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The Three-Component Biginelli Reaction: A Combined Experimental and Theoretical Mechanistic Investigation

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Dedicated to the memory of Professor Octavio A. C. Antunes for his friendship, leadership, and inspiring life and career. Professor Octavio A. C. Antunes, his wife Patricia, and their son Mateus were victims of the tragic accident involving flight AF 447 on May 31, 2009.

Abstract: Biginelli reactions have been monitored by direct infusion electrospray ionization mass spectrometry (ESI-MS) and key cationic intermediates involved in this three-component reaction have been intercepted and further characterized by tandem MS experiments (ESI-MS/MS). Density functional theory calculations were also used to investigate the feasibility of the major competing mechanisms proposed for the Biginelli reaction. The experimental and theoretical results were found to corroborate the iminium mechanism proposed by Folkers and Johnson, whereas no intermediates directly associated with either the more energy demanding Knoevenagel or enamine mechanisms could be intercepted.

Keywords: Biginelli reaction · density functional calculations · electrospray mass spectrometry · heterocyclic compounds · reaction mechanisms

Introduction

In 1893, Pietro Biginelli published his pioneering findings on a three-component reaction that has become known as the Biginelli reaction. This three-component one-pot reaction leads to the synthesis of dihydropyrimidines (**1**) typically by the reaction of a benzaldehyde (**2**), an acetoacetate (**3**), and an (thio)urea (**4**) under acid catalysis.[1] The Biginelli reaction is quite versatile as it can be performed with variations in all three components leading therefore to a myriad of dihydropyrimidines (Scheme 1).[2–12]

Bignelli reactions can be performed under a variety of conditions, and several improvements of the experimental procedures have been reported in recent years. Although it has been traditionally catalyzed by strong Brønsted acids, Lewis acids such as $LiClO_4$, $LaCl_3$, $InCl_3$, $Bi(OTf)_3$, $BiCl_3$, $Mn(OAc)_3$, $Cu(OTf)_2$, $FeCl_3$, $ZrCl_4$, or $SnCl_2$[13–17] are now being increasingly used. The use of ionic liquids,[18–20] microwave irradiation,[7,21–31] solid-phase reagents,[12,32,33] and polymer-supported catalysts have also been reported.[34,35] Two asymmetric versions of Biginelli reactions using $CeCl_3/InCl_3$ or $Yb(OTF)_3$ in the presence of chiral ligands have also been recently reported.[3,36–39] A driving force in developing synthetic methodologies for Bignelli products **1** is their similar pharmacological profile with analogous drugs, such as nifedipine (Scheme 1) which act as calcium channel modulators.[40]

Since its first report in 1893, a number of mechanisms have been forwarded for the Biginelli reaction. During the 1930s, Folkers and Johnson proposed that **5a**, **6a**, and **7a** (Scheme 2) could be involved.[41] The *N,N*-benzylidenebisurea (**5a**) would result from intermolecular condensation of benzaldehyde (**2a**) and two equivalents of urea (**4a**). Inter-

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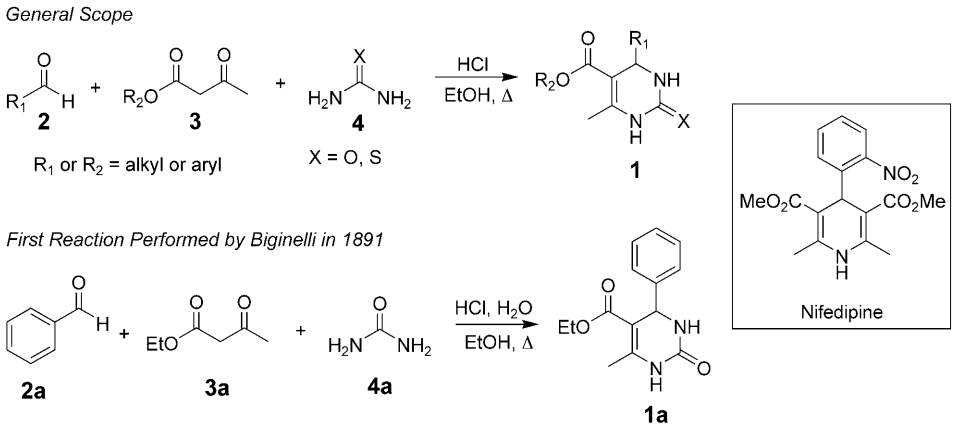
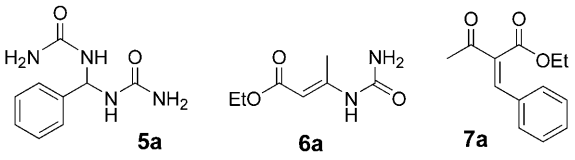


Scheme 1. The one-pot three-component Biginelli reaction.



Scheme 2. Intermediates proposed by Folkers and Johnson for the Biginelli reaction.[41]

mediate **6a** is an enamine formed by condensation of **3a** and **4a**, whereas intermediate **7a** is known as the Knoevenagel adduct formed by condensation of **2a** and **3a**.

In 1973, Sweet and Fissekis[42] proposed a more detailed mechanistic interpretation for the Biginelli reaction, which has became known as the Knoevenagel mechanism (mechanism C in Scheme 3). Their mechanism is based on the formation of a carbenium ion (**9a**) in the rate-limiting step of an acid-catalyzed Knoevenagel reaction between **2a** and **3a**. Intermediate **9a** was proposed to react with **4a** forming adduct **10a** (via **21a**), which would undergo an intramolecular condensation reaction to give the Biginelli dihydropyrimidine **1a**.

More recently, Kappe[43] used NMR to investigate Biginelli intermediates. Monitoring the reaction of benzaldehyde (**2a**) and ethyl acetoacetate (**3a**) in CD_3OH/HCl by ^1H and ^{13}C NMR spectroscopy, he found no evidence for an aldol reaction or any other reaction between the two components at room temperature. Further, Kappe also observed the formation of bisureide **5a** (Scheme 3) by ^1H NMR spectroscopy (CD_3OH, HCl), but no other intermediate (**11a** or **12a**) was detected (Scheme 3). Kappe assumed that the first addition step (**2a** + **4a** to give **11a**) is the rate-determining step and that both the subsequent acid-catalyzed dehydration (**11a** to **12a**) and the addition of a second equivalent of urea to the iminium ion (**12a** + **4a** to give **5a**) are fast steps, and therefore do not allow **11a** or **12a** to accumulate.

The presence of an enamine intermediate **6a** (mechanism B in Scheme 3) was also investigated by Kappe. Under the Biginelli reaction conditions, he found that the equilibrium lies to the side of the reagents, that is, **3a** and **4a**.

Recently, intermediates **13** and **14** (Scheme 4) were isolated employing sterically bulky[44] or electron-deficient acetoacetates ,[45] respectively, and dehydration of **14** gave **1b** using *p*-toluenesulfonic acid. A number of hexahydropyrimidines closely related to **1b** have been prepared by using perfluorinated 1,3-dicarbonyl compounds or β-keto esters as building blocks in the Biginelli condensation.[46,47]

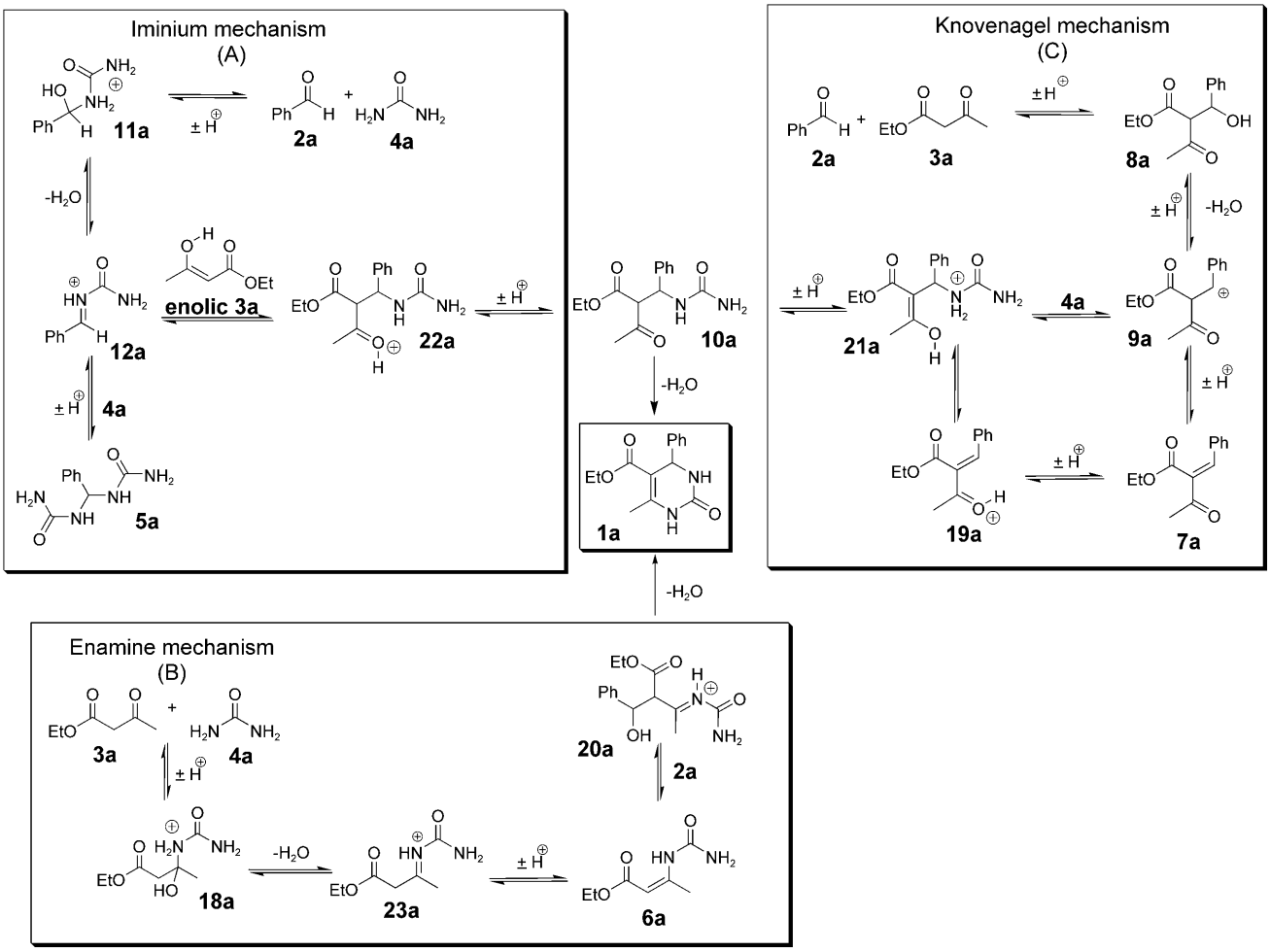
Recently, direct infusion electrospray ionization mass spectrometry (ESI-MS) has been incorporated to the set of major techniques for mechanistic studies of organic and inorganic reactions.[48,49] Owing to its outstanding ability to "fish" ionic or ionized intermediates directly from reaction solutions into the gas phase, with high sensitivity, speed and gentleness, ESI-MS and its tandem version ESI-MS/MS have provided continuous snapshots of the ionic composition of reaction solutions with on-line MS and MS/MS characterization of the intercepted intermediates. We rationalized therefore that ESI-MS and ESI-MS/MS, by its outstanding ability to intercept intermediates (even transient species) could provide a detailed picture of the Biginelli mechanism in light of its three alternative mechanisms (Scheme 3). Additionally, a theoretical investigation using DFT calculations to evaluate the feasibility of the three competing mechanisms was undertaken.

The Bignelli intermediates were expected to be transferred directly from solution to the gas phase and detected by ESI-MS in the positive-ion mode either in their natural cationic forms (such as **12a** and **9a**) or in protonated forms (Scheme 3). In ESI-MS/MS experiments, the structures of these gaseous cationic intermediates could then be investigated by collision-induced dissociation (CID) with argon.

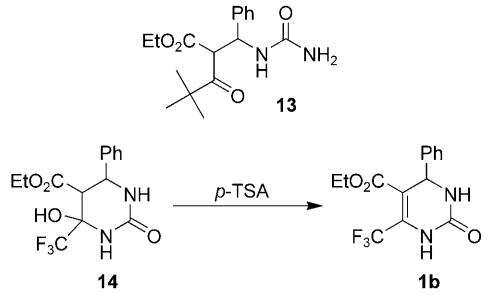
Results and Discussion

Based on the overall mechanistic view of Scheme 3, we first investigated the formation of the dormant bisureide **5a**. Benzaldehyde (**2a**, 1 mmol) and urea (**4a**, 2 mmol) were mixed in aqueous methanol (1:1 v/v, 5 mL) in the presence of a catalytic quantity of formic acid (0.1 mol%) and, most importantly, in the absence of ethyl acetoacetate (**3a**). After 5 min, a sample of the reaction solution was taken and its ESI(+)-MS recorded.

Figure 1 shows that ESI(+)-MS was able to intercept key cationic species: protonated bisureide [**5a**+H^+] of *m/z* 209; the iminium ion **12a** of *m/z* 149; its hydrated precursor **11a** of *m/z* 167 as well as the reagents, protonated benzaldehyde



Scheme 3. The iminium (A), enamine (B), and Knoevenagel (C) mechanisms for the Biginelli reaction.



Scheme 4. Intermediates **13** and **14** obtained from electron-deficient or sterically bulky acetoacetates.

$[\mathbf{2a}+\mathbf{H}]^+$ of *m/z* 107 and the protonated urea dimer **16a** of *m/z* 121. The intermediates intercepted by ESI-MS were then selected for further ESI(+)-MS/MS characterization which, by showing predictable dissociation routes, provided evidence for the proposed structures, see the Supporting Information.

We then performed the Biginelli reaction under the usual conditions with **2a**, **3a**, and **4a** (1 mmol each) in aqueous methanol (1:1 v/v, 5 mL) with a sub-stoichiometric amount of formic acid (0.1 mol%) as catalyst. Figure 2 shows the ESI(+)-MS collected after 5 min of reaction. Ions that were previously detected in the absence of **3a** (Figure 1) were again detected, but now three novel ions appeared which correspond to: a) intermediate **18a** of *m/z* 191; b) the final Biginelli product in its protonated form $[\mathbf{1a}+\mathbf{H}^+]$ of *m/z* 261 and c) $[\mathbf{10a}+\mathbf{H}^+]$ of *m/z* 279, that is most likely **22a** in Scheme 3 (perhaps in equilibrium with its isomeric form **21a**). These key ions were also characterized by ESI(+)-MS/MS (see the Supporting Information) and their dissociation chemistry was found to agree with the proposed structures.

Ions for the Knoevenagel mechanism such as the carbenium ion **9a** of *m/z* 219 or its isomer **19a** (Scheme 3) were not detected by ESI-MS (Figure 2), even after a reaction time of 2 h with continuous monitoring. However, the ion **[8a+H]** of *m/z* 237 was observed. The ESI(+)-MS interception of **11a**, **12a** and $[\mathbf{10a}+\mathbf{H}^+]$ are therefore more consistent with the iminium mechanism (Scheme 3).

Kappe has questioned the participation of enamine **6a** (Scheme 3) arguing that the equilibrium for its formation lies far to the side of the reactants **3a** and **4a**. By ESI(+)-

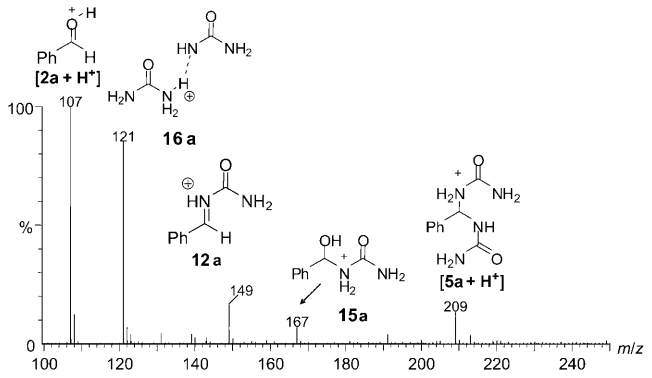


Figure 1. ESI(+)-MS for the reaction of **2a** with **4a**.

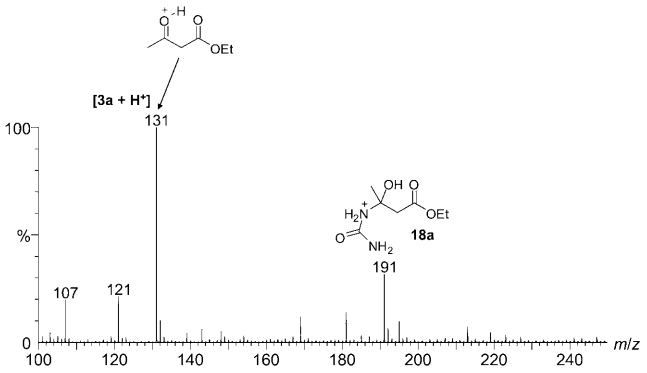


Figure 3. ESI(+)-MS for the reaction between **3a** and **4a**.

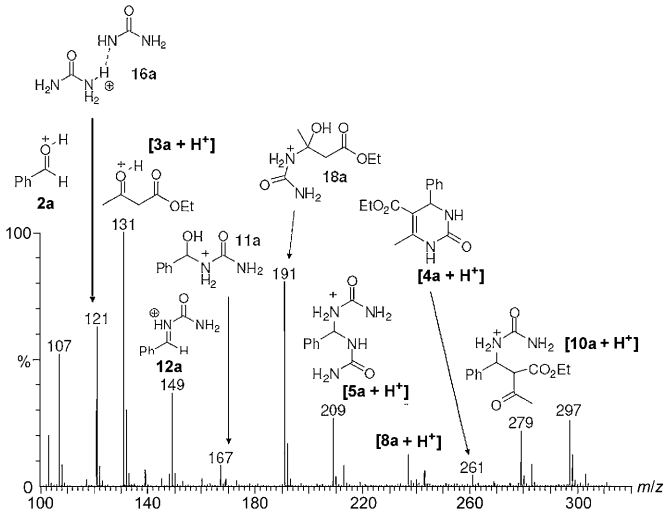


Figure 2. ESI(+)-MS for the three-component Biginelli reaction of **2a**, **3a** and **4a**.

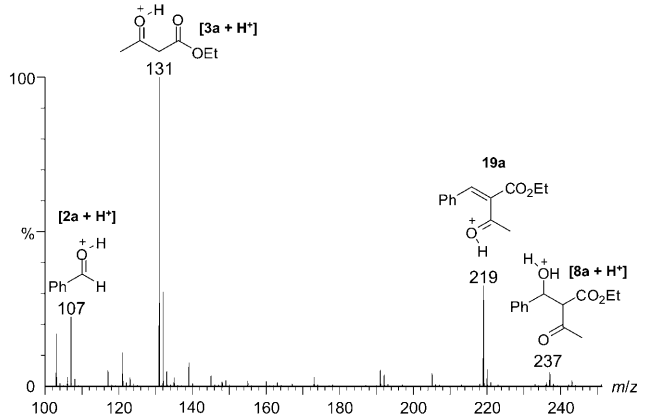


Figure 4. ESI(+) MS of the Knoevenagel condensation between **2a** and **3a** after a reaction period of 24 h.

MS monitoring we detected and characterized **18a** but failed to detect the enamine **6a** in its protonated form **23a** of *m/z* 173. To verify whether the failure to detect **6a** could be due to its transient nature (fast formation and/or consumption), **4a** (2 mmol) and **3a** (1 mmol) were mixed in aqueous methanol (1:1 v/v, 5 mL) in the absence of **2a** and in the presence of formic acid (0.1 mol%), as above. After 5 min, analysis by ESI(+)-MS (Figure 3) was unable to detect the protonated enamine **23a** although its postulated immediate precursor **18a** of *m/z* 191 was readily detected as an abundant ion.

We then monitored, by ESI(+)-MS, the Knoevenagel condensation between **2a** (1 mmol) and **3a** (1 mmol) in aqueous methanol (1:1 v/v, 5 mL) leading to **8a** in the presence of formic acid (0.1 mol%) and in the absence of **4a**. The reaction was monitored periodically and after 6 h only the protonated reactants were detected. The reaction solution was left stirring overnight and, after 24 h, the ESI(+)-MS was collected (see Figure 4). Analysis reveals that the protonated Knoevenagel adduct **19a** of *m/z* 219 and its protonated aldolic precursor **[8a+H+]** of *m/z* 237 were finally detected.

The Knoevenagel mechanism, evidenced by the detection of the intermediate **7a** (detected as its protonated form **19a**) after a reaction period of 24 h, seems to be feasible but too slow in comparison to the much shorter time scale of the Biginelli reaction to contribute significantly to product formation under the conditions used in this study.

To evaluate possible intermediates and transition states, and to compare the energetics of the proposed mechanisms: Folkers and Johnson (A), enamine (B), and Sweet and Fissekis (C) (see Scheme 3), DFT B3LYP/6-31G* calculations were performed. The effect of solvation was also investigated by use of the IEFPCM solvation model and single-point energies were calculated by using MP2/6-311++G**. The polarizable continuum model (PCM)[50,51] was chosen so as to mimic the effect of solvent. This model uses the physical properties of the solvent to simulate an artificial solvation environment without the explicit incorporation of solvent molecules on the structures calculated. Recently, Zhou and co-workers reported a short DFT study where they analyzed the iminium mechanism as proposed by Kappe.[52]

Figure 5 presents a potential energy surface for the three mechanisms and Figure 6 shows the calculated structures for the lowest energy pathway. Figure 5 shows that the formation of intermediates **11a** and **18a**, through the transition

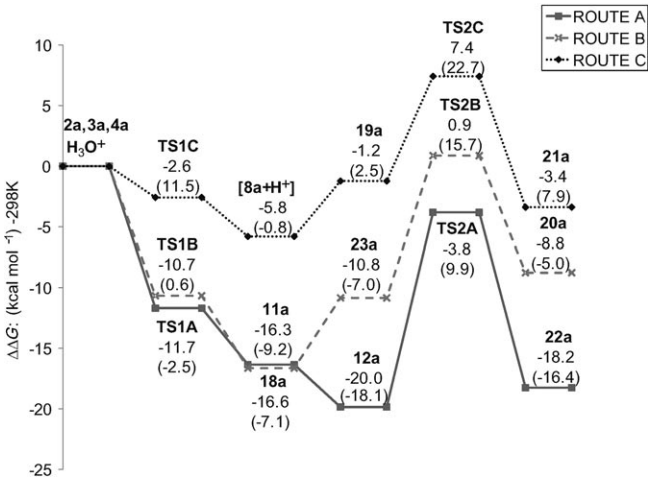


Figure 5. Potential energy surfaces for the three alternative Biginelli reaction mechanisms (routes A–C). Note that the energies of **TS1A**, **TS1B**, and **TS1C** are lower in energy than the reactants, but this is a consequence of the method of comparison of the relative energies (see the Supporting Information). The values in parentheses refer to MP2/6-311++G(d,p)//B3LYP/6-31+G(d) IEPFPCM calculations.

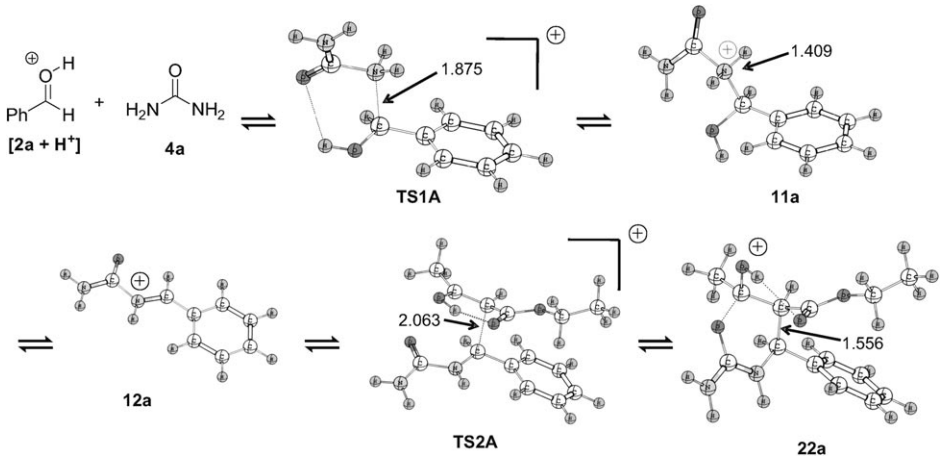


Figure 6. Optimized structures for key intermediates and transition states for the iminium mechanism of the Biginelli reaction with selected bond lengths [Å].

sates **TS1A** and **TS1B**, that is, the iminium (A) and enamine (B) mechanisms, respectively, are much more favored in comparison with the formation of **[8a+H$^+$]** via **TS1C** for the Knoevenagel mechanism (C). Intermediate **11a** readily undergoes dehydration to give the iminium ion **12a**. Note that both **12a** and **18a** were intercepted by ESI(+)-MS. Kappe,[43] as already mentioned, has shown that **12a** is in equilibrium with the diureide **5a**. Intermediate **12a** subsequently undergoes addition of enolic **3a** to give **22a** (via **TS2A**), which cyclizes to the final Biginelli product **1a**. The alternative enamine pathway via enamine **6a** passes through **TS2B**, which is 4.7 kcal mol^{-1} higher in energy than **TS2A**. Note that similar energy profiles were obtained when considering solvation effects via the IEFPCM solvation model or via the single point energies calculated using MP2/6-311++G** (values in parenthesis in Figure 5). The calculations that Figure 5 summarizes reveal that the iminium mechanism is kinetically and thermodynamically favored for the Biginelli reaction. This prediction is consistent with the experimental ESI(+)-MS/MS data.

Conclusions

ESI(+)-MS monitoring of the Biginelli reaction under three- and two-component conditions indicate that the Knoevenagel pathway is too slow and should not significantly contribute to formation of the Bignelli product. In accord with this finding, DFT calculations of the Knoevenagel pathway revealed a step with the largest activation barrier for the proposed mechanisms. A single early intermediate (**18a**) associated with the enamine mechanism was intercepted, but it is postulated to be a dormant species that reverts to reagents during the course of reaction. Several intermediates associated with the iminium mechanism were intercepted and characterized by ESI(+)-MS(/MS). DFT calculations, including solvent effects, have also indicated that the iminium mechanism is the kinetically and thermodynamically favored route to the Biginelli product. Therefore, the combined experimental and theoretical results support that the iminium mechanism (A in Scheme 3) is favored in Biginelli reactions. The most reasonable mechanistic interpretation would therefore assume three principal steps for the Biginelli reaction: 1) condensation of aldehyde **2** with the (thio)urea **4** in acidic media to form iminium ion **12** as the key intermediate; 2) addition of enolic acetoacetate **3** to **12** to form **10**, the immediate acyclic precursor of the final product and; 3) intramolecular addition leading to analogs of cyclized **14** and the formation of the final heterocyclic dihydropyrimidine product **1** via dehydration (Scheme 3).

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