CHAPTER II

SYNTHESIS OF $\beta$-AMINO CARBONYL COMPOUNDS USING IODINE AS CATALYST
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2.1. GENERAL INTRODUCTION

The development of new methods for the synthesis β-amino carbonyl compounds is an important area of research, because β-amino ketones and esters are extremely important as biologically active molecules.¹ β-Amino carbonyls are potentially useful intermediates for Wittig-type condensation²–⁸ and natural products,³,⁴ β-amino acids¹,⁹ and 1,3-amino alcohols¹⁰–¹² and are also found in natural products. Besides that these compounds have applications in plant protection and in paint and polymer chemistry.¹³ However, the most important application is in the area of pharmaceutical products. A collection of some pharmaceutically important products are represented in Figure 2.1.

Since β-amino carbonyl compounds are important building blocks for synthesis of various pharmaceutically important compounds, it will be useful if an efficient method can be developed for its synthesis.
Figure 2.1
Mannich reactions provide a useful route for synthesis of this \( \beta \)-amino carbonyl compounds.\(^{14}\) In the original Mannich reaction, formaldehyde is condensed with ammonia, in the form of its salt and a compound containing active hydrogen in presence of acid or base (Scheme 2.1).\(^{15}\)

\[
\begin{align*}
\text{HCHO} & + \text{NH}_4\text{Cl} + \text{RCO} & \overset{H^+ \text{ or } \text{OH}^-}{\longrightarrow} & \text{H}_2\text{NCO} \text{R}
\end{align*}
\]

Scheme 2.1

Instead of ammonia, primary or secondary amines or amides can also be used. In classical Mannich reaction, yield is low due to side reactions such as deamination. Therefore, a number of methods have been developed for indirect synthesis of \( \beta \)-amino carbonyl compounds These methods use preformed imines or iminium salts and preformed enolates.

This chapter deals with the development of a synthetic methodology for \( \beta \)-amino carbonyl compounds in presence of iodine as catalyst. This chapter is divided into two sections. The first section describes the synthesis of \( \beta \)-amino esters by three component Mannich-type reaction of aldehydes, silyl ketene acetals and benzyl carbamates and the second section describes the synthesis of \( \beta \)-amino ketones by direct three-component Mannich reaction of aldehydes, ketones and benzyl carbamates using iodine as catalyst.
2.2.1. INTRODUCTION

β-Amino esters have various applications in chemical as well as pharmaceutical industries. These compounds are used as catalyst in producing polyurethane polymers.\textsuperscript{16} Poly(ethylene oxide)-modified poly(β-amino ester) nanoparticles are used as a pH sensitive system for tumor-targeted delivery of hydrophobic drugs.\textsuperscript{17-20}

Amino sterol esters have interesting antibiotic and antiproliferation properties of certain types of cells.\textsuperscript{21} Polymeric β-amino ester compounds are used in the formation of nanoparticles and microparticles containing encapsulated agents. Polymeric β-amino ester compounds are also applicable for gene transfer.\textsuperscript{22,23}

Poly(β-amino esters) are end modified to form materials useful in the medical as well as non-medical field.\textsuperscript{24} The end-modified polymers may be used in any field where polymers have been found useful including the drug delivery arts.
2.2.2. REVIEW OF LITERATURE

Mannich reaction is one of the most important and widely used method for synthesis of β-amino ester compounds. The original protocol for three component Mannich reaction of amines, aldehydes and ketones in organic solvents include severe side reactions and have some substrate limitations, especially for enolizable aliphatic aldehydes. The classical intermolecular Mannich reaction is also plagued by a number of serious disadvantages because of the drastic reaction conditions and long reaction times. Numerous modified versions of the Mannich reaction have been developed to obviate the problems associated with the classical Mannich reaction. Most of these methods utilized preformed imines or iminium salts and preformed enolate equivalents such as silyl enol ether or silyl ketene acetics. In 1977, the reactions of imines with silyl enol ethers in the presence of a stoichiometric amount of TiCl₄ as a promoter were first reported (Scheme 2.2).

![Scheme 2.2](image)

Since then many methodologies were reported that uses catalytic amount of Lewis acid promoters such as TMSOTf, a diphosphonium salt, FeI₂, a trityl salt, montmorillonite, or B(C₆F₆)₃. However, these Lewis acid–catalyzed one-pot Mannich reactions had to be carried out under strict anhydrous conditions because many of the imines are hygroscopic and...
thermally unstable. Again, most Lewis acids could not be used in this reaction because they decompose or deactivate in the presence of the amines and water produced during imine formation.\(^{32}\)

Thus, the development of Mannich reaction methods is always in high demand. Several catalytic systems have been reported and applied to the Mannich-type reaction. Under those reaction conditions, imines could be activated effectively, and the Mannich reaction could proceed smoothly to afford the \(\beta\)-amino esters in good yields. Kobayashi et al.\(^{33-35}\) found that rare earth metal triflates such as ytterbium triflate \([\text{Yb(OTf)}_3]\) and scandium triflate \([\text{Sc(OTf)}_3]\) activate the imines effectively. They reported a highly efficient one-pot Mannich-type reaction aldehydes, amines and enolates for synthesis of \(\beta\)-amino esters in presence of these catalysts. They also developed a Mannich-type reaction of \(N\)-(\(\alpha\)-aminoalkyl)benzotriazoles with silyl enolates by using the same catalyst system (Scheme 2.3).\(^{36}\)

![Scheme 2.3](image)

The reactions with chiral amines provided \(\beta\)-amino ester compounds in moderate to excellent diastereoselectivities.\(^{37}\) Kobayashi et al.\(^{38}\) demonstrated the first Lewis acid catalyzed direct-type three component Mannich reactions of aldehydes, secondary amines and glycine derivatives (Scheme 2.4). The reaction with aromatic aldehydes affords the
corresponding *anti*-α,β-diamino ester derivatives in high yields with high diastereoselectivities.

\[
\begin{align*}
\text{R}^1 & \quad \text{HN}^2 \\
\text{Ar} & \quad \text{Ar}
\end{align*}
\]

**Scheme 2.4**

However, the reaction with an aliphatic aldehyde gave the product in lower diastereoselectivity. The rate of the reaction was largely accelerated in ionic liquids compared to in organic or water solvents. Lee and Park\(^3\) developed a novel methodology for synthesis of β-amino esters in environmentally benign ionic liquids using Yb(OTf)\(_3\) as catalyst. In this reaction, the ionic liquids acts as powerful reaction media and itself acts as a catalyst. Kobayashi *et al.*\(^4\) also developed a surfactant aided Lewis or Brønsted acid catalyzed three component Mannich-type reactions in aqueous media. These catalysts formed stable colloidal dispersion systems with organic substrates in water and catalyzed the Mannich reactions efficiently. Hydrophobic polystyrene-supported sulfonic acid (PS-SO\(_3\)H) was also found to be efficient for three component Mannich-type reactions in aqueous media.\(^4\) Later on, Akiyama and coworkers\(^5\) have found that Mannich-type reaction of aldehydes, amines, and silyl enolate could proceed smoothly in the presence of a catalytic amount of HBF\(_4\). Chen *et al.*\(^6\) attempted to examine this reaction in the presence of silica supported HBF\(_4\). Mannich-type reactions on solid phase were successfully carried out using scandium triflate [Sc(OTf)\(_3\)] as a catalyst.\(^7\) Microencapsulated
Sc(OTf)₃-catalyzed Mannich-type reactions were also reported. Loh et al. developed an indium chloride catalyzed three component Mannich-type reaction in aqueous media. It was found that the Mannich-type reaction involving aldehydes, amines, and silyl enol ethers/ketene silyl acetals proceeds smoothly in water under the catalysis of InCl₃ to afford the β-amino carbonyl compounds in high yields, but this method was limited to the addition of nonenolizable aldehydes and aromatic amines. Later on, they developed another indium chloride catalyzed method using MeOH as solvent. This method works with both aromatic and aliphatic aldehydes as well as with enolizable aldehydes. Ollevier and Nadeau reported a bismuth triflate catalyzed three component Mannich-type reaction where imines were formed in situ.

In 1991, Corey et al. reported the first example of the enantioselective synthesis of β-amino acid esters using chiral boronenolates (Scheme 2.5).

![Scheme 2.5](image)

Yamamoto et al. reported another enantioselective Mannich-type reaction using a stoichiometric amount of Brønsted acid-assisted chiral Lewis acid.
In 1997, Kobayashi et al.\textsuperscript{57,58} reported the first enantioselective Mannich-type reaction of imines with silyl enolates using a zirconium catalyst and the method showed high levels of enantioselectivity in the synthesis of chiral $\beta$-amino ester derivatives. Kobayashi\textsuperscript{59,60} reported that in the presence of catalytic amount of Cu(OTf)$_2$-chiral diamine complex, $N$-acyliminoesters react with silyl enol ethers to afford the Mannich-type adducts in high yields with high enantioselectivities (Scheme 2.6).

Josephsohn\textsuperscript{61} reported the synthesis of $\beta$-alkynyl $\beta$-amino esters by the same catalytic reaction. Urea derivatives also served as an efficient catalyst for asymmetric addition of silyl ketene acetalts to aldamines\textsuperscript{62}.
2.2.3. PRESENT WORK

OBJECTIVE

Mannich reaction is an important reaction for synthesis of \( \beta \)-amino ester compounds. A number of literature reports are found for synthesis of \( \beta \)-amino esters by Mannich reaction. However, there are limitations such as the use of toxic metal salts as catalysts, expensive reagents or catalysts, moisture sensitivity of the catalyst, low yield, etc. Moreover, most of these methods use anilines or benzyl amine as nitrogen source and hence deprotection of the resulting amino compound is difficult. So, the attempt to extend the applicability of catalytic protocols to less reactive compounds such as carbamate is one of the challenges. The objective of our work is to synthesize \( \beta \)-amino ester compounds using benzyl carbamate as nitrogen source and iodine as catalyst. We would like to carry out the synthesis by three component Mannich-type reaction of aldehydes, silyl ketene acetals and benzyl carbamates to afford the corresponding \( \beta \)-amino ester compounds (Scheme 2.7).

\[
\begin{align*}
\text{R} & \quad \text{H} + \quad \text{O} \quad \text{O} \quad \text{NH}_2 + \quad \text{OTMS} \quad \text{O} \quad \text{Me} & \quad \xrightarrow{\text{I}_2 (10 \text{ mol\%})} \quad \text{CH}_3\text{CN, r t}} & \quad \text{O} \quad \text{NH} \quad \text{O} \quad \text{Me} \\
\end{align*}
\]

Scheme 2.7
2.2.4. RESULTS AND DISCUSSION

Initial experiments were carried out taking benzaldehyde as a model substrate. The reaction was performed by adding 1-methoxy-2-methyl-1-(trimethylsilyloxy)-1-propene (1.2 mmol) to a solution of benzaldehyde (1 mmol), benzyl carbamate (1.05 mmol) and iodine (0.1 mmol) in acetonitrile at room temperature. The reaction gives 67% yield of the product. Further the same reaction was carried out by varying the concentration of iodine and also by changing the solvent (Table 2.1). Use of 20 mol% iodine increases the reaction rate but gives a relatively low yield of the product. Use of dichloromethane instead of acetonitrile leads to weaker result. Interestingly, Janda also reported similar iodine catalyzed three component reaction of aldehyde, aniline and silyl enol ether to get the corresponding β-amino ketones.⁶²

Table 2.1: Synthesis of Cbz-protected β-amino ester under different conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Iodine (mol%)</th>
<th>Time (h)</th>
<th>Yield* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₃CN</td>
<td>10</td>
<td>2.5</td>
<td>67</td>
</tr>
<tr>
<td>2</td>
<td>CH₃CN</td>
<td>20</td>
<td>2</td>
<td>45</td>
</tr>
<tr>
<td>3</td>
<td>CH₂Cl₂</td>
<td>10</td>
<td>2.5</td>
<td>40</td>
</tr>
</tbody>
</table>

*isolated yield

Under this optimized condition, a series of aldehydes are examined and the results are discussed in Table 2.2
Table 2.2: Synthesis of Cbz-protected β-amino ester

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>β-Amino ester</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₅CHO</td>
<td>OMe</td>
<td>2 5</td>
<td>67</td>
</tr>
<tr>
<td>2</td>
<td>ClCH₅CHO</td>
<td>OMe</td>
<td>2 5</td>
<td>67</td>
</tr>
<tr>
<td>3</td>
<td>BrCH₅CHO</td>
<td>OMe</td>
<td>2</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>BrCH₅CHO</td>
<td>OMe</td>
<td>2 5</td>
<td>64</td>
</tr>
<tr>
<td>5</td>
<td>MeOCH₅CHO</td>
<td>OMe</td>
<td>3</td>
<td>66</td>
</tr>
<tr>
<td>6</td>
<td>MeOCH₅CHO</td>
<td>OMe</td>
<td>3 2</td>
<td>73</td>
</tr>
<tr>
<td>7</td>
<td>O₂NCH₅CHO</td>
<td>OMe</td>
<td>5</td>
<td>32</td>
</tr>
</tbody>
</table>

*Isolated yield after chromatographic purification*
From Table 2.2, it can be concluded that substrates bearing electron donating group produced good yield while substrates bearing electron withdrawing group gave weaker result (Table 2.2, entry 7)

The products were characterized by IR and NMR spectroscopic method. In the IR spectrum of methyl 3-\[((benzyloxy)carbonyl]amino]-3-phenyl-2,2-dimethylpropanoate, presence of N-H and C=O group are ascertained by the bands at 3337 cm\(^{-1}\) and 1723 cm\(^{-1}\) respectively. Presence of bands at 1265 cm\(^{-1}\) and 1045 cm\(^{-1}\) are due to C-O stretching. The \(^1\)H NMR spectra shows a singlet signal at \(\delta = 4.90\) ppm for the CH proton attached to the nitrogen atom. The ten aromatic protons are observed as a multiplet at \(\delta = 7.36-7.19\) ppm A multiplet signal at \(\delta = 5\) 16-5.0 ppm is due to benzylic CH\(_2\) protons. The -OCH\(_3\) protons appear as a singlet at \(\delta = 3.73\) ppm while the six protons of the -C(CH\(_3\))\(_3\) group appear as two singlets at \(\delta = 1.15\) and 1.12 ppm.

Figure 2.2: \(^1\)H-NMR spectra of methyl 3-\[((benzyloxy)carbonyl]amino]-3-phenyl-2,2-dimethylpropanoate

The IR spectra of methyl 3-\[((benzyloxy)carbonyl]amino]-3-(4-methoxyphenyl)-2,2-dimethylpropanoate gives bands at frequency 3369...
cm\(^{-1}\), 1726 cm\(^{-1}\) and 1263 cm\(^{-1}\) which are due to N-H stretching, C=O stretching and C-O stretching respectively. The \(^1\)H NMR spectra shows a singlet signal at \(\delta = 4.85\) ppm for the CH proton attached to the nitrogen atom. A multiplet signal at \(\delta = 7.40-7.00\) and a doublet signal at \(\delta = 6.85\) ppm are observed due to the nine aromatic protons. The two protons of -OCH\(_2\)Ph group appears as a multiplet at \(\delta = 5.15-4.95\) ppm. The singlet signal at \(\delta = 3.80\) ppm is due to the methoxy protons attached to the aromatic ring. The other methoxy protons (\(\alpha\) to the keto group) also appear as a singlet at \(\delta = 3.72\) ppm. The two singlet signals at \(\delta = 1.14\) and 1.09 ppm are due to the two types of CH\(_3\) protons of the –C(CH\(_3\))\(_3\) group.

![Figure 2.3: \(^1\)H-NMR spectra of methyl 3-([(benzyloxy)carbonyl]amino)-3-(4-methoxyphenyl)-2,2-dimethylpropanoate](image)

The IR spectra of Methyl 3-([(benzyloxy)carbonyl]amino)-3-(4-bromophenyl)-2,2-dimethylpropanoate gives a band at frequency 3330 cm\(^{-1}\) for N-H stretching. Two bands at 1723 and 1643 cm\(^{-1}\) are due to C=O stretching in esters and amides. Another band is observed at 1265 cm\(^{-1}\) which is due to C-O stretching. In the \(^1\)H NMR spectra, the CH proton
attached to the nitrogen atom appears as a doublet signal at $\delta = 4.64$ ppm.

The nine aromatic protons are observed as a multiplet at $\delta = 7.45-7.10$ ppm and as a doublet at $\delta = 7.07$ ppm. A doublet signal is observed for the $-\text{NH}$ proton at $\delta = 6.34$ ppm. The two protons of $-\text{OCH}_2\text{Ph}$ group appears as a multiplet at $\delta = 5.15-5.0$ ppm. The singlet signal at $\delta = 3.64$ ppm is due to the three protons of $-\text{OCH}_3$ group. The two singlet signals at $\delta = 1.32$ and 1.09 are due to the two types of $\text{CH}_3$ protons of the $-\text{C(CH}_3)_3$ group.

![Figure 2.4: $^1$H-NMR spectra of methyl 3-{[(benzyloxy)carbonyl]amino}-3-(4-bromophenyl)-2,2-dimethylpropanoate](image)

2.2.5. PROBABLE MECHANISM

Mechanistically, the reaction proceeds through the formation of bisurethane (A) at the initial stage. Bisurethane is formed after a few minutes of the reaction. The bisurethane was isolated by quenching the reaction mixture at an intermediate stage and confirmed by correlating the melting point data with that reported in the literature. The reaction
proceeds further via the formation of intermediate acylimine (B), which undergoes nucleophilic attack by 1-methoxy-2-methyl-1-(trimethylsilyloxy)-1-propene to produce the corresponding β-amino ester (C).

\[
\begin{align*}
\text{R}^+ \text{C} = \text{N}-\text{H} - \text{I}_2 &\rightarrow \text{R}^+ \text{C} = \text{N}-\text{C} = \text{N} - \text{H} - \text{C} = \text{N}-\text{H} - \text{C} = \text{N} - \text{I}_2 \\
\text{A} &\rightarrow \text{B} \\
&\rightarrow \text{C}
\end{align*}
\]

Scheme 2.8

2.2.6. CONCLUSION

An efficient procedure has been developed for Mannich-type reaction for the synthesis of β-amino esters. The procedure is simple, one-pot and high-yielding. The catalyst molecular iodine is very cheap and easily available and only 10 mol% is sufficient for these reactions. Acetonitrile is found to be the best among the solvents studied for the reactions. Aromatic aldehydes bearing both electron-donating and electron-withdrawing groups give this reaction, however, yield is found better in case of first one.
2.2.7. EXPERIMENTAL SECTION

(A) General procedure for synthesis of Cbz-protected β-amino esters

To a solution of iodine (0.1 mmol) in acetonitrile (1 ml), aldehyde (1 mmol), benzyl carbamate (1.05 mmol) and 1-methoxy-2-methyl-1-(trimethylsilyloxy)-1-propene (1.2 mmol) were added successively at room temperature. After completion of the reaction (monitored by TLC), sodium thiosulfate was added. Then water was added and the reaction mixture was stirred for 20 minutes. It was then extracted with ether, washed with brine, dried over sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography over silica gel (60-120 mesh) with ethyl acetate-petroleum ether (10%) as eluent.

(B) Experimental Data

(1) Methyl 3-[[benzoyl]amino]-3-phenyl-2,2-Dimethylpropanoate

Yield: 67%

IR (Neat, cm⁻¹): 3337, 3056, 2986, 1723, 1504, 1425, 1265, 1340, 1045

¹H NMR (400 MHz, CDCl₃): 7.36-7.19 (m, 10H), 5.16-5.0 (m, 2H), 4.90 (s, 1H), 3.73 (s, 3H), 1.15 (s, 3H), 1.12 (s, 3H)
(2) Methyl 3-\{[[benzyloxy]carbonyl]amino\}_3-(4-chlorophenyl)-2,2-dimethylpropanoate

Yield: 67%

IR (Neat, cm\(^{-1}\)): 3057, 2924, 2945, 2842, 1717, 1653, 1507, 1462, 1264, 1193, 1135, 1093

\(^1\)H NMR (400 MHz, CDCl\(_3\)): 7.37-7.23 (m, 9H), 5.23-5.0 (m, 2H), 4.88 (s, 1H), 3.73 (s, 3H), 1.13 (s, 3H), 1.10 (s, 3H)

(3) Methyl 3-\{[[benzyloxy]carbonyl]amino\}_3-(4-bromophenyl)-2,2-dimethylpropanoate

Yield: 70%

IR (Neat, cm\(^{-1}\)): 3330, 3048, 2930, 2848, 1723, 1696, 1643, 1510, 1451, 1266, 1132, 1096, 1032, 743

\(^1\)H NMR (400 MHz, CDCl\(_3\)): 7.45-7.10 (m, 7H), 7.07 (d, J = 8.4 Hz, 2H), 6.34 (d, J = 7.8 Hz, 1H), 5.15-5.0 (m, 2H), 4.64 (d, J = 6.8 Hz, 1H), 3.64 (s, 3H), 1.32 (s, 3H), 1.09 (s, 3H)

(4) Methyl 3-\{[[benzyloxy]carbonyl]amino\}_3-(2-bromophenyl)-2,2-Dimethylpropanoate

Yield: 64%

IR (Neat, cm\(^{-1}\)): 3334, 3028, 2920, 2842, 1713, 1663, 1530, 1260

\(^1\)H NMR (400 MHz, CDCl\(_3\)): 7.39-7.20 (m, 7H), 7.08 (d, J = 8.4 Hz, 1H), 6.85 (d, J = 8.0 Hz, 1H), 6.38 (d, J = 7.8 Hz, 1H), 5.12-5.01 (m, 2H), 4.58 (d, J = 6.4 Hz, 1H), 3.70 (s, 3H), 1.14 (s, 3H), 1.07 (s, 3H)
(5) **Methyl 3-{{(benzyloxy)carbonyl]amino}-3-(4-methoxyphenyl)-2,2-dimethylpropanoate**

**Yield:** 66%

**IR (Neat, cm⁻¹):** 3369, 3057, 2972, 2944, 1726, 1611, 1513, 1464, 1263, 740

**¹H NMR (400 MHz, CDCl₃):** 7.40-7.00 (m, 7H), 6.85 (d, J = 8.8 Hz, 2H), 5.15-4.95 (m, 2H), 4.85 (s, 1H), 3.80 (s, 3H), 3.72 (s, 3H), 1.14 (s, 3H), 1.09 (s, 3H)

**¹³C NMR (100 MHz, CDCl₃):** 178.3, 159.1, 154.0, 132.1, 128.8, 128.7, 128.5, 113.2, 78.4, 55.2, 54.4, 52.1, 47.8, 23.1, 19.0

(6) **Methyl 3-{{(benzyloxy)carbonyl]amino}-3-(4-methylphenyl)-2,2-Dimethylpropanoate**

**Yield:** 73%

**IR (Neat, cm⁻¹):** 3347, 3054, 2979, 2941, 1728, 1611, 1510, 1456, 1266, 1194, 1136, 1089

**¹H NMR (400 MHz, CDCl₃):** 7.33-7.07 (m, 9H), 5.7-5.0 (m, 2H), 4.86 (s, 1H), 3.72 (s, 3H), 2.34 (s, 3H), 1.14 (s, 3H), 1.11 (s, 3H)

(7) **Methyl 3-{{(benzyloxy)carbonyl]amino}-3-(4-nitrophenyl)-2,2-Dimethylpropanoate**

**Yield:** 32%

**IR (Neat, cm⁻¹):** 3337, 3055, 2986, 1723, 1504, 1425, 1265, 1044

**¹H NMR (400 MHz, CDCl₃):** 8.2 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 8.0 Hz, 2H), 7.36-7.23 (m, 5H), 6.38 (d, J = 8.4 Hz, 1H), 5.08-5.04 (m, 2H), 4.44 (d, J = 7.2 Hz, 1H), 3.68 (s, 3H), 1.15 (s, 3H), 1.11 (s, 3H)
2.3.1. INTRODUCTION

\(\beta\)-Amino ketones are important building blocks for synthesis of biologically attractive compounds\(^6^4\) such as febrifugine and isofebrifugine (antimalarial agents)\(^6^5\) (Figure 2.5). Substituted \(\beta\)-amino ketones also possess antispasmodic,\(^6^6\) analgesic,\(^6^7\) local anesthetics\(^6^8\) and antibacterial activity.\(^6^9\) Cyclic \(\beta\)-amino ketones have exhibited anticonvulsant, analgetic and antiinflammatory activity.\(^7^0\) Some cyclic \(\beta\)-amino ketones inhibits pyruvic acid oxidation.\(^7^1\)

![Febrifugine and Isofebrifugine](image-url)

*Figure 2.5*
2.3.2. REVIEW OF LITERATURE

In the previous section, we have discussed a number of the literature reports on Mannich reactions for synthesis of \( \beta \)-amino ester compounds. In the Classical Mannich route to \( \beta \)-amino carbonyl compounds, yields are low due to side reactions occurred. The classical Mannich reaction has been modified and a number of reports are found in the literature. Lewis acid catalyzed Mannich-type reaction of imines (preformed) with silyl enolates is an excellent variant of the classical Mannich reaction and several reports are found in the literature. Kobayashi et al.\(^ {34,35} \) reported the synthesis of \( \beta \)-amino ketones by a three component Mannich-type reaction aldehydes, amines and enolates in presence of ytterbium triflate \([\text{Yb(OTf)}_3]\) and scandium triflate \([\text{Sc(OTf)}_3]\). They found that the catalyst \( \text{Yb(OTf)}_3 \) was also effective for the Mannich-type reaction of N-(\( \alpha \)-aminoalkyl)benzotriazoles with silyl enolates. Mannich-type reactions of 4-phenyl-2-trimethylsiloxy-1,3-butadiene with imines proceeded efficiently in the presence of water and Lewis acids like TMSOTf, BF\(_3\).Et\(_2\)O, Zn(OTf)\(_2\) etc.\(^ {54} \) Kobayashi\(^ {17} \) reported a lanthanide triflate catalyzed Mannich-type reaction in aqueous media. Other triflates like Cu(OTf)\(_2\)\(^ {40} \) or Sc(OTf)\(_3\)\(^ {41,42} \) could catalyzed the Mannich-type reaction efficiently in aqueous media in presence of sodium dodecyl sulfate (SDS). Dodecylbenzenesulfonic acid\(^ {43,73} \) is also found effective for synthesis of \( \beta \)-amino ketones in aqueous media. Various other catalysts like HCl\(^ {57,58} \), HBF\(_4\),\(^ {45-48} \) indium chloride,\(^ {52,53} \) hydrophobic polystyrene supported sulfonic
acid (PS-SO₃H),⁴⁴ heteropoly acids⁷⁵ catalyzed the Mannich-type reaction efficiently in aqueous medium. Shimizu et al.⁷⁶ has developed the Mannich reaction using water soluble calix[n]arene sulfonic acid as inverse phase transfer catalyst. Synthesis of β-amino ketones can be achieved efficiently in ionic liquids like [bmim][PF₆] using Yb(OTf)₃ as catalyst.³⁹,⁷⁷ In this reaction, the ionic liquids acts as powerful reaction media and itself acts as a catalyst. HBF₄ could also catalyzed the Mannich reaction efficiently in [bmim][BF₄] ionic liquids.⁷⁸ Microencapsulated Sc(OTf)₃-catalyzed Mannich-type reactions were also reported.⁵¹ A nanostructured-polymer supported Sc (III) catalyst was used by Gin et al.⁷⁹ for synthesis of β-amino ketones (Scheme 2.9)

\[
\begin{align*}
\text{CHO} & \quad + \quad \text{OSiMe}_3 & \quad + \quad \text{NH}_2 \\
\text{H}_2\text{O, r.t} & \quad \xrightarrow{\text{NP-Sc}} & \quad \text{NHPhO}
\end{align*}
\]

Scheme 2.9

β-Amino ketones are also synthesized in good yields and excellent stereoselectivities by silica sulfuric acid⁸⁰ catalyzed direct Mannich-type reaction. The bismuth triflate catalyzed Mannich-type reaction was first studied by Kobayashi et al.⁸¹ with preformed imines, but the yield was very low. Ollevier and Nadeau⁵⁴,⁸² reported that the yield could be improved when catalyst was used for three component Mannich-type reaction aldehydes, amines and silyl enolates in one pot. They have also carried out the reaction in aqueous medium.⁸³ Wang et al.⁸⁴ developed a NbCl₅ catalyzed Mannich-type reaction of aromatic aldehydes, acetophenone and
aromatic amines for synthesis of β-amino ketones. Recently, they have reported another method for preparation of β-amino ketones catalyzed by SnCl₂.⁸⁵

Shibasaki⁸⁶ reported the first direct catalytic asymmetric Mannich reaction with unmodified ketones. β-Amino aryl ketones were synthesized in good yields and with 31-44% ee by using a cooperative complex of AlLibis(binaphthoxide) (ALB) and La(OTf)₃ nH₂O (Scheme 2.10).⁸⁷

\[
\text{ALB (30 mol%) La(OTf)₃ nH₂O (30 mol%)}
\]
\[
\text{Tolene, 50 °C, 3Å-MS, rt}
\]

**Scheme 2.10**

Later on, the same group reported the direct asymmetric Mannich-type reaction using Et₂Zn/linked-BINOL complex as catalyst (Scheme 2.11).⁸⁸

\[
\text{Et₂Zn (4 mol%)}
\]
\[
\text{(S,S)-linked-BINOL complex (1 mol%)}
\]
\[
\text{3Å-MS, THF}
\]

**Scheme 2.11**

Kobayashi et al.⁸⁹ reported a ZnF₂ catalyzed asymmetric Mannich-type reaction using a chiral diamine in aqueous THF (Scheme 2.12)

\[
\text{ZnF₂ (50 mol%)}
\]
\[
\text{PhOH (10 mol%)}
\]
\[
\text{H₂O/THF (1/9), 0 °C}
\]

**Scheme 2.12**
However, direct application of this catalytic system to reactions in water without THF gave unsatisfactory results. Addition of TfOH as additive improves the yield. They also found that use of a catalytic amount of Cu(OTf)$_2$-chiral diamine complex can effectively promote the addition of N-acyliminoesters to silyl enol ethers$^{58,60,90}$ There were many other examples of asymmetric additions of enolates to imines reported by Sodeoka$^{93,94}$ and Lectca$^{93,94}$. Trost and co-workers$^{95}$ reported a dinuclear zinc complex catalyzed Mannich reaction with unmodified aromatic hydroxy ketones with excellent enantioselectivity (Scheme 2.13).

![Scheme 2.13](image)

List$^{96,97}$ also developed an asymmetric Mannich reaction of aldehydes, ketones and amines using proline as catalyst. Exceptionally high enantio-, diastereo-, regio- and chemoselectivity were observed in these reactions. However, yields are generally insufficient when acetone is used as the Mannich donor, while the Mannich acceptor should be electron-deficient and highly reactive. Hayashi and co-workers$^{98}$ have improved this method by using water-freezing induced-pressure method. Barbas and co-workers$^{99-101}$ also reported a L-proline catalyzed direct asymmetric Mannich reaction of $N$-PMP protected $\alpha$-imino ethyl glyoxylate with various unmodified aldehydes and ketones to afford $\alpha$-amino acid derivatives with excellent yields and enantioselectivities. They reported another proline catalyzed asymmetric Mannich reaction of unmodified aldehydes in...
aqueous medium.\textsuperscript{102} Later on, they demonstrated that in addition to proline, other amino acid derivatives like penicillamine derivative L-5,5-dimethylthiazolidine-4-carboxylic acid (DMTC) also catalyzed the direct asymmetric Mannich-type reaction with good enantioselectivity (Scheme 2.14).\textsuperscript{103}

They also reported the (S)-2-methylmethoxypyrrolidine (SMP)-catalyzed direct asymmetric Mannich-type reaction of unmodified aldehydes with N-PMP protected α-imino ethyl glyoxylate (Scheme 2.15).\textsuperscript{104}

Josephsohn \textit{et al.}\textsuperscript{105} reported an asymmetric Mannich reaction of enol ethers with aryl, alkyl, alkenyl and alkynyl imines by using silver catalyst.
2.3.3. PRESENT WORK

OBJECTIVE

Although there are several reports in literature, for synthesis of $\beta$-amino ketones by Mannich reaction, many of them fraught with limitations such as use of toxic metal salts as catalysts, expensive reagents or catalysts, moisture sensitivity of the catalyst, low yield, etc. Moreover, in many of those methods, the nitrogen sources are aniline or benzyl amine. In literature, we have found various organic transformations catalyzed by iodine. The objective of our present investigation is to study the catalytic activity of iodine for three component Mannich reaction of aldehydes, benzyl carbamate (nitrogen source) and acetophenones to prepare some of the protected $\beta$-amino ketones (Scheme 2.16).

Scheme 2.16
2.3.4. RESULTS AND DISCUSSION

To begin with, we have carried out the reaction by treating aldehydes with benzyl carbamate and acetophenone in presence of iodine at room temperature. Acetophenone was added to a solution of benzaldehyde, benzyl carbamate and iodine in acetonitrile at room temperature and was stirred for 24 hour. Initially, the reaction was examined by using 1 mmol of benzaldehyde, 1.5 mmol of benzyl carbamate, 5 mmol of acetophenone and 10 mol% of iodine in acetonitrile. The same reaction was further carried out with varying concentrations of iodine, acetophenone and benzyl carbamate. The variation of yield of the product under different conditions is discussed in Table 2.3. The reaction gives the best result when the ratio of benzaldehyde, acetophenone, benzyl carbamate and iodine is 1:1.5:1:0.1 When the reaction was carried under identical condition using dichloromethane as solvent, no improvement of yield was observed (Table 2.3, entry 10).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Benzaldehyde (mmol)</th>
<th>Acetophenone (mmol)</th>
<th>Benzyl carbamate (mmol)</th>
<th>Iodine (mol%)</th>
<th>Yield(^a) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>5</td>
<td>1.5</td>
<td>5</td>
<td>64</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>5</td>
<td>1.5</td>
<td>10</td>
<td>68</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>5</td>
<td>1.5</td>
<td>20</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>2.5</td>
<td>1.5</td>
<td>10</td>
<td>47</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>1.5</td>
<td>1.5</td>
<td>10</td>
<td>54</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>1.5</td>
<td>1.2</td>
<td>10</td>
<td>65</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>1.5</td>
<td>1.1</td>
<td>10</td>
<td>71</td>
</tr>
</tbody>
</table>

\(^{a}\) Yield calculated by GC analysis.
Then the scope of the reaction was examined using various aryl aldehydes and acetophenones. The results are described in Table 2.4.

**Table 2.4: Synthesis of β-amino ketones from various aldehydes**

| Entry | Aldehyde | Acetophenone | β-amino ketones | Yield<sup>a</sup> (%)
|-------|----------|--------------|-----------------|----------------
| 1     | ![image1](image1.png) | ![image2](image2.png) | ![image3](image3.png) | 78
| 2     | ![image4](image4.png) | ![image5](image5.png) | ![image6](image6.png) | 78
| 3     | ![image7](image7.png) | ![image8](image8.png) | ![image9](image9.png) | 82
| 4     | ![image10](image10.png) | ![image11](image11.png) | ![image12](image12.png) | 81
| 5     | ![image13](image13.png) | ![image14](image14.png) | ![image15](image15.png) | 78

<sup>a</sup>isolated yield after chromatographic purification

<sup>b</sup>dichloromethane was used as solvent
From Table 2.4, it was observed that aryl aldehydes having substituents CH$_3$, OCH$_3$, Cl and Br in para position reacted successfully to give the corresponding $\beta$-amino ketones. Although ortho- and para-substituted aldehydes shows good results, meta-substituted aldehydes such as 3-methoxybenzaldehyde (Table 2.4, entry 6) give no product.

The product $\beta$-amino ketones thus obtained are characterized by taking the mp data, elemental analysis data, IR and NMR spectral data. In the IR spectrum of benzyl 3-oxo-1,3-diphenylpropylcarbamate, bands at frequency 3321 cm$^{-1}$ and 1723 cm$^{-1}$ indicates the presence of N-H and C=O group in the compound. Bands at 1266 cm$^{-1}$ and 1081 cm$^{-1}$ are due to C-O stretching. In the $^1$H NMR spectrum, a multiplet signal is observed at $\delta$ = 5.36-5.30 ppm for the CH proton attached to the nitrogen atom. The doublet and multiplet signals at $\delta$ = 7.88 and 7.57-7.22 ppm respectively arises due to fifteen aromatic protons. A broad singlet is observed at $\delta$ =
5.89 ppm for the NH proton. Benzylic CH$_2$ protons appear as a singlet at $\delta$ = 5.09 ppm. A doublet signal at $\delta$ = 3.69 and a double doublet signal at $\delta$ = 3.44 ppm are due to the CH$_2$ protons that is $\alpha$ to the keto group. The $^{13}$C NMR spectra of the compound shows characteristic peaks at $\delta$ = 198.0, 155.7, 66.8, 51.8, 44.0 ppm. The signal at 198.0 ppm and 155.7 ppm are due to the carbon of the carbonyl group and the amide group respectively. The CH$_2$ carbon attached to the oxygen atom appears at 66.8 ppm. The CH$_2$ carbon attached to the carbonyl group and CH carbon attached to the nitrogen atom appear at 51.8 and 44.0 ppm respectively.

Figure 2.6: $^1$H-NMR spectra of benzyl 3-oxo-1,3-diphenylpropylcarbamate

Figure 2.7: $^{13}$C-NMR spectra of benzyl 3-oxo-1,3-diphenylpropylcarbamate
The IR spectra of benzyl 1-(4-methylphenyl)-3-oxo-3-phenylpropylcarbamate shows bands at frequency 3303 cm\(^{-1}\), 1687 cm\(^{-1}\) and 1251 cm\(^{-1}\) and 1035 cm\(^{-1}\) which are characteristic of N-H stretching, C=O stretching and C-O stretching respectively. In the \(^1\)H NMR spectrum, a multiplet signal is observed at \(\delta = 5.32-5.26\) ppm for the CH proton attached to the nitrogen atom. The signals for aromatic protons are observed at \(\delta = 7.89\) ppm (doublet) and 7.55-7 10 ppm (multiplet). Doublet signals are observed at \(\delta = 5.81\) ppm and 5.09 ppm which are due to NH proton and benzylic CH\(_2\) protons respectively Signals at \(\delta = 3.69\) ppm (doublet) and 3.43 ppm (double doublet) are due to the CH\(_2\) protons that is \(\alpha\) to the keto group. The three protons of the CH\(_3\) group attached to the aromatic ring appeared at \(\delta = 2.30\) ppm. In the \(^{13}\)C NMR spectrum, the characteristic peaks observed at \(\delta = 198.0, 155.7, 66.8, 51.6, 43.8\) and 21.0 ppm are due to the carbons bearing groups such as (>C=O), (-COO), (-OCH\(_2\)Ph), (-CH\(_2\)CO), (-CHNH) and (-CH\(_3\)) The mass spectra of the compound shows a peak at 396 for (M+Na)

![Diagram](image.png)

**Figure 2.8:** \(^1\)H-NMR spectra of benzyl 1-(4-methylphenyl)-3-oxo-3-phenylpropylcarbamate
Figure 2.9: $^{13}$C-NMR spectra of benzyl 1-(4-methylphenyl)-3-oxo-3-phenylpropylcarbamate

The IR spectra of benzyl 1-(4-chlorophenyl)-3-oxo-3-phenylpropylcarbamate give signals at frequency $3313 \text{ cm}^{-1}$ for N-H stretching band, $1683 \text{ cm}^{-1}$ for C=O stretching band. $1253 \text{ cm}^{-1}$ and $1087 \text{ cm}^{-1}$ for C-O stretching band. The $^1$H NMR spectra shows a multiplet signal at $\delta = 5.32-5.26 \text{ ppm}$ for the CH proton attached to the nitrogen atom. Four signals are observed at $\delta = 7.87$ (doublet), 7.59-7.54 (multiplet), 7.46-7.41 (multiplet) and 7.32-7.26 (multiplet) ppm for the fourteen aromatic protons. Two doublet signals observed at $\delta = 5.95 \text{ ppm}$ and 5.09 ppm are due to NH proton and benzylic CH$_2$ protons respectively. Two signals at $\delta = 3.68 \text{ ppm}$
(doublet) and 3.42 ppm (double doublet) are due to the $CH_2$ protons that is $\alpha$ to the keto group. The $^{13}$C NMR spectra of the compound shows characteristic peaks at $\delta = 197.7$, $155.7$, $66.9$, $51.2$ and $43.6$ ppm for the carbons bearing groups such as ($>C=O$), (-COO), (-OCH$_2$Ph), (-CH$_2$CO) and (-CHNH).

Figure 2.11: $^1$H-NMR spectra of benzyl 1-(4-chlorophenyl)-3-oxo-3-phenylpropylcarbamate

Figure 2.12: $^{13}$C-NMR spectra of benzyl 1-(4-chlorophenyl)-3-oxo-3-phenylpropylcarbamate

The IR spectra of benzyl 1-(4-chlorophenyl)-3-(4-methylphenyl)-3-oxopropylcarbamate gives signals at frequency 3339 cm$^{-1}$ and 1715 cm$^{-1}$ and 1681 cm$^{-1}$ which indicates the presence of NH and CO group respectively. The C-O stretching bands are observed at 1262 cm$^{-1}$ and
In the $^1$H NMR spectra, the CH proton attached to the nitrogen atom appears as a multiplet at $\delta = 5.28$-$5.18$ ppm. Two signals observed at $\delta = 7.80$ ppm (doublet) and 7.50-$7.08$ ppm (multiplet) are due to the thirteen aromatic protons. Benzyl CH$_2$ protons appear as a doublet signal at $\delta = 5.0$ ppm. Two double doublet signals at $\delta = 3.59$ ppm and 3 22 ppm are due to the CH$_2$ protons that is $\alpha$ to the keto group. The three protons of the CH$_3$ group attached to the aromatic ring appear at 2 40 ppm. The mass spectra of the same compound shows molecular ion peak (M$^+$) at 408 and (M$^+$+2) peak at 410. For this compound, molecular ion peak is the base peak. The other peaks at 274, 257, 119 and 91 are due to the fragments [PhCH$_2$OCONCHPh(p-Cl)]$^+$, [Ph(p-Me)COCH$_2$CHPh(p-Cl)]$^+$, [Ph(p-Me)CO]+ and tropylium ion respectively.

Figure 2.13: $^1$H-NMR spectra of benzyl 1-(4-chlorophenyl)-3-(4-methylphenyl)-3-oxopropylcarbamate
2.3.5. PROBABLE MECHANISM

The reaction proceeds through the same pathway as mentioned in SECTION A. The active acylimine (B) intermediate formed in situ undergoes nucleophilic attack by acetophenone to produce the corresponding β-amino ketone (C).

\[
\begin{align*}
\text{Acylhalide} + \text{Cbz-NH}_2 &\xrightarrow{I_2} \text{A} & \text{B} &\xrightarrow{I_2} \text{C}
\end{align*}
\]

Scheme 2.17
2.3.6. CONCLUSION

An efficient, simple, high yielding method is obtained for synthesis of $\beta$-amino carbonyl compounds. Use of 10 mol$\%$ is sufficient for this reaction. Aryl aldehydes having substituents CH$_3$, OCH$_3$, Cl and Br in para-position reacted successfully to give the corresponding $\beta$-amino ketones. Good yields are found for ortho and para-substituted aldehydes while meta-substituted aldehydes such as 3-methoxybenzaldehyde gives no product. Acetonitrile is found to be better solvent for these reactions.

2.3.7. EXPERIMENTAL SECTION

(A) General Procedure for Synthesis of $\beta$-amino ketones

To a solution of iodine (10 mol $\%$) in acetonitrile (1 ml), benzyl carbamate (1.01 mmol), aldehyde (1 mmol) and ketone (1.5 mmol) were added successively at room temperature. After stirring the reaction mixture for 24 h, iodine was destroyed by adding solid sodium thiosulfate. Water was added and the mixture was extracted with ethyl acetate. The organic phase was washed with brine, dried (sodium sulfate), filtered and evaporated. The crude product was purified by column chromatography over silica gel (60–120 mesh) using ethyl acetate–petroleum ether (12%) as eluent.
(B) **Experimental Data**

(1) Benzyl 3-oxo-1,3-diphenylpropylcarbamate

**Yield:** 78%

**Mp:** 110–111 °C

**IR (KBr, cm⁻¹):** 3321, 3058, 2932, 2862, 1723, 1524, 1347, 1266, 1081, 739, 699

**¹H NMR (300 MHz, CDCl₃):** 7.88 (d, J = 7.5 Hz, 2H), 7.57–7.22 (m, 13H), 5.89 (br s, 1H), 5.36–5.30 (m, 1H), 5.09 (s, 2H), 3.69 (d, J = 15.3 Hz, 1H), 3.44 (dd, J = 5.7 Hz, J = 16.8 Hz, 1H)

**¹³C NMR (75 MHz, CDCl₃):** 198.0, 155.7, 136.6, 136.4, 133.4, 128.6, 128.4, 128.0, 127.4, 126.3, 66.8, 51.8, 44.0

**Elemental analysis:** C 76.80%, H 5.95%, N 3.73% (requires C 76.86%, H 5.89%, N 3.90%)

(2) Benzyl 1-(4-chlorophenyl)-3-oxo-3-phenylpropylcarbamate

**Yield:** 78%

**Mp:** 120–121 °C

**IR (KBr, cm⁻¹):** 3313, 3048, 2950, 2891, 1683, 1535, 1489, 1450, 1348, 1253, 1201, 1087, 1036, 827, 757, 690

**¹H NMR (300 MHz, CDCl₃):** 7.87 (d, J = 8.4 Hz, 2H), 7.59–7.54 (m, 1H), 7.46–7.41 (m, 2H), 7.32–7.26 (m, 9H), 5.95 (d, J = 8.1 Hz, 1H), 5.32–5.26 (m, 1H), 5.09 (d, J = 2.1 Hz, 2H), 3.68 (d, J = 14.4 Hz, 1H), 3.42 (dd, J = 6.0 Hz, J = 17.1 Hz, 1H)

**¹³C NMR (75 MHz, CDCl₃):** 197.7, 155.7, 136.4, 136.2, 133.6, 133.2, 128.7, 128.5, 128.1, 128.0, 127.8, 66.9, 51.2, 43.6
Elemental Analysis: C 70.08%, H 5.16%, N 3.63% (requires C 70.14%, H 5.12%, N 3.56%)

(3) Benzyl 1-(4-methylphenyl)-3-oxo-3-phenylpropylcarbamate

Yield: 82%

Mp: 77-80 °C

IR (KBr, cm⁻¹): 3303, 3038, 2950, 1687, 1592, 1535, 1452, 1407, 1354, 1251, 1204, 1035, 813, 753, 691

¹H NMR (300 MHz, CDCl₃): 7.89 (d, J = 8.4 Hz, 2H), 7.55-7.10 (m, 12H), 5.81 (d, J = 6.3 Hz, 1H), 5.32-5.26 (m, 1H), 5.09 (d, J = 1.8 Hz, 2H), 3.69 (d, J = 14.7 Hz, 1H), 3.43 (dd, J = 6.3 Hz, J = 16.5 Hz, 1H), 2.30 (s, 3H)

¹³C NMR (75 MHz, CDCl₃): 198.0, 155.7, 137.1, 136.6, 136.4, 133.4, 129.3, 128.6, 128.4, 128.1, 128.0, 126.3, 66.8, 51.6, 43.8, 21.0

Elemental Analysis: C 77.24%, H 6.25%, N 3.69% (requires C 77.19%, H 6.21%, N 3.75%)

HRMS: Calculated mass (M + Na): 396.1576 (found: 396.1554)

(4) Benzyl 1-(4-methoxyphenyl)-3-oxo-3-phenylpropylcarbamate

Yield: 81%

Mp: 76-78 °C

IR (KBr, cm⁻¹): 3323, 3264, 3195, 3029, 2950, 2822, 1700, 1612, 1528, 1450, 1401, 1342, 1293, 1244, 1067, 1023, 822, 724, 689
\( ^1\text{H NMR (300 MHz, CDCl}_3\): 7.94 (d, \( J = 8.0 \text{ Hz, 2H} \)), 7.60-7.15 (m, 10H), 6.82 (d, \( J = 14.0 \text{ Hz, 2H} \)), 5.59 (br s, 1H), 5.30-5.15 (m, 1H), 5.05 (d, \( J = 4.0 \text{ Hz, 2H} \)), 3.79 (s, 3H), 3.66 (dd, \( J = 6.0 \text{ Hz, } J = 15.0 \text{ Hz, 1H} \)), 3.31 (dd, \( J = 6.0 \text{ Hz, } J = 18.0 \text{ Hz, 1H} \)).

**Elemental Analysis:** C 74.06 %, H 5.89 %, N 3.64 % (requires C 74.02 %, H 5.95 %, N 3.60 %)

**Mass (m/z, % rel. intensity):** 151 (25), 108 (100), 91 (29)

\[ (5) \text{ Benzyl 1-(2-methoxyphenyl)-3-oxo-3-phenylpropylcarbamate} \]

**Yield:** 78%

**Mp:** 96-99 °C

**IR (KBr, cm\(^{-1}\):** 3327, 3060, 2981, 2941, 2881, 2842, 1688, 1601, 1536, 1493, 1453, 1402, 1352, 1260, 1045, 1024, 834, 753, 694

\( ^1\text{H NMR (400 MHz, CDCl}_3\): 7.89 (d, \( J = 8.0 \text{ Hz, 2H} \)), 7.53 (d, \( J = 8.0 \text{ Hz, 2H} \)), 7.43-7.21 (m, 8H), 6.91-6.84 (m, 2H), 6.05 (br s, 1H), 5.55-5.45 (m, 1H), 5.2-5.06 (m, 2H), 3.85 (s, 3H), 3.6-3.45 (m, 2H)

\( ^{13}\text{C NMR (100 MHz, CDCl}_3): 198.3, 156.5, 155.6, 136.8, 136.5, 133.1, 128.7, 128.5, 128.1, 122.8, 120.8, 110.7, 66.7, 55.3, 49.7, 43.4 \)

**Elemental Analysis:** C 74.00%, H 5.83%, N 3.65% (requires C 74.02%, H 5.95%, N 3.60%)
(6) Benzyl 1-(2,4-dichlorophenyl)-3-oxo-3-phenylpropylcarbamate

Yield: 48%

Mp: 126-128 °C

IR (KBr, cm⁻¹): 3300, 3062, 2953, 2923, 1687, 1591, 1544, 1495, 1467, 1407, 1350, 1267, 1053, 823, 742, 690

¹H NMR (400 MHz, CDCl₃): 7.86 (d, J = 8.0 Hz, 2H), 7.57-7.18 (m, 11H), 6.24 (br s, 1H), 5.58-5.53 (m, 1H), 5.10-5.03 (m, 2H), 3.75-3.68 (d, J = 28 Hz, 1H), 3.46 (dd, J₁ = 4.0 Hz, J₂ = 16 Hz, 1H)

Elemental Analysis: C 64.62%, H 4.60%, N 3.25% (requires C 64.50%, H 4.47%, N 3.27%)

(7) Benzyl 3-(4-methylphenyl)-3-oxo-1-phenylpropylcarbamate

Yield: 75%

Mp: 82-84 °C

IR (KBr, cm⁻¹): 3362, 3029, 2950, 2881, 1719, 1674, 1605, 1522, 1450, 1406, 1366, 1290, 1230, 1020, 811, 754, 699

¹H NMR (200 MHz, CDCl₃): 8.03 (d, J = 8.0 Hz, 2H), 7.84 (d, J = 8.0 Hz, 2H), 7.62-7.00 (m, 10H), 5.34-5.23 (m, 1H), 5.03 (d, J = 4.0 Hz, 2H), 3.64 (dd, J = 8.0 Hz, J = 18 0 Hz, 1H), 3 25 (dd, J = 6 0 Hz, J = 18.0 Hz , 1H), 2.42 (s, 3H)

Elemental analysis: C 77.16%, H 6.23%, N 3.71% (requires C 77.19%, H 6.21%, N 3.75%)

Mass (m/z, % rel. intensity): 374 (M⁺+1, 100), 240 (15), 223 (2), 196 (2), 119 (10), 91 (2)
(8) Benzyl 1-(4-chlorophenyl)-3-(4-methylphenyl)-3-oxopropylcarbamate

Yield: 86%

Mp: 125-126 °C

IR (KBr, cm⁻¹): 3339, 3058, 2972, 2924, 1715, 1681, 1615, 1510, 1453, 1424, 1262, 1034, 743

¹H NMR (200 MHz, CDCl₃): 7.80 (d, J = 8.0 Hz, 2H), 7.50-7.08 (m, 11H), 5.28-5.18 (m, 1H), 5.00 (d, J = 4.0 Hz, 2H), 3.59 (dd, J = 6.0 Hz, J = 14.0 Hz, 1H), 3.22 (dd, J = 6.0 Hz, J = 16.0 Hz, 1H), 2.40 (s, 3H)

Elemental Analysis: C 70.71%, H 5.48%, N 3.39% (requires C 70.67%, H 5.44%, N 3.43%)

Mass (m/z, % rel. intensity): 410 (M⁺+2, 36), 408 (M⁺, 100), 274(9), 257 (3), 119 (22), 91 (3)

(9) Benzyl 1,3-bis(4-methylphenyl)-3-oxopropylcarbamate

Yield: 68%

Mp: 101-103 °C

IR (KBr, cm⁻¹): 3343, 3048, 2981, 2924, 1693, 1607, 1506, 1453, 1415, 1338, 1264, 1229, 1046, 814, 743, 700

¹H NMR (200 MHz, CDCl₃): 7.81 (d, J = 8.0 Hz, 2H), 7.40-7.00 (m, 11H), 5.25-5.15 (m, 1H), 5.00 (d, J = 4.0 Hz, 2H), 3.59 (dd, J = 6.0 Hz, J = 16.0 Hz, 1H), 3.22 (dd, J = 6.0 Hz, J = 16.0 Hz, 1H), 2.40 (s, 3H), 2.30 (s, 3H)
Elemental Analysis: C 77.58%, H 6.45%, N 3.65% (requires C 77.49%, H 6.50%, N 3.61%)

Mass (m/z, % rel. intensity): 387 (M⁺, 6), 296 (24), 254 (100), 211 (49), 134 (12), 120 (100), 91 (29), 65 (100)

(10) Benzyl 1-(4-methoxyphenyl)-3-(4-methylphenyl)-3-oxopropylcarbamate

Yield: 75%

Mp: 108-110 °C

IR (KBr, cm⁻¹): 3319, 3029, 2943, 2848, 1696, 1607, 1514, 1453, 1403, 1336, 1247, 1049, 815, 740, 698

¹H NMR (200 MHz, CDCl₃): 7.80 (d, J = 8.0 Hz, 2H), 7.47-7.10 (m, 8H), 7.00 (d, J = 8.0 Hz, 1H), 6.78 (d, J = 8.0 Hz, 2H), 5.20 (m, 1H), 5.00 (d, J = 4.0 Hz, 2H), 3.75 (s, 3H), 3.58 (dd, J = 6.0 Hz, J = 17.0 Hz, 1H), 3.23 (dd, J = 6.0 Hz, J = 17.0 Hz, 1H), 2.38 (s, 3H)

Elemental Analysis: C 74.49%, H 6.18%, N 3.43% (requires C 74.42%, H 6.25%, N 3.47%)

Mass (m/z, % rel. intensity): 373 (26), 207 (3), 161 (62), 143 (100)
(11) Benzyl 3-(4-chlorophenyl)-3-oxo-1-phenylpropylcarbamate

Yield: 66%

Mp: 97-99 °C

IR (KBr, cm\(^{-1}\)): 3332, 3302, 3037, 2939, 2861, 1685, 1585, 1539, 1489, 1449, 1395, 1332, 1258, 1209, 1088, 1030, 831, 750, 697

\(^1\)H NMR (300 MHz, CDCl\(_3\)): 7.80 (d, J = 8.1 Hz, 2H), 7.39-7.25 (m, 12H), 5.81 (br s, 1H), 5.34-5.27 (m, 1H), 5.08 (s, 2H), 3.66 (d, J = 14.7 Hz, 1H), 3.38 (dd, J = 4.5 Hz, J = 15.9 Hz, 1H)

\(^1^3\)C NMR (75 MHz, CDCl\(_3\)): 196.5, 155.6, 141.0, 139.8, 136.3, 134.9, 129.5, 128.9, 128.7, 128.4, 128.1, 127.6, 126.3, 66.8, 51.8, 44.

Elemental Analysis: C 70.11%, H 5.15%, N 3.59% (requires C 70.14%, H 5.12%, N 3.56%)

(12) Benzyl 1,3-bis(4-chlorophenyl)-3-oxopropylcarbamate

Yield: 75%

Mp: 124-125 °C

IR (KBr, cm\(^{-1}\)): 3322, 3234, 3047, 2939, 1708, 1670, 1585, 1484, 1449, 1400, 1338, 1265, 1209, 1058, 822, 728, 696

\(^1\)H NMR (300 MHz, CDCl\(_3\)): 7.80 (d, J = 8.4 Hz, 2H), 7.41-7.26 (m, 11H), 5.86 (d, J = 8.1 Hz, 1H), 5.30-5.24 (m, 1H), 5.08 (s, 2H), 3.64 (d, J = 14.1 Hz, 1H), 3.37 (dd, J = 6.0 Hz, J = 16.8 Hz, 1H)

\(^1^3\)C NMR (75 MHz, CDCl\(_3\)): 196.3, 155.6, 140.1, 139.6, 136.2, 134.7, 133.3, 129.4, 129.0, 128.8, 128.5, 128.1, 128.0, 127.8, 66.9, 51.2, 43.7
Elemental Analysis: C 64.52%, H 4.41%, N 3.23% (requires C 64.50%, H 4.47%, N 3.27%)

(13) Benzyl 3-(4-chlorophenyl)-1-(4-methylphenyl)-3-oxopropylcarbamate

Yield: 66%

Mp: 135-136 °C

IR (KBr, cm\(^{-1}\)): 3332, 3244, 3028, 2939, 2851, 1711, 1670, 1584, 1542, 1491, 1453, 1399, 1339, 1287, 1262, 1207, 1059, 819, 732, 696

\(^1\)H NMR (300 MHz, CDCl\(_3\)): 7.82 (d, \(J = 7.8\) Hz, 2H), 7.40-7.10 (m, 11H), 5.70 (br s, 1H), 5.30-5.23 (m, 1H), 5.08 (s, 2H), 3.66 (d, \(J = 14.7\) Hz, 1H), 3.38 (dd, \(J = 6.6\) Hz, \(J = 16.5\) Hz, 1H), 2.30 (s, 3H)

Elemental Analysis: C 70.64%, H 5.40%, N 3.46% (requires C 70.67%, H 5.44%, N 3.43%)

(14) Benzyl 3-(4-bromophenyl)-3-oxo-1-phenylpropylcarbamate

Yield: 70%

Mp: 106-108 °C

IR (KBr, cm\(^{-1}\)): 3342, 3293, 3058, 3028, 2930, 1684, 1583, 1540, 1495, 1447, 1395, 1376, 1331, 1258, 1207, 1068, 1030, 829, 748, 697
\(^1\)H NMR (300 MHz, CDCl\(_3\)): 7.70 (d, \(J = 7.8\) Hz, 2H) 7.52 (d, \(J = 8.1\) Hz, 2H), 7.30-7.04 (m, 10H), 5.86 (br s, 1H), 5.33-5.27 (m, 1H) 5.06 (s, 2H), 3.63 (d, \(J = 13.5\) Hz, 1H), 3.35 (dd, \(J = 5.7\) Hz, \(J = 17.1\) Hz 1H)

\(^{13}\)C-NMR (75 MHz, CDCl\(_3\)): 196.7, 155.6, 141.0, 136.2, 135.2, 129.5, 128.6, 128.5, 128.4, 128.0, 127.5, 126.3, 66.8, 51.7, 43.9.

Elemental Analysis: C 63.09\%, H 4.63\%, N 3.17\% (requires C 63.02\%, H 4.60\%, N 3.20\%)

(15) Benzyl 3-(4-bromophenyl)-1-(4-chlorophenyl)-3-oxopropylcarbamate

Yield: 42\%

Mp: 142-143 °C

IR (KBr, cm\(^{-1}\)): 3328, 3264, 2925, 2852, 1708, 1666, 1577, 1450, 1399, 1337, 1283, 1258, 1057, 1018, 812, 729, 694

\(^1\)H NMR (300 MHz, CDCl\(_3\)): 7.72 (d, \(J = 8.4\) Hz, 2H) 7.56 (d, \(J = 8.4\) Hz, 2H), 7.32-7.25 (m, 9H), 5.90 (br s, 1H), 5.30-5.23 (m, 1H), 5.08, 5.04 (m, 2H), 3.63 (d, \(J = 12.6\) Hz, 1H) 3.36 (dd, \(J = 5.4\) Hz, \(J = 16.8\) Hz, 1H)

\(^{13}\)C-NMR (75 MHz, CDCl\(_3\)): 196.7, 155.7, 139.6, 136.2, 135.1, 133.3, 132.0, 131.4, 129.5, 129.0, 128.8, 128.5, 128.0, 127.6, 67.0, 51.2, 43.7.

Elemental Analysis: C 58.40\%, H 4.09\%, N 3.02\% (requires C 58.43\%, H 4.05\%, N 2.96\%)
(16) Benzyl 3-(4-bromophenyl)-1-(4-methylphenyl)-3-oxopropylcarbamate

Yield: 68%

Mp: 124-126 °C

IR (KBr, cm⁻¹): 3303, 3028, 2921, 2842, 1705, 1584, 1547, 1492, 1459, 1400, 1339, 1259, 1056, 1013, 819, 734, 695

¹H NMR (300 MHz, CDCl₃): 7.75 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 8.7 Hz, 2H), 7.32-7.10 (m, 9H), 5.67 (br s, 1H), 5.29-5.25 (m, 1H), 5.08 (s, 2H), 3.66 (d, J = 16.2 Hz, 1H), 3.39 (dd, J = 6.6 Hz, J = 16.5 Hz, 1H), 2.30 (s, 3H)

Elemental Analysis: C 63.80%, H 4.87%, N 3.05% (requires C 63.73%, H 4.90%, N 3.10%)
2.4. REFERENCES


