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The Biginelli Reaction with an Imidazolium–Tagged Recyclable Iron Catalyst: Kinetics, Mechanism, and Antitumoral Activity

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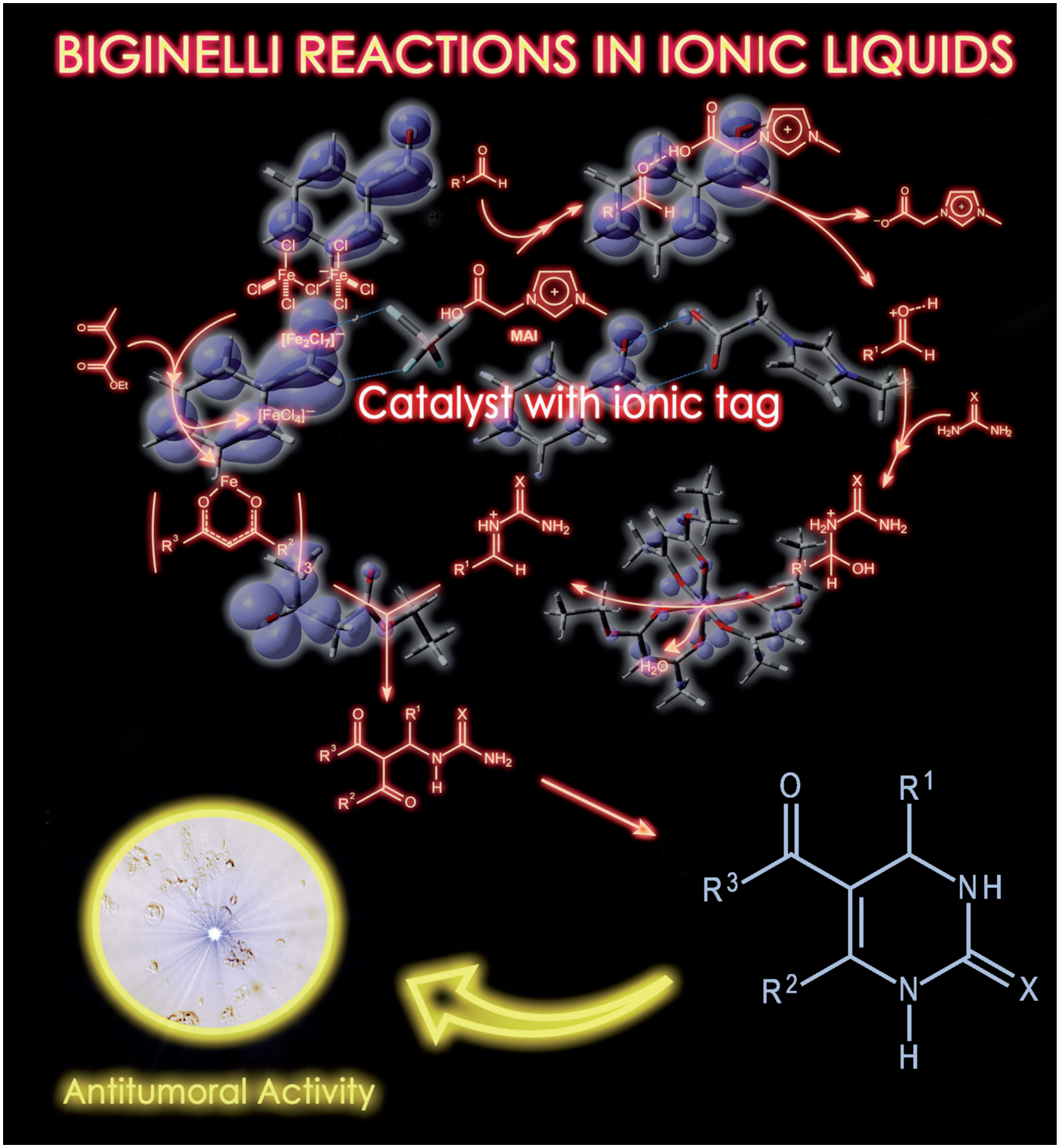
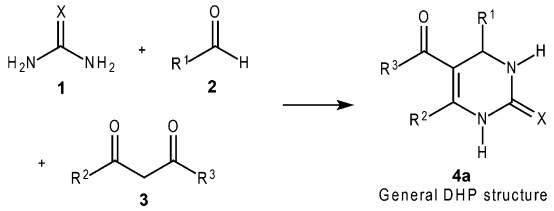


Abstract: The present work describes the synthesis, characterization, and application of a new ion-tagged iron catalyst. The catalyst was employed in the Biginelli reaction with impressive performance. High yields have been achieved when the reaction was carried out in imidazolium-based ionic liquids (BMI·PF_6, BMI·NTf_2, and BMI·BF_4), thus showing that the ionic-liquid effects play a role in the reaction. Moreover, the ion-tagged catalyst could be recovered and reused up to eight times without any noticeable loss in activity. Mechanistic studies performed by using high-resolution electrospray-ionization quadrupole-time-of-flight mass (HR-EI-QTOF) spectrometry and kinetic experiments indicate only one reaction pathway and rule out the other two possibilities under the development conditions. The theoretical calculations are in accordance with the proposed mechanism of action of the iron catalyst. Finally, the 37 dihydropyrimidinone derivatives, products of the Biginelli reaction, had their cytotoxicity evaluated in assays against MCF-7 cancer cell linages with encouraging results of some derivatives, which were virtually non-toxic against healthy cell linages (fibroblasts).

Keywords: density functional calculations · ionic liquids · iron · mass spectrometry · multicomponent reactions · NMR spectroscopy

Introduction

The multicomponent reaction (MCR) named the Biginelli reaction (Scheme 1), originally discovered by Pietro Biginelli,[1] is one of the most elegant methodologies used for the synthesis of dihydropyrimidinones (DHPs). The great interest in DHPs stems from the fact that this class of compounds and their derivatives has, in principle, pronounced biological activity.[2] As a consequence, many catalytic methodologies have been developed to improve the synthesis of this attractive family of compounds, as very recently reviewed.[3] Their biological properties include antitubercular,[4] antifungal,[5] antimicrobial,[6] antimitotic,[7] and anticancer,[8] amongst others.[9]



Scheme 1. The Biginelli reaction for dihydropyrimidinone (**4**) synthesis.

Ionic liquids (ILs) are commonly used as very efficient reaction media to support a plethora of catalysts (i.e., enzymes, organic catalysts, organometallic complexes, etc.).[10] In fact, ILs (especially those based on the imidazolium cation, Figure 1) are regarded as desirable solvents for MCRs with a positive synergy towards eco-compatible heterocyclic synthesis.[11] For instance, some derivatives have been synthesized by using ultrasound irradiation when dissolved in ILs with yields ranging from reasonable to excellent.[12] Dicationic acid ILs have also been successfully used to promote the Biginelli reaction.[13] Sulfonic acid-containing ILs have been employed as catalysts in the synthesis of DHPs derivatives.[14] There is no doubt about the potential of ILs as an attractive alternative to classic organic solvents to perform the Biginelli reaction,[15] whether they acting as media or as catalysts (or both) for the MCR. Surprisingly, ionic-liquid effects themselves have not been adequately exploited regarding MCR, and investigations into the mechanism of action of these salts in organic reactions are limited. Very recently, we have demonstrated the importance of the IL as the reaction medium for the Biginelli reaction and its role in the formation and stabilization of some new reactive intermediates.[16]

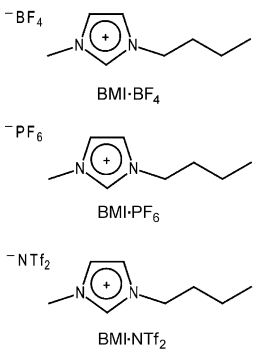


Figure 1. Imidazolium-based ionic liquids commonly used for catalytic reactions.

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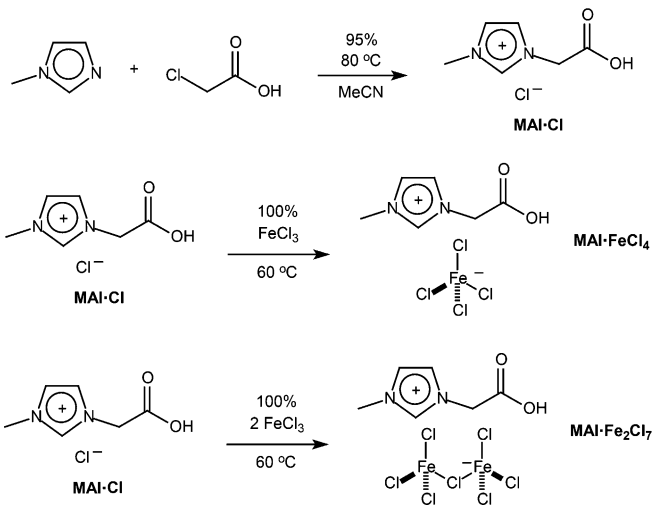
Due to the possibility of charged and polar intermediates in the Biginelli reaction pathways, it is reasonable to envisage ion-pairing formation of those species with ionic components (cations and anions), thus accelerating the product formation by lowering the activation barrier in the presence of ILs[17] when compared with reactions carried out in classical organic solvents. In other words, it is the so-called ionic-liquid effect.

Despite advances observed in the scientific literature to perform the Biginelli MCR,[18] there are still many questions to be answered and improvements to be achieved.[19] For example, the Biginelli mechanism is still under debate, with no consensus reached about the preferred pathway. Because there seems to be supporting evidence for the three mechanistic proposals depicted in Scheme 3 (see later), with many intermediates proposed, the discussion surrounding the mechanism of the Biginelli reaction is highly controversial. In the 1930s it was proposed that urea addition to the aldehyde was a key step for the synthesis of DHPs.[20] The Knoevenagel mechanism was later invoked.[21] Kappe then re-examined the Biginelli mechanism[22] and found that the experimental evidence aligned with an iminium-like mechanism. Due to our interest in the development of new ion-tagged catalysts[23] in reaction mechanism investigations,[24] in ionic-liquid effects on catalysis,[25] and on MCR reactions,[16] we describe herein the synthesis, characterization, and application of a new ion-tagged recyclable iron catalyst to the Biginelli reaction. Mass spectrometry, kinetics, and density functional theory are employed to investigate the mechanism by which the Biginelli reaction proceeds in the presence of the catalyst. In addition, the antitumoral activity of selected DHP derivatives synthesized in this work is described.

Results and Discussion

Catalyst synthesis and characterization: Aiming at a more efficient support in the selected reaction media and envisaging catalyst recyclability, two new ion-tagged iron catalysts were synthesized (Scheme 2). The choice of iron as the metal with the ionophilic ligand is compatible with green and sustainable processes. The ion-tagged catalyst would also allow an efficient support in the ionic media, thus improving the solubility/stability[26] of the catalyst and its electrostatic activation[27] favoring the ionic-liquid effect, that is, an auto-organization forming well-ordered nano-organized structures,[28] as discussed below. Moreover, ILs are regarded as promising candidates for green and sustainable processes.[29] Hence, this unique combination of ILs and ion-tagged iron catalysts is expected to be a powerful combination towards eco-friendly catalytic processes.

The ionophilic ligand (**MAI·Cl**) was obtained as previously described.[30] **MAI·Cl** was directly treated with $FeCl_3$, affording the new catalysts in quantitative yields (**MAI·$FeCl_4$** and **MAI·Fe_2Cl_7**). Both catalysts were characterized by high-resolution electrospray-ionization quadrupole time-of-flight mass spectrometry (ESI-QTOF-MS and MS/MS) (Figure 2).



Scheme 2. Synthesis of the two ion-tagged iron catalysts.

Notably, in the gas phase, the anion $[Fe_2Cl_7]^-$ from **MAI·Fe_2Cl_7** loses neutral $FeCl_3$ forming the anion $[FeCl_4]^-$. It has been recently demonstrated that in the presence of $[FeCl_4]^-$, additional quantities of $FeCl_3$ forces the formation of $[Fe_2Cl_7]^-$.[31]

Catalyst performance: Traditional conditions for the Biginelli reaction commonly require large excess of one of the reagents, large amounts of catalyst, high temperatures, several hours of reaction, and occasionally the presence of a co-catalyst.[32] In an attempt to find milder conditions, the activities of the new catalysts were tested in several organic solvents and ILs. The reaction of urea (3.00 mmol), benzaldehyde (3.00 mmol), and ethyl acetoacetate (3 mmol) in the presence of either **MAI·$FeCl_4$** (10 mol%) or **MAI·Fe_2Cl_7** (10 mol%) at 80 °C for 1 h was used as a model reaction. The results are summarized in Table 1.

As seen in Table 1, **MAI·Fe_2Cl_7** is more active than **MAI·$FeCl_4$** in all cases. This reaction has already been described with $FeCl_3$ as the promoter,[33] and it required large excess of one of the reagents (urea), iron (30 mol), additional catalytic amounts of HCl, and at least four hours to achieve reasonable yields. In the absence of solvent (Table 1, entries 1 and 2) the yields were comparable to reactions carried out in the presence of classical solvents (Table 1, entries 3–14). Conversely, reactions carried out in ionic media (Table 1, Entries 15–22) provided higher yields than those performed in organic solvents, except entries 15 and 16. To improve the results, we optimized the reaction conditions by using **MAI·Fe_2Cl_7** as the catalyst and the IL BMI BF_4 as the reaction medium (Table 1, entry 21). BMI·PF_6 resulted in the same yield as BMI·BF_4 (Table 1, entries 19 and 20), but the reaction medium turned dark, most probably due to anion degradation, as previously reported.[34] It has been reported that hexafluorophosphate (PF_6^-) degradation may be more pronounced in reactions involving metals, which can catalyze this decomposition.[35]

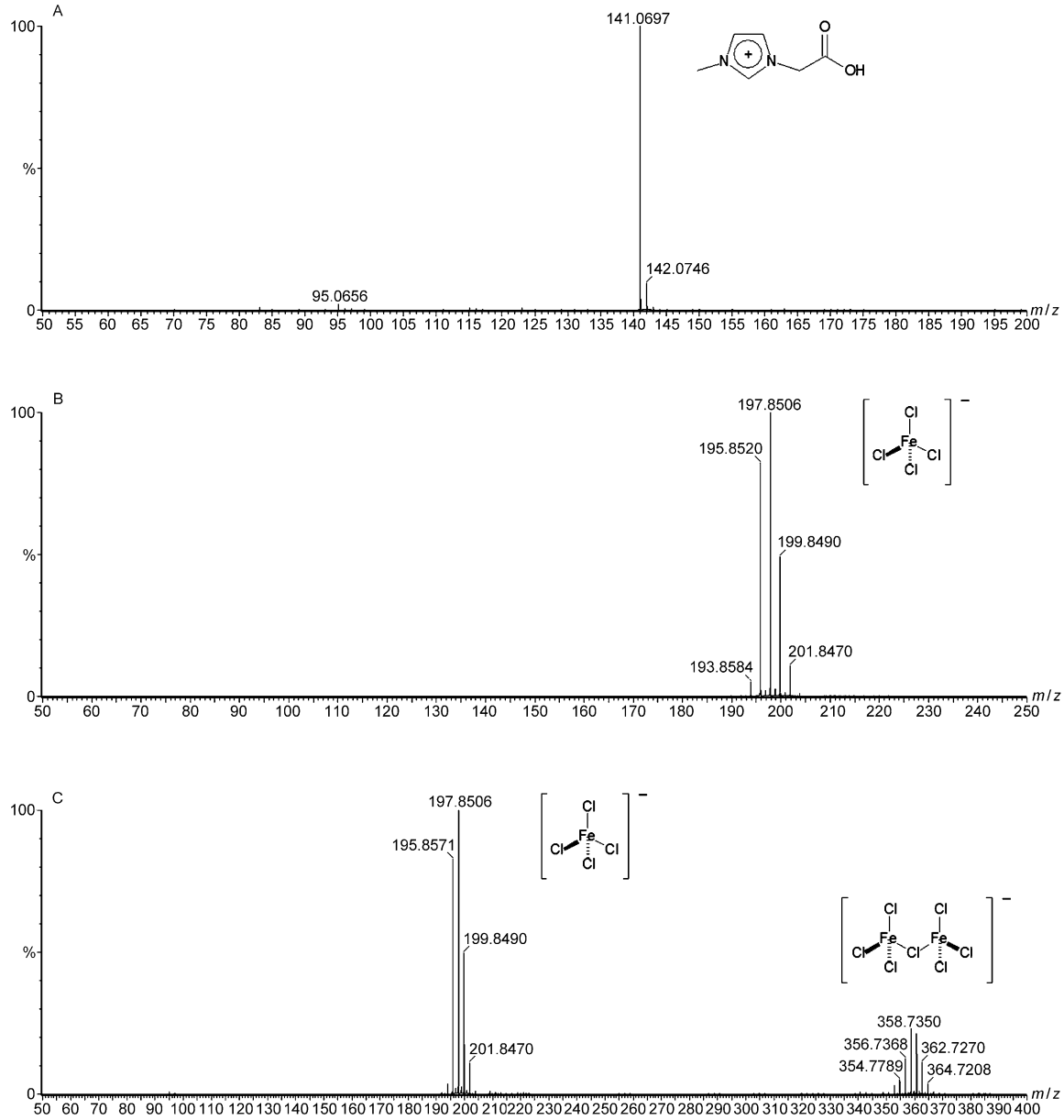
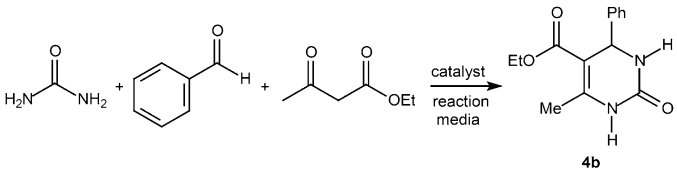


Figure 2. A) ESI-QTOF of the cation. B) ESI(−)-QTOF of the anion $[FeCl_4]^-$ from **MAI·FeCl$_4$** and C) ESI(−)-QTOF of the anion $[Fe_2Cl_7]^-$ from **MAI·Fe$_2$Cl$_7$**. Note that both catalysts have the same cation of $m/z = 141$ Da.

The effect of temperature on the reaction yield was investigated with the model reaction by using BMI·BF_4 as the reaction media and **MAI·Fe$_2$Cl$_7$** as the catalyst (Figure 3), and the best yields were achieved at 80 °C. The catalyst concentration also affected the reaction yield (Figure 4); the catalyst is prone to concentration-dependent yields due to the imidazolium moiety (catalyst aggregation effect), which probably explains the decrease in yield when the catalyst concentration is above 5 mol %. Overall, yields of up to 75 % are obtained with equimolar amounts of reagents, low catalyst concentration, and moderate temperature, presenting significant improvements in the synthesis of DHP.

Kinetics: To shed light on the preferred mechanism of the Biginelli reaction catalyzed by **MAI·Fe$_2$Cl$_7$**, the kinetics of product formation was analyzed for different reactant ratios (Figure S1, the Supporting Information). The observed rate constant (k_{obs}) was independent of the number of benzaldehyde or ethyl acetoacetate, but clearly decreased with excess urea (Figure 5). These observations are compatible with the iminium mechanism (Scheme 3), as excess of urea would displace the equilibrium between **b** and **c** towards the latter, and the rate of reversal of this equilibrium would contribute significantly to the overall rate of product formation. The enamine and Knoevenagel routes do not seem to provide a rationale for the decrease in k_{obs} with an excess of urea.

Table 1. Synthesis of DHP **4b** in different reaction media.[a]



Entry	Reaction media	Catalyst	Yield [%]
1	–	**MAI·Fe_2Cl_7**	26
2	–	**MAI·$FeCl_4$**	14
3	H_2O	**MAI·Fe_2Cl_7**	≈1
4	H_2O	**MAI·$FeCl_4$**	≈1
5	CH_2Cl_2	**MAI·Fe_2Cl_7**	12
6	CH_2Cl_2	**MAI·$FeCl_4$**	6
7	benzene	**MAI·Fe_2Cl_7**	5
8	benzene	**MAI·$FeCl_4$**	1
9	MeCN	**MAI·Fe_2Cl_7**	27
10	MeCN	**MAI·$FeCl_4$**	1
11	MeOH	**MAI·Fe_2Cl_7**	39
12	MeOH	**MAI·$FeCl_4$**	26
13	EtOH	**MAI·Fe_2Cl_7**	38
14	EtOH	**MAI·$FeCl_4$**	25
15	BMI·Cl	**MAI·Fe_2Cl_7**	19
16	BMI·Cl	**MAI·$FeCl_4$**	14
17	BMI·NTf_2	**MAI·Fe_2Cl_7**	40
18	BMI·NTf_2	**MAI·$FeCl_4$**	26
19	BMI·PF_6	**MAI·Fe_2Cl_7**	46
20	BMI·PF_6	**MAI·$FeCl_4$**	42
21	BMI·BF_4	**MAI·Fe_2Cl_7**	46
22	BMI·BF_4	**MAI·$FeCl_4$**	42

[a] All reactions were conducted at 80 °C over a period of 1 h with a catalyst load of 10 mol % and 3 mmol of each reagent added to 1 mL of solvent (or ionic liquid). Yields refer to the isolated product.

The time course for product formation is sigmoidal except when urea is in excess (the Supporting Information, Figure S1). This type of behavior is characteristic of autocatalysis; however, the proposed mechanisms do not readily provide an explanation for it. If we consider that the product precipitates in the reaction media, thus leaving the reactive phase, the equilibrium is displaced towards the product formation with a similar effect as in autocatalyzed reactions. This effect is reflected by the sigmoidal curves for most of the experiments. Nevertheless, with an excess of urea, the reaction yield decreases as a consequence of favoring a second addition to the iminium intermediate **a**. Under this situation, the normal course of the reaction (product formation) is no longer favored, rather the formation of **c** (second urea addition to **a**), thus the plot seems more like an exponential curve.

With all kinetics data and bearing the three mechanisms in mind (see Scheme 3), it was possible to make some important mechanistic inferences:

1) The iminium-based mechanism seems to be the more appropriate to explain the obtained data.

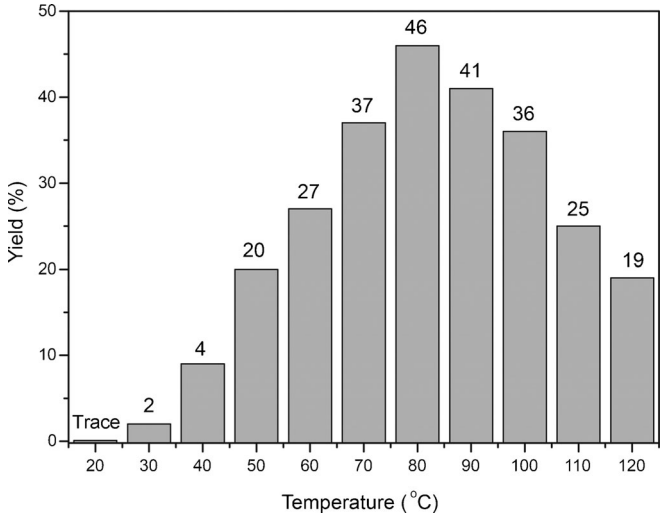


Figure 3. Temperature effect on the yield of the Biginelli reaction catalyzed by **MAI·Fe_2Cl_7** (10 mol %) in BMI·BF_4 (1 mL).

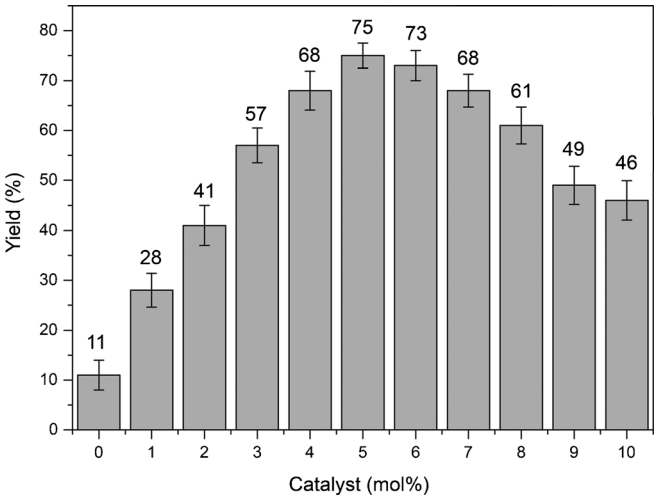


Figure 4. Effect of **MAI·Fe_2Cl_7** concentration on the Biginelli reaction in BMI·BF_4 (1 mL) at 80 °C. Bars represent the mean ± standard deviation of seven replicates for each concentration.

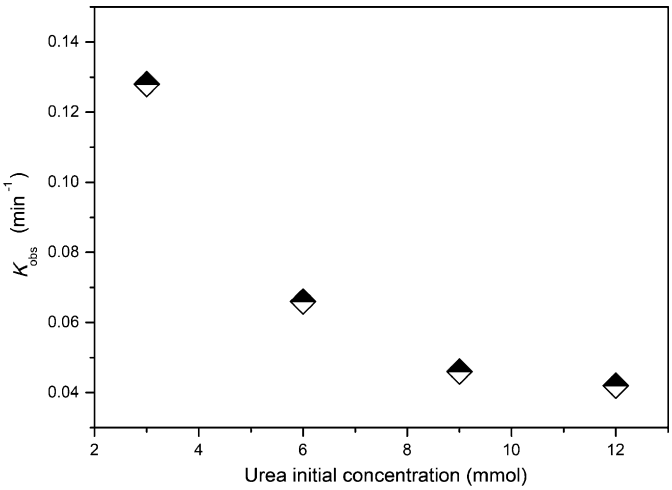
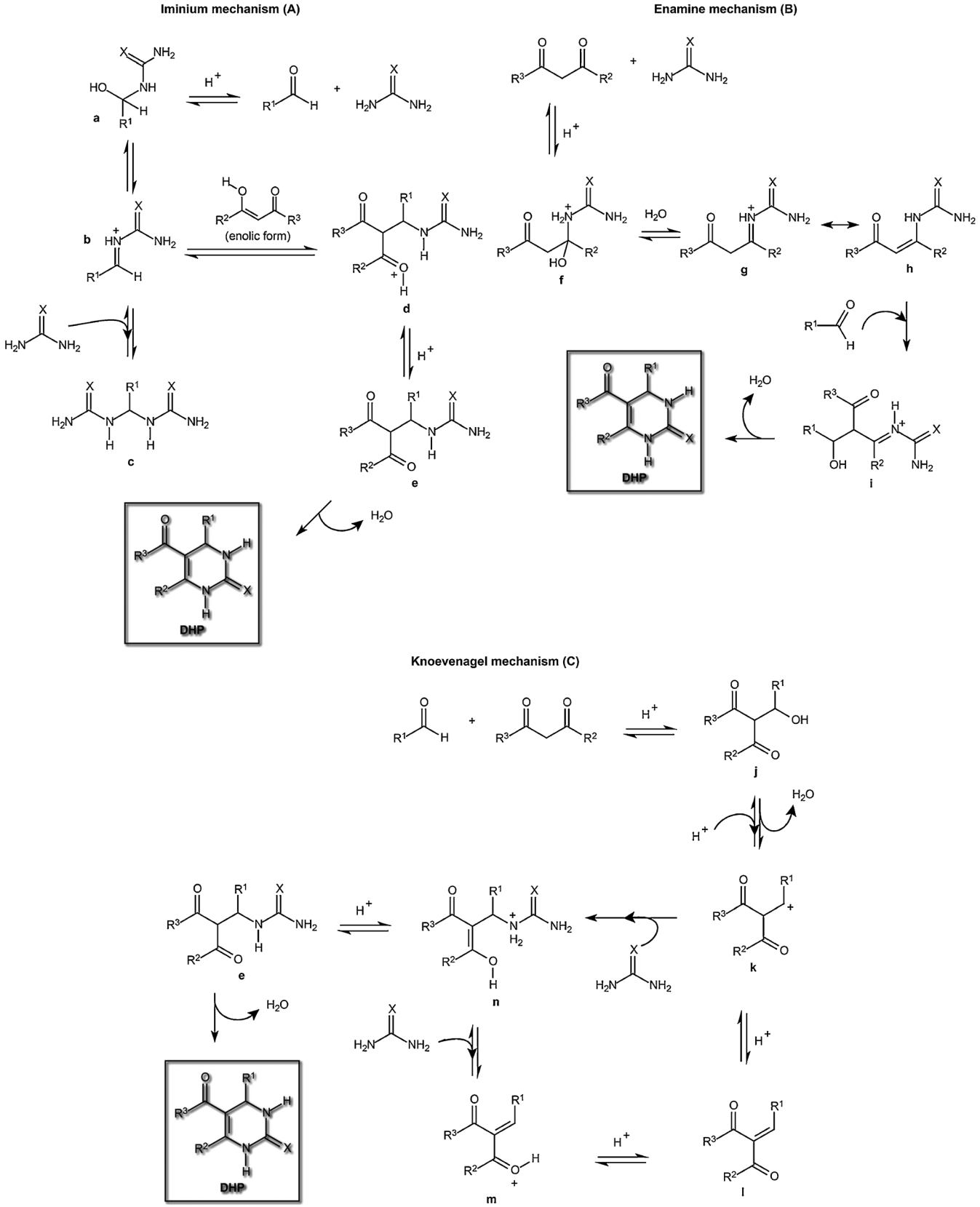


Figure 5. Dependence of k_{obs} on urea.



Scheme 3. Three proposed mechanisms for the Biginelli reaction, namely, iminium (A), enamine (B), and Knoevenagel (C) mechanisms. Several charged and polar intermediates are invoked (**a–n**).

2) Excess aldehyde favors the equilibrium to form intermediate **b** and avoids the second urea addition, which would lead to intermediate **c** formation (see Scheme 3). This issue is reflected in an augmentation of the yield with excess aldehyde.
3) Excess urea has a direct effect on the k_{obs} (slowing the reaction) favoring intermediate **b** formation, but the yield decreases (see Figure 5) mostly probably due to a second urea addition to the recently formed intermediate **b**. Above 9.00 mmol of urea the k_{obs} has no significant change in their values and it became a zero order for this reagent since it would be necessary the presence of additional quantities of benzaldehyde to consume it.
4) All kinetics data are not coherent whether evaluated based on the enamine mechanism or the Knoevenagel mechanism.
5) Excess aldehyde should not increase the reaction yield for the enamine mechanism, however it should increase with an excess of ethyl acetoacetate; and this effect was not observed with an excess of ethyl acetoacetate (see Scheme 3).
6) Excess urea excess should not have a direct influence on the k_{obs} considering the Knoevenagel mechanism because intermediate **k** (a carbocation) is very reactive and would be prompt trapped by urea (even at low concentrations); thus urea concentration is not the limitation for the Knoevenagel mechanism (see Scheme 3).

Based on the kinetics data it is more than reasonable to support the iminium mechanism as the preferred path under the developed conditions and to discard both the enamine and the Knoevenagel mechanisms. Indeed, all results described herein points firmly to the iminium mechanism as the correct one. To be sure on the mechanism of action of **MAI·Fe_2Cl_7** as the catalyst, mass spectrometry analyses and theoretical calculations were also conducted.

Mass spectrometric and NMR spectroscopic analyses: ESI-QTOF-MS and MS/MS analyses were conducted to further probe the Biginelli reaction catalyzed by **MAI·Fe_2Cl_7**. Samples from a mixture of all reagents (3 mmol each and 5 mol% of the catalyst at 80 °C) were directly injected and analyzed after 10, 30, 60, and 120 min with no significant difference in the MS spectra. Since the catalyst has a charge-tag in its structure, it was necessary to dilute the samples to form 100 μM solutions to avoid any signal suppression by the imidazolium moiety. By monitoring the reaction in acetonitrile solutions with in-line direct infusion ESI(+)-QTOF-MS(/MS), we were able to detect ions that were then structurally characterized by product ion spectrum experiments

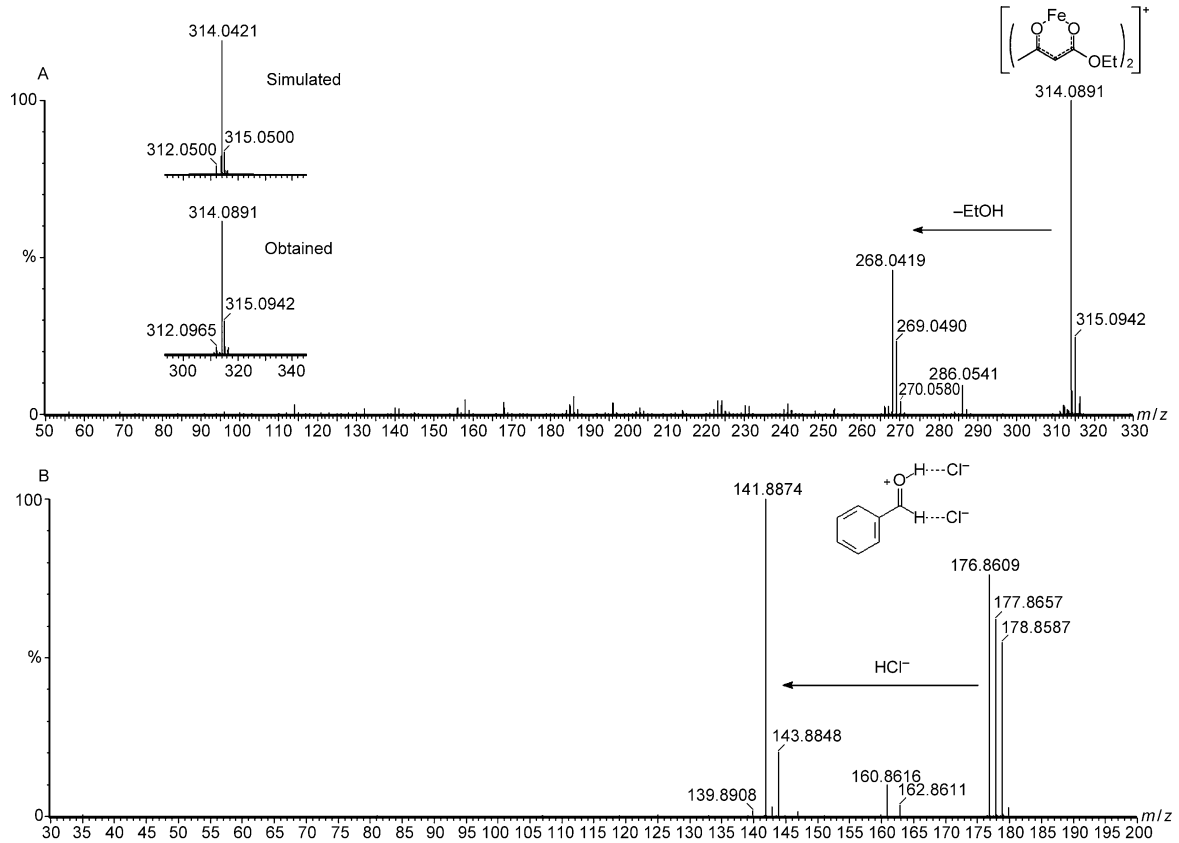
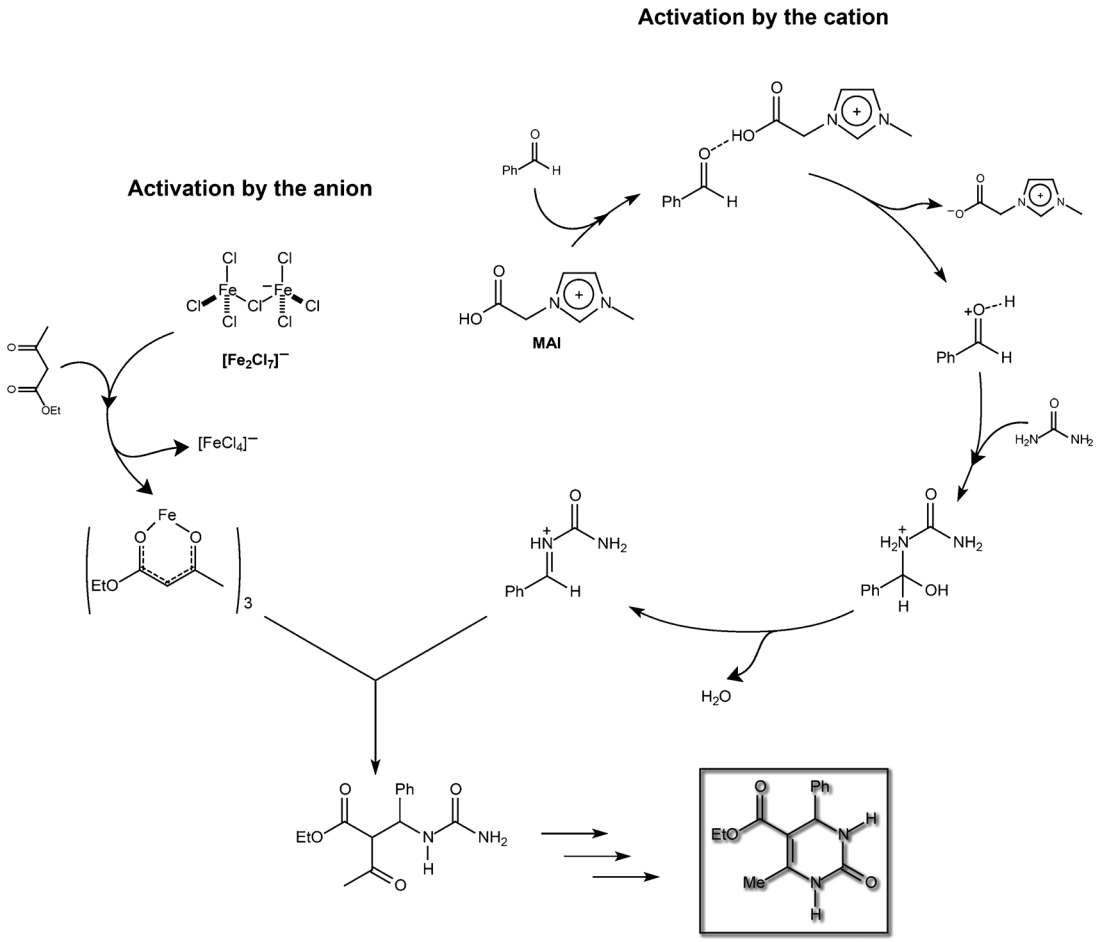
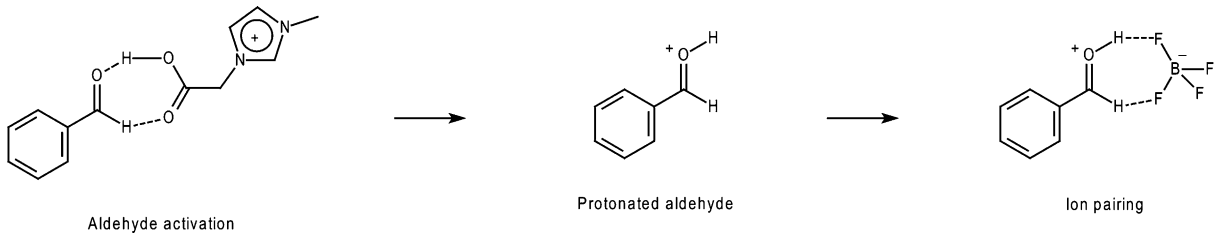


Figure 6. A) ESI(+)-QTOF product ion spectrum of iron-containing isotopologues of *m/z* ranging from 312 to 316. B) ESI(−)-QTOF product ion spectrum of isotopologues of $m/z = 176$ and 178.



Scheme 4. Proposed catalytic mechanism promoted by **MAI·Fe_2Cl_7**, in which both the anion (iron complex) and the cation (imidazolium) moieties play a role in promoting the reaction. Note that this proposed mechanism is compatible with the iminium mechanism for the Biginelli reaction.



Scheme 5. Aldehyde activation by the cation **MAI** and ionic-liquid effect (ion-pairing formation) in BMI·BF_4.

(Figure 6). A mechanism is proposed based on these findings (Scheme 4).

The Brønsted acid in the cation structure of **MAI** is responsible for the aldehyde carbonyl activation, similar to the mechanism by using 1-butyl-3-methylimidazolium derivatives as first proposed by the group of Dupont,[36] and followed by Yadav[37] and Raval.[38] The anion $Fe_2Cl_7^-$, a strong Lewis acid, is responsible for the in situ formation of the nucleophilic complex $Fe(acac)_3$, which in turn reacts with the iminium intermediate. $Fe(acac)_3$ is a better nucleophile than free ethyl acetoacetate, and, therefore, the dual activation promoted by the **MAI·Fe_2Cl_7** explains the superior efficiency of the ion-tagged iron catalyst.

It should be pointed out that ESI has already been used to study the Biginelli reaction promoted by a strong Brønsted acid (10 mol%) with the same reagents used herein.[39] In that report, the protonated intermediates shown in Scheme 3 were observed, such as **b**, **c**, **d**, and **e** from the iminium pathway. From the Knoevenagel mechanism, the protonated intermediates **j** and **l** were detected after reaction times of 2 and 24 h, respectively. In the present study, only intermediates arising from the iminium mechanism, **b**, **d**, and **e** were detected (data not shown). We failed to detect the protonated intermediate **c** or any derivative of it by using 3 mmol of urea, strongly indicating the efficiency of the developed reaction conditions to avoid the second urea

addition and to favor the reaction equilibrium towards DHP formation. Interestingly, no intermediates from the enamine and Knoevenagel pathways were observed, even with in-line direct infusions carried out after 2, 5, 10, 18, and 24 h of reaction from samples of the crude mixture. After 2 h we could detect the protonated DHP derivative, the protonated aldehyde, and the protonated intermediates **b**, **d**, and **e** but at considerably lower intensities. Analyses from longer reaction times showed no significant difference.

Other authors have developed different reaction conditions that favor an enamine-like mechanism;[40] their experiments ruled out the iminium and Knoevenagel-like pathways. In our case, however, a key step is the reaction of the urea-derived *N*-acyliminium ion with the π-nucleophile species, that is, the enolate-like iron complex (i.e., $Fe(acac)_3$) formed from ethyl acetoacetate (Scheme 4). Additions involving 1,3-dicarbonyl compounds and urea-derived *N*-acyliminium ions have been reported to yield derivatives of DHP.[41] Moreover, our experimental data (kinetics and mass spectrometry) corroborate those of Kappe's[22] Folkers and Johnson's[20] indicate urea addition to the aldehyde as the first step in the reaction.

^{13}C NMR spectroscopy experiments were also performed to probe the effect of the imidazolium moiety (**MAI·Cl**) on the reaction, and the results are shown in Figure 7. All experiments were performed using pure reagents (i.e., benzaldehyde, **MAI·Cl** and BMI·BF_4) in a sealed NMR tube containing a sealed capillary tube charged with $[D_6]$DMSO to set the scale (external standard). The carbonyl of the aldehyde shifts to a higher frequency (deshielded) in the presence of the acid ligand **MAI·Cl**, indicating that in the presence of the Brønsted acid, the carbon of the electrophile becomes more susceptible to nucleophilic attack. This effect is due to the cation, since the ligand has no metal center in its structure. The results confirm the aldehyde activation by the acid moiety of the cation, in accordance with the mechanism proposed based on kinetics and mass experiments.

Theoretical calculations: To investigate the efficiency of the catalytic system and the plausibility of the proposed mechanism of action of **MAI·Fe_2Cl_7**, theoretical calculations were performed. Fukui functions (f^+ and f^-) were calculated considering the proposed mechanism. All structures had their geometries fully optimized by quantum mechanics ab initio hybrid Hartree–Fock/density functional theory (DFT) calculations prior to the Fukui function determination. The results are depicted in Figure 8.

Highly elucidative values were obtained for the calculated Fukui functions. The nucleophilic species (ethyl acetoacetate) has an f^- of 0.02 for the CH_2 group (Figure 8). For the in situ complex formation ($Fe(acac)_3$), the f^- is 0.19, reflecting a far more reactive nucleophile than free ethyl acetoacetate. The Fukui functions clearly show anion-activation promoted by BMI·Fe_2Cl_7. In addition, a rationale is provided for the enamine mechanism not taking place under these conditions. As the ethyl acetoacetate is compromised to form a nucleophilic complex, it is not available to react with urea acting as an electrophilic species, as required in the enamine mechanism (Scheme 3).

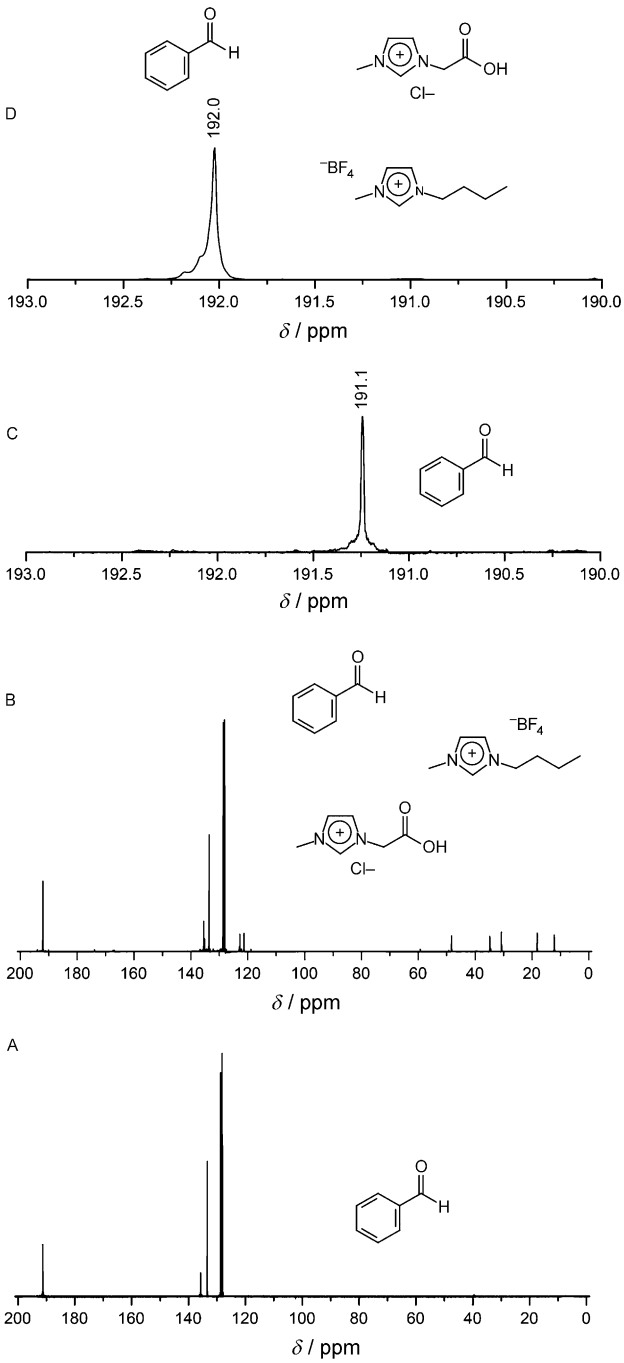


Figure 7. $^{13}C\{^1H\}$ NMR spectra. A) Pure benzaldehyde (0.8 mL). B) Mixture of all components (benzaldehyde (0.8 mL), **MAI·Cl** (≈50 mg) and BMI·BF_4 (0.8 mL)). C) Expansion from A. D) Expansion from B. $[D_6]$DMSO in a sealed capillary tube was used to set the scale as an external standard. Note the deshielding effect of the aldehyde C=O from $\delta = 191.1$ (C) to 192.0 ppm (D) in the mixture of the reagents. Also, note the low intensity of **MAI·Cl** signals in (B) due to its low concentration compared with the aldehyde and ionic-liquid concentrations.

The f^+ of the isolated benzaldehyde was determined to be 0.22. The protonated benzaldehyde displays a value of 0.31

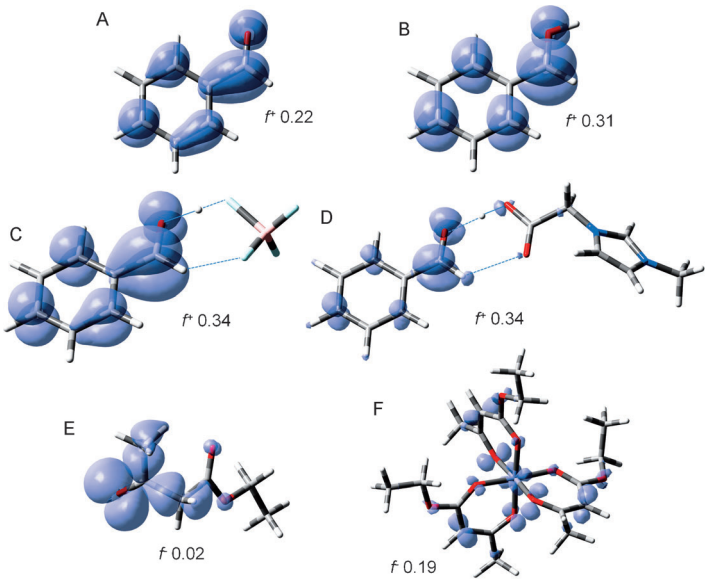


Figure 8. Optimized geometries and calculated Fukui functions (f^+ and f^-) of reactive intermediates from the Biginelli reaction and their isosurfaces by using the CAM-B3LYP/6-311+G(2df,p)/LANL2DZ level of theory. A) Benzaldehyde and f^+ (0.22) for the C=O carbon atom. B) Protonated benzaldehyde and f^+ (0.31) for the C=O$^+$–H carbon atom. C) Benzaldehyde coordinated with the anion (BF_4) of the ionic liquid (BMI·BF_4) and f^+ (0.34) for the C=O$^+$–H···B$^-$F$_4$ carbon atom. D) Benzaldehyde activation by the cation of the catalyst (**MAI**) and f^+ (0.34) for the C=O···**MAI** carbon atom. E) Ethyl acetoacetate and f^- (0.02) of the reactive CH_2 group (O=CCH_2C=O). F) Fe(acac)$_3$ complex (formed in situ) and f^- (0.19) of the reactive CH_2 group (O=CCH_2C=O). In the case of the complex, three f^- values for the CH_2 groups were obtained (0.19, 0.21, and 0.19).

and, as expected, is more electrophilic. It is worth remembering that Brønsted acids (the cation **MAI**) show a superacid behavior in ionic liquids, as reviewed elsewhere.[42] The reaction performed in BMI·BF_4 also showed two interesting features of ionic-liquid effect. The anion BF_4 was capable of coordinating (ion-pair formation) the protonated aldehyde, rendering its carbonyl carbon more susceptible to undergo nucleophilic addition (f^+ 0.34). Moreover, the aldehyde was also directly activated by the cation **MAI**, contributing to increase the electrophilicity of the carbonyl (f^+ 0.34), as shown in Scheme 5.

The calculated Gibbs free energy for ion-pair formation (BF_4 coordination) was -90.97 kcal mol^{-1} (more stable than the protonated aldehyde), indicating how these species become more stable in the ionic medium through the ionic-liquid effect, supplying additional rationale for the higher yields observed in the reactions performed in ILs. Moreover, two hydrogen bonds form upon **MAI** approximation (aldehyde-activation step), and two upon the anion (BF_4) coordination (Figure 8).

Recyclability and broad applicability of MAI·Fe_2Cl_7: An important goal in modern catalyst design is the development of recyclable, inexpensive, environmentally friendly, and efficient catalysts that must be active to form many derivatives of interest from the promoted reaction. In this context, **MAI·Fe_2Cl_7** possesses the hallmarks of an outstanding green catalyst.

The recycling reactions were performed with the optimized model reaction. Following formation of product, which precipitates, the system was filtered to isolate the product, and the reagents were recharged. At least 8 reactions were carried out with no noticeable loss of catalyst activity (Figure 9).

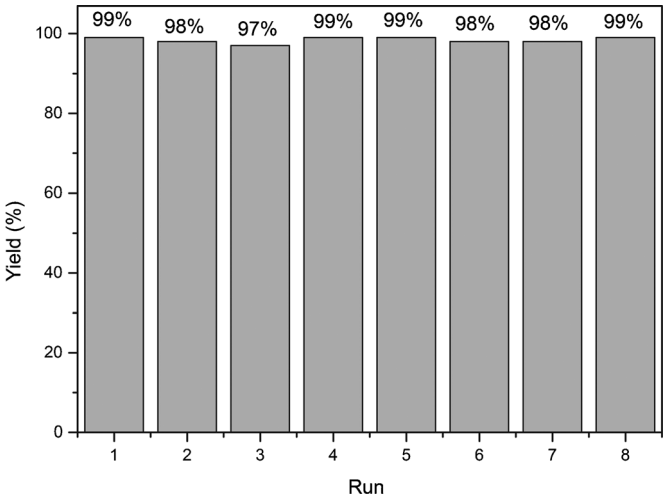
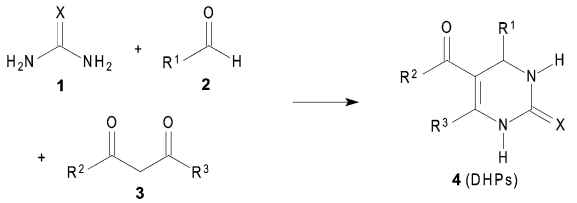


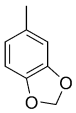
Figure 9. Recycling reactions using **MAI·Fe_2Cl_7** (5 mol%), BMI·BF_4 (1 mL), benzaldehyde (9.00 mmol), urea (3.00 mmol), and ethyl acetoacetate (3.00 mmol) at 80 °C for 2 h for each cycle.

Finally, **MAI·Fe_2Cl_7** was applied in the synthesis of DHP derivatives **4b–4bt**, with yields ranging from good to excellent (Table 2). The use of vanillin, a deactivated aldehyde (Table 2, Entries 25–28), resulted in the desired DHPs **4ba–bd** in impressive yields (80–98%). Compounds with promising biological activities were equally obtained in good to excellent yields, for instance, monastrol (Table 2, entry 11, 93%), piperastrol (Table 2, entry 39, 97%), enastron (Table 2, entry 42, 82%) and dimethylenastron (Table 2, entry 44, 80%). Furthermore, the application of **MAI·Fe_2Cl_7** allowed the direct synthesis of analogues of these interesting compounds.

Antitumoral activity: The promising antitumoral activity of this class of compounds is a subject of interest of many research groups.[43] Nevertheless, many of the previous reports are restricted to monastrol, piperastrol, enastron, and dimethylenastron (and their analogues). Here we evaluated the antitumoral activity of most of the synthesized compounds, beginning with cytotoxicity assays in MCF-7 cancer cell lines (mammalian human cells). Significant differences in the viability of treated and untreated cells were observed in cell viability assays (all performed with racemic DHPs). Many compounds have an inhibitory activity on cell proliferation in a dose- and time-dependent manner. However, some of them displayed considerable activity within 24 h

Table 2. Synthesis of DHP derivatives using **MAI·Fe_2Cl_7** (5 mol%), BMI·BF_4 (1 mL), aldehyde (9.00 mmol), urea or thiourea (3.00 mmol), and 1,3-dicarbonyl compound (3.00 mmol) at 80°C for 2 h.



Entry	Reagent				Product	Yield [%]	Entry	Reagent				Product	Yield [%]
	R^1	R^2	R^3	X				R^1	R^2	R^3	X		
1	Ph	OCH_2CH_3	Me	O	**4b**	99	25	4-OH-3-MeO-Ph	OCH_2CH_3	Me	O	**4ba**	98
2	Ph	Me	Me	O	**4c**	93	26	4-OH-3-MeO-Ph	Me	Me	O	**4bb**	80
3	Ph	OCH_2CH_3	Me	S	**4d**	83	27	4-OH-3-MeO-Ph	OCH_2CH_3	Me	S	**4bc**	85
4	Ph	Me	Me	S	**4e**	87	28	4-OH-3-MeO-Ph	Me	Me	S	**4bd**	85
5	4-Cl-Ph	OCH_2CH_3	Me	O	**4f**	82	29	H	OCH_2CH_3	Me	O	**4be**	96
6	4-Cl-Ph	Me	Me	O	**4g**	80	30	H	Me	Me	O	**4bf**	94
7	4-Cl-Ph	OCH_2CH_3	Me	S	**4h**	77	31	H	OCH_2CH_3	Me	S	**4bg**	86
8	4-Cl-Ph	Me	Me	S	**4i**	98	32	H	Me	Me	S	**4bh**	84
9	3-OH-Ph	OCH_2CH_3	Me	O	**4j**	80	33	Me	OCH_2CH_3	Me	O	**4bi**	82
10	3-OH-Ph	Me	Me	O	**4k**	93	34	Me	Me	Me	O	**4bj**	66
11[a]	3-OH-Ph	OCH_2CH_3	Me	S	**4l**	88	35	Me	OCH_2CH_3	Me	S	**4bk**	70
12	3-OH-Ph	Me	Me	S	**4m**	84	36	Me	Me	Me	S	**4bl**	60
13	2-OH-Ph	OCH_2CH_3	Me	O	**4n**	80	37		OCH_2CH_3	Me	O	**4bm**	87
14	2-OH-Ph	Me	Me	O	**4o**	84	38		Me	Me	O	**4bn**	79
15	2-OH-Ph	OCH_2CH_3	Me	S	**4p**	90	39[b]		OCH_2CH_3	Me	S	**4bo**	70
16	2-OH-Ph	Me	Me	S	**4q**	96	40		Me	Me	S	**4bp**	71
17	3-NO_2-Ph	OCH_2CH_3	Me	O	**4r**	97	41	3-OH-Ph			O	**4bq**	60
18	3-NO_2-Ph	Me	Me	O	**4s**	86	42[c]	3-OH-Ph			S	**4br**	72
19	3-NO_2-Ph	OCH_2CH_3	Me	S	**4t**	86	43	3-OH-Ph			O	**4bs**	70
20	3-NO_2-Ph	Me	Me	S	**4u**	70	44[d]	3-OH-Ph			S	**4bt**	70
21	2-NO_2-Ph	OCH_2CH_3	Me	O	**4v**	60	45		OCH_2CH_3	Me	O	**4bu**	66[f]
22	2-NO_2-Ph	Me	Me	O	**4x**	72	46		Me	Me	S	**4bv**	50[f]
23	2-NO_2-Ph	OCH_2CH_3	Me	S	**4y**	60[e]	47		OCH_2CH_3	Me	S	**4bx**	42[f]
24	2-NO_2-Ph	Me	Me	S	**4z**	98	48		Me	Me	O	**4by**	83

[a] Monastrol. [b] Piperastrol. [c] Enastron. [d] Dimethylenastron. [e] After 12 h of reaction. [f] Product formation is above 90%, but there is considerable loss in the purification procedure (chromatograph column).

(Figure S2 in the Supporting Information). The distribution of cell viability according to treatment and time is shown in Figures S2–4 in the Supporting Information.

Derivatives **4bo**, **4bq**, **4x**, and **4h** (Figures S2A, C, D and F, respectively) showed inhibitory activity greater than 50% at the highest tested concentration when compared with the control. Compounds derived from piperonal (Table 2, entries 37–40) had their highest concentration established based on previous studies, which showed that this group is about 30 times as potent as monastrol when tested against 5–7 different cancer cell linages.[2b]

DHP derivatives with benzaldehyde (Table 2, entries 1–4), 2-hydroxy- benzaldehyde (Table 2, entries 13–16) or 4-hydroxy-3-methoxy-benzaldehyde (Table 2, entries 25–28) and 4-chloro-benzaldehyde (Table 2, entries 5–8) also showed significant cytotoxic effects in 24 h at 1.00 mM, although these activities were smaller than 50% (Figure S2B and D, respectively). The class of acetaldehyde or formaldehyde derivatives did not show statistically significant activities.

After 48 h (Figure S3 in the Supporting Information), compounds **4bt**, **4bq**, **4m**, **4r**, **4p**, **4bc**, **4ba**, and **4i** (Figure S3C–E and S4G) have inhibitory activity higher than 50%, and in three of them their anti-proliferative activity was greater than 75%, **4bo** (79%), **4x** (87%), and **4h** (85%) (Figure S3A, G and D, respectively). After 72 h of treatment, 33 of the 37 tested compounds showed statistically significant inhibitory activity (Figure S4 in the Supporting Information) at the highest concentration. Among those, 20 compounds showed activity greater than 50%, which are **4bo, 4br, 4bs, 4bt, 4k, 4bq, 4j, 4m, 4v, 4x, 4t, 4u, 4p, 4bc, 4n, 4ba, 4bv, 4h, 4i**, and **4f** (Figure S4A, C–G). Groups treated with compounds **4bo** (500 μM), **4bt** (1.00 mM), **4x** (1.00 mM), **4t** (1.00 mM), **4bc** (1.00 mM), and **4h** (1.00 mM) had mean cell viabilities of 26, 11, 10, 9, 4, and 10%, respectively. This shows that these derivatives exert significant tox-

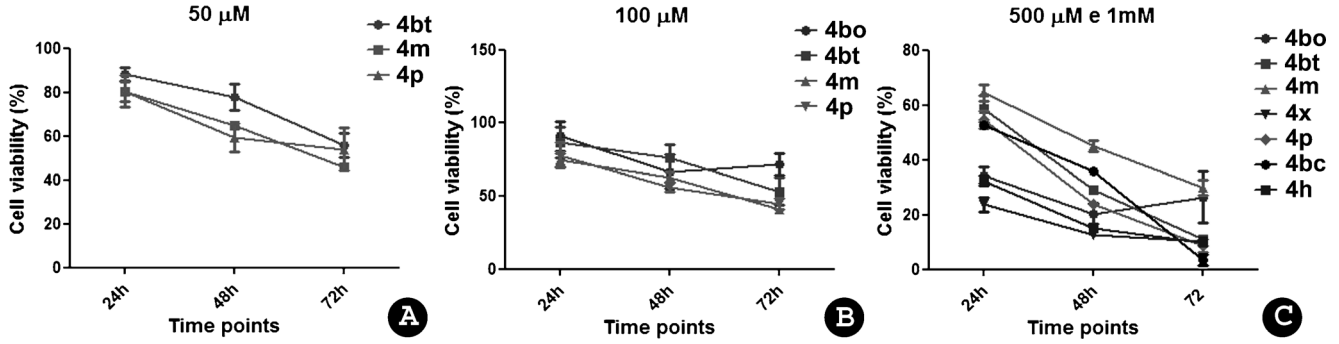


Figure 10. Cell viability versus time (24, 48, and 72 h) for the best cytotoxicity results at 50, 100, and 500 μM, and 1 mM concentration of the DHP derivatives.

icity on tumor cells (Figures S4A, C, D, E, and G in the Supporting Information). The highest concentration of DHPs with benzaldehyde and formaldehyde derivatives did not show satisfactory activity in any of the experiments.

Inhibitory activity was observed in cells treated with derivatives **4bt**, **4n**, and **4p** at lower doses when compared with untreated cells at 72 h (Figure S4C and E in the Supporting Information). These compounds may be promising chemotherapeutics for cancer treatment, since they could be cytotoxic and/or cytostatic for cancer cells with small doses with no considerable damage to normal cells. The best results of cytotoxicity time-dependence obtained by the treatment with the derivatives at 50, 100, 500 μM and 1 mM concentrations are shown in Figure 10.

Morphological alteration related to cell death after 72 h upon treatment of MCF-7 cells with derivatives **4bt** (800 μM), **4m** (1 mM), **4x** (800 μM), **4p** (400 μM), and **4bc** (1 mM) can be seen in Figure 11. All of these compounds showed high specific toxicity towards tumor cells at different concentrations. Figure 11 also shows round and detached cells (dead cells) and only a few attached cells, depending on the specific DHP effects. Compounds **4c** (dimethylenastron), **4p** and **4bc** showed the best results on the morphological alteration test, with almost no MCF-7 cells visible after 72 h. The few remaining attached cells showed enhanced morphological alterations, which are undoubtedly associated with cell-death processes, thus indicating the efficiency of such compounds against this cancer cells line.

Preliminary studies using healthy cells (fibroblasts) showed the virtual non-toxicity of the derivatives. Moreover, it shows the preference of this class of compounds to act against cancer cells, thus making these compounds potential new candidates for cancer therapy.

Conclusion

We have synthesized and applied a new ion-tagged iron catalyst as an efficient promoter of the Biginelli reaction. The ionic-liquid effect played a role in stabilizing the charged and polar intermediates formed during the reaction, explaining why yields performed in ILs were considerable higher than those obtained in classical organic solvents. The iron catalyst could be reused at least eight times with no noticeable loss in its activity. Moreover, the catalyst was applied in the synthesis of several DHP derivatives. Kinetic studies suggested the iminium mechanism is preferred under the present conditions. Additionally, ESI-QTOF experiments were consistent with the iminium mechanism. Theoretical calculations shed light on the atomic details of the proposed mechanism and are in agreement with the reactivity expected for the in situ-formed intermediates. Finally, 37 DHPs derivatives were evaluated against MCF-7 cancer cell line with promising results. Preliminary studies showed the virtual non-toxicity of the analyzed compounds when tested against healthy cells, which attests their apparent preference for rapidly proliferating cells.

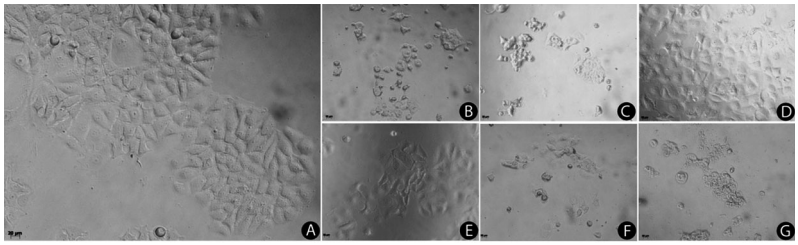


Figure 11. Morphological alterations in cells upon 72 h of DHP treatment. A) Untreated MCF-7 cells; no morphological changes observed. B) Monastrol (**4l**, 1 mM as the positive control); only a few attached round cells observed. C) Dimethylenastron (**4bt**, 800 μM); only a few attached round cells observed. D) Compound **4m** (1 mM); only a subtle effect on morphological features is observed. E) Compound **4x** (800 μM); remaining cells show conserved morphological aspect. F) Compound **4p** (400 μM); significant effect on the morphological aspects of MCF-7 cells. G) Compound **4bc** (1 mM); significant effect on the morphological aspects of MCF-7 cells.

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Multicomponent Reactions

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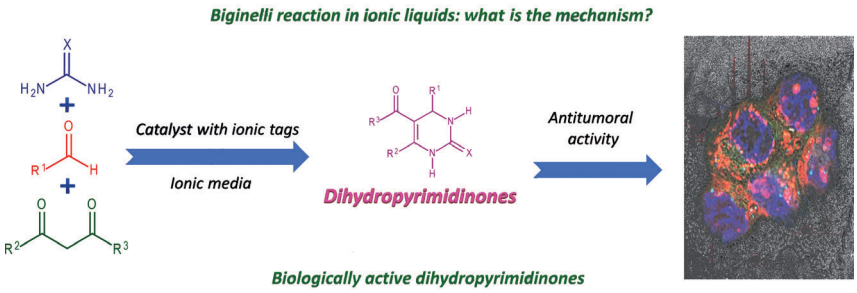
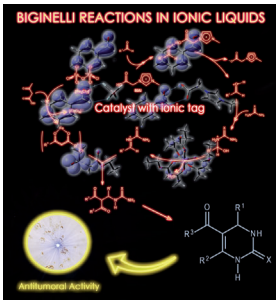
The Biginelli Reaction with an Imidazolium–Tagged Recyclable Iron Catalyst: Kinetics, Mechanism, and Antitumoral Activity



Ion/Iron will: The use of a new imidazolium-tagged iron catalyst as the promoter of the Biginelli reaction allowed the synthesis of several dihydropyrimidinones with attractive biological activity (see scheme). The mechanism of this interesting transformation was evaluated by means of kinetics, NMR spectroscopy, ESI-MS(/MS), and theoretical calculations.



Multicomponent Reactions

In their Full Paper on page■■, B. A. D. Neto and coworkers demonstrate the mechanism of the Biginelli reaction with an imidazolium-tagged iron catalyst with dual activation mode. For the first time, a kinetic study is conducted to demonstrate the iminium pathway is favoured under the developed conditions in ionic liquids. The combination of kinetics, NMR and ESI-MS(/MS) allowed an unambiguous assignment of the preferred reaction mechanism. Moreover, 37 racemic dihydropyrimidinones had their cytotoxicity evaluated in assays against MCF-7 cancer cell linages with encouraging results of some few derivatives, which were virtually non-toxic against healthy cell linages.