitrophenyl)(*m*-tolylamino)methyl]cyclohexanone (**6n**)

^{1}HNMR (500 MHz, $CDCl_3$): $\delta = 1.59$–1.67 (m, 1H, CH_2), 1.78–1.89 (m, 2H, CH_2), 1.99–2.01 (m, 1H, CH_2), 2.08–2.11 (m, 2H, CH_2), 2.24 (s, 3H, CH_3), 2.34–2.37 (m, 1H, CH_2), 2.41–2.46 (m, 1H, CH_2), 2.84–2.88 (m, 1H, CH), 4.69 (d, $^3J_{H,H} = 5.1$Hz, 0.53H, CH, *anti isomer*), 4.81 (d, $^3J_{H,H} = 4.47$ Hz, 0.47 H, CH, *syn isomer*), 4.85 (s, 1H, NH), 6.25 (t, $^3J_{H,H} = 7.77$ Hz, 1H, CH^{Ar}), 6.33 (s, 1H, CH^{Ar}), 6.49 (t, $^3J_{H,H} = 7.69$ Hz, 1H, CH^{Ar}), 6.94 (t, $^3J_{H,H} = 7.75$ Hz, 1H, CH^{Ar}), 7.59 (d, $^3J_{H,H} =$ 8.51Hz, 2H, CH^{Ar}), 8.18 (d, $^3J_{H,H} = 8.54$ Hz, 2H, CH^{Ar}) ppm.

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