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Mechanistic Studies on Lewis Acid Catalyzed Biginelli Reactions in Ionic Liquids: Evidence for the Reactive Intermediates and the Role of the Reagents

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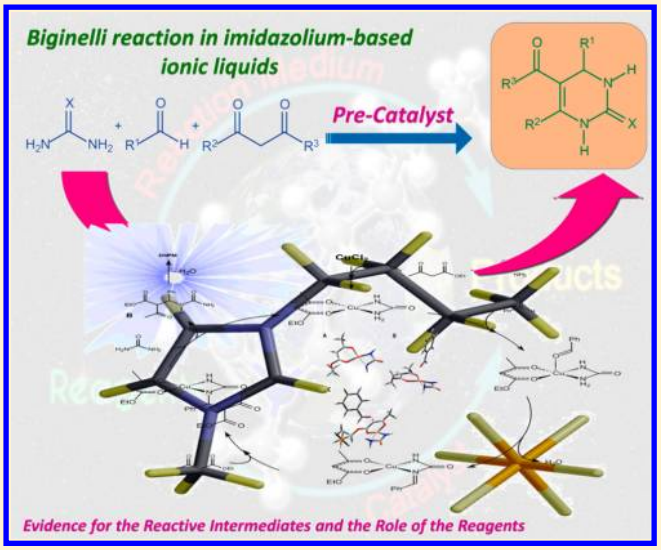
Supporting Information

ABSTRACT: This paper describes the use of common Lewis acids supported in imidazolium-based ionic liquids as the catalysts to promote the Biginelli reaction. The ionic liquid effect and the reaction mechanism are discussed on the basis of nuclear magnetic resonance (NMR), electrospray ionization mass spectrometry (ESI-MS), and theoretical calculations. Indeed, the results showed that the ionic medium plays a fundamental role in the synthesis of biologically active dihydropyrimidinones due to the stabilization of the charged intermediates proposed in the mechanism. When conducted in an ionic liquid as solvent, the reaction mechanism is more complex than in other Lewis acid catalyzed Biginelli reactions.



INTRODUCTION

Nowadays there is no doubt about the importance of ionic liquids (ILs) and how efficient and promising the multicomponent reactions (MCRs) are. A multicomponent synthesis performed in ILs has recently been described as "*a perfect synergy for eco-compatible heterocyclic synthesis*".[1] Somehow, this successful idea could be easily predicted, especially because ILs are regarded as a possible pathway toward sustainability.[2] Currently, it is possible to find many industrial processes carried out in ILs.[3] The tunable, unique, desired physicochemical properties of ILs make this class of substances highly studied and applied in many different areas.[4−6] Indeed, the impressive chemistry of ILs has been very recently reviewed.[7] In the search for multiple-bond-forming efficiency, MCRs play a central role, as recently reviewed.[8] The possibility of generating small molecule libraries, especially with biologically active compounds, has brought MCRs to prominence.[9] In this context, many examples of different approaches are found in the scientific literature to improve on both the chemical selectivity and yields of MCRs.[10−13]

The Biginelli multicomponent reaction, first reported in 1983[14] by Pietro Biginelli,[15] is a very elegant methodology to directly obtain 3,4-dihydropyrimidin-2(1*H*)-one (DHPMs) derivatives in a one-step procedure.[16] DHPMs usually display biological activity, and compounds such as enastron,[17] monastrol,[18] piperastrol[19] (and analogues), and other derivatives[20] (Figure 1) are known as biologically active compounds used as calcium channel modulators, adrenergic receptor antagonists, mitotic Kinesin inhibitors, antivirals, antibacterials, etc., as reviewed elsewhere.[21]

Since its discovery, the Biginelli MCR has experienced many drawbacks such as long reaction times, need of excess of one of the reactants, low yields, expansive catalysts, and others.[22−25] In this sense, ILs became a natural option for the observed efforts to improve on the reaction conditions, times, yields, and workup.[26] Task-specific ILs have been also employed as alternative acid[27,28] and basic[29,30] catalysts to perform this reaction. Ultrasonic irradiation[31] and metal-containing ILs (in

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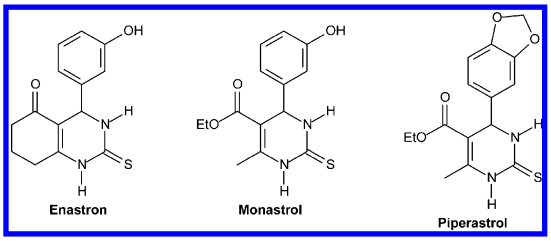


Figure 1. Some examples of biologically active dihydropyrimidinones (DHPMs).

the anion) such as $[InCl_4]^{-}$[32] and $[FeCl_4]^{-}$[33] have also been used as strategies to overcome all drawbacks associated with the Biginelli reaction.

It is well-known that some common Lewis acids ($SbCl_3$,[34] $Cu(OTf)_2$,[35] $ZrCl_4$,[36] $FeCl_3$,[37] $SnCl_2$,[38] $InBr_3$,[39] $ZnBr_2$, and others[40,41]) are capable of promoting the Biginelli reaction, despite the many problems associated with their use. The reaction mechanism of this MCR is so far indisputable (as will be discussed in due course). These metal catalysts are also commonly supported and used under high temperatures (typically above 100 °C), and in some cases, the presence of an additional Bronsted acid is required.[42]

On the basis of our experience using ILs and our interest in catalytic processes in this ionic media,[43−46] we describe herein that imidazolium-based ILs (Figure 2) are an excellent media to

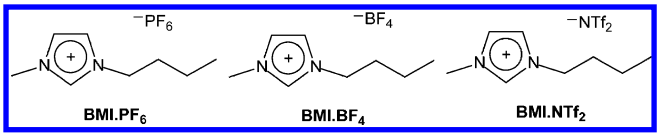


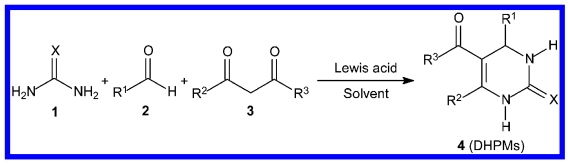
Figure 2. Imidazolium-based ionic liquids commonly used in biphasic catalysis.

support common metal Lewis acid with excellent results for the Biginelli reaction. The ionic liquid effect and the proposed reaction mechanism are also discussed.

RESULTS AND DISCUSSION

First, we investigated a series of Lewis acids as the Biginelli reaction promoters (Scheme 1), and results are summarized in Table 1.

Scheme 1. DHPMs Synthesis with Different Lewis Acids



It is worth highlighting that all tests were conducted with equimolar quantities of the three components of the Biginelli reaction and in only 60 min to evaluate the most active catalytic system among all tested.

It can be deduced from Table 1 that some Lewis acids such as $CeCl_3$, $InCl_3$, $FeCl_3$, $ZrOCl_2$, and $MgCl_2$, (Table 1, entries 6, 7, 17, 21, and 22) are promising catalysts and give the desired product above 60% of yield in the first reaction hour. Among these metals, there is no doubt about the importance of iron. For comparison purposes, it has been reported[37] that the use of $FeCl_3$ with an additional amount of HCl resulted in the same

Table 1. Lewis Acids Tested As Promoters of the Biginelli Reaction[a,b]

entry	catalyst	ionic liquid (or organic solvent)	yield[d] (%)
1			traces
2		$BMI{\cdot}BF_4$	3
3	CdO	$BMI{\cdot}BF_4$	5
4	$CdSO_4{\cdot}8H_2O$	$BMI{\cdot}BF_4$	42
5	$CdCl_2{\cdot}H_2O$	$BMI{\cdot}BF_4$	30
6	$CeCl_3{\cdot}7H_2O$	$BMI{\cdot}BF_4$	72
7	$InCl_3$	$BMI{\cdot}BF_4$	61
8	$Cr(CO)_6$	$BMI{\cdot}BF_4$	3
9	$SnCl_2$	$BMI{\cdot}BF_4$	40
10	$CoCl_2{\cdot}6H_2O$	$BMI{\cdot}BF_4$	59
11	MnO_2	$BMI{\cdot}BF_4$	5
12	Nb_2O_5	$BMI{\cdot}BF_4$	11
13	$BF_3{\cdot}OEt_2$	$BMI{\cdot}BF_4$	43
14	$AlCl_3{\cdot}6H_2O$	$BMI{\cdot}BF_4$	59
15	$FeSO_4{\cdot}7H_2O$	$BMI{\cdot}BF_4$	13
16	$FeCl_2{\cdot}4H_2O$	$BMI{\cdot}BF_4$	59
17	$FeCl_3$	$BMI{\cdot}BF_4$	66
18	$Ni(OAc)_2{\cdot}4H_2O$	$BMI{\cdot}BF_4$	4
19	$NiCl_2{\cdot}6H_2O$	$BMI{\cdot}BF_4$	58
20	$NiSO_4{\cdot}6H_2O$	$BMI{\cdot}BF_4$	30
21	$ZrOCl_2{\cdot}8H_2O$	$BMI{\cdot}BF_4$	68
22	$MgCl_2{\cdot}6H_2O$	$BMI{\cdot}BF_4$	66
23	$BaCl_2{\cdot}2H_2O$	$BMI{\cdot}BF_4$	52
24	$ZnCl_2$	$BMI{\cdot}BF_4$	49
25	$ZnSO_4{\cdot}7H_2O$	$BMI{\cdot}BF_4$	34
26	Cs_2CO_3[c]	$BMI{\cdot}BF_4$	7
27	CuO	$BMI{\cdot}BF_4$	9
28	$CuSO_4{\cdot}5H_2O$	$BMI{\cdot}BF_4$	54
29	$CuCl_2{\cdot}2H_2O$	$BMI{\cdot}BF_4$	73
30	$CuCl_2$	$BMI{\cdot}BF_4$	77
31	$CuCl_2$	$BMI{\cdot}NTf_2$	76
32	$CuCl_2$	$BMI{\cdot}PF_6$	87
33	$CuCl_2$	MeCN	46
34	$CuCl_2$	MeOH	52
35	$CuCl_2$	$CHCl_3$	48
36	$CuCl_2$	CH_2Cl_2	44
37	$CuCl_2$	THF	31
38	$CuCl_2$	H_2O	7

[a] R^1 = Ph, R^2 = Me, R^3 = OEt, X = O. [b] Benzaldehyde (3.00 mmol), ethyl acetoacetate (3.00 mmol), urea (3.00 mmol), 1 mL of solvent, and 10 mol % of the catalyst at 80 °C for 60 min to give **4a**. [c] Basic character. [d] Isolated yields.

product in 93% yield but after 4 h of reaction, indicating how promising the catalytic system shown here is. The use of copper catalysts, however, gave the best results (Table 1, entries 29 and 30), yielding the Biginelli adduct in 73% and 77% yield, respectively. Copper chloride is a cheap and readily available Lewis acid. Once the metal catalyst was selected ($CuCl_2$), it was tested in different ILs and other organic solvents to be sure about the benefits of using ionic media rather than a classic organic solvent (Table 1, entries 31−38). It is noted that the use of $BMI{\cdot}PF_6$ gave by far the best result (87%) for only 60 min of reaction (Table 1, entry 32), and it was also better than other commonly used solvents (Table 1, entries 33−38). It has been reported[42] that the use of a combined system with $CuCl/BF_3{\cdot}OEt_2$/AcOH in THF for 18 h gave the same product in a similar yield. The results indicated how efficient and promising

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this novel catalytic system (BMI·PF_6, $CuCl_2$) is, which was further optimized.

The reaction temperature was varied, and the results are better visualized in Figure 3. It is noted that the best reaction

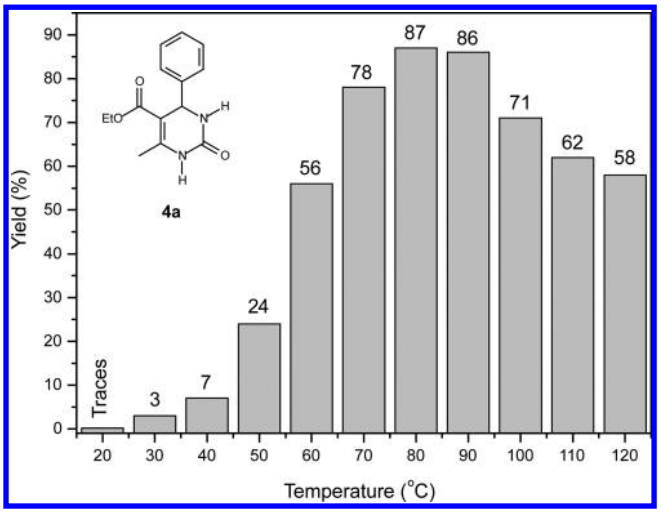


Figure 3. Temperature effect on the synthesis of DHPM **4a** in BMI·PF_6 and $CuCl_2$ as the catalyst.

temperatures were between 80 and 90 °C; thus, we decided to carry out the reactions at lower temperature, i.e., at 80 °C. Below this temperature, the isolated yields were not as good. It was also noted, nevertheless, that at 50 °C the system is relatively active and, in some cases, it may be a desired condition. Above 90 °C, yields decrease, despite the fact that the system remains active for all tested temperatures.

The reaction profile was also investigated and visualized in Figure 4.

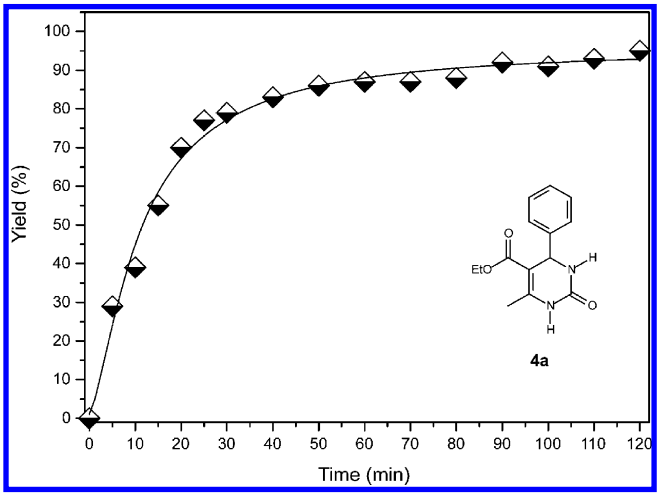
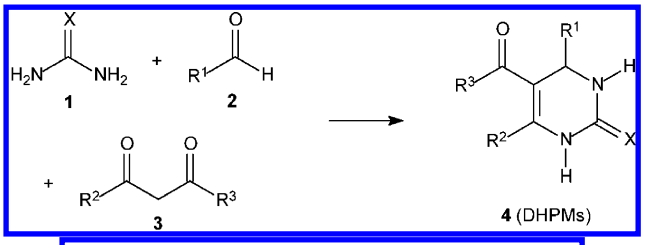


Figure 4. Reaction profile on the synthesis of DHPM **4a** using $CuCl_2$ as the catalyst and BMI·PF_6 as the reaction media.

It is noted that in only 5 min of reaction the yield is near 30% and that in 90 min yields are above 90%, reaching 95% of **4a** by the end of the reaction.

Once we optimized the reaction conditions, we decided to extend the methodology to the synthesis of different DHPMs. The results are summarized in Table 2.

Table 2. Dihydropyrimidinones Synthesized Using the Developed Conditions (80 °C, BMI·PF_6, $CuCl_2$)



DHPM	Reagent				Time	Yield
(**4a-p**)	R^1	R^2	R^3	X	(min)	(%)
4a	Ph	CH_3	CH_3CH_2O	O	120	95
4b	3-OH-Ph	CH_3	CH_3CH_2O	O	60	84
4c	3-OH-Ph	CH_3	CH_3	O	150	84
4d	3-OH-Ph	CH_3	CH_3CH_2O	S	60	80
4e	3-OH-Ph	CH_3	CH_3	S	360	82
4f	3-NO_2-Ph	CH_3	CH_3CH_2O	O	120	84
4g	3-NO_2-Ph	CH_3	CH_3	O	120	94
4h	3-NO_2-Ph	CH_3	CH_3	S	120	87
4i	H	CH_3	CH_3CH_2O	O	120	70
4j	H	CH_3	CH_3CH_2O	S	120	64
4k	Ph	CH_3	CH_3CH_2O	S	120	60
4l	Ph	CH_3	CH_3	O	120	98
4m	4-Cl-Ph	CH_3	CH_3	O	120	97
4n	4-Cl-Ph	CH_3	CH_3	S	120	68
4o	4-Cl-Ph	CH_3	CH_3CH_2O	O	120	66
4p	3-OH-Ph			O	60	77

The catalytic system showed to be active for different substrates and good to excellent yields were observed. The biologically active monastrol (**4d**) was obtained in 80% in only 1 h of reaction. Oxo-enastron (**4p**) was also obtained in 77% at the same time.

For long, the Biginelli reaction mechanism was the subject of many discussions. Currently, there are three major proposals accepted for this condensation: (i) The iminium mechanism, (ii) the Knoevenagel mechanism, and (iii) the enamine mechanism.[47−49] Recently, it has been demonstrated that electrospray ionization mass spectrometry (ESI-MS and -MS/MS) is an excellent tool to study the Biginelli intermediates formed during the transformation,[50] especially because ESI-MS is capable of "fishing" the formed ions from the solution, leading them directly to the gas phase.[51] The limitation, however, was that the study was conducted using a Bronsted acid,[50] which is usually not preferable for an actual Biginelli synthesis. Nevertheless, the potential of ESI-MS for studying this reaction was unequivocally demonstrated. Thus, we decided to use this important tool to evaluate which is the preferred mechanism under the studied reaction conditions. Fortunately, we were able to detect and characterize interesting intermediates and transient species, as will be shown and discussed. On the basis of these findings, a catalytic cycle was proposed (Scheme 2) and is analyzed (discussed) below.

In the presence of ethyl acetoacetate and urea, intermediate **I** is formed, which is found in equilibrium with intermediates **V** and **VI**, as shown in Scheme 2. Benzaldehyde coordinates to the metal center (copper) and forms **II**, which immediately leads to **III** with water release. Intermediate **III** is then trapped by ethyl acetoacetate forming **IV** through a direct addition to C═N. In the presence of urea, compound **B** is released restoring **I**. Intermediate **III** can equally proceed through two different pathways, i.e., (i) reacting with urea releasing compound **A** and restoring **I** (substitution reaction instead of an addition) or (ii) reacting with ethyl acetoacetate releasing

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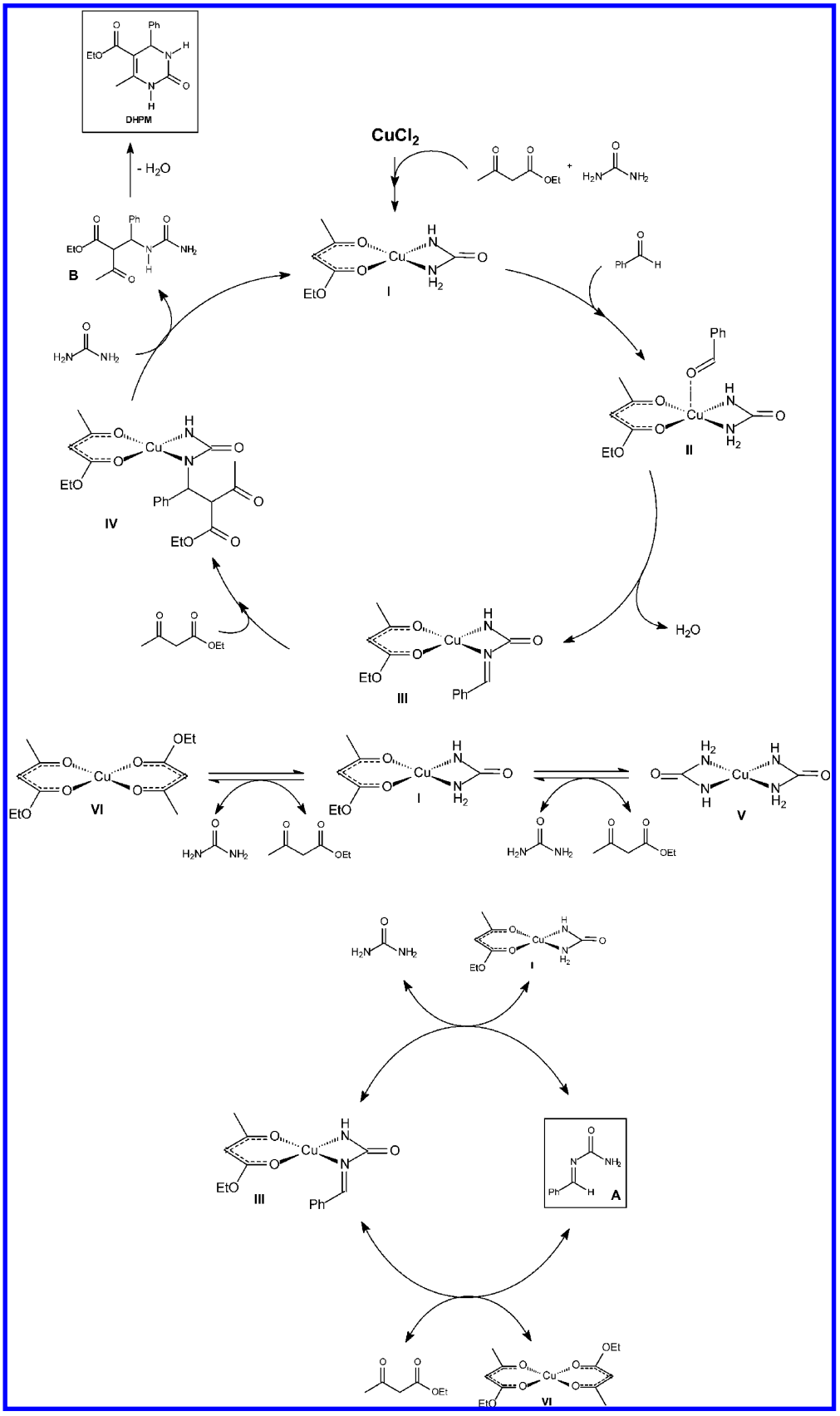
Scheme 2. Proposed Catalytic Cycle for the Synthesis of DHPMs



compound **A** giving **VI** (also a substitution reaction). In the proposed cycle, 1,3-dicarbonyl compound and/or urea act to stabilize the metal center and improve its reactivity. It is worth noting that many metals catalyze the Biginelli reaction, but the mechanism of the Lewis acid catalyzed reaction is much more accepted as following traditional and expected reaction

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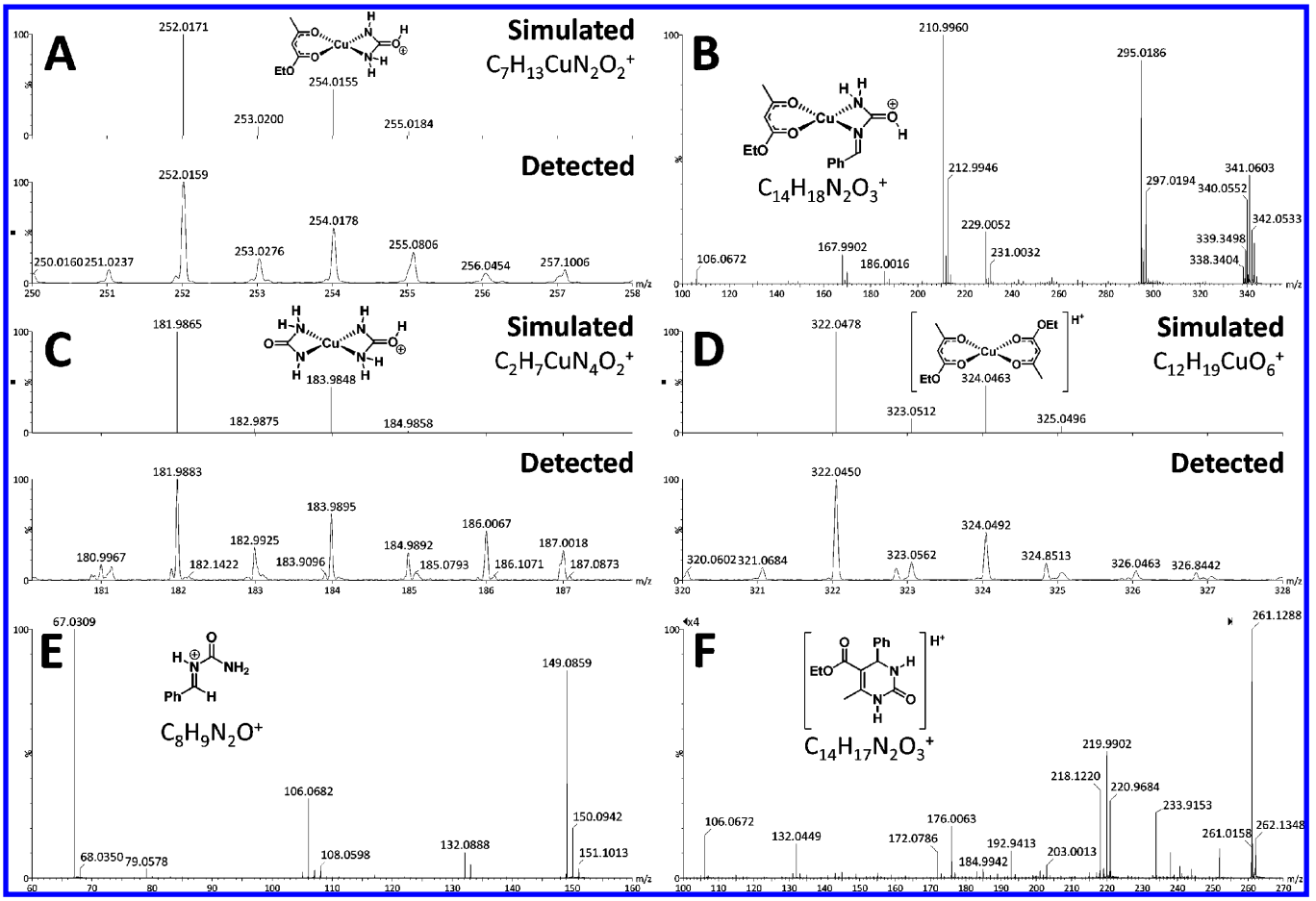

Figure 5. Key intermediates and products detected (and characterized) by ESI(+)-MS(/MS): (A) ESI(+)-MS of $[\mathbf{I} + H]^+$; (B) ESI(+)-MS/MS of $[\mathbf{III} + H]^+$; (C) ESI(+)-MS of $[\mathbf{V} + H]^+$; (D) ESI(+)-MS of $[\mathbf{VI} + H]^+$; (E) ESI(+)-MS/MS of the key Biginelli reaction intermediate $[\mathbf{A} + H]^+$, i.e., the so-called iminium intermediate; (F) ESI(+)-MS/MS of the Biginelli adduct $[DHPM + H]^+$.

pathways than properly asserted with scientific accuracy. Indeed, this kind of catalytic transformation seems more an assumption that has dominated the Biginelli MCR transformation. Using ESI(+)-MS(/MS); however, we were able to detect and characterize some key intermediates and products, as shown in Figure 5.

The online monitoring of the Biginelli reaction allowed us to detect and characterize exclusively the so-called iminium intermediate (intermediate **A**, Scheme 2) indicating that, under the development conditions, the preferred mechanistic pathway is the iminium mechanism. The unsuccessful detection of any intermediate of a direct addition of urea to the ethyl acetoacetate corroborates this proposition. No key intermediate of the enamine mechanism could be detected as well.

The proposed mechanism has a direct impact on many other previously published propositions of the Lewis acid catalyzed Biginelli reaction. The "text book" proposition mechanism for the Biginelli reaction, which starts with a direct coordination between the aldehyde and the metal center (used Lewis acid), despite being essentially correct, is not completely appropriate, since the Lewis acid is most likely acting as a precatalyst and not as the actual catalytic species, which in turn may be formed in situ with the components of the reaction itself. For many cases, this proposition allows a better understanding on the need of excess of some reagents and of high temperatures to facilitate the formation of those species.

To better understand the ionic liquid effect, NMR experiments (^{13}C and APT NMR) were performed. $^{13}C-\{^1H\}$ NMR gave interesting mechanistic insights, and the ionic liquid effect could be partially evaluated as well. All experiments were performed at 20 °C in a NMR tube containing a sealed capillary tube charged with DMSO-d_6 (external reference to set the scale at 39.5 ppm) and using pure reagents (BMI·PF_6, benzaldehyde, ethyl acetoacetate, urea, and $CuCl_2$) or mixtures of them. $CuCl_2$ was soluble in pure benzaldehyde or pure ethyl acetoacetate or in mixtures of any proportion. All mixture proportions used and the related signals can be found in the Supporting Information.

First, we investigated the deshielding effect of the aldehyde C═O in the presence of $CuCl_2$ and also considered the resulting effect from the presence of the IL in the mixture (aldehyde + $CuCl_2$ + BMI·PF_6). The results from these experiments can be visualized in Figure 6.

One can observe a signal related to the C═O group of benzaldehyde at 191.6 ppm. Upon $CuCl_2$ addition, almost no shift is noted (0.1 ppm only). The addition of BMI·PF_6, however, does affect the chemical shift of the C═O group. In the presence of the IL, the C═O group is deshielded to 192.8 ppm. It is worth noting that the temperature of the experiment is only 20 °C and that the reaction requires higher temperatures to achieve excellent yields. In the presence of all components (benzaldehyde, ethyl acetoacetate, urea, $CuCl_2$, and BMI·PF_6), the aldehyde signal is also observed at ∼192.8 ppm. This

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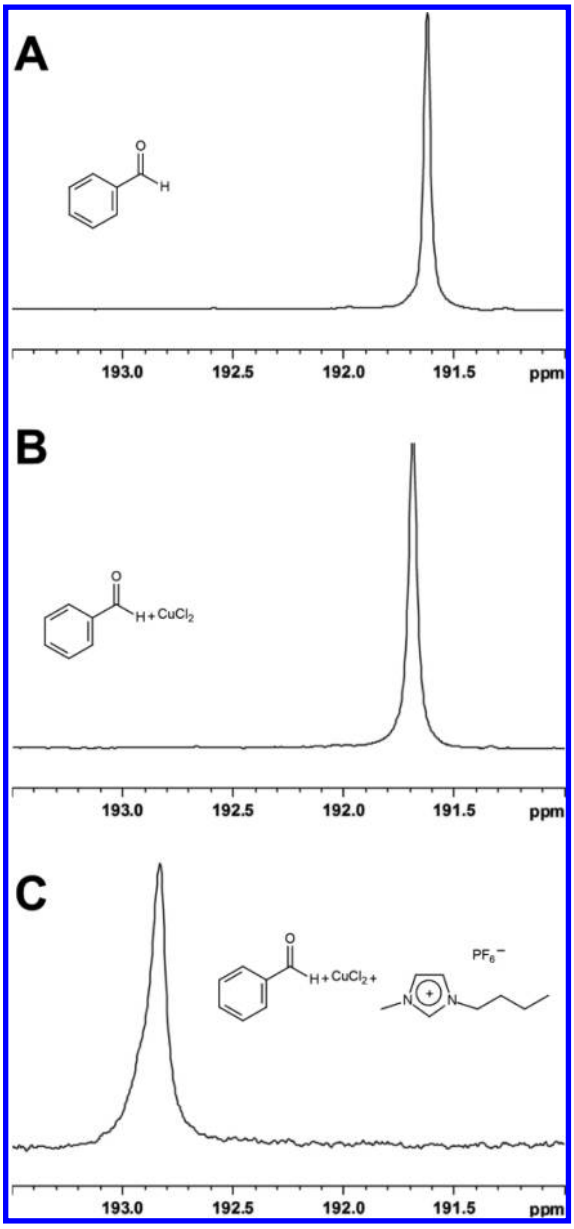

Figure 6. $^{13}C-\{^{1}H\}$ NMR expansion: (A) pure benzaldehyde; (B) mixture of benzaldehyde and $CuCl_2$; (C) mixture of benzaldehyde, $CuCl_2$ and BMI·PF_6. A sealed capillary tube charged with DMSO-d_6 was used as the external reference to set the scale (39.5 ppm).

subject was also further evaluated and discussed in the theoretical calculations.

The in situ formation of the copper complex **I** (Scheme 2) was also investigated by ^{13}C NMR experiments upon mixing of all components in the NMR tube. The results are shown in Figure 7.

We monitored the changes in chemical shift of the benzaldehyde hydrogens and clearly noted the appearance of novel species formed in situ, indicating the formation of the iminium intermediate and also suggesting the formation of **II** and **III**. The APT was recorded at 20 °C and after 4 h following the mixture. APT was used to follow the aromatic C−H from the aldehyde (or from its formed derivatives).

The effect of the IL over ethyl acetoacetate and the formation of species **VI** (Scheme 2) were equally followed by ^{13}C NMR (Figure 8).

Figure 8 clearly depicts the IL effect over the formation of species **VI**. After 4 h of reaction, the presence of **VI** was noted (∼166.6 ppm) and also the coordination of the aldehyde (∼167.9 ppm). It is also important to highlight that the ionic liquid effect over the ethyl acetoacetate is not as pronounced as was noticed for the benzaldehyde, and almost no changes in chemical shifts could be noted (see Figure 8A,C), once more indicating the preference of urea addition to the aldehyde (forming the intermediate **A**, Scheme 2) instead of any addition to the 1,3-dicarbonyl compound.

Theoretical calculations were also performed and discussed to contribute to the understanding of the ionic liquid effect and the activation of the catalytic species shown in the proposed catalytic cycle (Scheme 2). All structures had their geometries fully optimized by density functional theory (DFT) calculations.

In a first moment, we envisage the possibility of stabilizing the complexation of the aldehyde to the metal center considering the so-called 'text-book' mechanism, as shown in Figure 9.

The calculated length for the C═O bond of benzaldehyde is 1.2091 Å. In the presence of $CuCl_2$ this length slightly increases to 1.2384 Å. The O---Cu length is 1.9538 Å and H---Cl length 2.6523 Å. In the presence of the anion (hexafluorophosphate), both the O---Cu and H---Cl lengths are shorter (1.9275 and 2.6326 Å, respectively). In the meantime, the anion also favors lengthening of the C═O bond to 1.2426 Å. The Cl−Cu−Cl bond angle is 148.81° in the absence and 116.19° in the presence of $[PF_6]^-$; thus, a square planar complex geometry is much more likely. These results demonstrate the pronounced effect of the presence of IL on the system. The calculated benzaldehyde heat of formation (ΔH) is −9.21 kcal/mol (ΔG = +5.02 kcal/mol). The calculated binding energy for the aldehyde and the Lewis acid is −17.33 kcal/mol with ΔH = −16.91 kcal/mol (ΔG = −10.61 kcal/mol). In the presence of the anion, this binding energy becomes −29.87 kcal/mol with ΔH = −28.66 kcal/mol (ΔG = −14.45 kcal/mol), thus showing how spontaneous and stabilizing is the effect of the IL. Furthermore, these results help to understand the deshielded effect in the aldehyde observed by the NMR experiments, and in this case, experimental and theoretical approaches are in full accordance.

Despite the interesting results, we decided to investigate the same effect but considering the proposed catalytic cycle (see Scheme 2 and Figure 10) once these previous calculations could be used to corroborate the expected effect considering the actual mechanism for the transformation and explain the aldehyde activation by the presence of the IL.

The theoretical investigation was based on the key intermediates **I** and **II** and the association of **II** with $[PF_6]^-$. Intermediate **I** had its geometry optimized toward a better visualization of the benzaldehyde coordination effect to form **II**, which in turn is a key complex to form **A** (see Scheme 2). Considering the optimized geometry of **II**, the calculated ΔH is −2.72 kcal/mol (ΔG = +7.26 kcal/mol) and the binding energy is −3.47 kcal/mol. In the presence of $[PF_6]^-$, however, the effect of the IL was clearly observed. Upon $[PF_6]^-$ association, these values greatly changed, and ΔH was −16.96 kcal/mol (ΔG = +2.06 kcal/mol) and the binding energy was −18.54 kcal/mol. The results show the positive effect of the IL in the formation of the cycle's key intermediates, allowing a better understanding on the origin of the ionic liquid effect over the Biginelli reaction.

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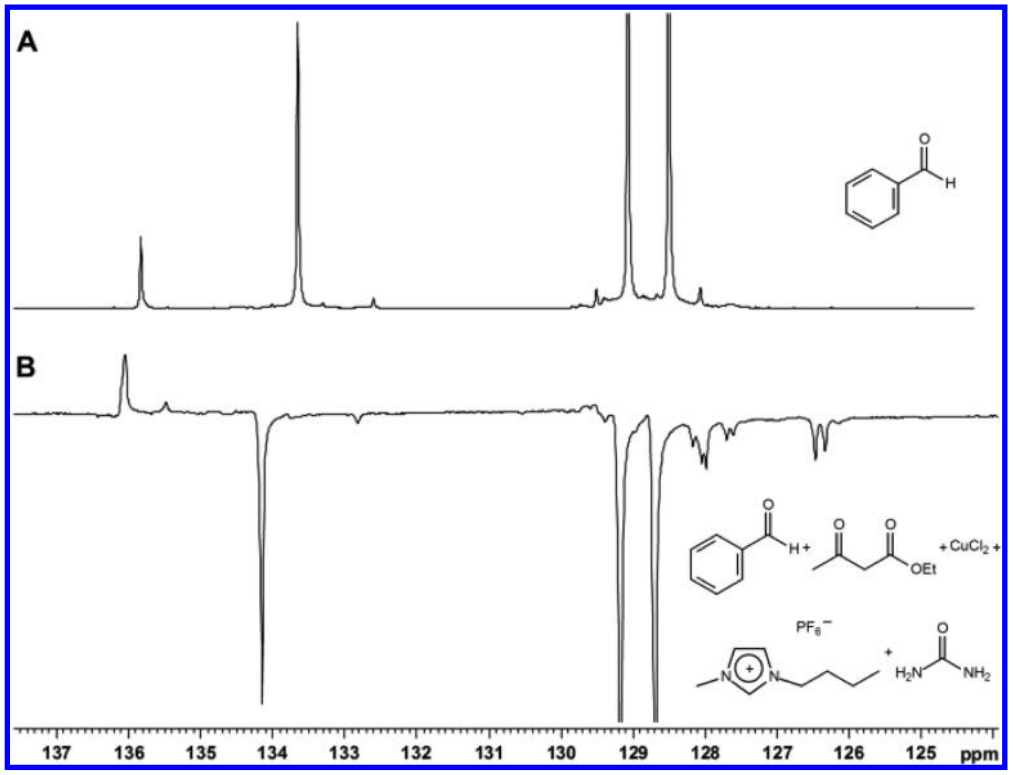

Figure 7. (A) $^{13}C-\{^{1}H\}$ NMR expansion of the C−H aromatic region of pure benzaldehyde. (B) $^{13}C-\{^{1}H\}$ NMR (APT) expansion of the C−H aromatic region of a mixture of benzaldehyde, ethyl acetoacetate, urea, BMI·PF_6, and $CuCl_2$. A sealed capillary tube charged with DMSO-d_6 was used as the external reference to set the scale (39.5 ppm).

Finally, the temperature effect (increase from 25 to 80 °C) was considered in the theoretical calculations, once all these previously discussed results were performed at room temperature (25 °C i.e. 298.15 K). Since the importance of the temperature to perform the Biginelli reaction under the developed conditions has been experimentally demonstrated (see Figure 3), we decided to calculate the same data for intermediate **II** and for **II** + $[PF_6]^-$ at the best reaction temperature (80 °C, i.e., 353.15 K). At this temperature (80 °C), ΔH values of −2.51 kcal/mol (ΔG = +8.97 kcal/mol) and −16.53 kcal/mol (ΔG = +5.35 kcal/mol) were obtained in the absence and presence of the anion, respectively. These results clearly demonstrate that the entropic effect plays an important role in the reaction, as demonstrated experimentally (see Figure 3), and they also showed interesting features on the positive ionic liquid effect over the reaction. Even at a higher temperature (80 °C), the ΔG value in the presence of the anion is lower than that observed at room temperature (25 °C) in its absence. This is in accordance with the expected effect of the IL by stabilizing polar and charged intermediates through ion-pairing and formation of supramolecular aggregates in a well ordered network.[52]

In summary, we have developed an efficient and simple protocol for DHPM synthesis in ILs. The novel proposed catalytic cycle for the Biginelli reaction and the ionic liquid effect were investigated by ESI-MS and -MS/MS, NMR, and theoretical calculations indicating the following:

i. The actual catalytic cycle is, indeed, more complex than the usually presented "text book" mechanism.
ii. The reagents used for the Biginelli reaction themselves are also responsible to form the active catalytic species with copper and to stabilize the metal center. Thus, for many cases, excess of the reagents is required.
iii. The IL is capable of facilitating the formation of the key catalytic intermediates (Scheme 2) and of stabilizing them through ion-pairing (and aggregate) formation, as indicated by theoretical calculations and NMR.
iv. The aldehyde activation is more efficient in the presence of the IL, as demonstrated by NMR, which is in full accordance with a previous report[53] and as we have recently observed for aminolysis reactions.[44]

Results presented herein, indeed, open up a new avenue toward the understanding of the Biginelli reaction mechanism and also allow a more rational design of new catalysts capable of promoting DHPMs syntheses under more sustainable conditions.

EXPERIMENTAL SECTION

General Methods. ESI-MS and ESI-MS/MS measurements were performed in the positive-ion mode (m/z 50−2000 range) on an HDMS instrument. This instrument has a hybrid quadrupole/ion mobility/orthogonal acceleration time-of-flight (oa-TOF) geometry and was used in the TOF V+ mode. All samples were dissolved in methanol to form 50 μM solutions and were directly infused into the ESI source at a flow rate of 10 μL/min after 5 min at 80 °C. ESI source conditions were as follows: capillary voltage 3.0 kV, sample cone 20 V, extraction cone 3 V. The theoretical treatment of the systems included in this work was performed using the density functional theory (DFT) approach of the Gaussian 09 series of programs. The geometry optimizations were carried out using the B3LYP/6-311G(d,p) level of calculation. At the same level of theory, the fundamental vibrational frequency calculations (using a scale factor of 0.967) were carried out to ensure the true minima and were also used to compute zero-point vibrational energy (ZPVE) and to derive the thermochemical corrections for the heat of formation, Gibbs free energy, and the

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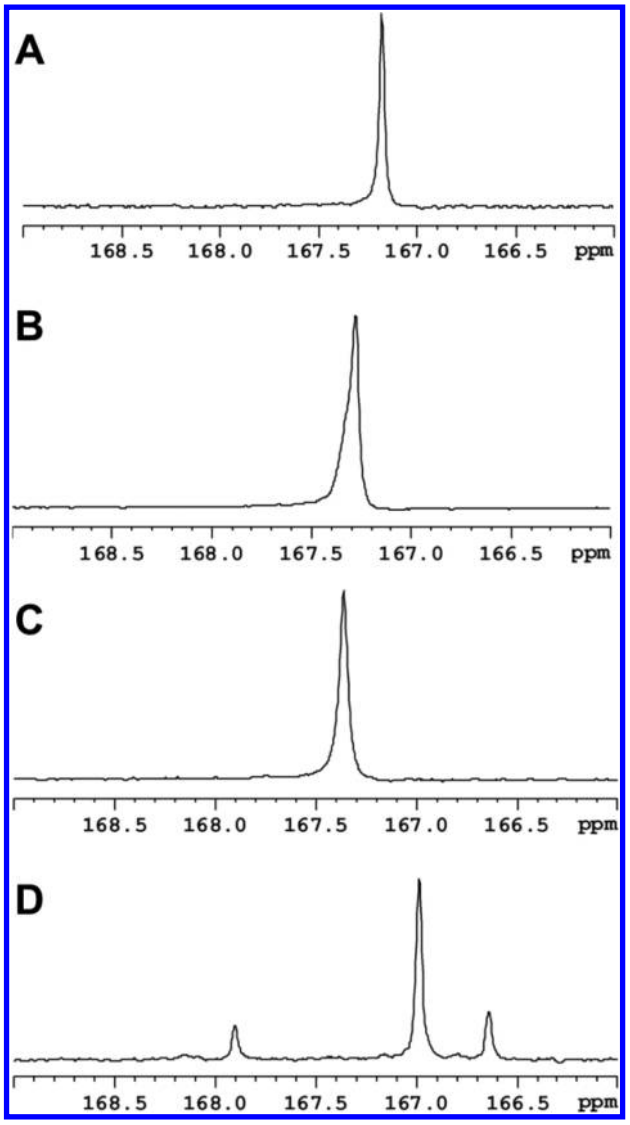

Figure 8. (A) $^{13}C-\{^{1}H\}$ NMR expansion of pure ethyl acetoacetate. (B) $^{13}C-\{^{1}H\}$ NMR expansion after $CuCl_2$ addition. (C) $^{13}C-\{^{1}H\}$ NMR expansion of a mixture of ethyl acetoacetate and $CuCl_2$ after addition of BMI·PF_6. (D) $^{13}C-\{^{1}H\}$ NMR expansion of a mixture of ethyl acetoacetate, $CuCl_2$, benzaldehyde, and BMI·PF_6 after 4 h. A sealed capillary tube charged with DMSO-d_6 was used as the external reference to set the scale (39.5 ppm).

binding energy. Zero-point energies and thermodynamic functions were calculated at 298.15 and 353.15 K and 1 atm. The optimized geometries were used for the single-point calculation at B98/6-311+G(3df,2p) level of calculation. To avoid a basis-set superposition error (BSSE) the heat of formation, Gibbs free energy and the binding energy were counter-poise corrected using a standard approach by Boys and Bernardi.[54] NMR spectra were recorded on a 7.05 T instrument using a 5-mm internal diameter probe operating at 300 MHz for ^{1}H and at 75 MHz for ^{13}C. Chemical shifts were expressed in parts per million (ppm) and referenced by the signals of the residual hydrogen atoms of the deuterated solvent (DMSO-d_6), as indicated in the legends. Investigative experiments were performed at 20 °C in a NMR tube containing a sealed capillary tube charged with DMSO-d_6 (external reference to set the scale at 39.5 ppm) and using pure reagents (BMI.PF_6, benzaldehyde, ethyl acetoacetate, urea, and $CuCl_2$) or homogeneous mixtures of them. Typically, $^{13}C-\{^{1}H\}$ NMR data were collected with 256 free induction decays (FIDs) and 64 K data points using a 15 μs pulse width (90° pulse angle). Prior to Fourier transformation (FT), the FIDs were zero-filled and an exponential

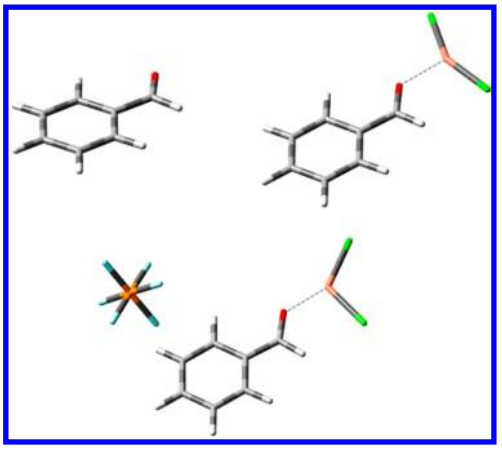

Figure 9. Optimized geometries of benzaldehyde and reactive intermediates considering the "text book" mechanism from the Biginelli reaction at the B3LYP/6-311G(d,p) level of theory.

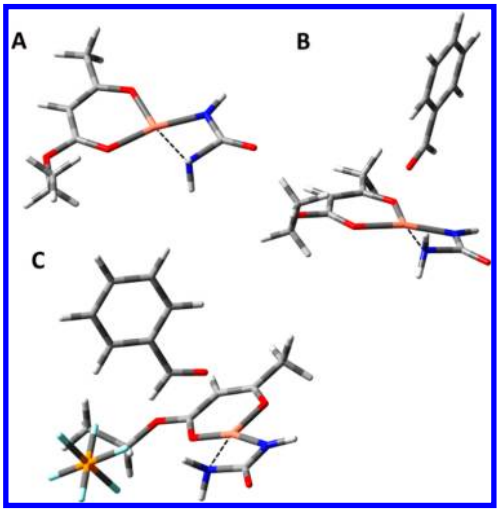

Figure 10. Optimized geometries of intermediates **I** (A), **II** (B), and **II** considering the association with the anion $[PF_6]^-$ (C) at the B3LYP/6-311G(d,p) level of theory.

weighing factor corresponding to line broadening to 1.0 Hz was applied.

General Procedure for the Biginelli Reactions. A sealed Schlenk tube containing 1 mL of BMI.PF_6, 3.00 mmol of the aldehyde, 3.00 mmol of the 1,3-dicarbonyl compound, 3.00 of urea (or thiourea), and $CuCl_2$ (10 mol %) was allowed to react at 80 °C. After the time indicated in Table 2, the substrates were purified by chromatographic column eluted with mixtures of hexane/ethyl acetate.

*Ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4a**):* ^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm 9.22 (s, 1H), 7.76 (s, 1H), 7.29–7.18 (m, 5H), 5.14 (s,1H), 3.97 (q, 2H, J = 6.8 Hz), 2.24 (s, 3H), 1.07 (t, 3H, J = 6.8 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ ppm 165.8, 152.6, 148.8, 145.3, 128.8, 127.7, 126.7, 99.7, 59.6, 54.4, 18.2, 14.5; FT- IR (KBr, cm^{-1}) 3252, 3109, 2972, 1728, 1689, 1645, 1468, 1230, 1097, 778; mp 212–213 °C (lit.[55] 213–214 °C); 95% (2.85 mmol, 742 mg).

*Ethyl 4-(3-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4b**):* ^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm 10.14 (s, 1H), 9.93 (s, 1H), 8.46(s, 1H), 7.65 (t, 1H, J = 7.9 Hz), 7.44–7.36 (m, 3H), 5.82 (d,1H, J = 2.7 Hz), 4.76 (q, 2H, J = 7.2 Hz), 2.99 (s, 3H), 1.87 (t, 3H, J = 7.1 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ ppm 165.9, 157.8, 152.7, 148.6, 146.7, 129.8, 128.8, 117.3, 114.6, 99.8, 59.6, 54.3, 18.2, 14.6; FT-IR (KBr, cm^{-1}) 3514, 3364, 3250, 3104, 2978, 1722, 1638, 1600, 1475, 1305, 1221, 1056, 771; mp 168–170 °C (lit.[56] mp 165–168 °C); 84% (2.52 mmol, 696 mg).

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*5-Acetyl-3,4-dihydro-4-(3-hydroxyphenyl)-6-methylpyrimidin-2(1H)-one (**4c**):* ^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm 10.18 (s, 1H), 9.94 (s, 1H), 8.56 (s, 1H), 7.88 (t, 1H, J = 7.1 Hz), 7.42 (t, 1H, J = 10.5 Hz), 5.94 (s,1H), 3.04 (s, 3H), 2.85 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ ppm 194.9, 157.9, 152.6, 148.4, 146.1, 130.0, 117.5, 114.8, 113.7, 110.0, 54.3, 30.7, 19.4.); FT-IR (KBr, cm^{-1}) 3248, 3107, 2942, 1707, 1657, 1606, 1462, 1235, 742; mp 214−215 °C; 84% (2.52 mmol, 621 mg).

*Ethyl 6-methyl-4-(3-hydroxyphenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4d**):* ^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm 10.28 (s, 1H), 9.59 (s, 1H), 9.44 (s, 1H), 7.09 (t, 1H, J = 7.9 Hz), 6.65 (m, 3H), 5.09 (d, 1H, J = 2.7 Hz), 3.98 (q, 2H, J = 6.7 Hz), 2.27 (s, 3H), 1.08 (t, 3H, J = 6.9 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ ppm 174.6, 165.6, 157.9, 145.3, 145.2, 129.9, 117.5, 115.0, 113.7, 101.2, 60.5, 54.4, 17.6, 14.4; FT-IR (KBr, cm^{-1}) 3304, 3179, 3109, 2982, 1662, 1573, 1479, 1375, 1293, 1196, 1117, 747; mp 180−181 °C (lite.[57] mp 180−183 °C); 80% (2.40 mmol, 702 mg).

*1-[1,2,3,4-Tetrahydro-4-(3-hydroxyphenyl)-6-methyl-2-thioxo-5-pyrimidinyl]ethanone (**4e**):* ^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm 10.24 (s, 1H), 9.70 (s, 1H), 9.47 (s, 1H), 7.10 (t, 1H, J = 6.9 Hz), 6.64 (d, 2H, J = 8.1 Hz), 5.19 (s, 1H), 3.44 (s, 1 H), 2.29 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ ppm 195.3, 174.3, 157.9, 144.8, 130.1, 117.6, 115.1, 113.8, 110.8, 54.2, 30.8, 18.7; FT-IR (KBr, cm^{-1}) 3514, 3272, 3184, 2993, 1621, 1582, 1486, 1372, 1193, 742, 571; mp 223−225 °C; 82% (2.46 mmol, 645 mg).

*Ethyl-6-methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4f**):* ^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm 9.39 (s, 1H), 8.16 −7.68 (m, 4H), 3.89 (q, 2H, J = 2.7 Hz), 2.28 (s, 3H), 1.10 (t, 3H, J = 6.9 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ ppm 165.1, 151.8, 149.5, 147.7, 147.0, 133.0, 130.3, 122.4, 121.0, 98.3, 59.4, 53.6, 17.9, 14.0; FT-IR (KBr, cm^{-1}) 3330, 3213, 3105, 2965, 1709, 1631, 1520, 1456, 1343, 1221, 1084, 810, 686, 530; mp 240−242 °C (lit.[58] mp 239−241 °C); 84% (2.52 mmol, 769 mg).

*5-Acetyl-3,4-dihydro-6-methyl-4-(3-nitrophenyl)pyrimidin-2(1H)-one (**4g**):* ^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm 9.37 (s, 1H), 8.14−7.6 (m, 4H), 5.4 (d, 1H, J = 3 Hz), 2.33 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ ppm 194.1, 152.0, 149.2, 147.9, 146.5, 133.0, 130.2, 122.4, 121.1, 109.5, 53.0, 30.7, 19.1; FT-IR (KBr, cm^{-1}) 3357, 3271, 3057, 1721, 1683, 1591, 1532, 1347, 1239, 764, 693, 578; mp 261−262 °C; 94% (2.82 mmol, 776 mg).

*[1,2,3,4-Tetrahydro-6-methyl-4-(3-nitrophenyl)-2-thioxo-5-pyrimidinyl]ethanone (**4h**):* ^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm 10.48 (s, 1H), 9.09 (s, 1H), 8.17−7.65 (m. 4H), 5.44 (d, 1H, J = 3.9 Hz), 2.38 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ ppm 199.9, 179.7, 153.1, 150.3, 150.1, 138.2, 135.6, 127.9, 115.4, 58.1, 35.9, 23.6; FT-IR (KBr, cm^{-1}) 3300, 3182, 3063, 1676, 1610, 1528, 1343, 1183, 1076, 764; mp 168−170 °C; 87% (2.61 mmol, 760 mg).

*1,2,3,4-Tetrahydro-6-methyl-2-oxo-5-pyrimidinecarboxylic acid ethyl ester (**4i**):* ^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm 4.58 (q, 2H, J = 3.7 Hz), 3.43 (d, 2H), 1.07 (t, 3H, J = 7.0 Hz); FT-IR (KBr, cm^{-1}): 3356, 2928, 1621, 1571, 1242, 664; mp 258−259 °C (lit.[59] mp 256−258 °C); 70% (2.10 mmol, 387 mg). This compound showed to be unstable and degradation is noted. The mp was measured just after purification in a sealed capillary tube.

*1,2,3,6-Tetrahydro-4-methyl-2-thioxo-5-pyrimidinecarboxylic acid, ethyl ester (**4j**):* ^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm 4.56 (m, 2H), 4.68 (m, 2H), 2.19 (s, 3H), 1.20 (t, 3H, J = 3.6 Hz); FT-IR (KBr, cm^{-1}) 3257, 2985, 2913, 1700, 1534, 1229, 1098, 920, 620; mp 212−213 °C; 64% (1.92 mmol, 385 mg). This compound showed to be unstable and degradation is noted. The mp was measured just after purification in a sealed capillary tube.

*Ethyl 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4k**):* ^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm 11.15 (s, 1H), 10.44 (s, 1H), 8.31- 80.4 (m, 5H), 5.94 (d,1H, J = 3.0 Hz), 4.75 (q, 2H, J = 6.7 Hz), 3.05 (s, 3H), 1.84 (t, 3H, J = 7.1 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ ppm 174.7, 166.9, 165.4, 145.9, 130.1, 129.0, 128.8, 100.7, 60.1, 53.9, 17.7, 14.6; FT-IR (KBr, cm^{-1}) 3322, 34663176, 3111, 1670, 1575, 1470, 1277, 1197, 1105, 696; mp 201−202 °C (lit.[60] mp 201 °C); 60% (1.80 mmol, 497 mg).

*5-Acetyl-4-phenyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**4l**):* ^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm 9.19 (s, 1H), 7.84 (s, 1H), 7.32−7.22 (m, 5H), 5.25 (s, 1H), 3.43 (q, J = 6.2 Hz), 1.06 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ ppm 194.7, 152.6, 148.6, 144.6, 128.9, 128.8, 110.0, 56.5, 30.7, 19.3; FT-IR (KBr, cm^{-1}) 3287, 3241, 2914, 1706, 603, 1466, 1248, 764; mp 238−240 °C (lit.[61] mp 238−240 °C); 98% (2.94 mmol, 677 mg).

*5-Acetyl-4-(4-chlorophenyl)-3,4-dihydro-6-methyl-2(1H)-pyrimidinone (**4m**):* ^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm 10.02 (s, 1H), 8.65 (s, 1H), 8.14 (d, 2H, J = 7.8 Hz), 8.03 (d, 2H, J = 8.1 Hz), 6.02 (s,1H), 4.02 (s, 2H), 1.81 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ ppm 194.64, 152.58, 148.98, 129.1, 129.3, 128.9, 110.0, 53.5, 30.9, 19.5; FT-IR (KBr, cm^{-1}) 3290, 3118,2998, 1696, 1613, 1493, 1430, 1225, 837, 563; mp 214−215 °C (lit.[62] mp 216 °C); 97% (2.91 mmol, 770 mg).

*1-[4-(4-Chlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl]ethanone (**4n**):* ^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm 11.11 (s, 1H), 10.75 (s, 1H), 8.55 (d, 2H, J = 8.4 Hz), 8.08 (d, 2H), 6.05 (d,1H, J = 3.6 Hz), 3.09 (s, 3H), 2.93 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ ppm 195.1, 174.7, 145.5, 142.3, 132.8, 131.7, 129.8, 110.8, 53.1, 31.0, 18.8; FT-IR (KBr, cm^{-1}) 3292, 3170, 2978, 1707, 1609, 1572, 1450, 1357, 1199, 1014, 826; mp 212−213 °C (lit.[56] mp 214−216 °C); 68% (2.04 mmol, 573 mg).

*Ethyl 4-(4-chlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4o**):* ^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm 9.24 (s, 1H), 7.77 (s, 1H), 7.34 (d, 2H, J = 7.2 Hz), 7.23 (d, 2H, J = 7.5 Hz), 5.14 (s,1H), 3.94 (q, 2H, J = 6.7 Hz), 2.24 (s, 3H), 1.07 (t, 3H, J = 7.1 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ ppm 165.9, 152.73, 149.3, 144.4, 132.4, 129.1, 128.8, 99.6, 59.9, 54.1, 19.5, 14.6; FT-IR (KBr, cm^{-1}) 3331, 3167, 3105, 2978, 1668, 1570, 1197, 747; mp 168−169 °C; 66% (1.98 mmol, 584 mg).

*4-(3-Hydroxyphenyl)-3,4,7,8-tetrahydroquinazoline-2,5(1H,6H)-dione (**4p**):* ^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm 9.88 (s, 1H), 9.54 (s, 1H), 9.23 (s, 1H), 7.09−6.86 (m, 1H), 6.66−6.39 (m, 3H), 4.87 (d, J = 3.6 Hz), 2.65−2.54 (m, 2H), 2.29- 2.16 (m, 2H), 1.66−1.57 (m, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ ppm 210.6, 205.1, 157.8, 155.9, 138.2, 129.9, 118.4, 115.9, 114.7, 86.9, 82.2, 56.5, 18.9, 14.4; FT-IR (KBr, cm^{-1}) 3464, 3349, 3170, 2949, 1678, 1663, 1621, 1592, 1514, 1460, 1170, 765, 632; mp 198−199 °C; 77% (2.31 mmol, 634 mg).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectra related with this manuscript and Cartesian coordinates and energy and thermal corrections for all of the calculated structures. These materials are available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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