Regioselective N-3 functionalization (acylation, alkoxy carbonylation, and alkylation) of 3,4-dihydropyrimidin-2(1H)-ones (DHPMs) is of considerable importance for the preparation of N-3 substituted DHPMs, related to the biologically important compounds SQ 32,926 1, SQ 32,547 2, L-771,668 3 and (S)-SNAP-7941 4 (Figure 1).1 Direct N-3 acylation (DMF/POCl₃) of a C-4 aryl substituted DHPM, furnished the N-3 formylated product (12% yield) but was attended by a 6H-1,3-thiazine derivative (47% yield).2 A rather high temperature (100-180°C) microwave-aided acylation, employing polymer-supported reagent and scavengers provided an attractive method,3 but lacked the economy and simplicity of a one-pot reaction. N-3 monoalkylated DHPMs are not formed in the alkylation of unsubstituted derivatives as well as through the use of monoalkyl ureas, the latter method furnished only N-1 alkylated DHPMs.4 In contrast to the acylation and alkylation, the alkoxy carbonylation of Biginelli DHPMs with, for example, ethyl chloroformate and base has been problematic owing to the formation of mixture of N-1 and N-3 substituted products, depending upon the substitution pattern around the DHPM ring.5

**Figure 1.** Therapeutically potent N-3 substituted DHPMs.
In one of the reports\textsuperscript{3a} aimed at the microwave assisted synthesis of N-3 acylated DHPMs through reaction of 5 with an acylating agent (Method A, Scheme 1), a minor amount of the N1,N3-diacylated product 6 was also formed along with the desired N-3 acylated DHPM 7. DHPM 6 was converted into the monoacyl 7 using amine based solid supported scavenging agents or upon treatment with water. Treating 5 (R\textsubscript{1} = Et, X = S, O) with n-BuLi, followed by quenching with various electrophiles, 7 were obtained along with N1,N3-diacylated DHPMs 6 (Method B, Scheme 1),\textsuperscript{6} the latter got converted into monoacyl DHPMs 7 upon stirring at room temperature in the presence of a base. In both of these methods (Method A and B, Scheme 1), diacyl DHPMs 6 were formed as a side product along with major product 7. Alternatively, 6 could also be synthesized from 7 upon reaction with appropriate acid chloride.\textsuperscript{3b} Thus, reaction of 5 with an acid chloride in the presence of potassium tert-butoxide and 18-crown-6, furnished 6 quantitatively.\textsuperscript{6}

Scheme 1

In the light of above observation, using method B (Scheme 1), the aim of the present investigation was to tune the reaction conditions for obtaining 6 as the exclusive product. Further, it was planned to trap the released ‘acyl group’ from N-1, by use of various nucleophiles to effect ‘acyl transfer’ and to develop 6 as ‘acyl group transfer agents’ (vide infra). The results of this investigation are presented in the following two sections.

7.2 Synthesis of N1,N3-diacylated DHPMs

7.3 Acyl group transfer property of N1,N3-diacylated DHPMs

DHPM 5 (R\textsubscript{1} = Et, X = O), used as precursor for further elaboration of N-1 and N-3 positions was obtained through the traditional three-component Biginelli condensation reaction of benzaldehyde with ethyl acetoacetate and urea.\textsuperscript{7} This compound has been well
characterized using spectroscopic and other techniques (*vide experimental*) and compared with an authentic sample.

In order to determine favorable reaction conditions for the high yielding synthesis of 6, *n*-BuLi was explored as base and propanoic anhydride was chosen as an acylating agent. Thus, when a THF solution of 5 (Scheme 2) was treated with *n*-BuLi (2.1 equiv.) at -20°C, under the blanket of purified anhydrous N₂ gas, a pale yellow colored solution resulted, which was quenched with propanoic anhydride (2.5 equiv.) at the same low temperature. After completion (TLC), the reaction was terminated at -78°C, by treating with saturated aqueous solution of ammonium chloride (Scheme 2) and two products [Rf 0.7 and 0.4 (ethyl acetate:hexane/30:70) (TLC)] were isolated after column chromatography.

The ¹H NMR (CDCl₃) spectrum (Figure 2), of the upper Rf (major) component showed signals at δ 0.95 (t, 3H, J 7.2 Hz, CH₃), 1.23 (t, 3H, J 7.2 Hz, CH₃), 1.29 (t, 3H, J 7.2 Hz, CH₃), 2.43 (m, 1H, CHH), 2.51 (s, 3H, C6-CH₃), 2.78 (m, 2H, CH₂), 3.11 (m, 1H, CHH), 4.25 (q, 2H, J 7.2 Hz, OCH₂), 6.77 (s, 1H, C4-H), 7.23 (m, 5H, ArH). The disappearance of resonances for both N-1 as well as N-3 protons of 5 (δ 5.59 and 7.80, respectively) and appearance of signals for two propionyl groups, indicated the substitution at both N-1 and N-3 atoms. This was further supported by its ¹³C NMR spectrum (Figure 2), which showed corresponding signals at δ 8.6, 9.0, 14.1, 19.6, 31.4, 31.6, 52.2, 61.2, 119.7, 126.3, 128.1, 128.7, 137.3, 149.2, 151.9, 164.3, 174.7 and 175.5. This data was further corroborated by the MS spectrum, which showed signal at m/z 395 (M⁺+23), corresponding to the molecular formula C₂₀H₂₄N₂O₅Na. On the basis of this data, structure 5-ethoxycarbonyl-6-methyl-1,3-dipropionyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one 6a (Scheme 2) has been assigned to this compound. It was isolated in 55% yield and depicted correct microanalytical data (*vide experimental*).
Synthesis of N1,N3-diacyl-3,4-dihydropyrimidin-2(1H)-ones. Acyl group transfer to amines: Synthesis of primary, secondary and tertiary amides

The $^1$H NMR (CDCl$_3$) spectrum (Figure 3), of lower Rf (minor) component showed signals at $\delta$ 1.17 (t, 3H, $J$ 7.2 Hz, CH$_3$), 1.25 (t, 3H, $J$ 7.2 Hz, CH$_3$), 2.40 (s, 3H, C6-CH$_3$), 2.80 (m, 1H, CHH), 3.08 (m, 1H, CHH), 4.17 (q, 2H, $J$ 7.2 Hz, OCH$_2$), 6.64 (s, 1H, C4-H), 7.29 (m, 5H, ArH), 7.92 (br, 1H, D$_2$O exchangeable, NH). The disappearance of N3-H ($\delta$ 7.92, upfield) and consequent downfield shift of the split singlet of C4-H of 5 ($\delta$ 5.39) to an unsplit singlet at $\delta$ 6.64, in the NMR spectra of the product, as well as appearance of signals corresponding to the propionyl group (Figure 3), hinted at N-3 propionylation. This data was further supported by the correct $^{13}$C NMR, MS and microanalytical analysis (vide experimental). On the basis of this data, structure 5-ethoxycarbonyl-6-methyl-3-propionyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one 7a (Scheme 2) is assigned to this compound.

It was observed that temperature and equivalents of the base significantly influenced the yield of 6a (Table 1). Thus, using 2.1 equiv. of n-BuLi at -78°C, 6a could be isolated in 35% yield along with N-3 monoacylated 7a (25%) (Table 1). However, using 2.1 equiv. of n-BuLi, but increasing the reaction temperature from -78°C to -20°C, 6a was isolated in 40% yield, upon quenching the reaction with aqueous NH$_4$Cl at -78°C. When equiv. of n-BuLi was decreased from 2.1 to 1.9, the yield of 6a was increased up to 50%. On further decreasing the n-BuLi equiv. to 1.7, the yield of 6a was increased up to 55%. Any further decrease in equiv. of n-BuLi did not lead to an increase in yield of 6a, but led to simultaneous increase in the proportion (TLC) of 7a. Very interestingly, it was also
observed from TLC examination, that when the reaction after addition of the electrophile, was warmed to room temperature, 6a gradually disappeared from the reaction (TLC) and the proportion of 7a (Scheme 2) was correspondingly increased. Thus, when the reaction was maintained at low temperature (-20°C) and quenched at -78°C with saturated aqueous solution of ammonium chloride, product 6a was isolated in 55% yield, along with 7a in 12% yield (Table 1).

**Table 1.** Optimization of reaction conditions for N1,N3-diacylation of DHPM 5 with propanoic anhydride.

<table>
<thead>
<tr>
<th>Equivalents of n-BuLi/temperature</th>
<th>Product</th>
<th>Isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1/-78°C</td>
<td>6a/7a</td>
<td>35/25</td>
</tr>
<tr>
<td>2.1/-20°C</td>
<td>6a/7a</td>
<td>40/20</td>
</tr>
<tr>
<td>1.9/-20°C</td>
<td>6a/7a</td>
<td>50/15</td>
</tr>
<tr>
<td>1.7/-20°C</td>
<td>6a/7a</td>
<td>55/12</td>
</tr>
</tbody>
</table>

Thus, exercising strict temperature control during the reaction as well as while quenching with ammonium chloride, either of 6a or 7a could be obtained. This property of 6a to transfer into 7a, prompted us to explore the possibility of utilizing the released acyl group for *in situ* acylation of nucleophilic substrates. Flexibility of using a number of
different acyl groups and their further transfer would add to the synthetic value of the overall transformation.

In the direction of achieving our aims, having optimized the reaction conditions \((n-\text{BuLi}, 1.7\ \text{equiv.}/-20^\circ\text{C})\), we investigated the acylation reaction of the metalated 5 with various acid anhydrides and acid chlorides to obtain corresponding products 6 as outlined in Scheme 3.

![Scheme 3](image)

**Scheme 3**

**Table 2.** Synthesis of N1,N3-diacylated DHPM derivatives.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R\textsuperscript{1}</th>
<th>Product</th>
<th>Isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Me</td>
<td>6\textbf{b}/7\textbf{b}</td>
<td>60/10</td>
</tr>
<tr>
<td>2.</td>
<td>(n)-Pr</td>
<td>6\textbf{c}/7\textbf{c}</td>
<td>78/5</td>
</tr>
<tr>
<td>3.</td>
<td>Ph</td>
<td>6\textbf{d}/7\textbf{d}</td>
<td>67/0</td>
</tr>
<tr>
<td>4.</td>
<td>4-OMeC\textsubscript{6}H\textsubscript{4}</td>
<td>6\textbf{e}/7\textbf{e}</td>
<td>64/0</td>
</tr>
</tbody>
</table>

Typically, when metalated DHPM 5 \((n-\text{BuLi}, 1.7\ \text{equiv.}/-20^\circ\text{C})\) was reacted with acetic anhydride, the formation of two products \([\text{Rf: 0.6 and 0.3 (ethyl acetate:hexane/25:75) (TLC) }]\) was detected. The higher Rf product in its \(^1\text{H}\) NMR (CDCl\textsubscript{3}) spectrum showed signals at \(\delta 1.29\) (t, 3H, J 7.2 Hz, CH\textsubscript{3}), 2.26 (s, 3H, C6-CH\textsubscript{3}), 2.53 (s, 3H, CH\textsubscript{3}), 2.59 (s, 3H, CH\textsubscript{3}), 4.26 (q, 2H, J 7.2 Hz, OCH\textsubscript{2}), 6.77 (s, 1H, C4-H), 7.25 (m, 5H, ArH). The 3H singlets at \(\delta 2.53\) and 2.59 could be assigned to the two N-acetyl groups. An unsplint singlet at \(\delta 6.77\), corresponding to the C4-H and disappearance of resonances for both N-1 (\(\delta 5.59\)) as well as N-3 (\(\delta 7.80\)) protons of the precursor 5, indicated the incorporation of two acetyl groups at these positions. From the \(^1\text{H}\) NMR, as well as the \(^{13}\text{C}\) NMR spectral data, correct microanalytical analysis data and MS \((m/z 367, \text{M}^+23)\) analysis, the structure 5-ethoxycarbonyl-6-methyl-1,3-diacetyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one 6\textbf{b} (60\%, Table 2) has been assigned to this compound.
In the $^1$H NMR (CDCl$_3$) spectrum of the lower Rf compound, a singlet at $\delta$ 2.56 could be assigned to an N-3 acetyl group. An unsplit singlet at $\delta$ 6.64 corresponding to the C4-H, indicated the incorporation of an acetyl group at the N-3 position. The other potential anionic site *i.e.*, N1-H remained unsubstituted and appeared at $\delta$ 7.58 (br, D$_2$O exchangeable, NH). From the $^1$H NMR data, as well as supporting $^{13}$C NMR spectral data and MS ($m/z$ 325, M$^+$+23) analysis the structure, 5-ethoxycarbonyl-6-methyl-3-acetyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one 7b (10%, Table 2) has been assigned to this compound. The compound exhibited correct microanalytical data (*vide experimental*).

Likewise, butyric anhydride was also used as electrophile for reaction with the metalated 5, using the optimized reaction conditions. The major product [Rf: 0.9 (ethyl acetate:hexane/30:70) (TLC)] of this reaction in its $^1$H NMR (CDCl$_3$) spectrum showed signals at $\delta$ 0.76 (t, 3H, $J$ 7.5 Hz, CH$_3$), 1.00 (t, 3H, $J$ 7.2 Hz, CH$_3$), 1.29 (t, 3H, $J$ 7.2 Hz, CH$_3$), 1.45 (m, 2H, CH$_2$), 1.67 (m, 2H, CH$_2$), 2.40 (m, 1H, CH$_2$), 2.52 (s, 3H, C6-CH$_3$), 2.74 (m, 2H, CH$_2$), 3.04 (m, 1H, CHH$_2$), 4.25 (q, 2H, $J$ 1.2 Hz, OCH$_2$), 6.76 (s, 1H, C4-H), 7.24 (m, 5H, ArH). The disappearance of resonance of both N-1 and N-3 protons and appearance of signals corresponding to the two butyryl groups indicated their incorporation at both the nitrogen atoms of the DHPM. Based on supporting data (*vide experimental*) structure, 5-ethoxycarbonyl-6-methyl-1,3-dibutyryl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one 6c has been assigned to this compound (78%, Entry 2, Table 2).

In analogy with the previous reactions, formation of N-3 butyryl DHPM derivative 7c (lower Rf component) was also observed in this reaction and it could be isolated in 5% yield (Table 2). The $^1$H NMR spectrum of this compound showed signals corresponding to only one butyryl group and unsplit singlet at $\delta$ 6.63 corresponding to C4-H, indicated the incorporation of butyryl group on N-3 position. Based on $^1$H NMR spectral assignments and other spectral/analytical data (*vide experimental*) structure, 5-ethoxycarbonyl-6-methyl-3-butyryl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one 7c has been assigned to this compound.

The scope of this methodology was further extended by using aromatic acid chlorides as electrophiles. Using typical reaction conditions, when metalated 5 was quenched with benzoyl chloride only a single product at Rf: 0.7 (ethyl acetate:hexane/30:70) (TLC) was isolated.

In its $^1$H NMR (CDCl$_3$) spectrum (Figure 4) signals were observed at $\delta$ 1.26 (t, 3H, $J$ 7.2 Hz, CH$_3$), 2.44 (s, 3H, C6-CH$_3$), 4.24 (m, 2H, OCH$_2$), 6.50 (s, 1H, C4-H), 7.14 (m,
2H, ArH), 7.39 (m, 11H, ArH), 7.56 (m, 2H, ArH). Appearance of the resonance corresponding to 15 aromatic protons was accompanied by the disappearance of signals of both N1-H and N3-H protons, indicating the incorporation of two benzoyl groups at both N-1 as well as N-3 atoms of 5. This was further supported by the \(^{13}\)C NMR (CDCl\(_3\)) spectrum (Figure 4), which showed signals at \(\delta\) 14.2, 16.8, 54.4, 61.2, 110.0, 126.8, 128.1, 128.3, 128.8, 130.1, 131.9, 132.6, 133.6, 134.7, 138.8, 146.4, 151.2, 165.0, 169.9 and 170.9. In its EIMS, parent ion peak appeared at \(m/z\) 491(M\(^+\)+23) corresponding to molecular formula C\(_{28}\)H\(_{24}\)N\(_2\)O\(_5\)+Na for the expected product. Based on the spectral as well microanalytical analysis (vide experimental), the structure, 5-ethoxycarbonyl-6-methyl-1,3-dibenzoyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one 6\(_d\) has been assigned to this compound. The corresponding N-3 acyl derivative 7\(_d\) was not detected (TLC) at any stage during the course of this reaction.

Figure 4. \(^1\)H NMR (300 MHz, CDCl\(_3\)) spectrum and \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) assignments of 6\(_d\).

Similar reaction with 4-methoxybenzoyl chloride furnished a single product in 64% yield (Entry 4, Table 2), which has been characterized as 5-ethoxycarbonyl-6-methyl-1,3-bis(4-methoxybenzoyl)-4-phenyl-3,4-dihydropyrimidin-2(1H)-one 6\(_e\), on the basis of spectral and microanalytical data (vide experimental). The corresponding N-3 acyl derivative 7\(_e\) was not detected (TLC) in this reaction also.

7.3 Acyl group transfer property of N1,N3-diacylated DHPM derivatives

Due to the inbuilt difference in basicity of N-1 (enaminoester nitrogen) and comparatively electron rich N-3 site of 6 (Section 7.2), the acyl group at N-1 position is
expected to be more electrophilic and hence susceptible to attack by nucleophiles more than the N-3 acyl group. As envisaged in section 7.2, we investigated the acyl transfer property of 6 as outlined in Scheme 4. The importance and synthetic utility of this transformation could be gauged from the fact that amine protection through an acylation reaction constitutes one of the most fundamental operations encountered during a diverse range of multi-step organic synthesis sequences, where protection of both basic as well as nucleophilic groups is necessitated. The objective is generally achieved by the use of an acid or base catalyzed direct acylation reaction using acids or activated derivatives of acids such as acyl halides and anhydrides and even esters, albeit under harsh conditions. Alternatively, acyl transfer reagents have also been employed in a number of instances. A useful chemoselective acylation reaction of amine in aqueous media has also been demonstrated in the ambit of “green” chemistry. Further, several enzymes, such as serine acetyltransferase are involved in direct transfer of the acyl groups during biosynthesis in bacteria and plants. Each method has its advantages (chemoselectivity, higher yields, formation of non-toxic by-products, if any, and mild reaction conditions), and disadvantages (expensive reagents, limitations for large scale preparations, exothermic nature of the reaction, formation of imide by-products in case of anhydrides, requirement of strongly basic catalysts and/or high pressure). Thus, acyl transfer using a readily accessible agent capable of performing chemoselective acylations under neutral conditions was highly desirable.

Scheme 4. Acyl transfer from 6 to amines.

In the following sections, we demonstrate the use of N1,N3-diacylated 6 as acyl transfer agents to various amines, culminating the synthesis of primary, secondary and tertiary amides.
7.3.1 Acyl group transfer to ammonia. Synthesis of primary amides

Initially reactions of 6 were performed with ammonia (Scheme 5). 5-Ethoxycarbonyl-6-methyl-1,3-dipropionyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one 6a was treated with ammonia gas\(^{\wedge}\) saturated THF solution at room temperature. After completion of the reaction (1 h, TLC), and removal of the solvent, two products at Rf: 0.5 and 0.2 (ethyl acetate:hexane/40:60) (TLC) were isolated after chromatographic purification of the residue.

![Diagram](image)

\(\text{Scheme 5}\)

The \(^1\text{H}\) NMR (CDCl\(_3\)) spectrum (Figure 5) of the lower Rf component which melted at 77-78\(^\circ\)C, showed signals at \(\delta\) 1.16 (t, 3H, \(J\) 7.5 Hz, CH\(_3\)), 2.24 (m, 2H, CH\(_2\)), 5.58 (br, 1H, D\(_2\)O exchangeable, NH), 5.88 (br, 1H, D\(_2\)O exchangeable, NH). The appearance of resonances for five aliphatic protons and D\(_2\)O exchangeable NH\(_2\) protons indicated the formation of an amide \(8\text{a}\) (82%, Table 3). This was further supported by its \(^{13}\text{C}\) NMR (CDCl\(_3\)) spectrum (Figure 5) which showed signals at \(\delta\) 9.2, 31.1 and 175.0 (Figure 5). In its EIMS, parent ion peak appeared at \(m/z\) 74 (M\(^{+}\)+1), corresponding to molecular formula C\(_7\)H\(_7\)NO for the expected product. Based on the spectral as well correct microanalytical analysis (\textit{vide experimental}), the compound was identified as, propionamide \(8\text{a}\).

From the reaction profile (Scheme 5) itself, the upper Rf component were expected to be the 5-ethoxycarbonyl-6-methyl-3-propionyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one \(7\text{a}\) and was isolated quantitatively (86%), at the end of the reaction. Since \(7\text{a}\) was already synthesized as described in Section 7.2, its identity could be easily established by comparison (TLC, m.p. and \(^1\text{H}\) NMR spectrum) with an authentic sample. The N-3

\(^{\wedge}\) Evolved by warming 30% aqueous ammonia solution using standard assembly and dried using KOH trap
propionylated DHPM 7a could be recycled back to diacetylated 6a (66%) upon refluxing in propanoic anhydride.

Likewise, when 5-ethoxycarbonyl-6-methyl-1,3-diacetyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one 6b (Scheme 5) was treated with ammonia dissolved in THF, the formation of two products [Rf: 0.7 and 0.2 (ethyl acetate:hexane/70:30) (TLC)] was observed analogously to the reaction of 6a. The $^1$H NMR (CDCl$_3$) spectrum of the lower Rf compound showed signals at $\delta$ 2.00 (s, 3H, CH$_3$), 6.03 (br, 1H, D$_2$O exchangeable, NH), 6.17 (br, 1H, D$_2$O exchangeable, NH). The $^{13}$C NMR (CDCl$_3$ and DMSO-$d_6$) spectrum depicted signals at $\delta$ 21.2 and 171.9. The EIMS showed parent ion peak at $m/z$ 60 (M$^+$+1), corresponding to molecular formula C$_2$H$_5$NO of acetamide 8b (Table 3), which was compared with commercial authentic sample.

Similar to the previous reaction, the higher Rf component were expected to be the N-3 acetylated 7b. Since 7b was already synthesized as described in Section 7.2, its identity could be easily established by comparison (TLC, m.p. and $^1$H NMR spectrum) with an authentic sample and it was also recycled back to 6b on refluxing with acetic anhydride (Scheme 5, 60%).

Likewise, reaction of N1,N3-dibutyryl DHPM 6c with ammonia saturated THF (Scheme 5), furnished a mixture of butyramide 8c (79%, Table 3) and the corresponding N-3 butyryl DHPM 7c (85%, Scheme 5). The latter was recycled to 6c (50%) upon refluxing with butyric anhydride. The structure could be assigned on the basis of
characteristic data (vide experimental), as well as comparison (TLC) with authentic sample.

**Table 3.** Preparation (THF/r.t) of primary amides 8 (R¹CONH₂) from ammonia.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Et</td>
<td>8a</td>
<td>82</td>
</tr>
<tr>
<td>2.</td>
<td>Me</td>
<td>8b</td>
<td>78</td>
</tr>
<tr>
<td>3.</td>
<td>n-Pr</td>
<td>8c</td>
<td>79</td>
</tr>
<tr>
<td>4.</td>
<td>Ph</td>
<td>8d</td>
<td>90</td>
</tr>
<tr>
<td>5.</td>
<td>4-CH₃OC₆H₄</td>
<td>8e</td>
<td>77</td>
</tr>
</tbody>
</table>

The scope of this methodology was further extended by preparing aromatic amides. The reaction of 5-ethoxycarbonyl-6-methyl-1,3-dibenzoyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one 6d (Scheme 5) with ammonia gas using the standard protocol furnished a mixture of two products [Rf: 0.5 and 0.3 (ethyl acetatae:hexane/50:50) (TLC)]. The ¹H NMR (CDCl₃) spectrum (Figure 6) of the lower Rf compound showed signals at δ 6.34 (br, 2H, D₂O exchangeable, NH₂), 7.46 (m, 3H, ArH), 7.82 (m, 2H, ArH). Further, its ¹³C NMR (CDCl₃) spectrum (Figure 6) depicted signals at δ 127.2, 128.5, 131.9, 133.3 and 169.6. In its EIMS, parent ion peak appeared at m/z 144 (M⁺+23), corresponding to molecular formula C₇H₇NO⁺Na of the expected product. Based on the spectral as well microanalytical analysis (vide experimental), the compound was identified as benzamide 8d (90%, Table 3).

**Figure 6.** ¹H NMR (300 MHz, CDCl₃) spectrum and ¹³C NMR (75 MHz, CDCl₃) assignments of 8d.
The mass spectrum of upper Rf component, showed a base peak at \( m/z \) 387 (\( M^+ + 23 \)), corresponding to the molecular formula \( \text{C}_{21}\text{H}_{20}\text{N}_2\text{O}_4\text{Na} \), expected for a mono-benzoeylated DHPM \( 7\text{d} \). The \( ^1\text{H} \) NMR (CDCl\(_3\)) spectrum depicted signals at \( \delta \) 1.28 (t, 3H, \( J \) 7.2 Hz, CH\(_3\)), 2.24 (s, 3H, C6-CH\(_3\)), 4.21 (q, 2H, \( J \) 7.2 Hz, OCH\(_2\)), 6.39 (s, 1H, C4-H), 7.38 (m, 10H, ArH), 7.67 (br, 1H, D\(_2\)O exchangeable, NH). Presence of 10 aromatic protons and a D\(_2\)O exchangeable broad NH at \( \delta \) 7.67 were characteristic of the expected N-3 benzoeylated DHPM \( 7\text{d} \). The spectral as well as microanalytical data (\textit{vide experimental}) established unequivocally the formation of \( 7\text{d} \) (72%, Scheme 5). Upon N-1 benzoeylation with benzoic anhydride, \( 7\text{d} \) was recycled to DHPM derivative \( 6\text{d} \) (33%).

Likewise, treatment of N1,N3-bis(4-methoxybenzoyl) DHPM \( 6\text{e} \) with ammonia gas dissolved in THF under optimized set of reaction conditions, furnished two products [Rf: 0.7 and 0.3 (ethyl acetate:hexane/70:30) (TLC)]. The compound at Rf 0.3 (ethyl acetate:hexane/70:30) was identified (\textit{vide experimental}) as 4-methoxybenzamide (77%, Table 3). While the other (Rf: 0.7) was identified as N-3 substituted DHPM \( 7\text{e} \) (77%, Scheme 5). However, \( 7\text{e} \) could not be recycled to \( 6\text{e} \) owing to the non availability of the corresponding anhydride.

### 7.3.2 Acyl group transfer to primary amines. Synthesis of secondary amides

Similar to the synthesis of primary amides as discussed in section 7.3.1, synthesis of secondary amides was planned through reaction of N1,N3-diacylated DHPM derivatives \( 6 \) with primary amines as outlined in Scheme 6. Reaction of 5-ethoxycarbonyl-6-methyl-1,3-dipropionyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one \( 6\text{a} \) (\( R^1 = \text{Et} \)) was first performed with aniline \( 9 \) (\( R^2 = \text{Ph} \)). Thus, when a THF solution of \( 9 \) (\( R^2 = \text{Ph} \), 1.0 equiv.) was treated with \( n-\text{BuLi} \) (1.0 equiv.) at \(-78^\circ\text{C}\), under the blanket of purified anhydrous N\(_2\) gas, a pale yellow colored solution resulted, which upon treatment with a solution of \( 6\text{a} \) (1.1 equiv.) in THF at the same low temperature yielded a mixture of two products with Rf 0.5 and 0.4 (ethyl acetate:hexane:30:70) (TLC).

The \( ^1\text{H} \) NMR (CDCl\(_3\)) spectrum (Figure 7) of the upper Rf component showed signals at \( \delta \) 1.25 (t, 3H, \( J \) 7.5 Hz, CH\(_3\)), 2.39 (q, 2H, \( J \) 7.5 Hz, CH\(_2\)), 7.09 (t, 2H, \( J \) 7.5 Hz, ArH), 7.15 (br, 1H, D\(_2\)O exchangeable, NH), 7.31 (t, 1H, \( J \) 7.5 Hz, ArH), 7.50 (d, 2H, \( J \) 7.5 Hz, ArH). The appearance of triplet and quartet at \( \delta \) 1.25 and 2.39, respectively, along with resonances corresponding to five aromatic protons, indicated the transfer of propionyl group to aniline. Its \( ^1\text{C} \) NMR (CDCl\(_3\)) spectrum (Figure 7) depicted signals at \( \delta \) 9.6, 30.7, 119.7, 124.1, 128.9, 137.9 and 172.0. In its EIMS, parent ion peak appeared at \( m/z \) 172 (\( M^+ + 23 \)),
corresponding to molecular formula C$_9$H$_{11}$NO+Na for the expected product. From the spectral as well as microanalytical analysis (vide experimental), the compound was identified as N-phenylpropionamide 10a (R$^1$ = Et, R$^2$ = Ph) (83%, Table 4).

As outlined in Scheme 6, the lower Rf component were expected to be the N-3 propionylated DHPM 7a and was isolated quantitatively (86%). Since 7a was already synthesized as described in Section 7.2, its identity could be easily established by comparison (TLC, m.p. and $^1$H NMR spectrum) with an authentic sample available in the laboratory. N-3 monoacylated DHPM 7a was recycled to N1,N3-dipropionylated derivative 6a (66%), upon refluxing with propanoic anhydride.

In order to simplify the reaction, by way of avoiding the use of n-BuLi, certain experiments were conducted. Initially, it was found that varying the temperature (-78°C to
r.t.), and changing the base, did not alter the yield of desired acylated product 10a (Table 4) in any significant way. Thus, when the reaction of 6a with 9 (R² = Ph) was performed in the presence of Et₃N at room temperature, the reaction proceeded to completion in 0.5 h and the desired secondary amide 10a was obtained in 81% yield (Table 4). Further, when THF solution of 6a (1.0 equiv.) was treated with 9 (R² = Ph, 1.0 equiv.) at room temperature, even without a base, the reaction proceeded to completion (TLC) in 0.5 h and furnished the product in almost quantitative (82%, Table 4) yield.

Table 4. Optimization of reaction conditions for reaction of 6a with 9 (R² = Ph).

<table>
<thead>
<tr>
<th>Base/temperature</th>
<th>Product</th>
<th>Isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n-BuLi/-78°C</td>
<td>10a</td>
<td>83</td>
</tr>
<tr>
<td>Et₃N/r.t.</td>
<td>10a</td>
<td>81</td>
</tr>
<tr>
<td>nil/r.t.</td>
<td>10a</td>
<td>82</td>
</tr>
</tbody>
</table>

Thus, for the synthesis of secondary amides 10 (Scheme 6), optimized conditions were found to be: THF/r.t. To further explore the applicability of these reaction conditions, we performed additional reactions of 6 with a range of primary amines and isolated the corresponding secondary amides 10 (Table 5) in a synthetically useful manner.

Typically, when THF solution of 6a was treated with 2-methoxyaniline 9 (R² = 2-OMeC₆H₄), two products [Rf 0.6 and 0.4 (ethyl acetate:hexane/30:70) (TLC)] were isolated. The ¹H NMR (CDCl₃) spectrum of upper Rf component depicted signals at δ 1.18 (t, 3H, J 7.5 Hz, CH₃), 2.36 (q, 2H, J 7.5 Hz, CH₂), 3.81 (s, 3H, CH₃), 6.89 (m, 3H, ArH), 7.70 (br, 1H, D₂O exchangeable, NH), 8.32 (dd, 1H, J 1.5, J 1.8 Hz, ArH). Its ¹³C NMR (CDCl₃) spectrum showed signals at δ 9.6, 31.0, 55.6, 109.7, 119.6, 121.0, 123.3, 127.7, 147.5 and 171.8. In its EIMS spectrum, a parent ion peak at m/z 202 (M⁺+23), corresponding to the molecular formula C₁₀H₁₃NO₂+Na was observed. From the spectral and microanalytical analysis (vide experimental) the compound was identified as N-(2-methoxyphenyl)propionamide 10b (90%, Table 5). The lower Rf component, as expected, was identified as 7a.

Likewise, reaction of N1,N3-diacetylated 6b (R¹ = Me) with o-toluidine 9 (R² = 2-MeC₆H₄), following the same procedure, furnished a product, N-2-tolylacetamide 10c in 65% yield (Table 5). The structure was confirmed from the spectral and microanalytical analysis (vide experimental).
**Table 5.** Preparation of secondary amides 10 (R²NHCOR¹) from primary amines 9 under neutral stirring conditions (Scheme 6).

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Et</td>
<td>Ph</td>
<td>10a</td>
<td>82</td>
</tr>
<tr>
<td>2.</td>
<td>Et</td>
<td>2-CH₃OC₆H₄</td>
<td>10b</td>
<td>90</td>
</tr>
<tr>
<td>3.</td>
<td>Me</td>
<td>2-CH₃C₆H₄</td>
<td>10c</td>
<td>65</td>
</tr>
<tr>
<td>4.</td>
<td>Me</td>
<td>n-Bu</td>
<td>10d</td>
<td>80</td>
</tr>
<tr>
<td>5.</td>
<td>Me</td>
<td>sec-Bu</td>
<td>10e</td>
<td>65</td>
</tr>
<tr>
<td>6.</td>
<td>Me</td>
<td>n-C₃H₇</td>
<td>10f</td>
<td>78</td>
</tr>
<tr>
<td>7.</td>
<td>Et</td>
<td>2-HOC₆H₄</td>
<td>10g</td>
<td>95</td>
</tr>
<tr>
<td>8.</td>
<td>Et</td>
<td>2-SHC₆H₄</td>
<td>10h</td>
<td>73</td>
</tr>
<tr>
<td>9.</td>
<td>Et</td>
<td>2-NHCOEtC₆H₄</td>
<td>10i</td>
<td>80</td>
</tr>
<tr>
<td>10.</td>
<td>Et</td>
<td>PhCH₂CH₂</td>
<td>10j</td>
<td>90</td>
</tr>
<tr>
<td>11.</td>
<td>Et</td>
<td>3,4-diMeOC₆H₃CH₂CH₂</td>
<td>10k</td>
<td>96</td>
</tr>
<tr>
<td>12.</td>
<td>Et</td>
<td>3-(1H-indolyl)CH₂CH₂</td>
<td>10l</td>
<td>90</td>
</tr>
<tr>
<td>13.</td>
<td>Et</td>
<td>D-3-(1H-indolyl)CH₂CH(COOMe)</td>
<td>10m</td>
<td>70</td>
</tr>
<tr>
<td>14.</td>
<td>Et</td>
<td>L-3-(1H-indolyl)CH₂CH(COOMe)</td>
<td>10n</td>
<td>62</td>
</tr>
<tr>
<td>15.</td>
<td>Et</td>
<td>DL-3-(1H-indolyl)CH₂CH(COOMe)</td>
<td>10o</td>
<td>60</td>
</tr>
</tbody>
</table>

In order to extend the scope of this methodology, when n-butylamine 9 (R² = n-C₃H₇) was treated with 6b, under optimized set of reaction conditions, two products [Rf 0.5 and 0.4 (ethyl acetate:hexane/40:60) (TLC)] were isolated. The ¹H NMR (CDCl₃) spectrum (Figure 8) of the upper Rf component depicted signals at δ 0.92 (t, 3H, J 6.9 Hz, CH₃), 1.33 (m, 2H, CH₂), 1.47 (m, 2H, CH₂), 1.97 (s, 3H, CH₃), 3.24 (q, 2H, J 7.2 Hz, CH₂), 5.40 (br, 1H, D₂O exchangeable, NH). The appearance of a 3H singlet at δ 1.97 confirmed the incorporation of an acetyl group on n-butylamine. Its ¹³C NMR (CDCl₃) spectrum (Figure 8) showed signals at δ 13.6, 19.9, 23.1, 31.5, 39.3 and 170.1. The appearance of the signal at δ 170.1 was assigned to C=O group. Additionally, microanalytical data and mass spectrum (m/z 116, M⁺+1) peaks, corresponded to the molecular formula C₆H₁₅NO, corresponding to N-butylacetamide 10d, isolated in 80% yield (Table 5).
Figure 8. $^1$H NMR (300 MHz, CDCl$_3$) spectrum and $^{13}$C NMR (75 MHz, CDCl$_3$) assignments of 10d.

Similar to the previous reaction, the lower Rf component was expected to be the N-3 acetylated DHPM 7b (86%). Since 7b was already synthesized as described in Section 7.2, its identity could be easily established by comparison (TLC, m.p. and $^1$H NMR spectrum) with authentic sample and it was recycled back to 6b on refluxing with acetic anhydride (60%).

Likewise, reaction of 6b with sec-butylamine (Scheme 6) furnished a product at Rf: 0.6 (ethyl acetate:hexane/30:70) (TLC). In its $^1$H NMR (CDCl$_3$) spectrum, signals were observed at $\delta$ 0.90 (t, 3H, $J$ 7.2 Hz, CH$_3$), 1.11 (d, 3H, $J$ 6.6 Hz, CH$_3$), 1.45 (m, 2H, CH$_2$), 1.98 (s, 3H, CH$_3$), 3.90 (m, 1H, CH), 5.23 (br, 1H, D$_2$O exchangeable, NH). The salient feature of the spectrum was the appearance of a 3H singlet of the acetyl group at $\delta$ 1.98. Further, the presence of signal at $\delta$ 169.4 in its $^{13}$C NMR spectrum was assigned to the C=O group of the amide. On the basis of NMR assignments, EIMS ($m/z$ 138, M$^+$+23) peak and correct microanalytical analysis (vide experimental), the formation of N-sec-butylacetamide 10e (65%, Table 5) was ascertained. The other compound at Rf: 0.3 (ethyl acetate:hexane/30:70) (TLC) was found to be 7b [identity could be easily established by comparison (TLC, m.p. and $^1$H NMR spectrum) with an authentic sample].

Thus the N1,N3-diacylated DHPMs 6 may be regarded as an efficient acyl transfer agents and transfer of N-1 acyl group to nucleophilic amine sites has clearly been demonstrated.

To evaluate the scope of acylation of amine substrates, bearing competitive nucleophilic sites, when 2-aminophenol was reacted with 6a in THF, two products [Rf 0.5
and 0.7 (ethyl acetate:hexane/40:60) (TLC)] were isolated (Scheme 6). The $^1$H NMR (CDCl$_3$) spectrum (Figure 9) of the upper Rf component showed signals at $\delta$ 1.29 (t, 3H, $J$ 7.5 Hz, CH$_3$), 2.50 (q, 2H, $J$ 7.5 Hz, CH$_2$), 6.85 (m, 1H, ArH), 7.00 (m, 2H, ArH), 7.13 (m, 1H, ArH), 7.45 (br, 1H, D$_2$O exchangeable, NH), 8.80 (br, 1H, D$_2$O exchangeable, OH). The presence of triplet and quartet signals at $\delta$ 1.29 and 2.50 corresponding to CH$_3$ and CH$_2$ groups of the propionyl group, respectively, ensured acylation process. Its $^{13}$C NMR (CDCl$_3$) spectrum (Figure 9) displayed signals at $\delta$ 9.8, 30.0, 119.7, 120.4, 122.0, 123.9, 127.0, 148.6 and 174.1. Its IR (KBr) spectrum was characteristic with the appearance of intense absorption band at 3415 cm$^{-1}$ assigned to OH, in addition to other absorptions. Additionally, microanalytical analysis and mass spectrum peak ($m/z$ 165, M$^+$), corresponded to the molecular formula C$_9$H$_{11}$NO$_2$ and led to the assignment of structure, N-(2-hydroxyphenyl)propionamide 10g (Table 5) to this compound, isolated in 95% yield. The lower Rf component was found to be N-3 substituted DHPM derivative 7a (86%) as expected from reaction profile (Scheme 6) and characterized as described earlier (Section 7.2).

![Figure 9](image)

**Figure 9.** $^1$H NMR (300 MHz, CDCl$_3$) spectrum and $^{13}$C NMR (75 MHz, CDCl$_3$) assignments of 10g.

Similar reaction of 6a with 2-aminothiophenol under optimized set of reaction conditions, furnished a compound N-(2-mercaptophenyl)propionamide 10h in 73% yield (Table 5). The identity of 10h was established from spectral and microanalytical data (vide experimental).

Thus, the reactions of 6a with 2-aminophenol and 2-aminothiophenol furnished products exclusively of N-acylation. The less basic and less nucleophilic OH and SH were not acylated under these conditions.
However, when 2-phenylenediamine 9 \( \text{R}^2 = 2\text{-NH}_2\text{C}_6\text{H}_4 \) (Scheme 6) was treated with two equivalents of 6a, at the end of the reaction two products \([\text{Rf} 0.5 \text{ and } 0.3 \text{ (ethyl acetate:hexane/40:60)} \text{ (TLC)}]\) were isolated. The \(^1\text{H NMR (CDCl}_3\) spectrum (Figure 10) of lower Rf component showed signals at \( \delta 1.22 \) (t, 6H, \( J 7.5 \text{ Hz, } 2\times\text{CH}_3 \)), 2.37 (q, 4H, \( J 7.5 \text{ Hz, } 2\times\text{CH}_2 \)), 7.17 (m, 2H, ArH), 7.33 (m, 2H, ArH), 8.17 (br, 2H, D\(_2\)O exchangeable, NH). The presence of triplet and quartet at \( \delta 1.22 \) and 2.37 respectively, corresponding to two ethyl groups ensured the acylation of both NH groups. Its \(^{13}\text{C NMR (CDCl}_3\) spectrum (Figure 10) displayed signals at \( \delta 9.7, 30.1, 125.5, 126.0, 130.5 \text{ and } 173.4 \). Additionally, correct microanalytical data and mass spectrum \((m/z 243, M^+ 23)\) led to the assignment of structure, N-(2-propionylaminophenyl)propionamide 10i to this compound, isolated in 80% yield (Table 5).

![Figure 10](image-url)

**Figure 10.** \(^1\text{H NMR (300 MHz, CDCl}_3\) spectrum and \(^{13}\text{C NMR (75 MHz, CDCl}_3\) assignments of 10i.**

Similar to the previous reaction, the upper Rf component was expected to be the N-3 acylated DHPM 7a (86%). Since 7a was already synthesized as described in Section 7.2, its identity could be easily established by comparison (TLC, m.p. and \(^1\text{H NMR spectrum) with authentic sample and it was recycled back to 6a on refluxing with propanoic anhydride (66%).**

N1,N3-dipropionylated DHPM derivatives were also explored for acyl transfers to biogenic amines. Thus, \(\beta\)-phenethylamine upon treatment with 6a in THF at room temperature, yielded two products \([\text{Rf} 0.5 \text{ and } 0.4 \text{ (ethyl acetate:hexane/40:60)} \text{ (TLC)}]\) (Scheme 6). The \(^1\text{H NMR (CDCl}_3\) spectrum (Figure 11) of lower Rf component showed signals at \( \delta 1.12 \) (t, 3H, \( J 7.5 \text{ Hz, } \text{CH}_3 \)), 2.15 (q, 2H, \( J 7.8 \text{ Hz, } \text{CH}_2 \)), 2.81 (t, 2H, \( J 6.9 \text{ Hz, }\text{CH}_2 \)), 243
CH$_2$), 3.52 (q, 2H, $J$ 6.9 Hz, NCH$_2$), 5.42 (br, 1H, D$_2$O exchangeable, NH), 7.25 (m, 5H, ArH). Presence of triplet and quartet at $\delta$ 1.12 and 2.15 respectively, indicated the propionylation of $\beta$-phenethylamine. $^1$H NMR spectrum was further supported by its $^{13}$C NMR (CDCl$_3$) spectrum (Figure 11), which displayed signals at $\delta$ 14.1, 18.8, 55.8, 60.0, 126.5, 127.9, 128.7, 145.9 and 173.0. Additionally, correct microanalytical data and mass spectrum ($m/z$ 178, M$^+$+1) peaks, corresponded to the molecular formula C$_{11}$H$_{15}$NO and led to the assignment of structure, N-phenethylpropionamide 10j to this compound, isolated in 90% yield (Table 5). The upper Rf compound was identified (vide experimental) as 7a (86%).

Likewise, homoveratrylamine furnished the corresponding amide 10k in 96% yield (Table 5) upon reaction with DHPM derivative 6a, using optimized set of reaction conditions. The structure of 10k was established from spectral and microanalytical data (vide experimental). 7a was also obtained in this reaction.

It is worth pointing out that $\beta$-arylethyl amide 10j and the dimethoxy analogue 10k are important intermediates, as upon treatment with anhydrous POCl$_3$ (Bischler-Napieralski reaction), 3,4-dihydroisoquinolines are formed, which are intermediates of isoquinoline alkaloids.$^{13}$

The scope of this methodology was further extended by using methyl tryptophanate (racemic as well as enantiomers). Thus, when D-methyl tryptophanate was reacted with DHPM 6a (Scheme 6), two products [Rf 0.5 and 0.2 (ethyl acetate:hexane/40:60) (TLC)]
were isolated. The \(^1\)H NMR (CDCl\(_3\)) spectrum (Figure 12) of lower Rf component displayed signals at \(\delta\) 1.09 (t, 3H, \(J 7.5\) Hz, CH\(_3\)), 2.16 (q, 2H, \(J 7.5\) Hz, CH\(_2\)), 3.33 (m, 2H, CH\(_2\)), 3.68 (s, 3H, CH\(_3\)), 4.95 (m, 1H, CH), 6.05 (d, 1H, \(J 7.5\) Hz, D\(_2\)O exchangeable, NH), 6.95 (d, 1H, \(J 2.4\) Hz, 1H-indole), 7.12 (m, 2H, ArH), 7.34 (d, 1H, \(J 8.1\) Hz, ArH), 7.51 (d, 1H, \(J 7.8\) Hz, ArH), 8.59 (br, 1H, D\(_2\)O exchangeable, NH). The appearance of signals of propionyl group assured the acylation of methyl tryptophanate. This was further supported by its \(^13\)C NMR (CDCl\(_3\)) spectrum (Figure 12), which displayed signals at \(\delta\) 9.5, 27.5, 29.5, 52.3, 52.8, 110.0, 111.2, 118.5, 119.6, 122.1, 122.6, 127.7, 136.0, 172.5 and 173.4. Additionally, correct microanalytical data and mass spectrum (\(m/z\) 297, M\(^+\)+23) peaks, corresponded to the molecular formula \(C_{15}H_{18}N_2O_3Na\) and led to the assignment of structure, D-3-\((1H\)-indol-3-yl)-2-propionylaminopropanoic acid methyl ester \(10m\) to this compound, isolated in 62\% yield (Table 5). The optical rotation of this compound was found to be \([\alpha]^{20}_D = -4.00\) (CHCl\(_3\), c = 0.5). Similar to the previous reaction, the upper Rf component were found to be N-3 propionyl DHPM \(7a\) (86\%).

Analogously, when L-methyl tryptophanate was reacted with DHPM \(6a\) (Scheme 6), two products [Rf 0.5 and 0.2 (ethyl acetate:hexane/40:60) (TLC)] were isolated. The \(^1\)H NMR (CDCl\(_3\)) spectrum (Figure 13) of lower Rf component displayed signals at \(\delta\) 1.11 (t, 3H, \(J 7.5\) Hz, CH\(_3\)), 2.18 (q, 2H, \(J 7.5\) Hz, CH\(_2\)), 3.35 (m, 2H, CH\(_2\)), 3.70 (s, 3H, CH\(_3\)), 4.96 (m, 1H, CH), 6.07 (br, 1H, D\(_2\)O exchangeable, NH), 6.97 (d, 1H, \(J 2.4\) Hz, 1H-indole), 7.15 (m, 2H, ArH), 7.35 (m, 1H, ArH), 7.52 (d, 1H, \(J 8.1\) Hz, ArH), 8.21 (br, 1H, D\(_2\)O exchangeable, NH). The appearance of signals of propionyl group assured the

![Figure 12. \(^1\)H NMR (300 MHz, CDCl\(_3\)) spectrum and \(^13\)C NMR (75 MHz, CDCl\(_3\)) assignments of \(10m\).](image-url)
Synthesis of N1,N3-diacyl-3,4-dihydropyrimidin-2(1H)-ones. Acyl group transfer to amines: Synthesis of primary, secondary and tertiary amides

acylation of methyl tryptophanate. $^{13}$C NMR spectrum, correct microanalytical data and mass spectrum ($m/z$ 297, M$^+$+23) peaks, corresponded to the molecular formula C$_{15}$H$_{18}$N$_2$O$_3$+Na, led to the assignment of structure, L-3-(1H-indol-3-yl)-2-propionylaminopropanoic acid methyl ester 10n to this compound, isolated in 60% yield (Table 5). The optical rotation of this compound $[[\alpha]_{D}^{20} = +4.00$ (CHCl$_3$, c = 0.5) was equal and with opposite sign to 10m. Similar to the previous reaction, the upper Rf component were found to be 7a.

Figure 13. $^1$H NMR (300 MHz, CDCl$_3$) spectrum and $^{13}$C NMR (75 MHz, CDCl$_3$) assignments of 10n.

Reactions of racemic methyl tryptophanate (DL) with 6a furnished corresponding racemic propionylated products 10o (vide experimental).

Similar to 10j or 10k, the products 10m, 10n and 10o could be visualized to be useful intermediates, which upon acid catalyzed cyclodehydration would furnish cis and/or trans 1,3-disubstituted 3,4-dihydro-β-carbolines, which are important intermediates of a variety of indole alkaloids.  

7.3.3 Acyl group transfer to secondary amines. Synthesis of tertiary amides

The importance of tertiary amides has been amply demonstrated. One of the important applications of tertiary amides is the activation of ortho hydrogen of aryl ring toward lithiation. After $o$-lithiation and substitution, tertiary amide can be easily converted to other functionalities such as aldehydes, amines, alcohols or alkyl groups. Thus, use of tertiary amides for $o$-lithiation gains additional significance. Through $o$-lithiation and Stille-coupling synthesis of a radiotracer of neurokinin B, which plays an important role in a range of central nervous system disorders, has also been reported. Tertiary amide
directing o-lithiation is also used for the synthesis of pharmacologically important isocoumarines.\textsuperscript{17} However, compiling methods of synthesis of tertiary amides is beyond the scope of this chapter.

Using N1,N3-diacylated DHPMs 6, we synthesized tertiary amides from corresponding secondary amines using the reaction conditions optimized for the synthesis of secondary amides 10 (Section 7.3.2).

Thus, when 5-ethoxycarbonyl-6-methyl-1,3-diacetyl-4-phenyl-3,4-dihydropyrimidin-2(1\textit{H})-one 6\textit{b} was reacted with diethyl amine 11 (R\textsubscript{2} = R\textsubscript{2} = Et) in THF at room temperature (Scheme 7), two products [Rf: 0.3 and 0.6 (ethyl acetate:hexane/30:70) (TLC)] were isolated after stirring the reaction at ambient temperature for 0.5 h.

![Scheme 7](image)

The upper Rf component in its \textit{\textit{1}}H NMR (CDCl\textsubscript{3}) spectrum (Figure 14) showed signals at \(\delta\ 1.12\) (t, 3H, J 7.2 Hz, CH\textsubscript{3}), 1.18 (t, 3H, J 7.2 Hz, CH\textsubscript{3}), 2.09 (s, 3H, COCH\textsubscript{3}), 3.34 (m, 4H, 2\times\textit{CH}_{2}). Appearance of the signals of one acetyl group ensured the acylation of diethyl amine. \textit{\textit{1}}H NMR spectrum was well supported by its \textit{\textit{13}}C NMR (CDCl\textsubscript{3}) data (Figure 14), which displayed signals at \(\delta\ 13.0, 14.0, 21.2, 40.0, 42.8\) and 169.9. Correct microanalytical analysis (\textit{vide experimental}) and mass spectrum (m/z 138, M\textsuperscript{+}+23), corresponding to molecular formula C\textsubscript{6}H\textsubscript{13}NO+Na and led to the identification of N,N-diethylacetamide 12\textit{a} (Table 6), obtained in 78% yield.

As expected, the lower Rf component was found to be 7\textit{b} and was isolated quantitatively (86\%) at the end of the reaction. Since 7\textit{b} was already synthesized as described in Section 7.2, its identity could be easily established by comparison (TLC, m.p. and \textit{\textit{1}}H NMR spectrum) with an authentic sample. Further, it was converted to the diacetylated derivative 6\textit{b} (60\%) upon refluxing with acetic anhydride.
Synthesis of N1,N3-diacyl-3,4-dihydropyrimidin-2(1H)-ones. Acyl group transfer to amines: Synthesis of primary, secondary and tertiary amides

Figure 14. $^1$H NMR (300 MHz, CDCl$_3$) spectrum and $^{13}$C NMR (75 MHz, CDCl$_3$) assignments of 12a.

Table 6. Preparation (THF/r.t) of tertiary amides 12 ($R^2-R^3$NOC $R^1$) from $R^2-R^3$NH.

<table>
<thead>
<tr>
<th>Entry</th>
<th>$R^1$</th>
<th>$R^2$</th>
<th>$R^3$</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Me</td>
<td>Et</td>
<td>Et</td>
<td>12a</td>
<td>78</td>
</tr>
<tr>
<td>2.</td>
<td>Me</td>
<td>-(CH$_2$)$_5$-</td>
<td></td>
<td>12b</td>
<td>80</td>
</tr>
<tr>
<td>3.</td>
<td>Me</td>
<td>-(CH$_2$)$_2$-O-(CH$_2$)$_2$-</td>
<td></td>
<td>12c</td>
<td>74</td>
</tr>
<tr>
<td>4.</td>
<td>$n$-Pr</td>
<td>Ph</td>
<td>Me</td>
<td>12d</td>
<td>70</td>
</tr>
<tr>
<td>5.</td>
<td>$n$-Pr</td>
<td>3,4-diMeOC$_6$H$_3$CH$_2$CH$_2$</td>
<td>Me</td>
<td>12e</td>
<td>93</td>
</tr>
</tbody>
</table>

Secondary cyclic amines were also used in order to further expand the scope of this reaction. Under optimized reaction conditions (Scheme 7), piperidine 11 ($R^2 = R^3 = -(CH$_2$)$_5$-) upon reaction with 6b furnished two products [Rf 0.4 and 0.6 (ethyl acetate:hexane/40:60) (TLC)]. The upper Rf component in its $^1$H NMR (CDCl$_3$) spectrum (Figure 15) displayed signals at $\delta$ 1.55 (m, 6H, 3$x$CH$_2$), 2.08 (s, 3H, CH$_3$), 3.38 (t, 2H, J 5.4 Hz, CH$_2$), 3.54 (t, 2H, J 5.4 Hz, CH$_2$). Appearance of signals of acetyl group indicated the acylation of amine. Its $^{13}$C NMR (CDCl$_3$) spectrum (Figure 15) depicted signals at $\delta$ 21.4, 24.4, 25.4, 26.3, 42.4, 47.4 and 168.7. In its EIMS analysis, a parent ion peak at $m/z$ 150 (M$^+$+23), corresponding to the molecular formula C$_7$H$_{13}$NO+Na was observed. Based on the spectral and correct microanalytical analysis (vide experimental) structure, 1-piperidin-yl-ethanone 12b (80%, Table 6) has been assigned to this compound.
The identity of the lower Rf component was conveniently established as 7b (86%) by comparison (TLC, m.p. and $^1$H NMR spectrum) with an authentic sample (Section 7.2).

Likewise, morpholine upon reaction with 6b furnished the corresponding tertiary amide 12c (74%, Table 6). The structure of 12c was established from spectral and microanalytical data (vide experimental).

Using similar reaction conditions, N-methylaniline 11 ($R_2$ = Ph, $R_3$ = Me) upon reaction with 5-ethoxycarbonyl-6-methyl-1,3-dibutyryl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one 6c furnished two products [Rf 0.7 and 0.4 (ethyl acetate:hexane/25:75) (TLC)] (Scheme 7). The $^1$H NMR (CDCl$_3$) spectrum of the upper Rf component showed signals at $\delta$ 0.82 (t, 3H, J 7.2 Hz, CH$_3$), 1.63 (m, 2H, CH$_2$), 2.04 (t, 2H, J 6.6 Hz, CH$_2$), 3.26 (s, 3H, CH$_3$), 7.29 (m, 5H, ArH). Appearance of signals of butyryl group indicated the acylation of amine. This was further supported by its $^{13}$C NMR (CDCl$_3$) spectral data, which displayed signals at $\delta$ 13.8, 18.9, 35.9, 37.2, 124.7, 127.3, 127.6, 128.9, 129.6, 144.2 and 173.2. In its EIMS spectrum, a parent ion peak at $m/z$ 178 (M$^+$+1) corresponded to the molecular formula C$_{11}$H$_{15}$NO was observed. Based on the spectral and correct microanalytical analysis (vide experimental) structure, N-methyl-N-phenylbutyramide 12d (70%, Table 6) has been assigned to this compound.

From the reaction profile (Scheme 7), the lower Rf component were expected to be 7c and was isolated quantitatively (85%) at the end of the reaction. Since 7c was already synthesized as described in Section 7.2, its identity could be easily established by
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7.4 Conclusions

Thus, we have demonstrated an efficient method for the preparation of primary, secondary and tertiary amides by reacting N1,N3-diacyl DHPMs with ammonia, primary and secondary amines, respectively. The fact that the transformation is accomplished under neutral reaction conditions, acylation of acid or base sensitive amines could also be performed. Further, the yields are high and isolation of the products is straightforward.

7.5 Experimental

7.5.1 General information

General experimental details are same as reported in Chapter 3 at page 115. For monitoring the progress of a reaction and for comparison purpose, thin layer chromatography (TLC) was performed on glass plates coated with silica gel-G for aliphatic amines and Merck (60F254, 0.2 mm) using an appropriate solvent system. The chromatograms were visualized under UV light and using iodine.

7.5.2 Materials and methods

The solvents: acetonitrile (P2O5), MeOH/EtOH (Na metal followed by Mg treatment), dichloromethane (DCM) (CaCl2), diethylether, hexane and tetrahydrofuran (THF) (Na-benzophenone ketyl), amines (KOH pellets) were adequately dried and drawn under N2 atmosphere using hypodermic glass syringes. The commercially available reagents (LR grade) were used as such without further purification. Liquids, low boiling reagents were at times distilled over 4Å molecular sieves as required. n-BuLi (2.0-2.3N in hexane) was prepared using the method reported in literature. Its strength was determined by titration against diphenylacetic acid following reported method. Reactions were run under a blanket of dry nitrogen gas in a sealed (rubber septum, Aldrich) round-bottomed flasks. Organometallic reagents were added using cannula and/or hypodermic glass syringes. The low temperature (-20°C and -78°C) was attained in Dewar flasks using organic solvent-liquid N2 slush.

7.5.3 Synthesis of 3,4-dihydropyrimidin-2(1H)-ones

A solution of ethyl acetoacetate (10.0 mmol), benzaldehyde (10.0 mmol), urea (15.0 mmol) in MeOH (5.0 ml) containing 1-2 drops of concentrated HCl was stirred at room temperature. After completion of the reaction, 3,4-dihydropyrimidin-2(1H)-one 5 got

comparison (TLC, m.p. and 1H NMR spectrum) with an authentic sample. DHPM 7c was converted to 6c (50%), upon refluxing with butyric anhydride.
precipitated. It was filtered and recrystallized from methanol. The characteristic data is presented below.

**5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (5)**

Colorless solid. Rf: 0.6 (ethyl acetate:hexane/50:50). Yield: 70%. m.p. 202-204°C (methanol). IR (KBr): \( \nu_{\text{max}} \) 1220, 1701, 1724, 3245 cm\(^{-1}\). \(^1\)H (300 MHz, CDCl\(_3\), 25°C): \( \delta \) 1.16 (t, 3H, \( J \) 6.9 Hz, ester-CH\(_3\)), 2.35 (s, 3H, C6-CH\(_3\)), 4.08 (m, 2H, ester-CH\(_2\)), 5.39 (d, 1H, \( J \) 0.9 Hz, C4-H), 5.59 (br, 1H, D\(_2\)O exchangeable, NH), 7.28 (m, 5H, ArH), 7.80 (br, 1H, D\(_2\)O exchangeable, NH). \(^13\)C NMR (75 MHz, CDCl\(_3\), 25°C): \( \delta \) 13.0, 17.0, 53.6, 58.3, 98.9, 125.4, 126.1, 127.1, 143.1, 146.7, 151.9 and 164.6. Anal. Calcd. for C\(_{14}\)H\(_{16}\)N\(_2\)O\(_3\): C, 64.62; H, 6.15; N, 10.77; Found: C, 64.40; H, 6.05; N, 10.35. MS: \( m/z \) 261 (M\(^+\)+1).

**7.5.4 General procedure for the synthesis of 5-ethoxycarbonyl-6-methyl-1,3-diacylated-4-phenyl-3,4-dihydropyrimidin-2(1H)-one**

To a stirred solution of DHPM 5 (1.92 mmol) in dry THF (20 ml) at -20°C, under a blanket of dry \( \text{N}_2 \) gas, freshly prepared 2.0 N \( n \)-BuLi in hexanes (3.26 mmol) was introduced using a syringe. The reaction was stirred at -20°C for 0.5 h after which an appropriate acid anhydride (in case of 6a-c)/acid chloride (in case of 6d-e) (4.8 mmol) dissolved in dry THF (10 ml) was added to the reaction mixture at the same low temperature. After completion (TLC), the reaction was quenched with saturated aqueous solution of NH\(_4\)Cl (-78°C) and the organic phase was washed with brine (10 ml) and extracted with ethyl acetate (3×30 ml). The extracts were dried over anhydrous sodium sulphate and evaporated under reduced pressure. The corresponding product 6a-e were isolated using column chromatography. The characteristic data of the compounds is given below.

**5-Ethoxycarbonyl-6-methyl-1,3-dipropionyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (6a)**

Colorless solid. Rf: 0.7 (ethyl acetate:hexane/30:70). Yield: 55%. m.p. 87°C (dichloromethane/hexane). IR (KBr): \( \nu_{\text{max}} \) 760, 1220, 1710, 3060 cm\(^{-1}\). \(^1\)H (300 MHz, CDCl\(_3\), 25°C): \( \delta \) 0.95 (t, 3H, \( J \) 7.2 Hz, CH\(_3\)), 1.23 (t, 3H, \( J \) 7.2 Hz, CH\(_3\)), 1.29 (t, 3H, \( J \) 7.2 Hz, ester-CH\(_3\)), 2.43 (m, 1H, CHH), 2.51 (s, 3H, C6-CH\(_3\)), 2.78 (m, 2H, CH\(_2\)), 3.11 (m, 1H, CHH), 4.25 (q, 2H, \( J \) 7.2 Hz, ester-CH\(_2\)), 6.77 (s, 1H, C4-H), 7.23 (m, 5H, ArH). \(^13\)C NMR (75 MHz, CDCl\(_3\), 25°C): \( \delta \) 8.6, 9.0, 14.1,
Synthesis of N1,N3-diacyl-3,4-dihydropyrimidin-2(1H)-ones. Acyl group transfer to amines: Synthesis of primary, secondary and tertiary amides

19.6, 31.4, 31.6, 52.2, 61.2, 119.7, 126.3, 128.1, 128.7, 137.3, 149.2, 151.9, 164.3, 174.7 and 175.5. Anal. Calcd. for C20H24N2O5: C, 64.52; H, 6.45; N, 7.53; Found: C, 64.78; H, 6.60; N, 7.30. MS: m/z 395 (M^+23).

5-Ethoxycarbonyl-6-methyl-1,3-diacetyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (6b)

Viscous liquid. Rf: 0.6 (ethyl acetate:hexane/25:75). Yield: 60%. IR (KBr): \( \nu_{\text{max}} \) 1220, 1600, 1650, 3015 cm\(^{-1}\). \(^1\)H (300 MHz, CDCl\(_3\), 25°C): \( \delta \) 1.29 (t, 3H, J 7.2 Hz, ester-CH\(_3\)), 2.26 (s, 3H, C6-CH\(_3\)), 2.53 (s, 3H, OCH\(_3\)), 2.59 (s, 3H, OCH\(_3\)), 4.26 (q, 2H, J 7.2 Hz, ester-CH\(_2\)), 6.77 (s, 1H, C4-H), 7.25 (m, 5H, ArH). \(^13\)C NMR (75 MHz, CDCl\(_3\), 25°C): \( \delta \) 14.0, 19.8, 25.8, 26.0, 51.9, 61.3, 120.7, 126.1, 128.1, 128.7, 136.9, 149.3, 152.2, 164.1, 170.3 and 171.4. Anal. Calcd. for C\(_{18}\)H\(_{20}\)N\(_2\)O\(_5\): C, 62.79; H, 5.81; N, 8.14; Found: C, 62.59; H, 5.92; N, 8.38. MS: m/z 367 (M^+23).

5-Ethoxycarbonyl-6-methyl-1,3-dibutyryl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (6c)

Viscous liquid. Rf: 0.9 (ethyl acetate:hexane/30:70). Yield: 78%. IR (KBr): \( \nu_{\text{max}} \) 1220, 1640, 1700, 3150 cm\(^{-1}\). \(^1\)H (300 MHz, CDCl\(_3\), 25°C): \( \delta \) 0.76 (t, 3H, J 7.5 Hz, CH\(_3\)), 1.00 (t, 3H, J 7.2 Hz, CH\(_3\)), 1.29 (t, 3H, J 7.2 Hz, ester-CH\(_3\)), 1.45 (m, 2H, CH\(_2\)), 1.67 (m, 2H, CH\(_2\)), 2.40 (m, 1H, CHH), 2.52 (m, 3H, C6-CH\(_3\)), 3.04 (m, 1H, CHH), 4.25 (q, 2H, J 1.2 Hz, ester-CH\(_2\)), 6.76 (s, 1H, C4-H), 7.24 (m, 5H, ArH). \(^13\)C NMR (75 MHz, CDCl\(_3\), 25°C): \( \delta \) 13.3, 13.6, 14.1, 17.7, 18.2, 19.7, 39.7, 39.8, 52.0, 61.3, 119.9, 126.3, 128.1, 128.7, 137.4, 149.4, 152.0, 164.3, 173.7 and 174.6. Anal. Calcd. for C\(_{22}\)H\(_{28}\)N\(_2\)O\(_5\): C, 66.00; H, 7.00; N, 7.00; Found: C, 65.78; H, 6.90; N, 7.20. MS: m/z 423 (M^+23).

5-Ethoxycarbonyl-6-methyl-1,3-dibenzoyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (6d)

Viscous liquid. Rf: 0.7 (ethyl acetate:hexane/30:70). Yield: 67%. IR (KBr): \( \nu_{\text{max}} \) 758, 1235, 1698, 1704, 3025 cm\(^{-1}\). \(^1\)H (300 MHz, CDCl\(_3\), 25°C): \( \delta \) 1.26 (t, 3H, J 7.2 Hz, ester-CH\(_3\)), 2.44 (s, 3H, C6-CH\(_3\)), 4.24 (m, 2H, ester-CH\(_2\)), 6.50 (s, 1H, C4-H), 7.14 (m, 2H, ArH), 7.39 (m, 11H, ArH), 7.56 (m, 2H, ArH). \(^13\)C NMR (75 MHz, CDCl\(_3\), 25°C): \( \delta \) 14.2, 16.8, 54.4, 61.2, 110.0, 126.8, 128.1,
128.3, 128.8, 130.1, 131.9, 132.6, 133.6, 134.7, 138.8, 146.4, 151.2, 165.0, 169.9 and 170.9. Anal. Calcd. for C\textsubscript{28}H\textsubscript{24}N\textsubscript{2}O\textsubscript{5}: C, 71.79; H, 5.12; N, 5.98; Found: C, 71.59; H, 5.22; N, 5.68. MS: \textit{m/z} 491(M\textsuperscript{+}+23).

5-Ethyoxycarbonyl-6-methyl-1,3-bis(4-methoxybenzoyl)-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (6e)

Viscous liquid. Rf 0.3 (ethyl acetate:hexane/60:40). Yield: 64%. IR (KBr): \(\nu_{\text{max}}\) 760, 1220, 1370, 1650, 1710, 3020 cm\(^{-1}\). \(^1\text{H}\) (300 MHz, CDCl\(_3\), 25\(^o\)C): \(\delta\) 1.30 (t, 3H, J 7.5 Hz, ester-CH\(_3\)), 2.48 (s, 3H, C6-CH\(_3\)), 3.79 (s, 3H, OCH\(_3\)), 3.82 (s, 3H, OCH\(_3\)), 4.31 (q, 2H, J 7.2 Hz, ester-CH\(_2\)), 6.50 (s, 1H, C4-H), 6.65 (d, 2H, ArH). 13\(^C\) NMR (75 MHz, CDCl\(_3\), 25\(^o\)C): \(\delta\) 14.2, 16.6, 54.4, 55.3, 55.5, 61.0, 110.2, 113.5, 114.1, 125.1, 126.8, 128.0, 128.7, 130.6, 132.9, 139.3, 146.6, 151.4, 162.7, 164.9, 165.2, 168.7 and 170.2. Anal. Calcd. for C\textsubscript{30}H\textsubscript{28}N\textsubscript{2}O\textsubscript{7}: C, 68.18; H, 5.30; N, 5.30; Found: C, 67.94; H, 5.10; N, 5.42. MS: \textit{m/z} 551(M\textsuperscript{+}+23).

7.5.5 General procedure for the reaction of ammonia with N1,N3-diacyl-3,4-dihydropyrimidin-2(1H)-one derivatives. Synthesis of primary amides

Appropriate N1,N3-diacyl-3,4-dihydropyrimidin-2(1H)-one derivative 6a-e (1.0 mmol), dissolved in THF (10 ml) was added to ammonia (evolved by warming 30% aqueous ammonia solution using standard assembly and dried through KOH trap) saturated THF solution and the reaction stirred for around 1 h at room temperature. After completion of the reaction (TLC), solvent was removed under reduced pressure and the residue chromatographed to isolate pure products 8 along with N-3 acyl DHPM derivatives 7. The characterization data of the compounds is given below.

\textbf{Propionamide (8a)}

Colorless solid. Rf: 0.2 (ethyl acetate:hexane/40:60). Yield: 82\%. m.p. 77-78\(^o\)C (dichloromethane/hexane). IR (KBr): \(\nu_{\text{max}}\) 1550, 1630, 3015, 3350 cm\(^{-1}\). \(^1\text{H}\) (300 MHz, CDCl\(_3\), 25\(^o\)C): \(\delta\) 1.16 (t, 3H, J 7.2 Hz, CH\(_3\)), 2.24 (m, 2H, CH\(_2\)), 5.58 (br, 1H, D\(_2\)O exchangeable, NH), 5.88 (br, 1H, D\(_2\)O exchangeable, NH). 13\(^C\) NMR (75 MHz, CDCl\(_3\), 25\(^o\)C): \(\delta\) 9.2, 31.1 and 175.0 Anal. Calcd. for C\textsubscript{4}H\textsubscript{7}NO: C, 49.32; H, 9.59; N, 19.18; Found: C, 49.10; H, 9.20; N, 18.90. MS: \textit{m/z} 74 (M\textsuperscript{+}+1).
Acetamide (8b)
Colorless solid. Rf: 0.2 (ethyl acetate:hexane/70:30). Yield: 78%. m.p. 77-79°C (dichloromethane/hexane). IR (KBr): \( \nu_{\text{max}} \) 1590, 1650, 3050 cm\(^{-1}\). \(^1\)H (300 MHz, CDCl\(_3\), 25°C): \( \delta \) 2.00 (s, 3H, OCH\(_3\)), 6.03 (br, 1H, D\(_2\)O exchangeable, NH), 6.17 (br, 1H, D\(_2\)O exchangeable, NH). \(^{13}\)C NMR (75 MHz, CDCl\(_3\), 25°C): \( \delta \) 21.2 and 171.9. Anal. Calcd. for C\(_2\)H\(_5\)NO: C, 40.68; H, 8.47; N, 23.73; Found: C, 40.30; H, 8.31; N, 23.50. MS: \( m/z \) 60 (M\(^+\)+1).

Butyramide (8c)
Colorless solid. Rf: 0.5 (ethyl acetate:hexane/80:20). Yield: 79%. m.p. 116-118°C (dichloromethane/hexane). IR (KBr): \( \nu_{\text{max}} \) 1610, 1670, 3090, 3180 cm\(^{-1}\). \(^1\)H (300 MHz, CDCl\(_3\), 25°C): \( \delta \) 0.89 (t, 3H, \( J \) 7.2 Hz, CH\(_3\)), 1.59 (m, 2H, CH\(_2\)), 2.13 (t, 2H, \( J \) 7.2 Hz, CH\(_2\)), 5.71 (br, 1H, D\(_2\)O exchangeable, NH), 6.15 (br, 1H, D\(_2\)O exchangeable, NH). \(^{13}\)C NMR (75 MHz, CDCl\(_3\), 25°C): \( \delta \) 13.6, 18.9, 37.8 and 175.5. Anal. Calcd. for C\(_4\)H\(_9\)NO: C, 55.17; H, 10.34; N, 16.09; Found: C, 54.84; H, 10.10; N, 15.80. MS: \( m/z \) 110 (M\(^+\)+23).

Benzamide (8d)
Colorless solid. Rf: 0.3 (ethyl acetate:hexane/50:50). Yield: 90%. m.p. 127-129°C (dichloromethane/hexane). IR (KBr): \( \nu_{\text{max}} \) 1610, 1660, 3010, 3250 cm\(^{-1}\). \(^1\)H (300 MHz, CDCl\(_3\), 25°C): \( \delta \) 6.34 (br, 2H, D\(_2\)O exchangeable, NH\(_2\)), 7.46 (m, 3H, ArH), 7.82 (m, 2H, ArH). \(^{13}\)C NMR (75 MHz, CDCl\(_3\), 25°C): \( \delta \) 127.2, 128.5, 131.9, 133.3 and 169.6. Anal. Calcd. for C\(_7\)H\(_7\)NO: C, 69.42; H, 5.79; N, 11.57; Found: C, 69.12; H, 5.54; N, 11.20. MS: \( m/z \) 122 (M\(^+\)+1).

4-Methoxybenzamide (8e)
Colorless solid. Rf: 0.3 (ethyl acetate:hexane/70:30). Yield: 77%. m.p. 165°C (dichloromethane/hexane). IR (KBr): \( \nu_{\text{max}} \) 1605, 1690, 2990, 3240 cm\(^{-1}\). \(^1\)H (300 MHz, CDCl\(_3\), 25°C): \( \delta \) 3.85 (s, 3H, OCH\(_3\)), 5.84 (br, 2H, D\(_2\)O exchangeable, NH\(_2\)), 6.93 (d, 2H, \( J \) 8.7 Hz, ArH), 7.77 (d, 2H, \( J \) 9.6 Hz, ArH). \(^{13}\)C NMR (75 MHz, CDCl\(_3\), 25°C): \( \delta \) 47.1, 105.5, 117.3, 121.0, 126.5, 154.3 and 160.6. Anal. Calcd. for C\(_8\)H\(_9\)NO\(_2\): C, 63.58; H, 5.96; N, 9.27; Found: C, 63.28; H, 5.64; N, 8.90. MS: \( m/z \) 152 (M\(^+\)+1).
5-Ethoxycarbonyl-6-methyl-3-propionyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (7a)
White crystalline solid. Rf: 0.4 (ethyl acetate:hexane/30:70). Yield: 86%. m.p. 202°C (dichloromethane). IR (KBr): $v_{\text{max}}$ 1690, 1780, 2975, 3140, 3200 cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$, 25°C): $\delta$ 1.17 (t, 3H, $J$ 7.2 Hz, CH$_3$), 1.25 (t, 3H, $J$ 7.2 Hz, ester-CH$_3$), 2.40 (s, 3H, C6-CH$_3$), 2.80 (m, 1H, CH$_H$), 3.08 (m, 1H, CHH$_H$), 4.17 (q, 2H, $J$ 7.2 Hz, ester-CH$_2$), 6.64 (s, 1H, C4-H), 7.29 (m, 5H, ArH), 7.92 (br, 1H, D$_2$O exchangeable, NH). $^{13}$C NMR (75 MHz, CDCl$_3$, 25°C): $\delta$ 9.1, 14.1, 17.7, 31.8, 53.6, 60.5, 105.5, 126.7, 127.9, 128.5, 140.0, 145.2, 152.1, 165.0 and 175.3. Anal. Calcd. for C$_{17}$H$_{20}$N$_2$O$_4$: C, 64.56; H, 6.33; N, 8.86; Found: C, 64.61; H, 6.22; N, 8.63. MS: m/z 317 (M$^+$+1).

5-Ethoxycarbonyl-6-methyl-3-acetyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (7b)
White crystalline solid. Rf: 0.3 (ethyl acetate:hexane/25:75). Yield: 86%. m.p. 170°C (dichloromethane/hexane). IR (KBr): $v_{\text{max}}$ 1650, 1712, 3130, 3230 cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$, 25°C): $\delta$ 1.25 (t, 3H, $J$ 7.2 Hz, ester-CH$_3$), 2.40 (s, 3H, C6-CH$_3$), 2.56 (s, 3H, COCH$_3$), 4.18 (q, 2H, $J$ 7.2 Hz, ester-CH$_2$), 6.64 (s, 1H, C4-H), 7.29 (m, 5H, ArH), 7.58 (br, 1H, D$_2$O exchangeable, NH). $^{13}$C NMR (75 MHz, CDCl$_3$, 25°C): $\delta$ 14.1, 17.8, 26.5, 53.4, 60.5, 105.6, 126.7, 127.9, 128.5, 139.7, 145.2, 152.2, 164.9 and 171.4. Anal. Calcd. for C$_{16}$H$_{18}$N$_2$O$_4$: C, 63.58; H, 5.96; N, 9.27; Found: C, 63.44; H, 6.14; N, 9.31. MS: m/z 325 (M$^+$+23).

5-Ethoxycarbonyl-6-methyl-3-butyryl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (7c)
White crystalline solid. Rf: 0.5 (ethyl acetate:hexane/30:70). Yield: 85%. m.p. 137°C (dichloromethane/hexane). IR (KBr): $v_{\text{max}}$ 1640, 1704, 3126, 3220 cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$, 25°C): $\delta$ 0.95 (t, 3H, $J$ 7.2 Hz, CH$_3$), 1.25 (t, 3H, $J$ 7.2 Hz, ester-CH$_3$), 2.1 (s, 3H, C6-CH$_3$), 2.40 (s, 3H, C6-CH$_3$), 2.64 (s, 1H, C4-H), 7.29 (m, 5H, ArH), 8.11 (br, 1H, D$_2$O exchangeable, NH). $^{13}$C NMR (75 MHz, CDCl$_3$, 25°C): $\delta$ 13.6, 14.1, 17.4, 18.3, 40.2, 53.4, 60.4, 105.5, 126.7, 127.8, 128.4, 139.9, 145.3, 152.5, 165.0 and 174.4. Anal. Calcd. for C$_{18}$H$_{22}$N$_2$O$_4$: C, 65.45; H, 6.67; N, 8.48; Found: C, 65.47; H, 6.53; N, 8.48. MS: m/z 353 (M$^+$+23).
5-Ethoxycarbonyl-6-methyl-3-benzoyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (7d)

White crystalline solid. Rf: 0.4 (ethyl acetate:hexane/30:70). Yield: 72%. m.p. 151°C (dichloromethane/hexane). IR (KBr): \( \nu_{\text{max}} \) 1639, 1704, 2977, 3130, 3234 cm\(^{-1}\). \(^1\)H NMR (300 MHz, CDCl\(_3\), 25°C): \( \delta \) 1.28 (t, 3H, \( J \) 7.2 Hz, ester-CH\(_3\)), 2.24 (s, 3H, C6-CH\(_3\)), 4.21 (q, 2H, \( J \) 7.2 Hz, ester-CH\(_2\)), 6.39 (s, 1H, C4-H), 7.38 (m, 10H, ArH), 7.67 (br, 1H, D\(_2\)O exchangeable, NH). \(^13\)C NMR (75 MHz, CDCl\(_3\), 25°C): \( \delta \) 14.2, 17.8, 55.6, 60.7, 106.4, 123.3, 126.6, 126.7, 127.7, 128.0, 128.5, 131.5, 135.7, 139.5, 145.3, 147.2, 152.1, 165.0 and 171.1. Anal. Calcd. for C\(_{21}\)H\(_{20}\)N\(_2\)O\(_4\): C, 69.23; H, 5.49; N, 7.69; Found: C, 69.45; H, 5.27; N, 7.54. MS: \( m/z \) 387 (M\(^+\)+23).

5-Ethoxycarbonyl-6-methyl-3-(4-methoxybenzoyl)-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (7e)

White crystalline solid. Rf: 0.7 (ethyl acetate:hexane/70:30). Yield: 77%. m.p. 160°C (dichloromethane/hexane). IR (KBr): \( \nu_{\text{max}} \) 1630, 1700, 2960, 3110, 3214 cm\(^{-1}\). \(^1\)H NMR (300 MHz, CDCl\(_3\), 25°C): \( \delta \) 1.28 (t, 3H, \( J \) 7.2 Hz, ester-CH\(_3\)), 2.33 (s, 3H, C6-CH\(_3\)), 3.83 (s, 3H, OCH\(_3\)), 4.22 (q, 2H, \( J \) 7.2 Hz, ester-CH\(_2\)), 6.33 (s, 1H, C4-H), 6.87 (m, 2H, ArH), 7.29 (m, 3H, ArH), 7.41 (m, 2H, ArH), 7.55 (m, 2H, ArH), 7.67 (br, 1H, D\(_2\)O exchangeable, NH). \(^13\)C NMR (75 MHz, CDCl\(_3\), 25°C): \( \delta \) 14.2, 17.7, 55.3, 55.8, 60.5, 106.3, 113.3, 126.5, 127.6, 127.9, 128.5, 130.4, 139.9, 145.6, 152.6, 162.5, 165.1 and 170.4. Anal. Calcd. for C\(_{22}\)H\(_{20}\)N\(_2\)O\(_5\): C, 69.00; H, 5.58; N, 7.11; Found: C, 66.75; H, 5.37; N, 7.24. MS: \( m/z \) 417 (M\(^+\)+23).

7.5.6 General procedure for the reaction of primary amines with N1,N3-diacyl-3,4-dihydropyrimidin-2(1H)-ones. Synthesis of secondary amides

Appropriate primary amine (1.0 mmol) (Table 5) was added to a solution of appropriate N1,N3-diacyl-3,4-dihydropyrimidin-2(1H)-one derivative 6a-b (1.0 mmol) in THF (10 ml) and the reaction was stirred for around 1 h at room temperature. After completion of the reaction (TLC), solvent was removed under reduced pressure and the residue chromatographed to isolate pure products 10 along with N-3 acyl DHPM derivatives 7. The characteristic data of the compounds is given below.
N-Phenylpropionamide (10a)
Colorless solid. Rf: 0.5 (ethyl acetate:hexane/30:70). Yield: 82%. m.p. 98-100\(^\circ\)C (dichloromethane/hexane). IR (KBr): \(\nu_{\text{max}}\) 756, 1440, 1600, 1655, 2990 cm\(^{-1}\). \(^1\)H (300 MHz, CDCl\(_3\), 25\(^\circ\)C): \(\delta\) 1.25 (t, 3H, J 7.5 Hz, CH\(_3\)), 2.39 (q, 2H, J 7.5 Hz, ArH), 7.09 (t, 2H, J 7.5 Hz, ArH), 7.15 (br, 1H, D\(_2\)O exchangeable, NH), 7.31 (t, 1H, J 7.5 Hz, ArH), 7.50 (d, 2H, J 7.5 Hz, ArH). \(^{13}\)C NMR (75 MHz, CDCl\(_3\), 25\(^\circ\)C): \(\delta\) 9.6, 30.7, 119.7, 124.1, 128.9, 137.9 and 172.0. Anal. Calcd. for C\(_9\)H\(_{11}\)NO: C, 72.48; H, 7.38; N, 9.39; Found: C, 72.20; H, 7.20; N, 9.10. MS: \(m/z\) 172 (M\(^+\)+23).

N-(2-Methoxyphenyl)propionamide (10b)
Viscous liquid. Rf: 0.6 (ethyl acetate:hexane/30:70). Yield: 90%. IR (KBr): \(\nu_{\text{max}}\) 1120, 1220, 1610, 1650, 3030 cm\(^{-1}\). \(^1\)H (300 MHz, CDCl\(_3\), 25\(^\circ\)C): \(\delta\) 1.18 (t, 3H, J 7.5 Hz, CH\(_3\)), 2.36 (q, 2H, J 7.5 Hz, COCH\(_2\)), 3.81 (s, 3H, OCH\(_3\)), 6.89 (m, 3H, ArH), 7.70 (br, 1H, D\(_2\)O exchangeable, NH), 8.32 (dd, 1H, J 1.5, J 1.8 Hz, ArH). \(^{13}\)C NMR (75 MHz, CDCl\(_3\), 25\(^\circ\)C): \(\delta\) 9.6, 31.0, 55.6, 109.7, 119.6, 121.0, 123.3, 127.7, 147.5 and 171.8. Anal. Calcd. for C\(_{10}\)H\(_{13}\)NO\(_2\): C, 67.04; H, 7.26; N, 7.82; Found: C, 66.82; H, 7.43; N, 7.55. MS: \(m/z\) 202 (M\(^+\)+23).

N-2-Tolylacetamide (10c)
Brownish solid. Rf: 0.8 (ethyl acetate:hexane/40:60). Yield: 65%. m.p. 120-122\(^\circ\)C (dichloromethane/hexane). IR (KBr): \(\nu_{\text{max}}\) 760, 1220, 1680, 3010 cm\(^{-1}\). \(^1\)H (300 MHz, CDCl\(_3\), 25\(^\circ\)C): \(\delta\) 2.20 (s, 3H, CH\(_3\)), 2.26 (s, 3H, COCH\(_3\)), 6.99 (br, 1H, D\(_2\)O exchangeable, NH), 7.08 (m, 1H, ArH), 7.20 (m, 2H, ArH), 7.74 (d, 1H, J 7.8 Hz, ArH). \(^{13}\)C NMR (75 MHz, CDCl\(_3\), 25\(^\circ\)C): \(\delta\) 17.7, 24.2, 123.5, 125.3, 126.6, 129.4, 130.4 and 168.0. Anal. Calcd. for C\(_9\)H\(_{11}\)NO: C, 72.40; H, 7.14; N, 9.62. MS: \(m/z\) 172 (M\(^+\)+23).

N-Butylacetamide (10d)
Viscous liquid. Rf: 0.5 (ethyl acetate:hexane/40:60). Yield: 80%. IR (KBr): \(\nu_{\text{max}}\) 760, 1210, 1650, 2950 cm\(^{-1}\). \(^1\)H (300 MHz, CDCl\(_3\), 25\(^\circ\)C): \(\delta\) 0.92 (t, 3H, J 6.9 Hz, CH\(_3\)), 1.33 (m, 2H, CH\(_2\)), 1.47 (m, 2H, CH\(_2\)), 1.97 (s, 3H, COCH\(_3\)), 3.24 (q, 2H, J 7.2 Hz, CH\(_2\)), 5.40 (br, 1H, D\(_2\)O exchangeable, NH). \(^{13}\)C NMR (75 MHz, CDCl\(_3\), 25\(^\circ\)C): \(\delta\) 13.6, 19.9, 23.1, 31.5, 39.3 and 170.1. Anal. Calcd. for C\(_6\)H\(_{13}\)NO: C, 62.61; H, 11.30; N, 12.17; Found: C, 62.32; H, 11.05; N, 12.10. MS: \(m/z\) 116 (M\(^+\)+1).
N-sec-Butylacetamide (10e)
Viscous liquid. Rf: 0.6 (ethyl acetate:hexane/30:70). Yield: 65%. IR (KBr): $\nu_{\max}$ 1225, 1670, 2990 cm$^{-1}$. $^1$H (300 MHz, CDCl$_3$, 25°C): $\delta$ 0.90 (t, 3H, $J$ 7.2 Hz, CH$_3$), 1.11 (d, 3H, $J$ 6.6 Hz, CH$_3$), 1.45 (m, 2H, CH$_2$), 1.98 (s, 3H, COCH$_3$), 3.90 (m, 1H, CH), 5.23 (br, 1H, D$_2$O exchangeable, NH). $^{13}$C NMR (75 MHz, CDCl$_3$, 25°C): $\delta$ 10.2, 20.3, 23.4, 29.6, 46.6 and 169.4. Anal. Calcd. for C$_6$H$_{13}$NO: C, 62.61; H, 11.30; N, 12.17; Found: C, 62.35; H, 11.37; N, 12.24. MS: m/z 138 (M$^+$+23).

N-Heptylacetamide (10f)
Viscous liquid. Rf: 0.5 (ethyl acetate:hexane/35:65). Yield: 78%. IR (KBr): $\nu_{\max}$ 1230, 1630, 2950 cm$^{-1}$. $^1$H (300 MHz, CDCl$_3$, 25°C): $\delta$ 0.88 (t, 3H, $J$ 6.9 Hz, CH$_3$), 1.29 (m, 8H, 4xCH$_2$), 1.50 (m, 2H, CH$_2$), 1.97 (s, 3H, COCH$_3$), 3.23 (q, 2H, $J$ 7.2 Hz, CH$_2$), 5.47 (br, 1H, D$_2$O exchangeable, NH). $^{13}$C NMR (75 MHz, CDCl$_3$, 25°C): $\delta$ 14.0, 22.5, 23.3, 26.8, 28.9, 29.5, 31.7, 39.6 and 169.1. Anal. Calcd. for C$_9$H$_{19}$NO: C, 68.79; H, 12.10; N, 8.92; Found: C, 68.66; H, 12.34; N, 9.17. MS: m/z 180 (M$^+$+23).

N-(2-Hydroxyphenyl)propionamide (10g)
Brownish solid. Rf: 0.7 (ethyl acetate:hexane/40:60). Yield: 95%. m.p. 62-64°C (dichloromethane/hexane). IR (KBr): $\nu_{\max}$ 755, 1300, 1665, 3330, 3415 cm$^{-1}$. $^1$H (300 MHz, CDCl$_3$, 25°C): $\delta$ 1.29 (t, 3H, $J$ 7.5 Hz, CH$_3$), 2.50 (q, 2H, $J$ 7.5 Hz, COCH$_2$), 6.85 (m, 1H, ArH), 7.00 (m, 2H, ArH), 7.13 (m, 1H, ArH), 7.45 (br, 1H, D$_2$O exchangeable, NH), 8.80 (br, 1H, D$_2$O exchangeable, OH). $^{13}$C NMR (75 MHz, CDCl$_3$, 25°C): $\delta$ 9.8, 30.0, 119.7, 120.4, 122.0, 123.9, 127.0, 148.6 and 174.1. Anal. Calcd. for C$_9$H$_{11}$NO$_2$: C, 65.45; H, 6.67; N, 8.48; Found: C, 65.20; H, 6.30; N, 8.10. MS: m/z 165 (M$^+$).

N-(2-Mercaptophenyl)propionamide (10h)
Colorless solid. Rf: 0.5 (ethyl acetate:hexane/40:60). Yield: 73%. m.p. 105°C (dichloromethane/hexane). IR (KBr): $\nu_{\max}$ 1240, 1670, 3010, 3300 cm$^{-1}$. $^1$H (300 MHz, CDCl$_3$, 25°C): $\delta$ 1.14 (t, 3H, $J$ 7.5 Hz, CH$_3$), 2.19 (q, 2H, $J$ 7.5 Hz, COCH$_2$), 7.00 (m, 1H, ArH), 7.42 (m, 2H, ArH), 7.98 (br, 1H, D$_2$O exchangeable, NH), 8.40 (d, 1H, $J$ 8.1 Hz, ArH). $^{13}$C NMR (75 MHz, CDCl$_3$, 25°C): $\delta$ 9.4, 29.9, 120.8, 123.0, 132.1, 136.4, 139.9, 155.2 and 174.0. Anal. Calcd. for
C₉H₁₁NOS: C, 59.67; H, 6.08; N, 7.73; S, 17.68; Found: C, 59.30; H, 6.30; N, 7.52; S, 17.40. MS: m/z 180 (M⁻⁻¹).

**N-(2-Propionylaminophenyl)propionamide (10i)**

Colorless solid. Rf: 0.3 (ethyl acetate:hexane/40:60). Yield: 80%. m.p. 115-118°C (dichloromethane/hexane). IR (KBr): ν max 760, 1445, 1665, 3300 cm⁻¹. ¹H (300 MHz, CDCl₃, 25°C): δ 1.22 (t, 6H, J 7.5 Hz, 2×CH₃), 2.37 (q, 4H, J 7.5 Hz, 2×COCH₂), 7.17 (m, 2H, ArH), 7.33 (m, 2H, ArH), 8.17 (br, 2H, D₂O exchangeable, NH). ¹³C NMR (75 MHz, CDCl₃, 25°C): δ 9.7, 30.1, 125.5, 126.0, 130.5 and 173.4. Anal. Calcd. for C₁₂H₁₆N₂O₂: C, 65.45; H, 7.27; N, 12.73; Found: C, 65.80; H, 7.50; N, 12.40. MS: m/z 243 (M⁺+23).

**N-Phenethylpropionamide (10j)**

Colorless solid. Rf: 0.4 (ethyl acetate:hexane/40:60). Yield: 90%. m.p. 52-54°C (dichloromethane/hexane). IR (KBr): ν max 1250, 1580, 1650, 3110, 3320 cm⁻¹. ¹H (300 MHz, CDCl₃, 25°C): δ 1.12 (t, 3H, J 7.5 Hz, CH₃), 2.15 (q, 2H, J 7.8 Hz, COCH₂), 2.81 (t, 2H, J 6.9 Hz, CH₂), 3.52 (q, 2H, J 6.9 Hz, CH₂), 5.42 (br, 1H, D₂O exchangeable, NH), 7.25 (m, 5H, ArH). ¹³C NMR (75 MHz, CDCl₃, 25°C): δ 14.1, 18.8, 55.8, 60.0, 126.5, 127.9, 128.7, 145.9 and 173.0. Anal. Calcd. for C₁₁H₁₅NO: C, 74.58; H, 8.47; N, 7.91; Found: C, 74.30; H, 8.20; N, 7.50. MS: m/z 178 (M⁺+1).

**N-[2-(3,4-Dimethoxyphenyl)ethyl]propionamide (10k)**

Light brown solid. Rf: 0.2 (ethyl acetate:hexane/50:50). Yield: 96%. m.p. 42-44°C (dichloromethane/hexane). IR (KBr): ν max 760, 1210, 1700, 3020 cm⁻¹. ¹H (300 MHz, CDCl₃, 25°C): δ 1.13 (t, 3H, J 3.6 Hz, CH₃), 2.16 (q, 2H, J 7.5 Hz, COCH₂), 2.75 (t, 2H, J 6.9 Hz, CH₂), 3.47 (q, 2H, J 6.9 Hz, CH₂), 3.85 (s, 6H, 2×OCH₃), 5.72 (br, 1H, D₂O exchangeable, NH), 6.75 (m, 3H, ArH). ¹³C NMR (75 MHz, CDCl₃, 25°C): δ 9.8, 29.6, 35.1, 40.5, 55.8, 111.3, 111.8, 120.5, 131.3, 147.0, 148.9 and 173.7. Anal. Calcd. for C₁₃H₁₉NO₃: C, 65.82; H, 8.02; N, 5.91; Found: C, 65.90; H, 7.80; N, 5.60. MS: m/z 260 (M⁺+23).

**N-[2-(1H-Indol-3-yl)ethyl]propionamide (10l)**

Viscous liquid. Rf: 0.2 (ethyl acetate:hexane/40:60). Yield: 90%. IR (KBr): ν max 740, 1210, 1710, 3010 cm⁻¹. ¹H (300 MHz, CDCl₃, 25°C): δ 1.10 (t, 3H, J 7.5 Hz, CH₃), 2.11 (q, 2H, J 7.5
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**D-3-(1H-Indol-3-yl)-2-propionylaminopropanoic acid methyl ester (10m)**

Viscous liquid. Rf: 0.2 (ethyl acetate:hexane/40:60). Yield: 62%. IR (KBr): $\nu_{\text{max}}$ 757, 1215, 1700, 3440 cm$^{-1}$. $^1$H (300 MHz, CDCl$_3$, 25°C): $\delta$ 1.09 (t, 3H, $J$ 7.5 Hz, CH$_3$), 2.16 (q, 2H, $J$ 7.5 Hz, COCH$_2$), 3.33 (m, 2H, CH$_2$), 3.68 (s, 3H, OCH$_3$), 4.95 (m, 1H, CH), 6.05 (d, 1H, $J$ 7.5 Hz, D$_2$O exchangeable, NH), 6.95 (d, 1H, $J$ 2.4 Hz, 1H-indole), 7.12 (m, 2H, ArH), 7.34 (d, 1H, $J$ 8.1 Hz, ArH), 7.51 (d, 1H, $J$ 7.8 Hz, ArH), 8.59 (br, 1H, D$_2$O exchangeable, NH). $^{13}$C NMR (75 MHz, CDCl$_3$, 25°C): $\delta$ 9.5, 27.5, 29.5, 52.3, 52.8, 110.0, 111.2, 118.5, 119.6, 122.1, 122.6, 127.7, 136.0, 172.5 and 173.4. Anal. Calcd. for C$_{15}$H$_{18}$N$_2$O$_3$: C, 65.69; H, 6.57; N, 10.22; Found: C, 65.30; H, 6.20; N, 9.90. MS: $m/z$ 297 (M$^+$+23). $[\alpha]_{D}^{20} = -4.00$ (CHCl$_3$, c = 0.5).

**L-3-(1H-Indol-3-yl)-2-propionylaminopropanoic acid methyl ester (10n)**

Viscous liquid. Rf: 0.2 (ethyl acetate:hexane/40:60). Yield: 60%. IR (KBr): $\nu_{\text{max}}$ 755, 1210, 1710, 3320 cm$^{-1}$. $^1$H (300 MHz, CDCl$_3$, 25°C): $\delta$ 1.11 (t, 3H, $J$ 7.5 Hz, CH$_3$), 2.18 (q, 2H, $J$ 7.8 Hz, COCH$_2$), 3.70 (s, 3H, OCH$_3$), 4.96 (m, 1H, CH), 6.07 (br, 1H, D$_2$O exchangeable, NH), 6.97 (d, 1H, $J$ 2.4 Hz, 1H-indole), 7.15 (m, 2H, ArH), 7.35 (m, 1H, ArH), 7.52 (d, 1H, $J$ 8.1 Hz, ArH), 8.21 (br, 1H, D$_2$O exchangeable, NH). $^{13}$C NMR (75 MHz, CDCl$_3$, 25°C): $\delta$ 9.5, 27.5, 29.5, 52.3, 52.8, 110.0, 111.2, 118.5, 119.6, 122.1, 122.6, 127.7, 136.0, 172.5 and 173.4. Anal. Calcd. for C$_{15}$H$_{18}$N$_2$O$_3$: C, 65.69; H, 6.57; N, 10.22; Found: C, 65.30; H, 6.30; N, 9.90. MS: $m/z$ 297 (M$^+$+23). $[\alpha]_{D}^{20} = +4.00$ (CHCl$_3$, c = 0.5).

**DL-3-(1H-Indol-3-yl)-2-propionylaminopropanoic acid methyl ester (10o)**

Colorless solid. Rf: 0.2 (ethyl acetate:hexane/40:60). Yield: 70%. m.p: 136°C (dichloromethane/hexane). IR (KBr): $\nu_{\text{max}}$ 750, 1210, 1700, 2900 cm$^{-1}$. $^1$H (300 MHz, CDCl$_3$, 25°C): $\delta$ 0.99 (t, 3H, $J$ 7.5 Hz, CH$_3$), 2.09 (q, 2H, $J$ 7.5 Hz, COCH$_2$), 3.24 (m, 2H, CH$_2$), 3.61 (s, 3H, OCH$_3$), 4.88 (m, 1H, CH), 5.94 (d, 1H, $J$ 7.5 Hz, D$_2$O)
exchangeable, NH), 6.87 (s, 1H, 1H-indole), 7.06 (m, 2H, ArH), 7.26 (d, 1H, J 7.8 Hz, ArH), 7.44 (d, 1H, J 7.5 Hz, ArH), 8.32 (br, 1H, D$_2$O exchangeable, NH). $^{13}$C NMR (75 MHz, CDCl$_3$, 25°C): δ 9.5, 27.5, 29.5, 52.3, 52.8, 110.0, 111.2, 118.5, 119.6, 122.2, 122.6, 136.0, 172.5 and 173.3. Anal. Calcd. for C$_{15}$H$_{18}$N$_2$O$_3$: C, 65.69; H, 6.57; N, 10.22; Found: C, 65.41; H, 6.46; N, 10.52. MS: m/z 297 (M$^+$+23).

7.5.7 General procedure for the reaction of secondary amines with N1,N3-diacyl-3,4-dihydropyrimidin-2(1H)-ones. Synthesis of tertiary amides

Appropriate secondary amine (1.0 mmol) (Table 6) was added to a solution of appropriate N1,N3-diacyl-3,4-dihydropyrimidin-2(1H)-one derivative 6b-c (1.0 mmol) in THF (10ml) and the reaction was stirred for around 1 h at room temperature. After completion of the reaction (TLC), solvent was removed under reduced pressure and the residue chromatographed to isolate pure products 12 along with N-3 acyl DHPM derivatives 7. The characteristic data of the compounds is given below.

N, N-Diethylacetamide (12a)

Viscous liquid. Rf: 0.6 (ethyl acetate:hexane/30:70). Yield: 78%. IR (KBr): $\nu_{\text{max}}$ 1215, 1730, 3020 cm$^{-1}$. $^1$H (300 MHz, CDCl$_3$, 25°C): δ 1.12 (t, 3H, J 7.2 Hz, CH$_3$), 1.18 (t, 3H, J 7.2 Hz, CH$_3$), 2.09 (s, 3H, COCH$_3$), 3.34 (m, 4H, 2×CH$_2$). $^{13}$C NMR (75 MHz, CDCl$_3$, 25°C): δ 13.0, 14.0, 21.2, 40.0, 42.8 and 169.9. Anal. Calcd. for C$_6$H$_{13}$NO: C, 62.61; H, 11.30; N, 12.17; Found: C, 62.30; H, 10.95; N, 11.97. MS: m/z 138 (M$^+$+23).

1-Piperidin-1-yl-ethanone (12b)

Viscous liquid. Rf: 0.6 (ethyl acetate:hexane/40:60). Yield: 80%. IR (KBr): $\nu_{\text{max}}$ 1215, 1710, 3320 cm$^{-1}$. $^1$H (300 MHz, CDCl$_3$, 25°C): δ 1.55 (m, 6H, 3×CH$_2$), 2.08 (s, 3H, COCH$_3$), 3.38 (t, 2H, J 5.4 Hz, CH$_2$), 3.54 (t, 2H, J 5.4 Hz, CH$_2$). $^{13}$C NMR (75 MHz, CDCl$_3$, 25°C): δ 21.4, 24.4, 25.4, 26.3, 42.4, 47.4 and 168.7. Anal. Calcd. for C$_7$H$_{13}$NO: C, 66.14; H, 10.24; N, 11.02; Found: C, 66.01; H, 9.90; N, 10.80. MS: m/z 150 (M$^+$+23).

1-Morpholin-4-yl-ethanone (12c)

Viscous liquid. Rf: 0.5 (ethyl acetate:hexane/40:60). Yield: 74%. IR (KBr): $\nu_{\text{max}}$ 1240, 1655, 1700, 2750, 3350 cm$^{-1}$. $^1$H (300 MHz, CDCl$_3$, 25°C): δ 2.09 (s, 3H, COCH$_3$), 3.46 (t, 2H, J 4.8 Hz, CH$_2$), 3.66 (m, 6H, 3×CH$_2$). $^{13}$C NMR (75 MHz, CDCl$_3$, 25°C): δ 21.0, 41.7, 46.5, 66.5, 66.7 and 169.1. Anal. Calcd. for
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C₉H₁₁NO₂: C, 55.81; H, 8.53; N, 10.85; Found: C, 55.61; H, 8.40; N, 10.78. MS: m/z 152 (M⁺+23).

N-methyl-N-phenylbutyramide (12d)
Viscous liquid. Rf: 0.7 (ethyl acetate:hexane/25:75). Yield: 70%. IR (KBr): νₓ max 1215, 1760, 3320 cm⁻¹. ¹H (300 MHz, CDCl₃, 25°C): δ 0.82 (t, 3H, J 7.2 Hz, CH₃), 1.63 (m, 2H, CH₂), 2.04 (t, 2H, J 6.6 Hz, COCH₂), 3.26 (s, 3H, N-CH₃), 7.29 (m, 5H, ArH). ¹³C NMR (75 MHz, CDCl₃, 25°C): δ 13.8, 18.9, 35.9, 37.2, 124.7, 127.3, 127.6, 128.9, 129.6, 144.2 and 173.2. Anal. Calcd. for C₁₁H₁₅NO: C, 74.58; H, 8.47; N, 7.91; Found: C, 74.20; H, 8.10; N, 7.78. MS: m/z 178 (M⁺+1).

N-(3,4-dimethoxyphenethyl)-N-methylbutyramide (12e)
Viscous liquid. Rf: 0.8 (ethyl acetate:hexane/60:40). Yield: 93%. IR (KBr): νₓ max 757, 1260, 1730, 2970 cm⁻¹. ¹H (300 MHz, CDCl₃, 25°C): δ 0.87 (t, 3H, J 7.5Hz, CH₃), 1.63 (m, 2H, CH₂), 2.05 (t, 2H, J 7.8 Hz, COCH₂), 2.78 (t, 2H, J 7.5 Hz, CH₂), 2.89 (s, 3H, N-CH₃), 3.55 (m, 2H, CH₂), 6.76 (m, 3H, ArH). ¹³C NMR (75 MHz, CDCl₃, 25°C): δ 13.8, 18.4, 33.3, 34.4, 35.8, 49.8, 51.6, 55.7, 111.7, 120.6, 130.7, 131.7, 147.4, 148.8 and 172.8. Anal. Calcd. for C₁₅H₂₃NO₃: C, 67.92; H, 8.68; N, 5.28; Found: C, 67.70; H, 8.35; N, 5.01. MS: m/z 288 (M⁺+23).

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