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Communication

Cerium Chloride ($CeCl_3 \cdot 7H_2O$) as a Highly Efficient Catalyst for One-Pot Three-Component Mannich Reaction

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Nós demonstramos a utilização de $CeCl_3 \cdot 7H_2O$ como catalisador altamente eficiente para reação de Mannich de três componentes para fornecer compostos β-amino carbonílicos em bons a excelentes rendimentos em curto período de reação. O processo é brando, eficiente e ambientalmente amigável com o uso de pequena quantidade de catalisador.

We have demonstrated the use of $CeCl_3 \cdot 7H_2O$ as highly efficient catalyst for one-pot three-component Mannich reaction to afford β-amino carbonyl compounds in good to excellent yield within shorter period of reaction time. The process is mild, efficient, environmentally benign with the use of little amount of catalyst.

Keywords: Mannich reaction, $CeCl_3 \cdot 7H_2O$, aromatic aldehydes, amines, β-amino carbonyl compounds

Introduction

Three-component reactions have emerged as a useful method, since the combination of three-components to generate new products in a single step is extremely economical, among the multi-component reaction.[1-5]

Our research group focuses on finding efficient chemical transformation using three or more components in a single step by a catalytic process since it avoids use of stoichiometric toxic reagents, large amounts of solvents and expensive purification techniques which is also the fundamental targets of modern organic synthesis.[6]

There are many types of three-component reaction reported in the literature and Mannich reaction is one of the most important C-C bonds forming reaction. Basically, Mannich reaction is the synthesis of β-amino carbonyl compounds and as such is one of the most important reaction in organic synthesis.[7,8] The gaining impetus of the Mannich reaction has been fuelled by the ubiquitous nature of nitrogen containing compounds in drugs[9] and natural products.[10]

However, the classical Mannich reaction is plagued by a number of serious disadvantages with limited applications.[11,12] Therefore, numerous modern versions of Mannich reaction have been developed to overcome the negative aspect of this classical method. In general, improved methodologies rely on two-component system using preformed electrophiles such as imines and stable nucleophiles such as enolates, enols, ethers and enamines,[13,14] but the preferable route is the use of a one-pot three-component strategy as it facilitates wide range of structural variations, but these early three-component reactions were hampered due to a number of serious limitations.[15]

The conventional catalyst for the synthesis of β-amino carbonyl compounds of aldehydes, ketones and amines involve mainly organic and mineral acids like proline,[16-18] acetic acid,[19] *p*-dodecyl benzene sulfonic acid[20] and other Lewis acids.[21,22] They often suffer the drawbacks of long reaction times, harsh reaction conditions, toxicity and difficulty in product isolation. While searching for economical and better catalyst, we thought its worthwhile to perform a controlled reaction for one-pot three-component Mannich reaction catalyzed by cerium(III) chloride heptahydrate ($CeCl_3 \cdot 7H_2O$), which has attracted considerable attention because of its diverse application as a promoter in organic synthesis.[23]

Cerium halides are relatively an effective Lewis acid catalyst,[24] as it is water tolerant, non-toxic, easy to handle, inexpensive and can be reused without further purification.

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In this work, we have found $CeCl_3 \cdot 7H_2O$ as an efficient catalyst for the synthesis of β-amino carbonyl compounds at room temperature through a one-pot three-component reaction of aromatic aldehydes, ketones and aromatic amines in methanol (Scheme 1). It is also noteworthy to mention that our environmentally benign reaction does not generate any toxic waste products.

Results and Discussion

In order to verify the efficient catalytic behavior of $CeCl_3 \cdot 7H_2O$, a controlled reaction was performed using benzaldehyde (1 mmol), aniline (1 mmol) and acetophenone (1 mmol) in methanol (5 mL) at room temperature. In the absence of $CeCl_3 \cdot 7H_2O$, the reaction resulted in the formation of a fused product after 8 h at 50 °C (10% yield). However under same condition by employing 1 mol% of $CeCl_3 \cdot 7H_2O$, the reaction afforded expected products up to 94% yield within 4 h of reaction time.

With this optimistic result in hand, we further investigated the best reaction conditions by using different amounts of $CeCl_3 \cdot 7H_2O$. An increase in the quantity of $CeCl_3 \cdot 7H_2O$ from 1 mol% to 3 mol% not only decreased the reaction time from 4 h to 2 h but also increased the product yield slightly from 85% to 93%. Thus the use of 3 mol% $CeCl_3 \cdot 7H_2O$ is sufficient to push the reaction forward for the optimum yield of β-amino carbonyl compounds (Table 1).

Table 1. Optimization of the concentration of $CeCl_3 \cdot 7H_2O$ in the Mannich reaction[a]

entry	$CeCl_3 \cdot 7H_2O$/mol%	time/h	Yield/(%)[b]
1	0	8	10
2	1	4	85
3	2	2	90
4	3	2	93

[a]Reaction conditions: acetophenone (1 mmol), benzaldehyde (1 mmol) and aniline (1 mmol), x mol% $CeCl_3 \cdot 7H_2O$; solvent methanol; r.t. [b]Isolated yields.

Further, we have also scrutinized this reaction by employing various Lewis acids such as $CuSO_4$, $CeCl_3 \cdot 7H_2O$, $CuCl_2$, $ZnCl_2$, and $AlCl_3$ and we found that $CeCl_3 \cdot 7H_2O$ showed the best result among all the catalysts (Table 2, entry 2). Remarkably, catalyst with high Lewis acidity such as $ZnCl_2$ and $AlCl_3$ failed to catalyze the reaction efficiently and resulted in lower yields of the corresponding product (Table 2).

Table 2. Optimization of various Lewis acids for the Mannich reaction[a]

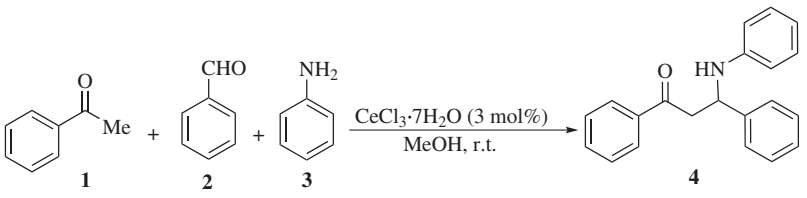
entry	Catalyst	time/h	Yield/(%)[b]
1	$CuSO_4$	2	55
2	$CeCl_3 \cdot 7H_2O$	2	93
3	$CuCl_2$	2	40
4	$ZnCl_2$	2	15
5	$AlCl_3$	2	12

[a]Reaction conditions: acetophenone (1 mmol), benzaldehyde (1 mmol) and aniline (1 mmol), 3 mol% catalyst; solvent: methanol; r.t. [b]Isolated and unoptimized yields.

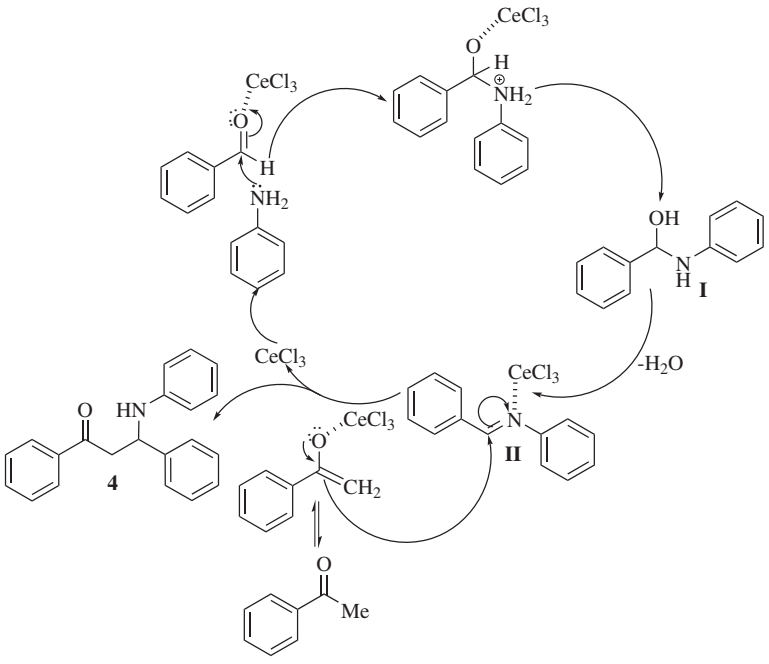
A possible mechanism of $CeCl_3 \cdot 7H_2O$ catalyzed Mannich reaction is shown in Scheme 2. The role of catalyst is the activation of precursors through coordination leading the desired product in good yield with less reaction time. First it coordinates with the carbonyl oxygen of aldehyde and activating it, and then nucleophilic attack by amine gives **I** which in turns gets converted to intermediate imine **(II)** after dehydration. The intermediate **II** again activated by the catalyst through coordination by $CeCl_3$ and then the attack by enol to imine gives the desired product **4**.

Encouraged by these remarkable results, we screened a variety of aromatic aldehydes and amines having electron-withdrawing as well as electron-donating groups and in each case we observed good to excellent yields, however, when *ortho*-substituted anilines were used as substrates, the reaction gave no product probably due to steric hindrance of *ortho*-substituents. In the investigation of various substituted benzaldehydes, it was found that *p*-methylbenzaldehyde is the most reactive substrate in the reaction (Table 3, entry 3). It was observed that the catalyst had no catalytic activity for the reactions when aliphatic aldehydes and amines were used as substrate.

In order to ascertain the scope and limitation of this $CeCl_3 \cdot 7H_2O$ catalyzed Mannich reaction, we have also extended the use of this catalytic systems to the reaction

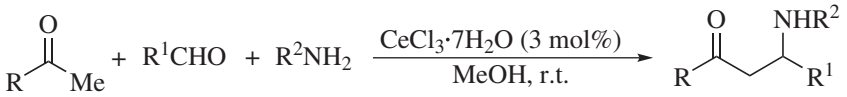


Scheme 1. $CeCl_3 \cdot 7H_2O$-catalyzed Mannich reaction.



Scheme 2. Proposed mechanism of $CeCl_3 \cdot 7H_2O$ catalyzed Mannich reaction.

Table 3. Synthesis of various β-amino carbonyls using $CeCl_3 \cdot 7H_2O$[a]



entry	Ketone	R^1	R^2	time/h	Yield/(%)[b]	mp/(°C)	TON[c]
1	Acetophenone	Ph	4-MeC_6H_4	2.5	96	164-167	32
2	Acetophenone	Ph	Ph	2	93	168-170	31
3	Acetophenone	4-MeC_6H_4	Ph	2.5	97	129-130	32
4	Acetophenone	Ph	4-$OMeC_6H_4$	3	91	162-163	30
5	Acetophenone	Ph	4-$NO_2C_6H_4$	8	73	184-185	24
6	Acetophenone	Ph	4-ClC_6H_4	2.5	95	172-173	31
7	Acetophenone	Ph	3,4-$(Me)_2C_6H_3$	3.5	92	145-146	30
8	Acetophenone	4-$OMeC_6H_4$	Ph	3	91	135-137	30
9	Acetophenone	4-$NO_2C_6H_4$	Ph	8	74	103-104	31
10	Acetophenone	4-$OMeC_6H_4$	4-IC_6H_4	4	76	173-175	25
11	Acetophenone	4-ClC_6H_4	Ph	5	91	118-120	30
12	Acetophenone	Ph	4-IC_6H_4	3	89	168-170	29
13	*p*-Methylacetophenone	Ph	Ph	5	85	138-140	28
14	*p*-Nitroacetophenone	Ph	Ph	5	87	146-148	29
15	Cyclohexanone	Ph	Ph	3	88	137-138	29
16	Cyclohexanone	Ph	4-MeC_6H_4	3.5	90	116-117	30
17	Cyclohexanone	4-$OMeC_6H_4$	Ph	4	83	133-134	27
18	Cyclohexanone	Ph	4-ClC_6H_4	5	91	137-138	30

[a]Reaction conditions: acetophenone (1 mmol), aldehydes (1 mmol) and anilines (1 mmol), 3 mol% $CeCl_3 \cdot 7H_2O$; solvent methanol; r.t. [b]Isolated yields. [c]Turnover number (TON).

of cyclohexanone with various aldehydes and amines as depicted in Table 3. Cyclohexanone showed antiselectivities determined by ^1H NMR analysis of crude products.

Mannich reaction was very sensitive to reaction temperature. The high temperature could improve the reaction rate and shorten the reaction time, but favor side reactions and the oxygenolysis of aldehyde and amine.[25] In our investigation for the effect of temperature we found that $CeCl_3 \cdot 7H_2O$ efficiently catalyzed the Mannich reaction at room temperature.

Table 4. Effect of solvent on the synthesis of β-amino carbonyl ketones[a]

Solvent No.	Solvent	entry 1 (Table 3)		entry 7 (Table 3)	
		time/h	Yield/(%)[b]	time/h	Yield/(%)[b]
1	Ethanol	2	92	2	66
2	PEG 200	2	90	2	62
3	Methanol	2	98	2	70
4	DMF	2	60	2	40
5	DMSO	2	55	2	43
6	MeCN	2	72	2	55
7	Solvent Free	2	-	2	-

[a]Reaction conditions: acetophenone (1 mmol), aldehydes (1 mmol) and anilines (1 mmol), 3 mol% $CeCl_3 \cdot 7H_2O$; solvent methanol; r.t. [b]Isolated yields.

Conclusions

In conclusion, we have developed a novel and efficient catalytic method for Mannich reaction of aldehydes, amines and ketones. We have shown that the reaction proceeds much faster when $CeCl_3 \cdot 7H_2O$ is employed as a catalyst compare to uncatalyzed reaction. The most attractive part of this work is that only small amount of catalyst is needed for catalyzing the reaction. The simple experimental procedures, fast reaction rates and easy isolation of products make this procedure very useful and environment friendly. In addition, our method does not require expensive reagents and high temperature for the synthesis of β-amino carbonyl compounds compared to the traditional protocols and has broad substrate applicability with ease and much improved yields.

Experimental

General experimental procedures

All chemicals were purchased from Sigma-Aldrich and Lancaster and were used as such. All reactions and purity of β-amino carbonyl compounds were monitored by thin layer chromatography (TLC) using aluminium plates coated with silica gel (Merck) using 20% and 80% petroleum ether as an eluent. The isolated products were further purified by column chromatography using silica gel G (particle size 10-40 microns, 300 mesh) purchased from Spectrochem Pvt. Ltd. Mumbai, India and purified product were recrystallized. Melting points are determined on Buchi 530. IR spectra were recorded on Perkin-Elmer FTIR-1710 spectrophotometer using KBr. ^{1}H NMR spectra were recorded on a Bruker Avance Spectrospin 300 (300 MHz) using TMS as internal standard and chemical shift are in δ. GC-MS mass spectra were recorded on a Waters LCT Micromass. The temperature of the reaction mixture was measured through a non-contact infrared thermometer (AZ, Mini Gun type, Model 8868).

Typical experimental procedure for the synthesis of β-aminocarbonyls

In a 50 mL round bottom flask, acetophenone (1 mmol), aromatic aldehydes (1 mmol) and aromatic amines (1 mmol) in MeOH (5 mL) were mixed and stirred at room temperature. To this, $CeCl_3 \cdot 7H_2O$ (cerium chloride heptahydrate) (3 mol%) was added. The progress of reaction mixture was monitored by TLC (using petroleum ether/AcOEt = 80:20 as an eluent). After completion of the reaction, the solid product was collected by filtration at pump and washed with methanol and water. The crude product was subjected to purification by recrystalization using ethanol, was subjected to further purification by silica gel column chromatography using 15% ethyl acetate, and 85% petroleum ether as an eluent to yield the β-amino carbonyl compounds. The structures of all the products were unambiguously established on the basis of their spectral analysis (IR, ^{1}H NMR and GC/MS mass spectral data). All the products are known compounds.

Supplementary Information

Supplementary data are available free of charge at http://jbcs.sbq.org.br, as PDF file.

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Cerium Chloride ($CeCl_3 \cdot 7H_2O$) as a Highly Efficient Catalyst for One-Pot Three-Component Mannich Reaction

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*1,3-Diphenyl-3-p-tolylamino-propan-1-one, (**1**)*

A white solid; R_f = 0.70 (petroleum ether/AcOEt = 80:20); IR (KBr) ν_{max}/cm^{-1}: 3383 (NH), 1698 (CO). ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 2.47 (s, 3H, $-CH_3$), 3.62-3.45 (m, 2H), 4.47 (t, 1H), 6.91 (d, *J* 8.5 Hz, 2H, Ar-H), 6.97 (d, *J* 7.9, 2H, Ar-H), 7.07-7.03 (m, 2H, Ar-H), 7.15 (d, *J* 6.3 Hz, 2H, Ar-H), 7.32-7.28 (m, 1H, Ar-H), 7.49-7.46 (m, 2H, Ar-H), 7.69-7.66 (m, 1H, Ar-H), 7.83 (d, *J* 7.9 Hz, 2H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.3, 45.5, 56.7, 113.1, 120.5, 122.5, 128.9, 128.3, 130.4, 133.1, 135.3, 144.6, 196.6. *m/z* (GC-MS, HRMS): 313.362 (M^+). Anal. Calc. for $C_{22}H_{21}NO$: C, 83.78; H, 6.71; N, 4.44. Found: C, 82.98; H, 6.81; N, 4.42.

*1,3-Diphenyl-3-phenylamino-propan-1-one, (**2**)*

A white solid; R_f = 0.68 (petroleum ether/AcOEt = 80:20); IR (KBr) ν_{max}/cm^{-1}: 3386 (NH), 1671 (CO). ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 3.47-3.32(m, 2H), 4.98 (t, 1H), 6.51 (d, *J* 8.0 Hz, 2H, Ar-H), 6.63-6.69 (m, 1H, Ar-H). 7.04-7.00 (m, 2H, Ar-H), 7.20(d, *J* 6.5 Hz, 2H, Ar-H), 7.26-7.23(m, 1H, Ar-H), 7.41-7.38 (m, 2H, Ar-H), 7.51-7.45 (m, 1H, Ar-H), 7.57-7.53(m, 2H, Ar-H), 7.84 (d, *J* 7.8 Hz, 2H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 46.3, 54.2, 115.3, 119.4, 126.4, 128.6, 128.8, 129.5, 132.3, 135.8, 146.2, 197.0. *m/z* (GC-MS, HRMS): 301.368 (M^+). Anal. Calc. for $C_{20}H_{18}NO$: C, 83.30; H, 6.29; N, 4.86. Found: C, 82.98; H, 6.15; N, 4.23.

*1-Phenyl-3-phenylamino-3-p-tolyl-propan-1-one, (**3**)*

A white solid; R_f = 0.61 (petroleum ether/AcOEt = 80:20); IR (KBr) ν_{max}/cm^{-1}: 3387 (NH), 1667 (CO). ^1H NMR (300 MHz, TMS , $CDCl_3$): δ 2.27 (s, 3H, $-CH_3$), 3.45-3.31 (m, 2H), 4.82 (t, 1H), 6.75 (d, *J* 8.1 Hz, 2H, Ar-H), 6.83-6.91 (m, 1H, Ar-H), 7.08-7.04 (m, 2H, Ar-H), 7.10 (d, *J* 7.8 Hz, 2H, Ar-H), 7.21 (d, *J* 7.38-7.27 (4 Hz, 2H, Ar-H), 7.41-7.36 (m, 2H, Ar-H), 7.49-7.41 (m, 1H, Ar-H), 7.89 (d, *J* 8.1 Hz, 2H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.7, 42.7, 54.5, 111.4, 119.5, 123.6, 127.4, 128.6, 131.9, 132.3, 135.4, 143.2, 190.6. *m/z* (GC-MS, HRMS): 317.402 (M^+). Anal. Calc. for $C_{22}H_{21}NO$: C, 83.78; H, 6.71; N, 4.44. Found: C, 82.85; H, 6.56; N, 4.37.

*3-(4-Methoxy-phenylamino)-1,3-diphenyl-propan-1-one, (**4**)*

A white solid; R_f = 0.64 (petroleum ether/AcOEt = 80:20); IR (KBr) ν_{max}/cm^{-1}: 3385 (NH), 1675 (CO). ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 3.44-3.39 (m, 2H), 3.58 (s, 3H, $-OCH_3$), 4.86 (t, 1H), 6.51 (d, *J* 8.6 Hz, 2H, Ar-H), 6.71 (d, *J* 8.9, 2H, Ar-H), 6.96-7.05 (m, 1H, Ar-H), 7.15 (d, *J* 8.3 Hz, 2H, Ar-H), 7.30-7.24 (m, 2H, Ar-H), 7.41-7.38 (m, 2H, Ar-H), 7.53-7.33 (m, 1H, Ar-H), 7.81 (d, *J* 7.5 Hz, 2H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 46.2, 55.3, 58.2, 115.2, 122.7, 126.2, 127.1, 128.6, 128.8, 128.9, 129.3, 132.5, 138.5, 141.7, 1510.2, 195.6. *m/z* (GC-MS, HRMS): 332.473 (M^+). Anal. Calc. for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.23. Found: C, 79.58; H, 6.73; N, 4.37.

*3-(4-Nitro-phenylamino)-1,3-diphenyl-propan-1-one, (**5**)*

A white solid; R_f = 0.48 (petroleum ether/AcOEt = 80:20); IR (KBr) ν_{max}/cm^{-1}: 3364 (NH), 1627 (CO). ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 3.67 (d, *J* 6.8 Hz, 2H), 5.12 (t, 1H), 6.37 (brs, 2H, Ar-H), 6.64 (d, *J* 6.4, 2H, Ar-H), 7.24-7.20 (m, 1H, Ar-H), 7.38-7.29 (m, 2H, Ar-H), 7.37 (d, *J* 7.7 Hz, 2H, Ar-H), 7.67-7.59 (m, 1H, Ar-H), 8.01 (d, *J* 7.2 Hz, 2H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 45.2, 53.1, 111.7, 125.9, 126.1, 127.4, 128.9, 128.2, 128.1, 130.5, 132.8, 136.7, 138.6, 140.0, 197.8. *m/z* (GC-MS, HRMS): 348.637 (M^+). Anal. Calc. for $C_{21}H_{18}N_2O_3$: C, 72.82; H, 5.24; N, 8.09. Found: C, 72.42; H, 5.76; N, 7.96.

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*3-(4-Chloro-phenylamino)-1,3-diphenyl-propan-1-one, (**6**)*

A white solid; R_f = 0.79 (petroleum ether/AcOEt = 80:20); IR (KBr) ν_{max}/cm^{-1}: 3325 (NH), 1654 (CO). ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 3.54-3.37 (m, 2H), 4.91 (t, 1H), 6.35 (d, *J* 8.4 Hz, 2H, Ar-H), 6.68 (d, *J* 8.1, 2H, Ar-H), 7.11 (d, *J* 6.6 Hz, 2H, Ar-H), 7.28-7.22 (m, 2H, Ar-H), 7.34-7.31 (m, 2H, Ar-H), 7.42-7.38 (m, 2H, Ar-H), 7.51-7.47 (m, 1H, Ar-H), 7.86 (d, *J* 7.8 Hz, 2H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 44.08, 55.1, 116.4, 122.5, 125.7, 127.3, 128.4, 128.7, 129.3, 133.6, 137.5, 140.6, 197.4. *m/z* (GC-MS, HRMS): 335.832 (M^+). Anal. Calc. for $C_{21}H_{18}ClNO$: C, 75.11; H, 5.40; N, 4.17. Found: C, 75.41; H, 5.36; N, 4.31.

*3-(3,4-Dimethyl-phenylamino)-1,3-diphenyl-propan-1-one, (**7**)*

A white solid; R_f = 0.73 (petroleum ether/AcOEt = 80:20); IR (KBr) ν_{max}/cm^{-1}: 3410 (NH), 1702 (CO). ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 2.35 (s, 6H, $-CH_3$), 3.10 (d, *J* 6.1, 2H), 4.56 (t, 1H), 6.28 (s, 1H, Ar-H), 6.29 (d, *J* 6.8 Hz, 2H, Ar-H), 6.65 (d, *J* 8.1, 2H, Ar-H), 7.05-7.11 (m, 1H, Ar-H), 7.28 (d, *J* 6.7 Hz, 2H, Ar-H), 7.31-7.28 (m, 2H, Ar-H), 7.34-7.30 (m, 2H, Ar-H), 7.49-7.42 (m, 1H, Ar-H), 7.93 (d, *J* 7.8 Hz, 2H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.3, 42.4, 55.7, 115.4, 123.2, 126.5, 128.6, 128.7, 129.7, 129.8, 131.3, 137.4, 141.4, 192.5. *m/z* (GC-MS, HRMS): 327.432 (M^+). Anal. Calc. for $C_{23}H_{23}NO$: C, 83.85; H, 7.04; N, 4.25. Found: C, 82.89; H, 7.18; N, 4.10.

*3-(4-Methoxy-phenyl)-1-phenyl-3-phenylamino-propan-1-one, (**8**)*

A white solid; R_f = 0.67 (petroleum ether/AcOEt = 80:20); IR (KBr) ν_{max}/cm^{-1}: 3401 (NH), 1679 (CO). ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 3.47-3.40 (m, 2H), 3.62 (s, 3H, $-OCH_3$), 4.96 (t, 1H), 6.47 (d, *J* 8.1 Hz, 2H, Ar-H), 6.52 (t, 1H, Ar-H), 6.90-6.86 (m, 2H, Ar-H), 7.23 (d, *J* 8.2 Hz, 2H, Ar-H), 7.33-7.28 (m, 2H, Ar-H), 7.44-7.41 (m, 2H, Ar-H), 7.54-7.51 (m, 1H, Ar-H), 7.89 (d, *J* 7.5 Hz, 2H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 47.6, 54.2, 56.2, 113.2, 113.9, 116.4, 128.6, 128.1, 127.9, 129.4, 132.9, 134.2, 137.7, 160.2, 198.2. *m/z* (GC-MS, HRMS): 331.423 (M^+). Anal. Calc. for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.23. Found: C, 79.64; H, 6.48; N, 4.31.

*3-(4-Nitro-phenyl)-1-phenyl-3-phenylamino-propan-1-one, (**9**)*

A white solid; R_f = 0.54 (petroleum ether/AcOEt = 80:20); IR (KBr) ν_{max}/cm^{-1}: 3372 (NH), 1681 (CO). ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 3.52 (d, *J* 6.1 Hz, 2H), 5.13 (t, 1H), 6.52 (d, *J* 6.5 Hz, 2H, Ar-H), 6.66-6.70 (m, 1H, Ar-H), **7**.07-7.11 (m, 2H, Ar-H), 7.48-7.43 (m, 2H, Ar-H), 7.59-7.55 (m, 2H, Ar-H), 7.65 (d, *J* 7.5 Hz, 2H, Ar-H), 7.87 (d, *J* 8.0 Hz, 2H, Ar-H), 8.16 (d, *J* 9.6 Hz, 2H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 46.4, 54.1, 112.8, 116.8, 123.4, 128.2, 128.4, 128.6, 129.3, 132.6, 137.6, 140.2, 143.6, 146.4, 198.4. *m/z* (GC-MS, HRMS): 346.381 (M^+). Anal. Calc. for $C_{21}H_{18}N_2O_3$: C, 72.82; H, 5.24; N, 8.09. Found: C, 72.92; H, 5.13; N, 8.16.

*3-(4-Bromo-phenyl)-1-phenyl-3-phenylamino-propan-1-one, (**10**)*

A white solid; R_f = 0.59 (petroleum ether/AcOEt = 80:20); IR (KBr) ν_{max}/cm^{-1}: 3385 (NH), 1670 (CO). ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 3.41 (d, *J* 5.6, 2H), 3.69 (s, 3H, $-OCH_3$), 4.91 (t, 1H), 6.48 (d, *J* 7.6 Hz, 2H, Ar-H), 6.70 (d, *J* 6.9 Hz, 2H, Ar-H), 7.04 (d, *J* 6.7 Hz, 2H, Ar-H), 7.33 (d, *J* 7.6 Hz, 2H, Ar-H), 7.46-7.41 (m, 2H, Ar-H), 7.58-7.54 (m, 1H, Ar-H), 7.90 (d, *J* 6.7 Hz, 2H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 47.2, 54.4, 56.8, 112.8, 113.9, 86.8, 127.8, 128.3, 128.1, 138.6, 132.9, 134.2, 137.7, 160.7, 197.8. *m/z* (GC-MS, HRMS): 457.348 (M^+). Anal. Calc. for $C_{22}H_{20}NO_2$: C, 57.78; H, 4.41; N, 3.06. Found: C, 57.92; H, 4.33; N, 3.17.

*3-(4-Chloro-phenyl)-1-phenyl-3-phenylamino-propan-1-one, (**11**)*

A white solid; R_f = 0.70 (petroleum ether/AcOEt = 80:20); IR (KBr) ν_{max}/cm^{-1}: 3382 (NH), 1690 (CO). ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 3.48 (d, *J* 5.8 Hz, 2H), 5.18 (t, 1H), 6.60 (d, *J* 6.2 Hz, 2H, Ar-H), 6.68-6.73 (m, 1H, Ar-H), 7.07-7.12 (m, 2H, Ar-H), 7.28 (d, *J* 7.6 Hz, 2H, Ar-H), 7.52 (d, *J* 8.1 Hz, 2H, Ar-H), 7.60-7.67 (m, 2H, Ar-H), 7.71-7.76 (m, 1H, Ar-H), 7.96 (d, *J* 9.1 Hz, 2H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 47.9, 53.7, 111.5, 115.3, 128.1, 128.6, 128.7, 128.9, 129.6, 131.8, 136.5, 141.1, 144.5, 196.6. *m/z* (GC-MS, HRMS): 337.416 (M^+). Anal. Calc. for $C_{21}H_{18}ClNO$: C, 75.11; H, 5.40; N, 4.17. Found: C, 75.32; H, 5.67; N, 4.23.

*3-(4-Iodo-phenylamino)-1,3-diphenyl-propan-1-one, (**12**)*

A white solid; R_f = 0.63 (petroleum ether/AcOEt = 80:20); IR (KBr) ν_{max}/cm^{-1}: 3383 (NH), 1669 (CO). ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 3.34 (m, 2H), 4.64 (t, 1H), 6.24 (d, *J* 7.0 Hz, 2H, Ar-H), 6.96 (d, *J* 8.1 Hz, 2H, Ar-H), 7.06-7.02 (m, 1H, Ar-H), 7.14-7.10 (m, 2H, Ar-H), 7.25 (d, *J* 6.3 Hz, 2H, Ar-H), 7.34-7.29 (m, 2H, Ar-H), 7.45-7.42 (m, 1H, Ar-H), 7.83 (d, *J* 8.1 Hz, 2H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 46.4, 55.3, 113.2, 126.2, 126.4, 127.8, 128.5, 128.7, 128.9, 132.3, 132.5, 137.5, 138.8, 142.8, 198.2. *m/z* (GC-MS, HRMS): 346.382 (M^+). Anal. Calc. for $C_{21}H_{18}INO$: C, 59.03; H, 4.25; N, 3.28. Found: C, 59.12; H, 4.17; N, 3.34.

*3-Phenyl-3-phenylamino-1-p-tolyl-propan-1-one, (**13**)*

A white solid; R_f = 0.74 (petroleum ether/AcOEt = 80:20); IR (KBr) ν_{max}/cm^{-1}: 3380 (NH), 1670 (CO). ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 2.42 (s, 3H, $-CH_3$), 3.45 (d, *J* 5.9 Hz, 2H), 4.93 (t, 1H), 6.43 (d, *J* 7.8 Hz, 2H, Ar-H), 6.58 (m, 1H, Ar-H). 6.98 (m, 2H, Ar-H), 7.11 (d, *J* 6.4 Hz, 2H, Ar-H), 7.27-7.19 (m, 3H, Ar-H), 7.43 (d, 7.8 Hz, 2H, Ar-H), 7.86 (d, *J* 7.2 Hz, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.7, 44.2, 52.3, 109.2, 113.5, 124.2, 126.3, 127.3, 127.5, 128.1, 128.4, 131.5, 140.2, 141.7, 194.3. *m/z* (GC-MS, HRMS): 316.374 (M^+). Anal. Calc. for $C_{22}H_{21}NO$: C, 83.78; H, 6.71; N, 4.44. Found: C, 83.92; H, 6.61; N, 4.37.

*1-(4-Nitro-phenyl)-3-phenyl-3-phenylamino-propan-1-one, (**14**)*

A white solid; R_f = 0.49 (petroleum ether/AcOEt = 80:20); IR (KBr) ν_{max}/cm^{-1}: 3400 (NH), 1678 (CO). ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 3.44-3.57 (m, 2H), 5.10 (t, 1H), 6.48 (d, *J* 6.2 Hz, 2H, Ar-H), 6.69-6.63 (m, 2H, Ar-H). 6.80-6.83 (m, 1H, Ar-H), 7.14 (d, *J* 7.6 Hz, 2H, Ar-H), 7.23-7.26 (m, 1H, Ar-H), 7.31-7.35 (m, 2H, Ar-H), 7.62 (d, *J* 6.3 Hz, 2H, Ar-H); 7.92 (d, *J* 7.2 Hz, 2H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 46.2, 53.4, 110.1, 114.9, 122.7, 123.5, 126.1, 127.9, 128.3, 128.8, 142.6, 141.3, 151.8, 196.4. *m/z* (GC-MS, HRMS): 346.217 (M^+). Anal. Calc. for $C_{21}H_{18}N_2O_3$: C, 72.82; H, 5.24; N, 8.09. Found: C, 72.96; H, 5.34; N, 8.11.

*2-(Phenyl-phenylamino-methyl)-cyclohexanone, (**15**)*

A white solid; R_f = 0.68 (Petroleum Ether/AcOEt = 80:20); IR (KBr) ν_{max}/cm^{-1}: 3390 (NH), 1690 (CO). ^1H NMR (300 MHz, TMS, $CDCl_3$, syn/anti = 48:52): δ 1.25-1.76 (m, 6H), 2.28-2.44 (m, 2H), 2.73-2.78 (m, 1H), 4.62 (d, 0.52H, *J* 7.6 Hz), 4.70 (brs, 1H), 4.79 (d, 0.48H, *J* 4.8 Hz), 6.37 (d, *J* 7.3 Hz, 2H, Ar-H), 6.51-6.63 (m, 1H, Ar-H), 7.02-7.07 (m, 2H, Ar-H), 7.19-7.26 (m, 1H, Ar-H), 7.29-7.37 (m, 2H, Ar-H), 7.60 (d, *J* 7.8 Hz, 2H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.2, 24.5, 28.3, 36.7, 52.1, 57.4, 108.6, 113.5, 123.1, 127.5, 128.9, 138.6, 140.4, 203.8. *m/z* (GC/MS, HRMS): 283.329 (M^+). Anal. Calc. for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.34; H, 7.45; N, 5.23.

*2-(phenyl-p-tolylamino-methyl)-cyclohexanone, (**16**)*

A white solid; R_f = 0.62 (petroleum ether/AcOEt = 80:20); IR (KBr) ν_{max}/cm^{-1}: 3406 (NH), 1702 (CO). ^1H NMR (300 MHz, TMS, $CDCl_3$, syn/anti = 34:66): δ 1.33-1.89 (m, 6H), 2.14 (s, 3H, $-CH_3$), 2.36-2.57 (m, 2H), 2.97-3.04 (m, 1H), 4.52 (d, 0.34H, *J* 5.2 Hz), 4.52 (d, 0.66H, *J* 6.8 Hz), 4.77 (brs, 1H), 6.45 (d, *J* 7.5 Hz, 2H, Ar-H), 6.84 (d, *J* 8.2 Hz, 2H, Ar-H), 7.02-7.18 (m, 1H, Ar-H), 7.32-7.42 (m, 2H, Ar-H), 7.62 (d, *J* 7.1 Hz, 2H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.0, 23.2, 25.7, 32.9, 43.3, 55.1, 57.3, 113.3, 127.6, 126.8, 126.4, 127.1, 128.9, 140.4, 142.5, 209.2. *m/z* (GC/MS, HRMS): 296.106 (M^+). Anal. Calc. for $C_{20}H_{23}NO$: C, 81.87; H, 7.90; N, 4.77. Found: C, 81.69; H, 7.56; N, 4.13.

*(2-(4-Methoxy-phenyl)-phenylamino-methyl)-cyclohexanone, (**17**)*

A white solid; R_f = 0.69 (petroleum ether/AcOEt = 80:20); IR (KBr) ν_{max}/cm^{-1}: 3332 (NH), 1690 (CO). ^1H NMR (300 MHz, TMS, $CDCl_3$, syn/anti = 42:58): δ 1.68-1.93 (m, 6H), 2.42-2.47 (m, 2H), 2.72-2.76 (m, 1H), 3.89 (s, 3H, OCH_3), 4.08 (d, 0.58H, *J* 7.3 Hz), 4.63 (d, 0.42H, *J* 4.4 Hz), 4.71 (br, s, 1H), 6.64-6.61 (m, 1H, Ar-H), 6.68 (d, *J* 8.3 Hz, 2H, Ar-H), 7.10-7.03 (m, 2H, Ar-H), 7.16 (d, *J* 7.6 Hz, 2H, Ar-H), 7.27 (d, *J* 8.4 Hz, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.8, 23.2, 27.8, 30.9, 41.3, 57.2, 56.3, 113.1, 117.2, 126.8, 128.6, 128.8, 136.4, 138.2, 147.0, 212.7. *m/z* (GC/MS, HRMS): (M^+). Anal. Calc. for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.43; H, 7.58; N, 4.59.

*(2-(4-Chloro-phenylamino)-phenyl-methyl)-cyclohexanone, (**18**)*

A yellowish solid; R_f = 0.73 (petroleum ether/AcOEt = 80:20); IR (KBr) ν_{max}/cm^{-1}: 3378 (NH), 1674 (CO). ^1H NMR (300 MHz, TMS, $CDCl_3$, syn/anti = 28:72): δ 1.60-1.92 (m, 6H), 2.28-2.31 (m, 2H), 2.65-2.61 (m, 1H), 4.10 (d, 0.72H, *J* 8.2 Hz), 4.30 (d, 0.28H, *J* 4.1 Hz), 4.56 (brs, 1H), 6.58 (d, *J* 7.3 Hz, 2H, Ar-H), 6.98 (d, *J* 8.7 Hz, 2H, Ar-H), 7.22-7.17 (m, 1H, Ar-H), 7.41-7.48 (m, 2H, Ar-H), 7.56 (d, *J* 8.9 Hz, 2H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.9, 25.1, 28.7, 40.1, 54.6, 57.3, 112.6 120.1, 124.9, 128.1, 138.6, 140.5, 210.4. *m/z* (GC/MS, HRMS): 344.281 (M^+). Anal. Calc. for $C_{19}H_{20}ClNO$: C, 72.72; H, 6.42; N, 4.46. Found: C, 72.68; H, 6.32; N, 4.41.