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Stereoselective Synthesis of β-Amino Ketones via Direct Mannich-Type Reactions, Catalyzed with $ZrOCl_2 \cdot 8H_2O$ under Solvent-Free Conditions

Bagher Eftekhari-Sis,[a] Amir Abdollahifar,[a] Mohammed M. Hashemi,*[a] and Maryam Zirak[b]

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At room temperature, zirconium oxychloride ($ZrOCl_2 \cdot 8H_2O$) efficiently catalyzes the direct Mannich-type reaction of a variety 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 stereoselectivities. The catalyst can be recycled for subsequent reactions without any appreciable loss of efficiency.

Introduction

Multi-component reactions (MCRs) performed either in the solid phase or in solution,[1] have emerged as powerful tools in combinatorial chemistry for the generation of small-molecule libraries. The goal is to aid the discovery of new leads for drug development and optimization of processes or to identify novel biologically active substrates.

β-Amino carbonyl compounds are attractive targets for chemical synthesis because of their wide use as biologically active molecules.[2] Therefore, the development of new synthetic methods leading to β-amino carbonyl compounds or their derivatives has attracted much attention in organic synthesis. The Mannich reaction is a classical method for the preparation of β-amino ketones and aldehydes,[2,3] and has been one of the most important basic reactions in organic chemistry for its use in natural product and pharmaceutical syntheses. However, due to the drastic reaction conditions and the long reaction times, the classical intermolecular Mannich reaction is plagued by a number of serious disadvantages.[3] However, catalytic Mannich reactions have been reported by several groups as an efficient method to prepare β-amino carbonyl compounds.[4]

Due to the ease of availability,[5] and low toxicity,[6] Zr^{IV} salts have recently attracted much attention.[7] This has been reflected in their applications in several organic transformations such as electrophilic amination of activated arenes,[8a] transthioacetylization of acetals,[8b] deoxygenation of heterocyclic *N*-oxides,[8c] reduction of nitro compounds,[8d] conversion of carbonyl compounds to 1,3-oxathiolanes,[8e] synthesis of nitriles from *O*-arylaldoximes,[8f] Michael reactions of 1,3-dicarbonyl compounds and enones,[8g] opening of epoxide rings by amines,[8h] reactions of indole, 1-methylindole, and pyrrole with α,β-unsaturated ketone,[8i] and other organic transformations.[8j–8w] There have been only a few reports on metal-oxysalt-based organic reactions.[9]

Recently, we have reported[10] that $ZrOCl_2 \cdot 8H_2O$ supported on montmorillonite K10 catalyzes the synthesis of β-amino esters and ketones via the conjugated addition of amines to α,β-unsaturated carbonyl compounds. The results encouraged us to work on the synthesis of β-amino ketones via three-component Mannich reactions catalyzed with $ZrOCl_2 \cdot 8H_2O$.

As part of our research on chemical transformations,[10,11] in this paper we report a simple and environmentally benign methodology for the stereoselective synthesis of β-amino ketones via direct Mannich-type reactions between aldehydes, anilines, and ketones under neutral, solvent-free conditions at room temp. using $ZrOCl_2 \cdot 8H_2O$ as the catalyst. We report herein that excellent *anti* selectivity was observed in $ZrOCl_2 \cdot 8H_2O$-catalyzed direct Mannich-type reactions of cyclic ketones and aldimines under solvent-free conditions.

Results and Discussion

The $ZrOCl_2 \cdot 8H_2O$-catalyzed Mannich reaction was first studied using imines. *N*-Benzylideneaniline and cyclohexanone were treated with 15 mol% $ZrOCl_2 \cdot 8H_2O$ under solvent-free conditions for 25 min at room temp. The corresponding β-amino ketone was isolated in high yield (95%),

[a] Department of Chemistry, Sharif University of Technology, P. O. Box 11365-9516, Tehran, Iran
Fax: +98-21-600-5718
E-mail address: mhashemi@sharif.edu
[b] Department of Organic Chemistry, Faculty of Chemistry, Tabriz University, P. O. Box 51664, Tabriz, Iran

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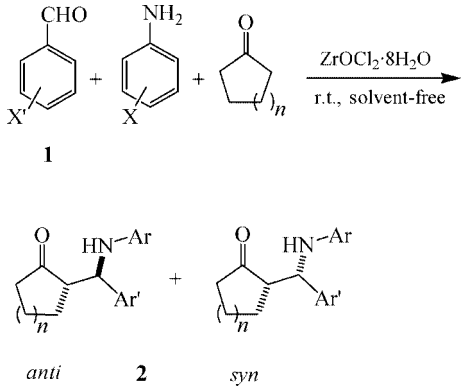
with 100% *anti* selectivity. Consequently, a one-pot sequence involving the formation of the imine and its in situ Mannich reaction was investigated. The overall reaction is shown in Scheme 1.



Scheme 1. Direct Mannich-type reaction between aldehydes of type **1**, anilines, and cyclic ketones.

To examine the optimal conditions for the Mannich reaction of benzaldehyde, aniline, and cyclohexanone using $ZrOCl_2·8H_2O$ as the catalyst, to afford the corresponding β-amino carbonyl adduct, we carried out experiments 1a–1j. A summary of the results is provided in Table 1. Entries 1a–1e show the effect of various solvents and solvent-free conditions on the yield and stereoselectivity of the reaction. Interestingly, the Mannich reaction exhibited an intriguing solvent effect; excellent *anti* selectivity was observed under solvent-free conditions, whereas the reaction in aqueous or organic solvent showed low stereoselectivity. Therefore, we chose solvent-free conditions for high yield and high *anti* selectivity of the reaction and environmental acceptability. Entry 1e describes the yields of three consecutive additions leading to the corresponding β-amino ketones. In these experiments the product was isolated by filtration, the solid residues were washed with dichloromethane, and the remaining catalyst reloaded with fresh reagents for further runs after reactivation (35 °C, vacuum). No considerable decrease in the yield was observed demonstrating that $ZrOCl_2·8H_2O$ can be reused as a catalyst in direct Mannich-type reactions. The optimum amount of catalyst (0.15 mmol of $ZrOCl_2·8H_2O$) was determined from experiments corresponding to entries 1e–1g. Entry 1h shows the catalytic effect of $ZrOCl_2·8H_2O$ in the three-component Mannich reaction of benzaldehyde, aniline, and cyclohexanone. The optimum amount of cyclohexanone was determined to be 3 equiv. as shown in entries 1e, 1i, and 1j.

The reaction of benzaldehyde, aniline, and cyclohexanone in the presence of $ZrOCl_2·8H_2O$ gives the β-amino ketone adduct in high yield over a short reaction time with excellent *anti* selectivity. Details of this reaction are summarized in Table 2. The data in Table 2 clearly show that the reaction of different aromatic aldehydes of type **1**, anilines, and cyclic ketones give the corresponding β-amino ketones in good to high yield with good to excellent *anti* selectivity at room temp. without using any solvent.

Table 1. Mannich reactions of benzaldehyde (1 mmol), aniline (1 mmol), and cyclohexanone under different conditions.

Entry	Solvent	$ZrOCl_2·8H_2O$ [mol-%]	Yield [%]	*anti*/*syn*
1a	MeCN	15	68[a]	58:42
1b	MeOH	15	45[a]	53:47
1c	EtOAc	15	70[a]	61:39
1d	H_2O	15	–[a][b]	–
1e	solvent-free	15	93, 86, 80[a][c]	100:0
1f	solvent-free	10	57[a]	98:2
1g	solvent-free	20	95[a]	100:0
1h	solvent-free	0	5[a]	–
1i	solvent-free	15	43[d]	82:18
1j	solvent-free	15	92[e]	99:1

[a] 3 equiv. of cyclohexanone was used. [b] Main product was imine. [c] Catalyst was used over three runs. [d] 1 equiv. of cyclohexanone was used. [e] 5 equiv. of cyclohexanone was used.

Table 2. Direct Mannich-type reactions of aromatic aldehydes, anilines, and cyclic ketones (see also Scheme 1).[a]

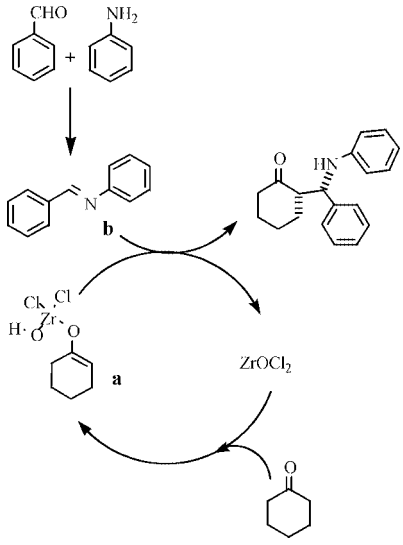
	n	X	X′	Time [min]	Yield[b] [mg]	[%]	*anti*/*syn*[c]
2a	1	H	4-Me	6	220	79	99:1
2b	1	H	4-Cl	7	239	80	97:3
2c	2	H	H	20	259	93	100:0
2d	2	H	4-Cl	15	257	88	99:1
2e	2	H	4-NO_2	25	298	92	74:26
2f	2	H	furfural	10	223	83	92:8
2g	2	4-MeO	H	15	262	85	99:1
2h	2	3-Me	H	15	240	82	85:15
2i	2	4-Cl	H	12	247	79	81:19
2j	2	3-Me	4-NO_2	20	317	94	72:28
2k	2	3-Me	4-Cl	15	252	77	100:0
2l	2	4-Cl	4-Me	15	206	63	87:13
2m	3	H	H	50	219	75	94:6
2n	3	H	4-Cl	45	245	75	83:17
2o	3	3-Me	H	55	233	76	89:11

[a] Reaction conditions: To aniline (1 mmol), aldehyde (1 mmol), cycloalkanone (3 equiv.), and $ZrOCl_2·8H_2O$ (0.05 g, 15 mol-%) were added successively at room temp. and stirred for the time listed in Table 2. [b] Yields refer to isolated products. [c] Diastereomeric ratio measured by ^{1}H-NMR spectroscopic analysis of the crude reaction mixture.

As shown in Table 2, high *anti* selectivity is obtained with various substituted benzaldehydes except for nitro-substituted benzaldehydes (see compounds **2e**, **2j**).

The proposed mechanism involves the attack of in-situ-generated enolate **a** on the in-situ-generated aldimine **b** as shown in Scheme 2. $ZrOCl_2$, used in catalytic amounts, is recycled in the reaction and can be reused for subsequent reactions.

Four possible transition states are shown in Scheme 3. Transition states **I** and **IV** provide the *anti* isomer, whereas the *syn* isomer forms via **II** and **III**. In **III** and **IV** the two phenyl groups of aldimine are *syn* to each other, so they are unfavorable. Also in **III** and **IV** steric repulsion exists between the hydrogen atoms of cyclohexanone's methylene groups and phenyl and hydroxy (or chloro) groups, respectively. Steric repulsion in **IV** is less than in **III**; therefore,



Scheme 2. Proposed reaction mechanism for Mannich reactions of benzaldehyde, anilines, and cyclohexanone.

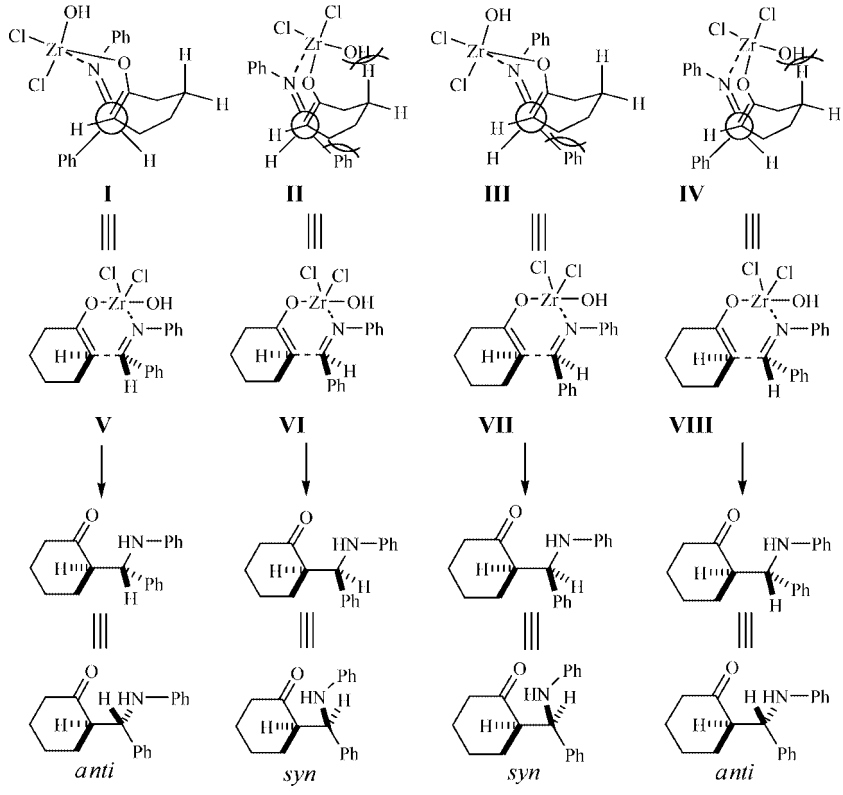
since **IV** leads to the *anti* isomer, this contributes to product formation more than in **III**. The phenyl groups of aldimine in **I** and **II** are *anti* to each other, therefore **I** and **II** should be more stable than **III** and **IV**. However, the existence of greater steric repulsion in **II** between the methylene groups of cyclohexanone and phenyl group on the carbon atom and the hydroxy (or chloro) on the Zr atom causes **II** to be less favorable. **I** is the most stable transition state that produces the *anti* isomer.

As shown in **VI** and **VII**, the phenyl group on carbon is *syn* to the methylene group of cyclohexanone, in which the steric repulsion between the phenyl group on the carbon atom and cyclohexanone methylene group causes **VI** and **VII** to be unfavorable.

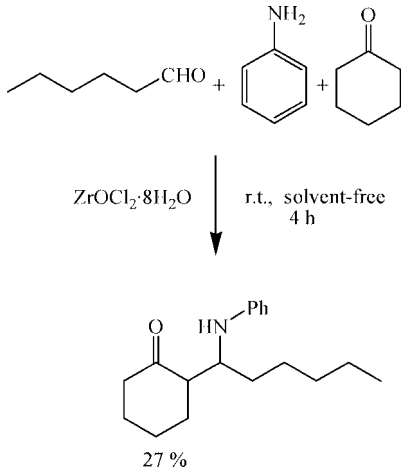
Mannich reactions of hexanal and anilines with cyclohexanone were investigated, Scheme 4 clearly shows that the reaction of the aliphatic aldehyde, anilines, and cyclohexanone afford the corresponding β-amino ketones in low yields over long reaction times.

The *anti*/*syn* ratio was determined by ^{1}H NMR, using the intensity of the H^a (Scheme 5). $J_{Ha,Hb}$ signal of the *anti* isomer which is higher than that of the *syn* isomer. According to the ^{1}H NMR spectrum, the H^a signal for the *anti* isomer has a lower δ value than that for the *syn* isomer. For instance, in the ^{1}H NMR spectra of 2-[(*p*-chlorophenylamino)phenylmethyl]cyclohexanone (**2i**), the signal at δ = 4.58 ppm (J = 6.9 Hz) is contributed by the *anti* isomer, while the one at 4.87 ppm (J = 3.7 Hz) is contributed by the *syn* isomer.

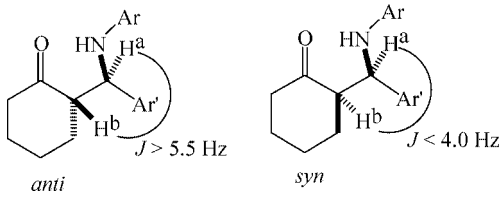
Similarly, Mannich reactions of aldehydes and anilines with acyclic ketones such as acetone and acetophenone were investigated, the overall reaction is best formulated in Scheme 6.



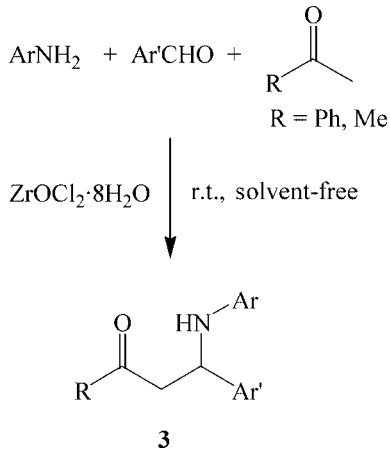
Scheme 3. Four possible transition states.



Scheme 4. Reaction conditions: to aniline (1 mmol), hexanal (1 mmol), cyclohexanone (3 equiv.), and $ZrOCl_2{\cdot}8H_2O$ (0.05 g) were added successively at room temp. and stirred for 4 h.



Scheme 5. Identification of *anti* and *syn* isomer by ^1H NMR spectroscopy.



Scheme 6. Mannich reaction of aromatic aldehydes, anilines, and acyclic ketones.

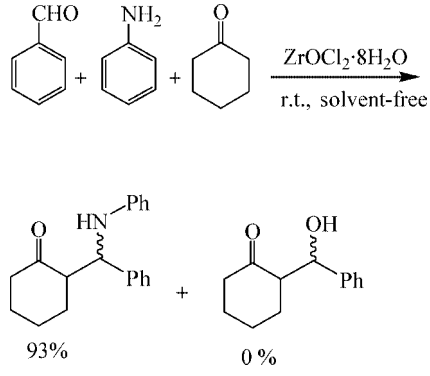
The reaction of aldehydes, anilines, and acyclic ketones in the presence of $ZrOCl_2{\cdot}8H_2O$ gives the β-amino ketone adducts in good yields over short reaction times at room temp. without using any solvent. The required time for the completion of the reaction in the case of acetophenone is longer than for acetone. The results are summarized in Table 3.

Table 3. Mannich reaction of aromatic aldehydes, anilines, and acyclic ketones (see also Scheme 6).

	R	Ar	Ar′	Time [h]	Yield[a] [mg]	[%]
3a	Me	3-MeC_6H_4	Ph	0.75	189	65
3b	Me	4-ClC_6H_4	Ph	0.75	205	93
3c	Ph	Ph	Ph	4	195	65
3d	Ph	4-ClC_6H_4	Ph	4	211	63
3e	Ph	Ph	4-ClC_6H_4	4	221	66

[a] Yields refer to isolated products, and products are characterized using ^1H NMR and ^{13}C NMR spectroscopy.

Another characteristic feature of the present protocol is the high chemoselectivity of cyclohexanone toward aldimines, in preference to aldehydes, prepared in situ from the reaction of aldehydes and amines as shown in Scheme 7.



Scheme 7. Chemoselectivity of cyclohexanone toward aldimine in preference to aldehydes.

Although conventional Lewis acids activate aldehydes preferentially, in this media, aldehydes do not undergo an aldol reaction by means of $ZrOCl_2{\cdot}8H_2O$ at room temp. under solvent-free conditions. The high chemoselectivity is rationalized by considering the higher basicity of nitrogen over oxygen. A related phenomenon was recently reported for the difference in the reactivity between aldimines and aldehydes by the use of proline, HBF_4, and dibutyltin dimethoxide.[12]

The following features are noteworthy in these reactions.

i. A 1:1:3 mixture of benzaldehyde, *p*-anisidine, and cyclohexanone with 15 mol% of $ZrOCl_2{\cdot}8H_2O$ gives the Mannich adduct in 85% yield in 15 min under solvent-free conditions (**2g**). This is in contrast to 84% yield for a reaction performed in water (1 day), catalyzed by HCl/40 mol-% SDS (sodium dodecyl sulfate).[13]

ii. It is known that the Mannich reaction of cyclohexanone tends to exhibit high *anti* stereoselectivity, but these methods have some disadvantages such as long reaction times.[4b,13] In the present work we obtained Mannich adducts in good to excellent *anti* selectivity in short reaction times without using any solvent.

iii. Anilines substituted with electron-withdrawing groups and aldehydes substituted with electron-donating groups give only low yields (**2l**).

iv. Not only benzaldehyde, but also heteroaromatic aldehydes, such as furfural, work well (**2f**).

v. For the reactions of cyclic ketones and acetone, 3 equiv. of the ketone are needed to avoid polyaminoalkylation.
vi. Increase in ring size leads to an increase in the reaction times (**2b**, **2d**, **2n**).
vii. Mannich reactions of aliphatic aldehydes and anilines with ketones are not interesting due to low yields and long reaction times.

Conclusion

In summary, three-component Mannich reactions of aldehydes, anilines, and ketones are efficiently catalyzed by $ZrOCl_2 \cdot 8H_2O$ 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 $ZrOCl_2 \cdot 8H_2O$-catalyzed Mannich reactions of cyclic ketones and aromatic aldimines in very short times, at room temp. under solvent-free conditions.

Experimental Section

General: All chemicals were purchased and used without any further purification. NMR spectra were recorded at 500 MHz for proton and at 125 MHz for carbon nuclei in ($CDCl_3$/CCl_4). Elemental analyses were carried out using a Vario EL III, Elementar. The products were purified by column chromatography carried out on silica gel using ethyl acetate/petroleum ether mixtures. All compounds were characterized by their spectroscopic data (IR, NMR) by comparison with those reported in the literature. Reactions were carried out at room temp. All aldehydes, ketones, and amines employed are commercially available.

General Reaction Procedure: To aniline derivative (1 mmol), benzaldehyde derivative (1 mmol), cyclohexanone (3 equiv.), and $ZrOCl_2 \cdot 8H_2O$ (0.05 g, or 15 mol-%) were added successively at room temp. (20–25 °C) and stirred at the same temperature for 20 min. After completion of the reaction, ethyl acetate (15 mL) was added, and catalyst was removed by filtration. Filtrates were washed with a saturated aqueous $NaHCO_3$ solution and brine, dried with anhydrous Na_2SO_4, and concentrated to dryness. The crude mixture was washed with hexane to afford the 2-[phenyl-(phenylamino)methyl]cyclohexanone in (259 mg) 93% as a 100:0 *anti*/*syn* mixture. Products **2** were obtained almost in pure form. Further purification carried out by column chromatography on silica gel using petroleum ether/ethyl acetate.

2-[(Phenylamino)(*p*-tolyl)methyl]cyclopentanone (2a): IR (KBr): $\tilde{\nu}$ = 3393 (NH), 3039, 2955, 2871 (CH), 1724 (CO), 1603, 1510 (C=C), 1313 (NH) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.73–1.81 (m, 2 H, CH_2), 1.93–1.95 (m, 2 H, CH_2), 2.09–2.17 (m, 1 H, CH_2), 2.32–2.36 (m, 1 H, CH_2), 2.38 (s, 3 H, CH_3), 2.45–2.50 (m, 1 H, CH), 4.05 [d, ^3J(H,H) = 7.44 Hz, 1 H, CH, *anti* isomer], 5.12 (s, 1 H, NH), 6.51 (d, $^3J_{H,H}$ = 7.69 Hz, 2 H, CH^{Ar}), 6.64 (t, $^3J_{H,H}$ = 7.31 Hz, 1 H, CH^{Ar}), 7.04 (t, $^3J_{H,H}$ = 7.43 Hz, 2 H, CH^{Ar}), 7.13 (d, $^3J_{H,H}$ = 7.89 Hz, 2 H, CH^{Ar}), 7.27 (d, $^3J_{H,H}$ = 7.98 Hz, 2 H, CH^{Ar}) ppm. $C_{19}H_{21}NO$ (279.38): calcd. C 81.68, H 7.58, N 5.01; found C 81.47, H 7.71, N 4.92.

2-[(*p*-Chlorophenyl)(phenylamino)methyl]cyclopentanone (2b): IR (KBr): $\tilde{\nu}$ = 3358 (NH), 3032, 2959, 2868 (CH), 1725 (CO), 1602, 1518 (C=C), 1310 (NH), 761 (C–Cl) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.70–1.79 (m, 2 H, CH_2), 1.93–1.99 (m, 2 H, CH_2), 2.10–2.17 (m, 1 H, CH_2), 2.35–2.40 (m, 1 H, CH_2), 2.45–2.48 (m, 1 H, CH), 4.53 (d, $^3J_{H,H}$ = 7.31 Hz, 1 H, CH, *anti* isomer), 5.18 (br. s, 1 H, NH), 6.49 (d, $^3J_{H,H}$ = 7.88 Hz, 2 H, CH^{Ar}), 6.68 (t, $^3J_{H,H}$ = 7.30 Hz, 1 H, CH^{Ar}), 7.07 (t, $^3J_{H,H}$ = 8.35 Hz, 2 H, CH^{Ar}), 7.30–7.41 (m, 4 H, CH^{Ar}) ppm. $C_{18}H_{18}ClNO$ (299.79): calcd. C 72.11, H 6.05, N 4.67; found C 72.33, H 6.24, N 4.41.

2-[(*p*-Nitrophenyl)(phenylamino)methyl]cyclohexanone (2e): IR (KBr): $\tilde{\nu}$ = 3373 (NH), 3032, 2948, 2858 (CH), 1699 (CO), 1601 (C=C), 1515, 1346 (NO_2), 1287 (NH) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.59–1.68 (m, 1 H, CH_2), 1.78–1.87 (m, 2 H, CH_2), 1.99–2.00 (m, 1 H, CH_2), 2.06–2.08 (m, 2 H, CH_2), 2.34–2.38 (m, 1 H, CH), 2.41–2.49 (m, 1 H, CH2), 2.84–2.88 (m, 1 H, CH), 4.71 (d, $^3J_{H,H}$ = 4.84 Hz, 0.74 H, CH, *anti* isomer), 4.83 (d, $^3J_{H,H}$ = 3.42 Hz, 0.26 H, CH, *syn* isomer), 4.93 (s, 1 H, NH), 6.48 (d, $^3J_{H,H}$ = 7.77 Hz, 2 H, CH^{Ar}), 6.67 (d, $^3J_{H,H}$ = 7.37 Hz, 1 H, CH^{Ar}), 7.07 (t, $^3J_{H,H}$ = 8.09 Hz, 2 H, CH^{Ar}), 7.58 (t, $^3J_{H,H}$ = 8.49 Hz, 2 H, CH^{Ar}), 8.17 (d, $^3J_{H,H}$ = 8.64 Hz, 2 H, CH^{Ar}) ppm. $C_{19}H_{20}N_2O_3$ (324.37): calcd. C 70.35, H 6.21, N 8.64; found C 70.56, H 5.98, N 8.49.

2-[Phenyl(*m*-tolylamino)methyl]cyclohexanone (2h): IR (KBr): $\tilde{\nu}$ = 3351 (NH), 3038, 2944 (CH), 1702 (CO), 1602, 1538 (C=C), 1306 (NH) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.74–1.82 (m, 2 H, CH_2), 1.92–2.01 (m, 4 H, CH_2), 2.25 (s, 3 H, CH_3), 2.37–2.39 (m, 1 H, CH_2), 2.46–2.49 (m, 1 H, CH_2), 2.74–2.78 (m, 1 H, CH), 4.63 (d, $^3J_{H,H}$ = 6.96 Hz, 0.85 H, CH, *anti* isomer), 4.77 (d, $^3J_{H,H}$ = 3.47 Hz, 0.15 H, CH, *syn* isomer), 4.70 (br. s, 1 H, NH), 6.31 (d, $^3J_{H,H}$ = 6.37 Hz, 1 H, CH^{Ar}), 6.38 (s, 1 H, CH^{Ar}), 6.46 (d, $^3J_{H,H}$ = 7.34 Hz, 1 H, CH^{Ar}), 6.95 (t, $^3J_{H,H}$ = 7.66 Hz, 1 H, CH^{Ar}), 7.25 (t, $^3J_{H,H}$ = 7.15 Hz, 1 H, CH^{Ar}), 7.34 (t, $^3J_{H,H}$ = 7.42 Hz, 2 H, CH^{Ar}), 7.40 (d, $^3J_{H,H}$ = 7.70 Hz, 2 H, CH^{Ar}) ppm. $C_{20}H_{23}NO$ (293.40): calcd. C 81.87, H 7.90, N 4.77; found C 82.01, H 7.69, N 4.88.

2-[(*p*-Nitrophenyl)(*m*-tolylamino)methyl]cyclohexanone (2j): IR (KBr): $\tilde{\nu}$ = 3373 (NH), 2948, 2858 (CH), 1699 (CO), 1601 (C=C), 1516, 1345 (NO_2), 1300, 1100 (NH) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.59–1.67 (m, 1 H, CH_2), 1.78–1.89 (m, 2 H, CH_2), 1.99–2.01 (m, 1 H, CH_2), 2.08–2.11 (m, 2 H, CH_2), 2.24 (s, 3 H, CH_3), 2.34–2.37 (m, 1 H, CH_2), 2.41–2.46 (m, 1 H, CH_2), 2.84–2.88 (m, 1 H, CH), 4.69 (d, $^3J_{H,H}$ = 5.1 Hz, 0.72 H, CH, *anti* isomer), 4.81 (d, $^3J_{H,H}$ = 4.47 Hz, 0.28 H, CH, *syn* isomer), 4.85 (br. s, 1 H, NH), 6.25 (t, $^3J_{H,H}$ = 7.77 Hz, 1 H, CH^{Ar}), 6.33 (s, 1 H, CH^{Ar}), 6.49 (t, $^3J_{H,H}$ = 7.69 Hz, 1 H, CH^{Ar}), 6.94 (t, $^3J_{H,H}$ = 7.75 Hz, 1 H, CH^{Ar}), 7.59 (d, $^3J_{H,H}$ = 8.51 Hz, 2 H, CH^{Ar}), 8.18 (d, $^3J_{H,H}$ = 8.54 Hz, 2 H, CH^{Ar}) ppm. $C_{20}H_{22}N_2O_3$ (338.40): calcd. C 70.99, H 6.55, N 8.28; found C 80.20, H 6.32, N 8.51.

2-[(*p*-Chlorophenyl)(*m*-tolylamino)methyl]cyclohexanone (2k): IR (KBr): $\tilde{\nu}$ = 3349 (NH), 3045, 2939, 2865 (CH), 1703 (CO), 1603, 1531 (C=C), 1487, 1300 (NH), 710 (C–Cl) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.72–1.85 (m, 3 H, CH_2), 1.96–2.01 (m, 3 H, CH_2), 2.64 (s, 3 H, CH_3), 2.35–2.36 (m, 1 H, CH_2), 2.43–2.47 (m, 1 H, CH_2), 2.72–2.75 (m, 1 H, CH), 4.60 (d, $^3J_{H,H}$ = 6.18 Hz, 1 H, CH, *anti* isomer), 4.74 (s, 1 H, NH), 6.29 (d, $^3J_{H,H}$ = 7.98 Hz, 1 H, CH^{Ar}), 6.35 (s, 1 H, CH^{Ar}), 6.48 (d, $^3J_{H,H}$ = 7.43 Hz, 1 H, CH^{Ar}), 6.96 (t, $^3J_{H,H}$ = 7.72 Hz, 1 H, CH^{Ar}), 7.31 (d, $^3J_{H,H}$ = 8.35 Hz, 2 H, CH^{Ar}), 7.35 (d, $^3J_{H,H}$ = 8.46 Hz, 2 H, CH^{Ar}) ppm. $C_{20}H_{22}ClNO$ (327.85): calcd. C 73.27, H 6.76, N 4.27; found C 73.49, H 6.56, N 4.46.

2-[Phenyl(*m*-tolylamino)methyl]cycloheptanone (2o): IR (KBr): $\tilde{\nu}$ = 3344 (NH), 3029, 2944, 2872 (CH), 1702 (CO), 1597, 1531 (C=C), 1501, 1322 (NH) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.31–1.37 (m, 2 H, CH_2), 1.49–1.63 (m, 2 H, CH_2), 1.73–1.75 (m, 1 H, CH_2), 1.93–1.95 (m, 3 H, CH_2), 2.26 (s, 3 H, CH_3), 2.35–2.39 (m, 1 H,

CH_2), 2.50–2.56 (m, 1 H, CH_2), 2.90–2.95 (m, 1 H, CH), 4.52 (d, $^3J_{H,H}$ = 7.47 Hz, 0.89 H, CH, *anti* isomer), 4.64 (d, $^3J_{H,H}$ = 4.53 Hz, 0.11 H, CH, *syn* isomer), 4.94 (br. s, 1 H, NH), 6.34 (d, $^3J_{H,H}$ = 8.24 Hz, 1 H, CH^{Ar}), 6.41 (s, 1 H, CH^{Ar}), 6.47 (d, $^3J_{H,H}$ = 7.47 Hz, 1 H, CH^{Ar}), 6.97 (t, $^3J_{H,H}$ = 7.72 Hz, 2 H, CH^{Ar}), 7.25–7.27 (m, 1 H, CH^{Ar}), 7.30–7.39 (m, 4 H, CH^{Ar}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.1, 25.4, 28.4, 29.6, 29.8, 42.9, 58.9, 60.7, 110.7, 110.9, 114.8, 118.8, 127.5, 127.6, 128.8, 128.9, 129.3, 138.9, 142.0, 147.3, 215.4 ppm. $C_{21}H_{25}NO$ (307.43): calcd. C 82.04, H 8.20, N 4.56; found C 81.83, H 8.43, N 4.34.

4-Phenyl-4-(*m*-tolylamino)butan-2-one (3a): IR (KBr): $\tilde{\nu}$ = 3358 (NH), 3038, 2959 (CH), 1700 (CO), 1602, 1538 (C=C), 1308 (NH) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.14 (s, 3 H, CH_3), 2.27 (s, 3 H, CH_3), 2.90 (d, $^3J_{H,H}$ = 6.25 Hz, 2 H, CH_2), 4.42 (s, 1 H, NH), 4.81 (t, $^3J_{H,H}$ = 6.21 Hz, 1 H, CH), 6.28 (d, $^3J_{H,H}$ = 8.27 Hz, 1 H, CH^{Ar}), 6.35 (s, 1 H, CH^{Ar}), 6.52 (d, $^3J_{H,H}$ = 7.37 Hz, 1 H, CH^{Ar}), 6.97 (t, $^3J_{H,H}$ = 7.73 Hz, 1 H, CH^{Ar}), 7.21–7.35 (m, 5 H, CH^{Ar}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 30.5, 30.9, 31.1, 31.5, 51.3, 54.0, 54.2, 110.8, 111.5, 114.5, 114.8, 115.3, 115.5, 119.1, 119.6, 120.1, 128.0, 129.3, 129.7, 133.4, 138.9, 141.6, 146.7, 205.9 ppm. $C_{17}H_{19}NO$ (253.34): calcd. C 80.60, H 7.56, N 5.53; found C 80.32, H 7.29, N 5.78.

4-(*p*-Chlorophenylamino)-4-phenylbutan-2-one (3b): IR (KBr): $\tilde{\nu}$ = 3349 (NH), 3030, 2940, 2876 (CH), 1706 (CO), 1597, 1535 (C=C), 1497, 1320 (NH), 726 (C–Cl) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.11 (s, 3 H, CH_3), 2.92 (d, $^3J_{H,H}$ = 5.64 Hz, 2 H, CH_2), 4.60 (s, 1 H, NH), 4.76 (t, $^3J_{H,H}$ = 6.11 Hz, 1 H, CH), 6.45 (d, $^3J_{H,H}$ = 8.83 Hz, 1 H, CH^{Ar}), 7.03 (d, $^3J_{H,H}$ = 8.85 Hz 2 H, CH^{Ar}), 7.24–7.30 (m, 1 H, CH^{Ar}), 7.34–7.36 (m, 4 H, CH^{Ar}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 30.7, 51.2, 54.8, 55.0, 114.7, 115.2, 115.7, 123.1, 126.5, 127.9, 129.2, 129.4, 142.4, 145.6, 206.3 ppm. $C_{16}H_{16}ClNO$ (273.76): calcd. C 70.20, H 5.89, N 5.12; found C 69.92, H 6.08, N 5.60.

Supporting Information (see also the footnote on the first page of this article): IR, ^1H and ^{13}C NMR spectroscopic data of compounds **2c**, **2d**, **2f**, **2g**, **2i**, **2l**, **2m**, **2n**, **3d**, and **3e**.

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