A three-component condensation protocol based on ionic liquid phase bound acetoacetate for the synthesis of Biginelli 3,4-dihydropyrimidine-2(1*H*)-ones

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Abstract
A novel and efficient task-specific ionic liquid synthesis of Biginelli compounds has been developed. Ionic liquid-phase bound acetoacetate reacted with (thio)ureas and various aldehydes with a cheap catalyst to afford ionic liquid-phases supported 3,4-dihydropyrimidine-2-(thi)ones. The desired 3,4-dihydropyrimidine-2-(thi)ones were easily cleaved from the ionic liquid-phase by transesterification under mild conditions in good yields and high purity. The task-specific ionic liquid technology represents an attractive alternative to the classical solid- and solution-phase synthesis strategies and combines the advantage of performing homogeneous chemistry for multicomponent reactions.

Keywords: Ionic liquid phase, Biginelli reaction, three-component synthesis, solventless reaction, transesterification, 3,4-dihydropyrimidine

Introduction

Multicomponent reactions (MCRs) have become an increasingly important method[1] for developing new drug candidates for fighting diseases. In 1893, Italian chemist Pietro Biginelli anticipated intuitively the synthetic potential of multicomponent reactions[2] by combining in a single flask the reactants of two different reactions leading to the same product. The original Biginelli protocol for the preparation of 3,4-dihydropyrimidine-2(1*H*)-ones (DHPMs) consisted in heating a mixture of the three components (aldehyde, β-ketoester and urea) in ethanol

containing a catalytic amount of HCl. Since that time, the "Biginelli reaction" has been known as an efficient one-pot reaction protocol to prepare 3,4-DHPMs with different pharmacological properties. The dihydropyrimidine core structure has emerged as integral backbones of several calcium channel blockers [3], α_{1a}-adrenergic receptor antagonism[4] and mitotic inhibitor[5]. In addition, several marine alkaloids containing the dihydropyrimidine-5-carboxylate moiety also show interesting biological activities[6]. To make new DHPM derivatives available to drug research, the immobilization strategies on solid or liquid phases have been receiving special attention in drug discovery efforts by the adaptation of conventional solution phase to solid or liquid phase protocols. However, one of the challenges of solid or liquid phase technologies for drug discovery is developing synthetic routes for the traceless tethering of compounds to the polymer supports. This is because complications may arise if these appendages are redundant and affect the activities of the compounds. In this regard, for the preparation of DHPM derivatives on solid or liquid phase, three different strategies can be envisioned (Figure 1). The first-one makes use of immobilized aldehyde and Biginelli protocols depending on immobilized aldehydes on usual solid- or liquid-phases were not found. The second involves the use of an immobilized β-ketoester[7]. This approach was initially reported by Hamper *et al.*[8] for attachment of a malonic monoester from macroporous Wang resin and Meldrum's acid.

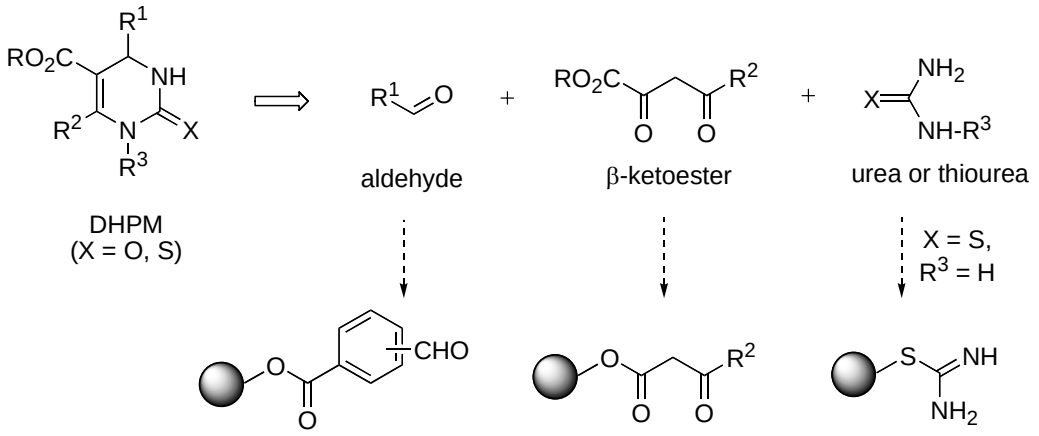


Figure 1. Immobilization strategies used for the preparation of Biginelli DHPM derivatives.

And the third one uses a S-linked isothiouronium salt[9] by application of the so-called "Atwal's modification" or a N-linked urea with a sylil[10] or a sulfone linker[11] to the solid support. Wipf developed an original solid-phase modification of the Biginelli condensation and Cunningham[12] by using γ-amino butyric acid derived urea attached to Wang resin. An interesting variation of this protocol, is that the Biginelli reaction was also adapted to fluorous-phase conditions[13]. This is based on the concept that fluorinated reagents dissolve preferentially in perfluoroalkanes, the fluorous phase ("fluorous tag"). In the field of combinatorial chemistry, solid-phase synthesis along high-throughput screening has emerged as a powerful tool for the discovery of novel drug[14] candidates. Despite its great success, solid-phase synthesis still

exhibits several drawbacks such as the difficulties to monitor reaction progress and the heterogeneous reaction conditions. By replacing insoluble cross-linked resins with soluble supports (polyethylene glycol (PEG) and non-cross linked polystyrene), the familiar reaction condition of classical organic chemistry is facilitated. However, some limitations were expressed for the use of soluble polymers such as limited solubility during the reaction progress, insolubility in ether solvents and low loading capacity[15]. So, the idea of searching alternative soluble supports for high-throughput organic synthesis has been advocated.

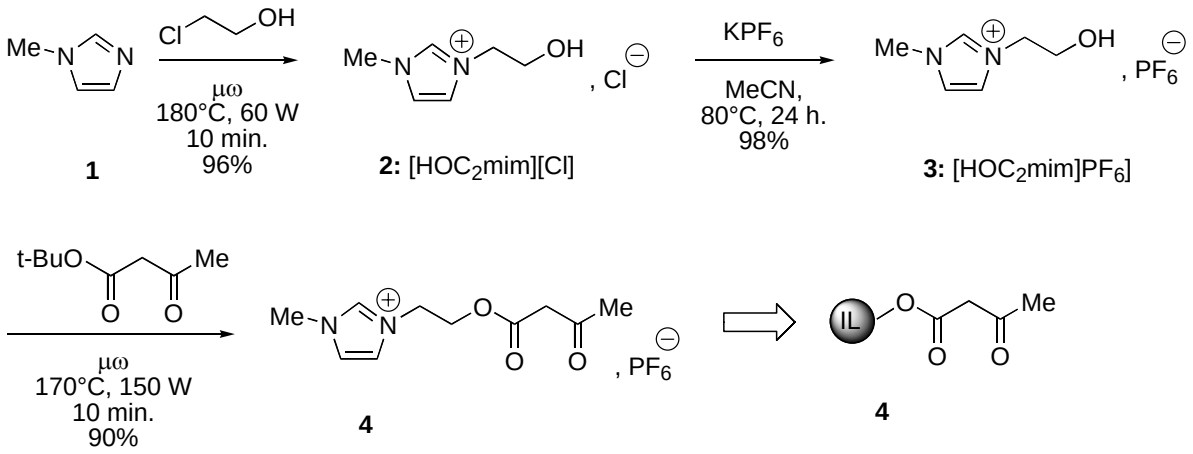
The so-called room temperature ionic liquids or ionic liquids (ILs) have demonstrated to have versatile applications[16] in organic synthesis as environmentally benign reaction media owing to their many fascinating and intriguing properties. Numerous chemical reactions can be carried out in Ils because their solubility can be turned readily by the choice of cation and anion. Recently, the scope of ILs has been expanded by the introduction of additional functional groups designed to exhibit particular properties or reactivities[17]. These task-specific ionic liquids (TSILs) can be utilised as alternatives to classical polymeric matrices in combinatorial chemistry. By example, the alcohol functionalized TSILs[18] have been studied in our laboratory and other groups as replacements for solid polymer supports in the heterogeneous phase synthesis of heterocyclic molecules[19] and peptides[20] in which the excess reagents and by-products in the multi-step reactions can be removed easily by simple washings with a solvent.

In connection with our research program on exploitation of the TSILs as tools in "liquid phase organic synthesis (LPOS)", we report on the generation of the 3,4-dihydropyrimidine-2(1*H*)-ones *via* Biginelli three component condensation.

Results and Discussion

As shown in scheme 1, the ionic liquid-phase bound acetoacetate **4** was synthesized according to the three-step process developed in our laboratory. The first step is the solventless quaternization reaction[18] of chloroethanol on commercial imidazole **1** (96%) under microwave dielectric heating[21] at 180°C for 10 minutes followed by the anionic metathesis of [HOC_2mim][Cl] **2**. For the anion exchange in the second step, the corresponding coordinating anion used was PF_6^- from the commercially available starting salt KPF_6. The anion-metathesis reaction was carried out in dry acetonitrile and stirring at 80°C under nitrogen for 24 hours (98%). Then the insoluble salt (KCl) was filtered off and the solution of crude reaction mixture was also re-filtered on a pad of Celite® to remove halide waste trapped in [HOC_2mim][PF_6] **3**, followed by evaporation of acetonitrile *in vacuum*. Eventually, the halide impurities were evaluated by volumetric titration using Volhard's method. Halide contaminants in ILs are problematic because the halide content can affect potentially the usefulness of a TSIL for a given chemical reaction. The presence of chloride ions decreases the density and increases the viscosity of ILs[22]. Finally in the third step, the ILP bound acetoacetate **4** was obtained in good yield (90%) under microwave irradiations (150 W) after 10 minutes from *tert*-butyl acetoacetate and **3** with a stoechiometry of 1/2.6. It is

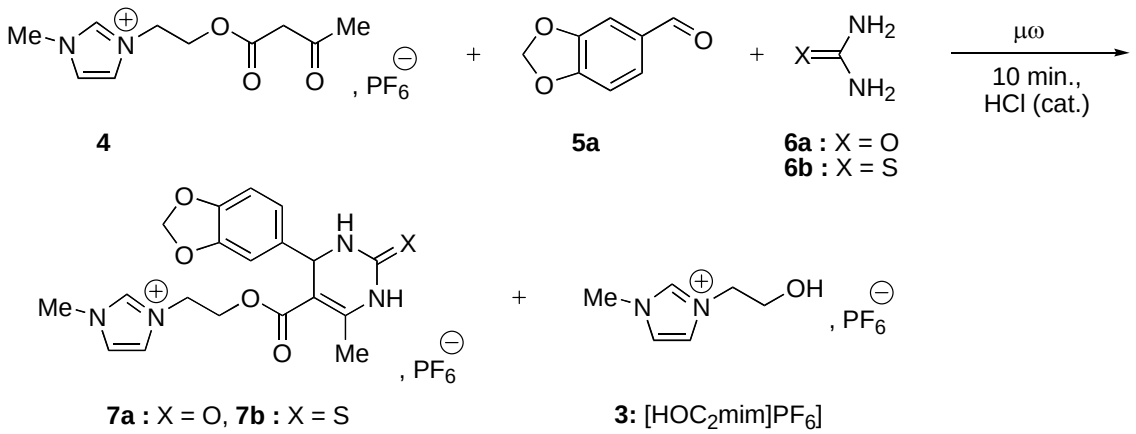
noteworthy that the choice PF_6 anion[23] was guided by the facile purification of **4** after microwave dielectric heating: ILP bound acetoacetate **4** is immiscible in AcOEt and the excess of *tert*-butyl acetoacetate and eventually unreacted starting product **3** were eliminated by washings with AcOEt.



Scheme 1. General route used for the synthesis of Ionic Liquid Phase bound acetoacetate **4**.

A variety of different combinatorial protocols based on the Biginelli MCR[24] has been advanced and the standard procedure for this condensation involves one-pot condensation of the three components in a solvent such as ethanol, using a strongly acidic catalyst, i.e. hydrochloric acid and eventually with Lewis acids[25] for the synthesis of complex DHPMs. Recently, several groups have also developed solvent-free microwave-assisted procedures[26] for performing rapid chemical synthesis associated to the generation of high-quality libraries in an automated fashion.

In order to be able to carry out such Biginelli condensations in a faster and more efficient way –eliminating the use of a solvent and reflux conditions- we started to examine the influence of MW irradiation (monomode microwave cavity: Synthewave® 402 reactor[27]) on a neat mixture of ILP bound acetoacetate **4**, piperonaldehyde **5a**, (thio)ureas **6a,b** and a catalytic amount of hydrochloric acid (Scheme 2). The results of this model Biginelli reaction under microwave (μω) are presented in Table 1.



Scheme 2. Evaluation of a model Biginelli reaction under microwave irradiation (μω).

For preliminary runs, we have decided to use a 1:1:3 mixture of ILP **4**, piperonaldehyde **5a** and (thio)ureas **6a,b** for the development of a microwave-assisted solvent-free three component condensation. Entries 1-2 show that at high temperature (120°C) low yield for **7** (5%) associated to the formation of undesired starting ILP **3** (40-50%) are observed. At lower reaction temperature (entries 3-4) the conversion of the starting products into the desired 3,4-DHPM **7b** increases (60-70%) and the unwanted by-product **3** decreases (15%). From these experiences with microwave-assisted Biginelli condensation, it became evident that combination of hydrochloric acid and microwave at high temperature was not the appropriate reaction protocol because of inadvertent decomposition of the starting ILP bound acetoacetate **4** and probably urea **6**, leading to unknowed by-products.

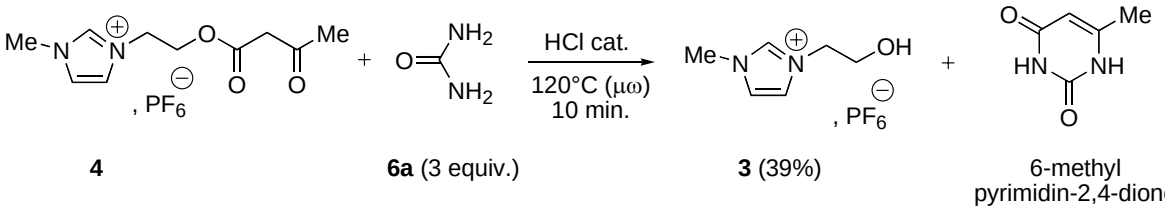
Table 1. Effect of microwave irradiation in a model Biginelli reaction

Entry	Starting urea		Reaction	Conversion (%) of **4** into	
	6	X	temperature (°C)	**7**[a]	**3**[b]
1	**6b**	S	120	5	40
2	**6a**	O	120	5	50
3	**6b**	S	80	60	-
4	**6b**	S	90	70	15

[a] Conversion of **4** and **5a** into **7** estimated by ^{1}H NMR until disappearance of the starting products **4** and **5a**.
[b] Conversion of **4** into **3** estimated by ^{1}H NMR until disappearance of **4**.

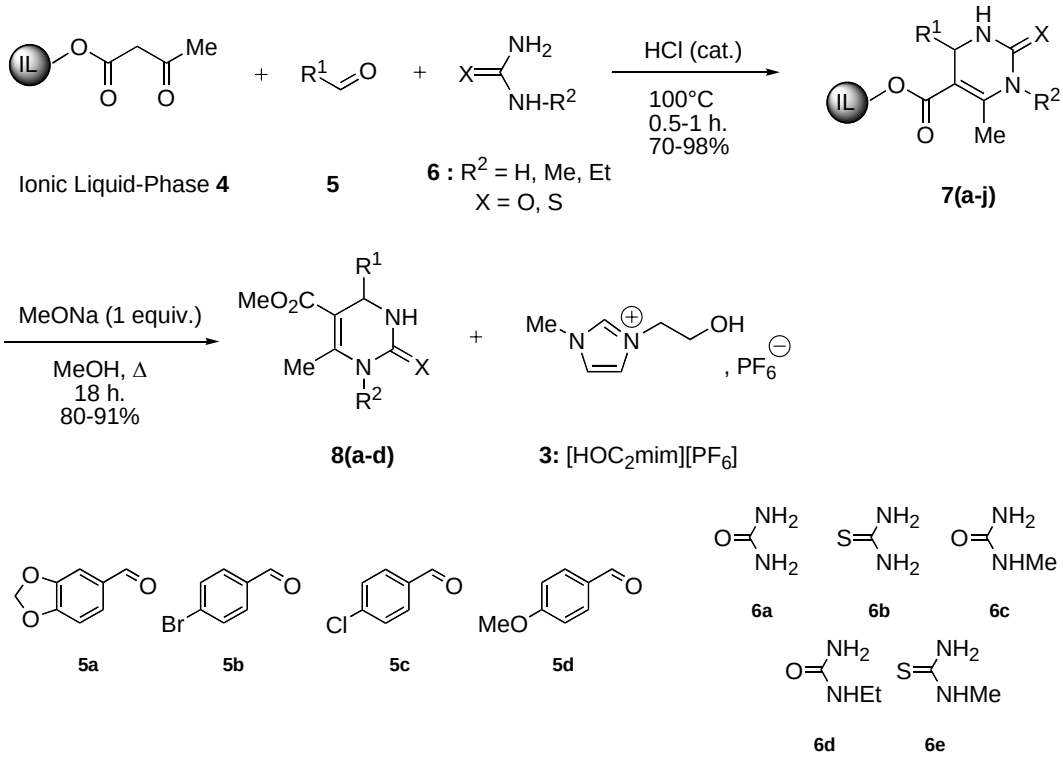
It is noteworthy that solvent-free reaction (Scheme 3) of **4** with 3 equivalents of urea **6a** and catalytic amount of hydrochloric acid at 120°C for 10 minutes under microwave led to 39% of [HOC_2mim][PF_6] **3** and traces (5%) of 6-methylpyrimidine-2,4-dione[28]. The assigned structure of 6-methyl pyrimidine-2,4-dione was substantiated by observation of a singlet at δ 5.83 ppm for

H-5 proton and another singlet located at δ 2.03 ppm for the methyl group attached to the C-6 carbon after analysis of the crude reaction mixture by ^{1}H NMR. We therefore considered the use of a conventional oil bath for heating. After a few optimization cycles, we discovered that 100°C proved to be a very efficient reaction temperature for transformation of the starting products with HCl as cheap catalyst: no by-product was detected in the crude reaction mixture.



Scheme 3. reaction of ILP bound acetoacetate **4** with urea **6a** under catalytic microwave irradiations.

For the model reaction (Scheme 4) involving piperonaldehyde **5a** and (thio)urea **6a** or **6b** with ILP bound acetoacetate **4**, a total reaction time of 30 minutes at 100°C resulted in high yield (Table 2) of pure product (**7a:** 98% and **7b:** 96%). With the others monosubstituted (thio)ureas **6(c-e),** an increase in reaction time to 30 minutes (global reaction time: 1 hour) produced the expected 3,4-DHPMs without traces of impurities.



Scheme 4: Preparation of 4-aryl-3,4-dihydropyrimidine **8** by solventless three-component reaction followed by transesterification detachment of the ionic liquid phase **7**.

After heating in oil bath, the excess of (thio)urea **6** and the acidic catalyst (HCl) could be easily removed by simple washings with cold deionised water (1:10 w/v) and the ILP bound 3,4-DHPM **7** precipitated directly in the reaction mixture after a short active cooling period of 10 minutes (Figure 1) and showed no traces of impurities by ^{1}H NMR (see Figure 2 of **7f** after precipitation). For the examples given in table 2, this one-pot three component Biginelli condensation protocol based on ionic liquid-phase bound acetoacetate gave yields ranging from 70 to 98% and are in general comparable or higher than the yields obtained using the classical solution-phase protocols under reflux conditions.

Table 2. Results for the preparation of 3,4-DHPMs **8** from the ILPs **7**

Compound	Starting products	R^1	R^2	X	Yield (%)[a]
7a	**5a** + **6a**	3,4-$(CH_2O)C_6H_3$	H	O	98
7b	**5a** + **6b**	3,4-$(CH_2O)C_6H_3$	H	S	96
7c	**5d** + **6a**	4-$MeOC_6H_4$	H	O	90
7d	**5c** + **6b**	4-ClC_6H_4	H	S	90
7e	**5c** + **6a**	4-ClC_6H_4	H	O	90
7f	**5b** + **6c**	4-BrC_6H_4	Me	O	93
7g	**5c** + **6c**	4-ClC_6H_4	Me	O	96
7h	**5c** + **6e**	4-ClC_6H_4	Me	S	70
7i	**5c** + **6d**	4-ClC_6H_4	Et	O	89
7j	**5b** + **6d**	4-BrC_6H_4	Me	O	81
8a	**7i**	4-ClC_6H_4	Et	O	90
8b	**7j**	4-BrC_6H_4	Et	O	89
8c	**7d**	4-ClC_6H_4	H	S	85
8d	**7a**	3,4-$(CH_2O)C_6H_3$	H	O	91

[a] Yield of isolated product.

As illustrated in table 2, the versatility of this protocol was demonstrated through the preparation of a small library of ten 3,4-DHPMs **7(a-j)** grafted on the ionic liquid-phase and the products formed were estimated directly by ^{1}H NMR without detaching the material from the ionic liquid-phase.

Finally, the target compounds **8** were released from the ionic liquid-phase **7** by treatment with sodium methoxide (1 equivalent) in refluxed MeOH. Complete cleavage of the compounds **7** was determined by the observation of a new singlet at δ 3.56 ppm for the methyl ester group of **8** and also the upfield shift of the α-methylene protons of the side chain appended on the imidazolium cation of the ILP from δ 4.42 ppm to 4.00 ppm in the ^{1}H NMR. If the peaks of the α-methylene protons was still present after NMR checking, the recovered ILP bound 3,4-DHPM

7 could be resubmitted to the same reaction conditions until a complete scission was achieved. Normally, cleavage was complete using the above reaction conditions (MeONa 1 equiv./refluxed MeOH) after 18 hours.

It is worth noting that, in contrast to the various restrictions on the analysis of reaction progress in solid-phase synthesis, this ionic liquid-phase protocol allowed the use of routine analytical techniques (NMR, TLC,…) to monitor reaction progress without the need of cleavage and check procedure. Importantly, the purity of the transesterified products **8** cleaved from the ionic liquid-phase was high enough for NMR (^{1}H, ^{13}C) and mass spectrometry (HRMS) characterization and no further purification by gel chromatography were necessary. As it can be seen from inspection of the data presented in table 2, the esters **8(a-d)** were prepared in good yields (85-91%) after washings with deionised water and drying under reduced pressure. Additionaly, the ionic liquid-phase [HOC_2mim][PF_6] **3** issued from transesterification cleavage can be eventually reused after purification by elimination of water and solvent washings (AcOEt: 1/5 w/v).

Figure 2. Treatment of the crude Biginelli reaction mixture **7** with deionised water: the upper aqueous layer contains excess of urea or thiourea **6** and the ionic liquid phase bound 3,4-DHPM **7** is insoluble.

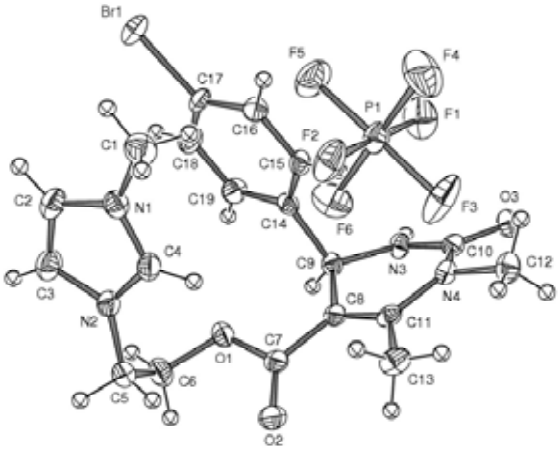


Figure 3. Ortep diagram of the 1-[2-[4-(4-Bromophenyl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidin-5-ylcarbonyloxy]ethyl]-3-methylimidazolium hexafluorophosphate **7f**.

Conclusions

In summary, this work shows that attachment of one of the reactants in the Biginelli reaction to ionic liquid-phase allows a straightforward separation of the heterocyclic product by solvent washings to replace the solid support polymer in combinatorial synthesis. In contrast to most solid phase syntheses, reaction can be run in homogeneous phase and can be followed by spectroscopic standard techniques at each step of the multistep synthesis. This general solvent-free protocol involved the used of a cheap catalyst (HCl) and afforded 3,4-dihydropyrimidine-2-(thi)one grafted on the ionic liquid-phase with high purity and improved yields compared to the classical solution-phase reaction. The advantage of the presented method is the possibility to perform the crystallization of the ILP linked 3,4-DHPM and thus purification step is facilited for elimination of (thio)urea excess which cannot be achieved by solid supported or polymer supported chemistry. Detachment by transesterification provides the corresponding organic products in good yields without the need of column chromatography for purification. Considering the simple experimental techniques used in this Ionic Liquid-Phase Organic Synthesis (IoLiPOS) methodology, automation should be feasible, thus allowing the preparation of small libraries of heterocyclic molecules. Further applications of this methodology for more complex 3,4-DHPMs by multicomponent reaction are currently being pursued.

Experimental Section

General Procedures. Melting points were determined on a Kofler melting point apparatus and were uncorrected. Thin-layer chromatography (TLC) was accomplished on 0.2-mm precoated plates of silica gel 60 F-254 (Merck) or neutral alumina oxide gel 60F 254 (Merck).

Visualization was made with ultraviolet light (254 and 365 nm) or with a fluorescence indicator. IR spectra were recorded on a BIORAD FTS 175C spectrophotometer. ^{1}H NMR spectra was recorded on BRUKER AC 300 P (300 MHz) spectrometer, ^{13}C NMR spectra on BRUKER AC 300 P (75 MHz) spectrometer. Chemical shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard. The mass spectra (HRMS) were taken respectively on a MS/MS ZABSpec TOF Micromass (EBE TOF geometry) at an ionizing potential of 8 eV for the ILPs and on a VARIAN MAT 311 at an ionizing potential of 70 eV for the other compounds in the Centre Régional de Mesures Physiques de l'Ouest (CRMPO, Rennes). Reactions under microwave irradiations were realized in the Synthewave® 402 apparatus (Merck Eurolab, Div. Prolabo, France) in quartz open reactor vessel fitted with a condenser The microwave instrument consists of a continuous focused microwave power output from 0 to 300W. All the experiments were performed using stirring option. The target temperature was reached with a ramp of 3 minutes and the chosen microwave power stay constant to hold the mixture at this temperature. The reaction temperature is monitored using calibrated infrared sensor and the reaction time include the ramp period. Solvents were evaporated with a BUCHI rotary evaporator. All reagents were purchased from Acros, Aldrich Chimie, and Fluka France were used without further purification. The starting [HOC_2mim][X] ionic liquid phases **2** (X = Cl), **3** (X = PF_6)[18] and the ILP bound acetoacetate **4**[23] were synthesized according to ours previous methods.

Standard procedure for the three-component synthesis of 3,4-DHPMs 7(a-e) from urea 6a or thiourea 6b

A mixture of 1-[2-(acetoacetyloxy)ethyl]-3-methylimidazolium hexafluorophosphate **4** (409 mg, 1.15 mmol), commercial aldehyde **5** (1.15 mmol., 1 equiv.), commercial urea **6a** (207 mg, 3.45 mmol., 3 equiv.) or thiourea **6b** (262.2 mg, 3.45 mmol., 3 equiv.) and concentrated HCl (0.5% mol.) as catalyst was stirred vigorously at 100°C without solvent for 30 minutes. After cooling down to room temperature, deionised water (10 mL) was added in the crude reaction mixture. The desired insoluble 3,4-DHPM **7** was collected by filtration and was purified by washing with diethyl ether (2 x 5 ml). The expected 3,4-DHPM **7** was further dried under high *vacuum* (10^{-2} torr) at 25°C for 3 hours. The pure product **7** was characterized by ^{1}H, ^{13}C NMR and HRMS.

1-[2-[4-(1,3-Benzodioxol-5-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidin-5-ylcarbonyloxy]ethyl]-3-methylimidazolium hexafluorophosphate (7a). Yield = 98%. Orange foam. ^{1}H NMR ($(CD_3)_2SO$, 300 MHz) δ = 2.21 (s, 3H, CH_3); 3.81 (s, 3H, NCH_3); 4.35-4.40 (m, 4H, NCH_2CH_2O); 5.00 (d, 1H, *J* = 2.9 Hz, H-4'); 6.00 (d, 2H, *J* = 2.7 Hz, OCH_2O); 6.58 (dd, 1H, *J* = 8, 1.4 Hz, H-6''); 6.65 (d, 1H, *J* = 1.3 Hz, H-2''); 6.82 (d, 1H, *J* = 8 Hz, H-5''); 7.58 (s, 1H, H-4 or H-5); 7.63 (s, 1H, H-4 or H-5); 7.77 (br s, 1H, NH); 9.03 (s, 1H, H-2); 9.32 (br s, 1H, NH). ^{13}C NMR ($(CD_3)_2SO$, 75 MHz) δ = 18.07 (CH_3); 35.84 (NCH_3); 48.13 (CH_2N); 53.45 (C-4'); 61.55 (CH_2O); 98.16 (C-5'); 101.14 (OCH_2O); 106.72 (C-2''); 108.15 (C-5''); 119.32 (C-6''); 122.44-123.60 (C-4, C-5); 136.81 (C-2); 138.52 (C-1''); 146.51-147.37 (C-4'', C-3''); 150.21-152.08 (C-6', C-2'); 164.94 ($CO_2CH_2CH_2$). HRMS, *m/z*: 385.1508 found (calculated for $C_{19}H_{21}N_4O_5$, C^+ requires 385.1512).

1-[2-[4-(1,3-Benzodioxol-5-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-ylcarbonyloxy]ethyl]-3-methylimidazolium hexafluorophosphate (7b). Yield = 96%. Pink foam. ^{1}H NMR ($(CD_3)_2SO$, 300 MHz) δ = 2.24 (s, 3H, CH_3); 3.81 (s, 3H, NCH_3); 4.40 (m, 4H, NCH_2CH_2O); 5.02 (d, 1H, *J* = 3.5 Hz, H-4'); 6.01 (d, 2H, *J* = 2.2 Hz, OCH_2O); 6.57 (dd, 1H, *J* = 1.5 Hz, *J* = 8 Hz, H-6''); 6.64 (d, 1H, *J* = 1.3 Hz, H-2''); 6.85 (d, 1H, *J* = 8 Hz, H-5''); 7.59 (s, 1H, H-4 or H-5); 7.64 (s, 1H, H-4 or H-5); 9.03 (s, 1H, H-2); 9.68 (br s, 1H, NH); 10.41 (br s, 1H, NH). ^{13}C NMR ($(CD_3)_2SO$, 75 MHz) δ = 17.42 (CH_3); 35.82 (NCH_3); 48.01 (CH_2N); 53.45 (C-4'); 61.85 (CH_2O); 99.56 (C-5'); 101;23 (OCH_2O); 106.79 (C-2''); 108.21 (C-5''); 119.65 (C-6''); 122.40-123.56 (C-4, C-5); 136.93 (C-2); 137.08 (C-1''); 146.65-146.79-147.34 (C-3'', C-4'', C-6'); 164.72 ($CO_2CH_2CH_2$), 173.98 (C-2'). HRMS, *m/z*: 401.1287 found (calculated for $C_{19}H_{21}N_4O_4S$, C^+ requires 401.1284).

1-[2-[4-(4-Methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidin-5-ylcarbonyloxy]ethyl]-3-methylimidazolium hexafluorophosphate (7c). Yield = 90%. Mp = 162-164°C. ^{1}H NMR ($(CD_3)_2SO$, 300 MHz) δ = 2.19 (s, 3H, CH_3); 3.73 (s, 3H, OCH_3); 3.80 (s, 3H, NCH_3); 4.33-4.38 (m, 4H, NCH_2CH_2O); 5.02 (d, 1H, *J* = 2.9 Hz, H-4'); 6.85 (d, 2H, *J* = 8.6 Hz, H-3'', H-5''); 7.04 (d, 2H, *J* = 8.6 Hz, H-2'', H-6'') 7.56 (s, 1H, H-4 or H-5); 7.63 (s, 1H, H-4 or H-5); 7.75 (br s, 1H, NH); 9.00 (s, 1H, H-2); 9.30 (br s, 1H, NH). ^{13}C NMR ($(CD_3)_2SO$, 75 MHz) δ = 18.03 (CH_3); 35.80 (NCH_3); 48.11 (CH_2N); 53.14 (C-4'); 55.16 (CH_3O), 61.50 (CH_2O); 98.41 (C-5'); 113.83 (C-3'', C-5''), 122.44-123.61 (C-4, C-5); 127.43 (C-2'', C-6''); 136.68 (C-1'); 136.74 (C-2); 149.89-152.11 (C-6', C-2'); 158.58 (C-4'); 164.95 ($CO_2CH_2CH_2$). HRMS, *m/z*: 371.1710 found (calculated for $C_{19}H_{23}N_4O_4$, C^+ requires 371.1719).

1-[2-[4-(4-Chlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-ylcarbonyloxy]ethyl]-3-methylimidazolium hexafluorophosphate (7d). Yield = 90%. Brown foam. ^{1}H NMR ($(CD_3)_2SO$, 300 MHz) δ = 2.24 (s, 3H, CH_3); 3.81 (s, 3H, NCH_3); 4.41 (m, 4H, NCH_2CH_2O); 5.12 (d, 1H, *J* = 3.6 Hz, H-4'); 7.14 (d, 2H, *J* = 8.5 Hz, H-2'', H-6''); 7.40 (d, 1H, *J* = 8.4 Hz, H-3'', H-5''); 7.61 (s, 1H, H-4 or H-5); 7.64 (s, 1H, H-4 or H-5); 9.07 (s, 1H, H-2); 9.75 (br s, 1H, NH); 10.48 (br s, 1H, NH). ^{13}C NMR ($(CD_3)_2SO$, 75 MHz) δ = 17.43 (CH_3); 35.79 (NCH_3); 47.94 (CH_2N); 53;14 (C-4'); 61.90 (CH_2O); 99.21 (C-5'); 122.41-123.55 (C-4, C-5); 128.31 (C-2'', C-6''); 128.63 (C-3'', C-5''); 132.35 (C-4''); 136.94 (C-2); 141.96-146.87 (C-1'', C-6'); 164.60 ($CO_2CH_2CH_2$), 174.20 (C-2'). HRMS, *m/z*: 391.1002 found (calculated for $C_{18}H_{20}N_3O_2{}^{35}ClS$, C^+ requires 391.0996).

1-[2-[4-(4-Chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidin-5-ylcarbonyloxy]ethyl]-3-methylimidazolium hexafluorophosphate (7e). Yield = 90%. Yellow foam. ^{1}H NMR ($(CD_3)_2SO$, 300 MHz) δ = 3.20 (s, 3H, CH_3); 3.81 (s, 3H, NCH_3); 4.40 (m, 4H, NCH_2CH_2O); 5.07 (d, 1H, *J* = 3.2 Hz, H-4'); 7.14 (d, 2H, *J* = 8.4 Hz, H-2'', H-6''); 7.36 (d, 1H, *J* = 8.4 Hz, H-3'', H-5''); 7.60 (s, 1H, H-4 or H-5); 7,64 (s, 1H, H-4 or H-5); 7,85 (br s, 1H, NH); 9.02 (s, 1H, H-2); 9.38 (br s, 1H, NH). ^{13}C NMR ($(CD_3)_2SO$, 75 MHz) δ = 18.07 (CH_3); 35.82 (NCH_3); 48.06 (CH_2N); 53.16 (C-4'); 61.55 (CH_2O); 97.74 (C-5'); 122.45-123.58 (C-4, C-5); 128.15 (C-2'', C-6''); 128.49 (C-3'', C-5''); 131.95 (C-4''); 136.75 (C-2); 143.40 (C-1');

150.46-151.89 (C-2'; C-6'); 164.79 ($CO_2CH_2CH_2$). HRMS, *m/z*: 375.1228 found (calculated for $C_{18}H_{20}N_4O_3$, C^+ requires 375.1224).

Standard procedure for the three-component synthesis of 3,4-DHPMs 7(f-j) from methylurea 6c, ethylurea 6d or methylthiourea 6e

A mixture of 1-[2-(acetoacetyloxy)ethyl]-3-imidazolium hexafluorophosphate **4** (483.1 mg, 1.35 mmol), commercial aldehyde **5** (1.35 mmol., 1 equiv.), commercial methylurea **6c** (300.4 mg, 4.06 mmol., 3 equiv.) or ethylurea **6d** (357.3 mg, 4.06 mmol., 3 equiv.) or methylthiourea **6e** (365.4 mg, 4.06 mmol., 3 equiv.) and concentrated HCl (0.5% mol.) as catalyst was stirred vigorously at 100°C without solvent for one hour. After cooling down to room temperature, deionised water (10 mL) was added in the crude reaction mixture. The desired insoluble 3,4-DHPM **7** was collected by filtration and was purified by washing with diethyl ether (2 x 5 ml). The expected 3,4-DHPM **7** was further dried under high *vacuum* (10^{-2} torr) at 25°C for 3 hours. The pure product **7** was characterized by ^1H, ^{13}C NMR and HRMS.

1-[2-[4-(4-Bromophenyl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidin-5-ylcarbonyloxy]ethyl]-3-methylimidazolium hexafluorophosphate (7f). Yield = 93%. Yellow needles. Mp = 184-186°C. ^1H NMR ($(CD_3)_2SO$, 300 MHz) δ = 2.46 (s, 3H, CH_3); 3.08 (s, 3H, $CONCH_3$); 3.80 (s, 3H, NCH_3); 4.42 (m, 4H, NCH_2CH_2O); 5.05 (d, 1H, *J* = 3.7 Hz, H-4'); 7.06 (d, 2H, *J* = 8.4 Hz, H-2'', H-6''); 7.49 (d, 1H, *J* = 8.4 Hz, H-3'', H-5''); 7.59 (s, 1H, H-4 or H-5); 7.62 (s, 1H, H-4 or H-5); 8.10 (d, 1H, *J* = 3.8 Hz, NH); 9.00 (s, 1H, H-2). ^{13}C NMR ($(CD_3)_2SO$, 75 MHz) δ = 16.16 (CH_3); 29.85 ($CONCH_3$); 35.82 (NCH_3); 47.94 (CH_2N); 51.58 (C-4'); 61.75 (CH_2O); 100.56 (C-5'); 120.53 (C-4''); 122.39-123.55 (C-4, C-5); 128.34 (C-2'', C-6''); 131.39 (C-3'', C-5''); 136.72 (C-2); 143.00 (C-1''); 152.83-152.75 (C-2'; C-6'); 164.96 ($CO_2CH_2CH_2$). HRMS, *m/z*: 433.0878 found (calculated for $C_{19}H_{21}N_4O_3{}^{79}Br$, C^+ requires 433.0875).

X-Ray Crystallographic data for (7f). Crystal data for $C_{19}H_{21}N_4O_3Br$, PF_6, Mr = 1158.57, monoclinic, C2/c, a = 34.679(1), b = 12.2504(4), c = 10.7844(4) Å, β = 99.989(3)°, V = 4512.1(3) $Å^3$, Z = 8, D_X = 1.706 $Mg.m^{-3}$, λ(MoKα) = 0.71073 Å, μ = 19.73 cm^{-1}, F(000) = 2336, T = 120(1) K. The sample (0.18∗0.16∗0.14 mm) is studied on an Oxford Diffraction Xcalibur Saphir 3 diffractometer with graphite monochromatized MoKα radiation. The data collection ($2\theta_{max}$ = 54°, omega scan frames via 0.75° omega rotation and 20 s per frame, range HKL: H 0.44 K 0.15 L 13.13) gives 16184 reflections. The data leads to 4894 independent reflections from which 3691 with I>2.0σ(I). The structure was solved with SIR-97[29] that reveals the non-hydrogen atoms of the molecule. After anisotropic refinement, many hydrogen atoms may be found with a Fourier Difference. The whole structure was refined with SHELXL 97 by the full-matrix least-square techniques (use of F square magnitude; x, y, z, β_{ij} for Br, F, P, C, N and O atoms, x, y, z in riding mode for H atoms; 307 variables and 3691 observations with I>2.0σ(I); calculated $w = 1/[\sigma^2(Fo^2) + (0.069P)^2]$ where $P = (Fo^2+2Fc^2)/3$ with the resulting R = 0.036, R_W = 0.105 and S_W = 1.067, Δρ < 0.7 $eÅ^{-3}$. Atomic scattering factors were from International Tables for X-ray Crystallography. Ortep views were realized with PLATON 98.

1-[2-[4-(4-Chlorophenyl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidin-5-ylcarbonyloxy]ethyl]-3-methylimidazolium hexafluorophosphate (7g). Yield = 96%. White needles. Mp = 170-172°C. ^{1}H NMR ($(CD_3)_2SO$, 300 MHz) δ = 2.46 (s, 3H, CH_3); 3.08 (s, 3H, $CONCH_3$); 3.79 (s, 3H, NCH_3); 4.42 (m, 4H, NCH_2CH_2O); 5.07 (d, 1H, *J* = 3.8 Hz, H-4'); 7.12 (d, 2H, *J* = 8.4 Hz, 2H, H-2'', H-6''); 7.36 (d, 1H, *J* = 8.4 Hz, H-3'', H-5''); 7.59 (s, 1H, H-4 or H-5); 7.63 (s, 1H, H-4 or H-5); 8,12 (d, 1H, *J* = 3.8 Hz, NH); 9.02 (s, 1H, H-2). ^{13}C NMR ($(CD_3)_2SO$, 75 MHz) δ = 16.14 (CH_3); 29.84 ($CONCH_3$); 35.78 (NCH_3); 47.93 (CH_2N); 51.53 (C-4'); 61.73 (CH_2O); 100.62 (C-5'); 122.38-123.53 (C-4, C-5); 127.97 (C-2'', C-6''); 128.46 (C-3'', C-5''); 131.98 (C-4''); 136.71 (C-2); 142.58 (C-1''); 152.75-152.80 (C-2'; C-6'); 164.97 ($CO_2CH_2CH_2$). HRMS, *m/z*: 389.1383 found (calculated for $C_{19}H_{22}N_4O_3{}^{35}Cl$, C^+ requires 389.1380).

1-[2-[4-(4-Chlorophenyl)-1,6-dimethyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-ylcarbonyloxy]ethyl]-3-methylimidazolium hexafluorophosphate (7h). Yield = 70%. Orange needles. Mp = 145-147°C. ^{1}H NMR ($(CD_3)_2SO$, 300 MHz) δ = 2.49 (s, 3H, CH_3); 3.47 (s, 3H, $CSNCH_3$); 3.81 (s, 3H, NCH_3); 4.46 (br s, 4H, NCH_2CH_2O); 5,10 (d, 1H, *J* = 4 Hz, H-4'); 7.12 (d, 2H, *J* = 8.2 Hz, H-2'', H-6''); 7.40 (d, 1H, *J* = 8.2 Hz, H-3'', H-5''); 7.61 (s, 1H, H-4 or H-5); 7.64 (s, 1H, H-4 or H-5); 9.02 (s, 1H, H-2); 9.98 (d, 1H, *J* = 4.3 Hz, NH). ^{13}C NMR ($(CD_3)_2SO$, 75 MHz) δ = 16.29 (CH_3); 35.79 (NCH_3); 36.27 ($CSNCH_3$); 47.83 (CH_2N); 51.41 (C-4'); 62.15 (CH_2O); 103.67 (C-5'); 122.38-123.55 (C-4, C-5); 128.01 (C-2'', C-6''); 128.61 (C-3'', C-5''); 132.40 (C-4''); 136.74 (C-2); 140.63-149.85 (C-1'', C-6'); 164.62 ($CO_2CH_2CH_2$), 177.96 (C-2'). HRMS, *m/z*: 405.1146 found (calculated for $C_{19}H_{22}N_4O_2{}^{35}ClS$, C^+ requires 405.1152).

1-[2-[4-(4-Chlorophenyl)-1-ethyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidin-5-ylcarbonyloxy]ethyl]-3-methylimidazolium hexafluorophosphate (7i). Yield = 89%. White foam. ^{1}H NMR ($(CD_3)_2SO$, 300 MHz) δ = 1.05 (t, 3H, *J* = 6.9 Hz, CH_2CH_3); 2.47 (s, 3H, CH_3); 3.60 (m, 1H, *J* = 7 Hz, CH_2CH_3); 3.77 (m, 1H, CH_2CH_3); 3.80 (s, 3H, NCH_3); 4.40 (m, 4H, NCH_2CH_2O); 5.05 (d, 1H, *J* = 3.1 Hz, H-4'); 7.11 (d, 2H, *J* = 8.3 Hz, H-2'', H-6''); 7.37 (d, 1H, *J* = 8.3 Hz, H-3'', H-5''); 7.58 (s, 1H, H-4 or H-5); 7,63 (s, 1H, H-4 or H-5); 8.03 (d, 1H, *J* = 3.5 Hz, NH); 9.00 (s, 1H, H-2). ^{13}C NMR ($(CD_3)_2SO$, 75 MHz) δ = 14.75 (CH_2CH_3); 15.60 (CH_3); 35.78 (NCH_3); 37.14 (CH_2CH_3); 47.94 (CH_2N); 51.66 (C-4'); 61.75 (CH_2O); 101.03 (C-5'); 122.37-123.54 (C-4, C-5); 127.97 (C-2'', C-6''); 128.46 (C-3'', C-5''); 131.97 (C-4''); 136.71 (C-2); 142.70-151.66-152.20 (C-1'', C-6', C-2'); 165.00 ($CO_2CH_2CH_2$). HRMS, *m/z*: 403.1542 found (calculated for $C_{20}H_{24}N_4O_3{}^{35}Cl$, C^+ requires 403.1537).

1-[2-[4-(4-Bromophenyl)-1-ethyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidin-5-ylcarbonyloxy]ethyl]-3-methylimidazolium hexafluorophosphate (7j). Yield = 81%. Yellow foam. ^{1}H NMR ($(CD_3)_2SO$, 300 MHz) δ = 1.05 (t, 3H, *J* = 6.5 Hz, CH_2CH_3); 2.47 (s, 3H, CH_3); 3.61 (m, 1H, CH_2CH_3); 3.77 (m, 1H, CH_2CH_3); 3.80 (s, 3H, NCH_3); 4.37 (m, 4H, NCH_2CH_2O); 5.03 (sl, 1H, H-4'); 7.05 (d, 2H, *J* = 8 Hz, H-2'', H-6''); 7.50 (d, 1H, *J* = 8 Hz, H-3'', H-5''); 7.59 (s, 1H, H-4 or H-5); 7.63 (s, 1H, H-4 or H-5); 8.03 (br d, 1H, *J* = 2.5 Hz, NH); 9.00 (s, 1H, H-2). ^{13}C NMR ($(CD_3)_2SO$, 75 MHz) δ = 14.75 (CH_2CH_3); 15.60 (CH_3); 35.81 (NCH_3); 37.16

(CH_2CH_3); 47.93 (CH_2N); 51.71 (C-4'); 61.76 (CH_2O); 100.97 (C-5'); 120.51 (C-4''); 122.37-123.54 (C-4, C-5); 128.33 (C-2'', C-6''); 131.37 (C-3'', C-5''); 136.72 (C-2); 143.10-151.67-152.19 (C-1'', C-6', C-2'); 164.98 ($CO_2CH_2CH_2$). HRMS, *m/z*: 447.1033 found (calculated for $C_{20}H_{24}N_4O_3{}^{79}Br$, C^+ requires 447.1032).

General procedure for the synthesis of 3,4-DHPMs 8(a-d) by transesterification of ionic liquid-phase bound 3,4-DHPM 7

To a solution of compound **7** (0.57 mmole) in anhydrous methanol (10 mL) was added commercial sodium methoxide (31 mg, 0.57 mmole, 1 equiv.) in one portion under nitrogen. After vigorous stirring at 78°C for 18 h., the solvent was eliminated *in vacuum*. Then 10 mL of deionised water was added to the crude reaction mixture and a crude solid (**8**) was obtained after 30 min. of stirring. The precipitated methyl ester **8** was filtered, washed with deionised water (2 x 5 mL) and dried under reduced pressure (10-2 Torr) during 3 h.

Methyl 4-(4-chlorophenyl)-1-ethyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidin-5-carboxylate (8a). Yield = 90%. White needles. Mp = 140-142°C. ^{1}H NMR ($(CD_3)_2SO$, 300 MHz) δ = 1.05 (t, 3H, *J* = 7 Hz, CH_2CH_3); 2.50 (s, 3H, CH_3); 3.56 (s, 3H, OCH_3); 3.58 (m, 1H, *J* = 7 Hz, CH_2CH_3); 3.78 (m, 1H, *J* = 7 Hz, CH_2CH_3); 5.12 (d, 1H, *J* = 3.4 Hz, H-4); 7.22 (d, 2H, *J* = 8.3 Hz, H-2', H-6'); 7.38 (d, 1H, *J* = 8.4 Hz, H-3', H-5'); 7.96 (d, 1H, *J* = 3.5 Hz, NH). ^{13}C NMR ($(CD_3)_2SO$, 75 MHz) δ = 14.78 (CH_2CH_3); 15.55 (CH_3); 37.02 (CH_2CH_3); 51.12 (OCH_3); 51.86 (C-4); 102.14 (C-5); 127.98 (C-2', C-6'); 128.47 (C-3', C-5'); 131.94 (C-4'); 142.96-150.15-152.39 (C-1', C-5, C-2); 165.98 (CO_2CH_3). IR (KBr): 1490, 1607, 1689, 1711, 2981, 3101, 3208, 3520 cm^{-1}. HRMS, *m/z*: 308.0911 found (calculated for $C_{13}H_{17}N_2O_3{}^{35}Cl$, M^+ requires 308.0928).

Methyl 4-(4-bromophenyl)-1-ethyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidin-5-carboxylate (8b). Yield = 89%. White needles. Mp = 120-122°C. ^{1}H NMR ($(CD_3)_2SO$, 300 MHz) δ = 1.05 (t, 3H, *J* = 6.8 Hz, CH_2CH_3); 2.50 (s, 3H, CH_3); 3.56 (br s, 4H, OCH_3, CH_2CH_3); 3.78 (m, 1H, *J* = 7 Hz, CH_2CH_3); 5.11 (d, 1H, *J* = 2.6 Hz, H-4); 7.16 (d, 2H, *J* = 8.1 Hz, H-2', H-6'); 7.52 (d, 1H, *J* = 8.2 Hz, H-3', H-5'); 7.95 (d, 1H, *J* = 2.7 Hz, NH). ^{13}C NMR ($(CD_3)_2SO$, 75 MHz) δ = 14.78 (CH_2CH_3); 15.55 (CH_3); 37.00 (CH_2CH_3); 51.13 (OCH_3); 51.90 (C-4); 102.05 (C-5); 120.44 (C-4'); 128.32 (C-2', C-6'); 131.38 (C-3', C-5'); 143.35-150.15-152.35 (C-1', C-6, C-2); 165.96 (CO_2CH_3). IR (KBr) : 1486, 1608, 1682, 1712, 2945, 2980, 3242 cm^{-1}. HRMS, *m/z*: 352.0417 found (calculated for $C_{13}H_{17}N_2O_3{}^{79}Br$, M^+ requires 352.0423).

Methyl 4-(4-chlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-carboxylate (8c). Yield = 85%. Brown viscous oil. ^{1}H NMR ($(CD_3)_2SO$, 300 MHz) δ = 2.31 (s, 3H, CH_3); 3.57 (s, 3H, OCH_3); 5.18 (d, 1H, *J* = 3 Hz, H-4); 7.24 (d, 2H, *J* = 8.3 Hz, H-2', H-6'); 7.44 (d, 2H, *J* = 8.3 Hz, H-3', H-5'); 9.71 (br s, 1H, NH); 10.43 (br s, 1H, NH). ^{13}C NMR ($(CD_3)_2SO$, 75 MHz) δ = 17.27 (CH_3); 51.16 (OCH_3); 53.34 (C-4); 100.06 (C-5); 128.27 (C-2', C-6'); 128.66 (C-3',C-5'); 132.33 (C-4'); 142.19 (C-1'); 145.66 (C-6); 165.52 (CO_2Me); 174.30 (C-2). IR (KBr): 1488, 1556, 1697, 1714, 2992, 3160 cm^{-1}. HRMS, *m/z*: 296.0382 found (calculated for $C_{13}H_{13}N_2O_2{}^{35}Cl$, M^+ requires 296.0386).

Methyl 4-(1,3-benzodioxol-5-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-carboxylate (8d). Yield = 91%. White needles. Mp = 238-240°C. ^{1}H NMR ($(CD_3)_2SO$, 300 MHz) δ = 2.25 (s, 3H, CH_3); 3.53 (s, 3H, OCH_3); 5.06 (s, 1H, H-4); 5.98 (s, 2H, OCH_2O); 6.68 (d, 1H, *J* = 7.6 Hz, H-6'); 6.74 (s, 1H, H-2'); 6.84 (d, 1H, *J* = 7.8 Hz, H-5'); 7.70 (br s, 1H, NH); 9.21 (br s, 1H, NH). ^{13}C NMR ($(CD_3)_2SO$, 75 MHz) δ = 17.90 (CH_3); 50.87 (OCH_3); 53.61 (C-4); 99.11 (C-5); 101.03 (OCH_2O); 106.74 (C-2'); 108.13 (C-5'); 119.32 (C-6'); 138.74 (C-1'); 146.48-147.37 (C-4', C-3'); 148.69-152.22 (C-6, C-2); 165.89 (CO_2Me). IR (KBr): 1230, 1486, 1647, 1693, 1712, 2951, 3099, 3206, 3363, 3517 cm^{-1}. HRMS, *m/z*: 296.0391 found (calculated for $C_{14}H_{14}N_2O_5$, M^+ requires 296.0393).

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