

Article

Highly Efficient Synthesis of Substituted 3,4-Dihydropyrimidin-2-(1*H*)-ones (DHPMs) Catalyzed by Hf(OTf)₄: Mechanistic Insights into Reaction Pathways under Metal Lewis Acid Catalysis and Solvent-Free Conditions

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Academic Editor: Romano V. A. Orru

Received: 2 January 2019; Accepted: 18 January 2019; Published: 21 January 2019



Abstract: In our studies on the catalytic activity of Group IVB transition metal Lewis acids, Hf(OTf)₄ was identified as a highly potent catalyst for “one-pot, three-component” Biginelli reaction. More importantly, it was found that solvent-free conditions, in contrast to solvent-based conditions, could dramatically promote the Hf(OTf)₄-catalyzed formation of 3,4-dihydro-pyrimidin-2-(1*H*)-ones. To provide a mechanistic explanation, we closely examined the catalytic effects of Hf(OTf)₄ on all three potential reaction pathways in both “sequential bimolecular condensations” and “one-pot, three-component” manners. The experimental results showed that the synergistic effects of solvent-free conditions and Hf(OTf)₄ catalysis not only drastically accelerate Biginelli reaction by enhancing the imine route and activating the enamine route but also avoid the formation of Knoevenagel adduct, which may lead to an undesired byproduct. In addition, ¹H-MMR tracing of the H-D exchange reaction of methyl acetoacetate in MeOH-*d*₄ indicated that Hf(IV) cation may significantly accelerate ketone-enol tautomerization and activate the β-ketone moiety, thereby contributing to the overall reaction rate.

Keywords: hafnium triflate; 3,4-dihydropyrimidin-2-(1*H*)-ones; solvent-free; Biginelli reaction; mechanism

1. Introduction

As one of the most prominent multicomponent reactions (MCRs), Biginelli reaction has been utilized for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones (DHPMs) via acid-catalyzed one-pot condensation of aldehyde, β-ketoester, and urea in refluxing ethanol since its discovery in 1893 [1–4]. In past several decades, the identification of DHPM core structure in bioactive marine alkaloids including crambescidins [5], batzelladines [6], and monanchocidins [7], and a broad spectrum of pharmacological applications of both natural and synthetic DHPMs as antiviral, antibacterial, antitumor, anti-inflammatory, antihypertensive, and anti-epileptic agents, α_{1A} receptor antagonist, and calcium channel blocker, etc. [3,4,8] have elicited much attention to Biginelli reaction once again. In addition, DHPMs have also found applications as functional polymers [9], adhesives [10], and fabric dyes [11] in materials science.

Though the conventional Brønsted acid-catalyzed Biginelli reaction provides a reliable access to DHPMs, however, this method is limited by moderate yields and long reaction time. To improve the

efficacy of Biginelli reaction, a large number of metal Lewis acids, such as FeCl_3 [12], $\text{Yb}(\text{OTf})_3$ [13], $\text{Mn}(\text{OAc})_3$ [14], $\text{InCl}_3/\text{InBr}_3/\text{In}(\text{OTf})_3$ [15–17], $\text{ZrCl}_4/\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$ [18,19], $\text{CuCl}_2/\text{Cu}(\text{OTf})_2$ [20, 21], SmI_2 [22], RuCl_3 [23], $\text{Sr}(\text{OTf})_2$ [24], $\text{Ce}(\text{NO}_3)_3$ [25], TaBr_5 [26], $\text{Bi}(\text{NO}_3)_2$ [27], SbCl_3 [28], $\text{GaI}_3/\text{Ga}(\text{OTf})_3$ [29,30], and TiCp_2Cl_2 [31] have been proved as effective catalysts for this purpose. Generally, the reaction conditions of metal Lewis acid-catalyzed DHPM synthesis fall into two categories. The first one is performed in organic solvents, such as EtOH, CH_3CN , or tetrahydrofuran (THF). These methods typically need 10 mol% catalyst and 4–8 h to complete. The second one is conducted under solvent-free conditions, typically requires less catalyst (5%), and completes faster (0.5–1 h). In contrast, a Brønsted base-catalyzed Biginelli reaction (10 mol% *t*-BuOK) required much longer (3–8 h) to complete under the same solvent-free conditions [32].

In recent years, organometallic complexes of Bi(V) [33] and Cu(I) [34] have also been employed for the synthesis of DHPMs. In addition, the fast development of heterogeneous catalysts such as mesoporous materials [35], metal oxide nanoparticles [36], supported solid acids [37], and metal-coordinated polymers [38] has provided an alternative approach to DHPMs with improved catalyst recyclability. However, the preparation of these specific catalysts greatly limits their value in practical applications. In most of recent medicinal research, DHPMs were synthesized with easily accessible metal Lewis acid catalysts [39–42]. Therefore, the identification of highly potent, commercially available, affordable, and non-toxic metal Lewis acid catalysts for Biginelli reaction are still awaiting exploration.

Another fascinating aspect of Biginelli reaction is the revelation of reaction mechanism. The so-called imine, enamine, and Knoevenagel routes featuring different bimolecular condensation intermediates had been proposed [3,4]. In 1997, Kappe reexamined the mechanism and established that the imine route is the major pathway leading to the HCl-catalyzed formation of DHPMs [43], which are supported by the following mechanistic studies based on ESI-MS [44,45], NMR [45], and theoretical calculations [44,46]. However, most of the mechanisms proposed for metal Lewis acid-catalyzed Biginelli reactions were simply in favor of the imine route without much supporting evidence except Guo's recent work on TiCp_2Cl_2 [31]. It should be noticed that Cepanec's experimental results showed that SbCl_3 inhibited both the imine and Knoevenagel routes and the reaction proceeded via the enamine route [28], which suggests that the mechanism of metal Lewis acid-catalyzed Biginelli reaction may vary from that based on HCl catalysis. Currently, more and more research has revealed that the reactions under solvent-free conditions could be of huge difference from those under solvent-based conditions in terms of yield, reaction rate, or even stereoselectivity [47,48]. However, the mechanistic explanation for the remarkably enhanced reactivity under solvent-free conditions over that in organic solvents has rarely been discussed in previous research.

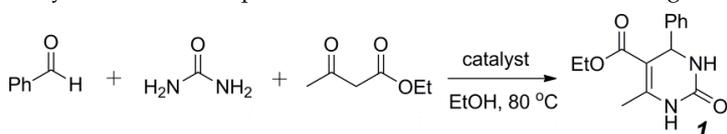
Our ongoing research on the catalytic activity of Group IVB transition metal (Zr(IV) and Hf(IV)) salts showed that they have strong activation capability on carbonyl-transformation reactions, and Hf(IV) salts exhibit even superior reactivity to Zr(IV) salts in many reactions [49,50]. Inspired by these precedent results, we envisioned that Hf(IV) salts may promote Biginelli reaction via its strong interactions with aldehyde and β -ketoester. It has to be mentioned that, earlier, Chen et al. reported the catalytic activity of $\text{Hf}(\text{OTf})_4$ over several rare earth metal triflates on 2-selenoxo DHPM synthesis (5 mol%, 120 °C, 20 min–2 h) [51], whereas our independent research focused on the elucidation of reactivity of Hf(IV) salts on 2-oxo/thio DHPM synthesis and, more importantly, the underlying mechanism of catalysis. We report herein the identification of $\text{Hf}(\text{OTf})_4$ as a highly potent catalyst for Biginelli synthesis of 2-oxo/thio DHPMs under solvent-free conditions (1 mol%, 80 °C, 20–30 min). The catalytic effects of $\text{Hf}(\text{OTf})_4$ on all three potential reaction pathways were systematically investigated in both 'sequential bimolecular condensations' and 'one-pot, three-component' manners under solvent-free conditions. Our experimental results suggest that both the promotion of imine route and activation of enamine route by $\text{Hf}(\text{OTf})_4$ under solvent-free conditions are crucial for the marked enhancement of reaction efficacy.

2. Results and Discussion

2.1. Optimization of Hf(OTf)₄-Catalyzed Biginelli Reaction Conditions

In the preliminary experiment, we compared the catalytic activity of Zr(IV) and Hf(IV) salts at 10 mol% level in a model reaction, which contained benzaldehyde, ethylacetoacetate, and urea in 1:1:1.2 molar ratio and was refluxed in ethanol. The results in Table 1 showed that ZrCl₄- and ZrOCl₂·8H₂O-catalyzed reactions (~80%, 9–12 h) were significantly faster and higher-yielding than the conventional Biginelli reaction catalyzed by conc. HCl (65%, 18 h). ZrCp₂Cl₂ was less potent (62%, 18 h) than the other two Zr(IV) catalysts possibly due to the more hindered catalytic center. In contrast, HfCl₄ (81%, 9 h) and HfCp₂Cl₂ (73%, 12 h) exhibited higher activity than their Zr(IV) counterparts, whereas Hf(OTf)₄ appeared as the most potent catalyst and afforded **1** in 88% yield within only 9 h.

Table 1. Catalytic effect of Group IVB transition metal Lewis acids on Biginelli reaction.

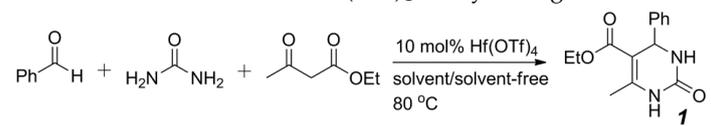


| | Catalyst | Reaction Time (h) | Yield of 1 (%) |
|---|---|-------------------|-----------------------|
| 1 | no | 24 | no reaction |
| 2 | conc. HCl | 18 | 65 |
| 3 | ZrCl ₄ (10 mol%) | 12 | 80 |
| 4 | ZrCp ₂ Cl ₂ (10 mol%) | 12 | 62 ¹ |
| 5 | ZrOCl ₂ ·8H ₂ O (10 mol%) | 9 | 78 |
| 6 | HfCp ₂ Cl ₂ (10 mol%) | 12 | 73 ¹ |
| 7 | HfCl ₄ (10 mol%) | 9 | 81 |
| 8 | Hf(OTf) ₄ (10 mol%) | 9 | 88 |

¹ The starting materials were not completely consumed when the reaction reached equilibrium.

In the following research, the solvent effect was investigated. As listed in Table 2, the reactions in toluene, dichloroethane, THF, and acetonitrile were hard to go to completion in the presence of 10 mol% Hf(OTf)₄. In comparison, ethanol was a superior solvent for the Hf(OTf)₄-catalyzed Biginelli reaction. To our surprise, when the reaction was performed under solvent-free conditions at 80 °C, it completed within only 5 min in 96% yield. Further lowering the amount of Hf(OTf)₄ showed that as low as 1 mol% Hf(OTf)₄ was sufficient enough to catalyze high-yielding conversion to **1** (95%, 20 min). We also noticed that the reaction could proceed at 80 °C in the absence of catalyst under solvent-free conditions, which is in agreement with a previous report [52]. However, the reaction was much slower and less efficient (63%, 8 h).

Table 2. Solvent effect on the Hf(OTf)₄-catalyzed Biginelli reaction.



| | Solvent | Reaction Time (h) | Yield of 1 (%) |
|---|--------------------|-------------------|-----------------------|
| 1 | toluene | 12 | 52 ¹ |
| 2 | 1,2-dichloroethane | 9 | 56 ¹ |
| 3 | THF | 9 | 63 ¹ |
| 4 | CH ₃ CN | 9 | 65 ¹ |
| 5 | EtOH | 9 | 88 |
| 6 | solvent-free | 5 min | 96 |

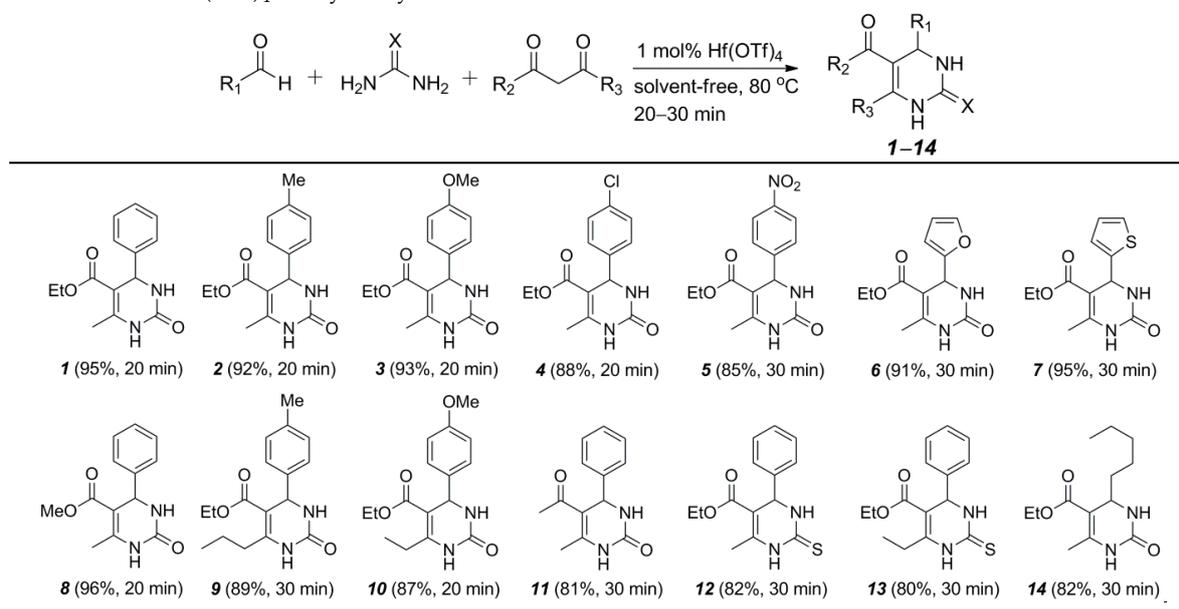
¹ The starting materials were not completely consumed when the reaction reached equilibrium.

As another key factor for Biginelli reaction, the reaction temperature was varied to achieve the best result. It was found that lowering the temperature to 60 °C had negative effect on the reaction (87%, 40 min). When the temperature was increased to 100 °C, the reaction completed faster, but the yield dropped (76%, 5 min) due to the formation of polar byproducts.

2.2. Scope of Hf(OTf)₄-Catalyzed Biginelli Reaction under Solvent-Free Conditions

With the optimized conditions, 1 mol% Hf(OTf)₄ was applied to the synthesis of a diversity of 2-oxo/thio DHPMs. As shown in Table 3, benzaldehydes with electron-donating and electron-withdrawing groups (2–5), heteroarylaldehydes (6,7), and different β-ketoesters (8–10) were well tolerated by this method (>85%, 20–30 min). When acetylacetone (11), thiourea (12,13), or an aliphatic aldehyde (14) were employed, the corresponding DHPMs were obtained in only slightly lowered yields.

Table 3. Hf(OTf)₄-catalyzed synthesis of substituted DHPMs 1–14 under solvent-free conditions.

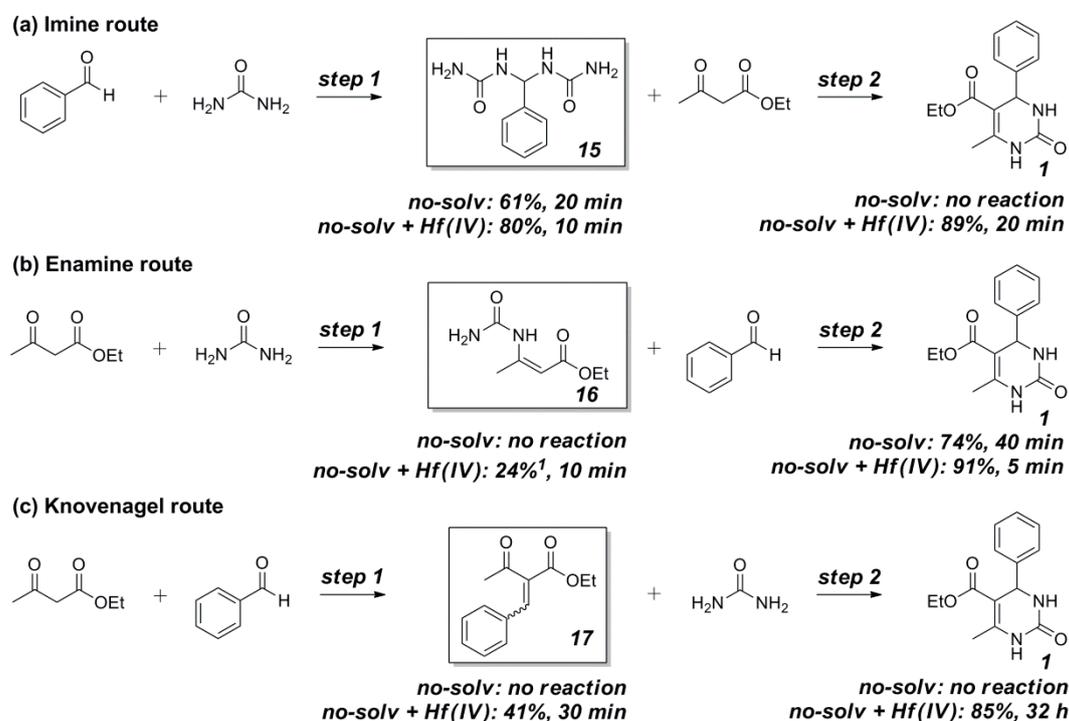


2.3. Mechanistic Investigation on the Reaction Pathways of the Hf(OTf)₄-Catalyzed Biginelli Reaction under Solvent-Free Conditions

Compared to that of metal Lewis acid-catalyzed Biginelli reactions performed in organic solvents, the mechanism of those under solvent-free conditions was simply interpreted as the same in most previous reports [13,20,24,29]. However, the huge difference in terms of catalyst needed, reaction rate, and yield between the two types of reaction conditions, as was observed in our and others' research [13,23–25,27,30], urged us to reconsider how solvent-free conditions affect the outcome of Biginelli reaction from a mechanistic perspective. Our investigation started with the preparation of the three key intermediates **15**, **16**, and **17**, which correspond to the imine, enamine, and Knoevenagel routes, respectively. As described in previous reports, **15** is obtained as a white solid and poorly soluble in most organic solvent. Meanwhile, both **16** and **17** are found stable for TLC analysis.

In the next stage, we closely analyzed the individual routes by tracing the sequential bimolecular condensations in the presence or absence of Hf(OTf)₄ under solvent-free conditions. Compared to the reactions in ethanol (either with or without Hf(OTf)₄), which barely generated much insoluble bisureide **15**, the bimolecular reaction between benzaldehyde and urea quickly formed a significant amount of white precipitation of **15** at 80 °C (61%, 20 min), indicating that the neat conditions promote the condensation (Scheme 1a). The presence of 1 mol% Hf(OTf)₄ further enhanced the formation of **15** (80%, 10 min). However, in the second step, only in the presence of Hf(OTf)₄ could **15** react with ethyl

acetoacetate to form desired DHPM **1** (89%, 20 min). This result showed that $\text{Hf}(\text{OTf})_4$ catalyzed both the reversion of bisureide **15** back to the proposed imine intermediate **18** and its subsequent annulation with ethyl acetoacetate. The solvent-free conditions and the metal Lewis acid synergistically strengthen the imine pathway, which largely explains the remarkable acceleration of $\text{Hf}(\text{IV})$ -catalyzed Biginelli reaction under solvent-free conditions over that under solvent-based conditions.



Scheme 1. The three “sequential bimolecular condensation reactions” (a–c) under solvent-free conditions in the presence or absence of $\text{Hf}(\text{OTf})_4$. ¹ Determined by ¹H-NMR in $\text{DMSO}-d_6$.

In solvent-based reaction, enamine **16** has been proved unable to react with benzaldehyde to yield **1** experimentally and theoretically. Therefore, the enamine route has not been regarded as a contribution in most previous research. However, we found that, under solvent-free conditions, $\text{Hf}(\text{OTf})_4$ could promote the quick condensation between ethyl acetoacetate and urea to give enamine **16** (24%, 10 min). The isolation by flash column chromatography indicated that **16** is easy to decompose in the presence of solvent, but is rather stable in solid form. More importantly, the subsequent annulation of **16** with benzaldehyde was fast and high-yielding in the presence of catalyst (91%, 5 min, Scheme 1b). This unexpected result strongly indicated that the presence of $\text{Hf}(\text{OTf})_4$ under solvent-free conditions activates the enamine route and opens the second pathway to reach the desired DHPM product.

Then, the reaction between benzaldehyde and ethyl acetoacetate was examined. The data in Scheme 1c shows that $\text{Hf}(\text{OTf})_4$ plays a key role for the Knoevenagel condensation. Compared to that of **15** and **16**, the $\text{Hf}(\text{IV})$ -catalyzed formation of **17** under solvent-free conditions was slower (41%, 30 min). Moreover, its subsequent annulation with urea afforded **1** in an extremely slow rate (85%, 32 h). Considering that $\text{Hf}(\text{IV})$ -catalyzed ‘one-pot, three-component’ Biginelli reaction is quite fast (20 min) under solvent-free conditions, the Knoevenagel route could hardly be fitted into the reaction time frame of the ‘one-pot, three-component’ Biginelli reaction.

Since the real “three-component” Biginelli reaction is more complicated, it was carefully reanalyzed under solvent-free conditions with $\text{Hf}(\text{OTf})_4$ to confirm the observations based on individual sequential bimolecular condensations. It was found that the originally clear reaction solution instantly generated a large amount of gel-like solid in the presence of $\text{Hf}(\text{IV})$ upon heating at 80 °C (2 min, Figure 1a). At this point, only a small amount of **1** and enamine **16** were observed on TLC, suggesting a large portion of the white solid obtained at this point might be bisureide, which was

isolated and confirmed as **15**. As the reaction proceeded, the amount of white solid decreased and the viscosity of the reaction system dropped remarkably (5 min, Figure 1a) possibly due to the Hf(IV)-catalyzed reversion of **15** to imine intermediate **18**. Afterwards, as more and more DHPM **1** accumulated via the imine and enamine routes as white precipitate, the viscosity of the reaction system increased again (from 10 to 20 min, Figure 1a). Although it is hard to determine the contributions from imine and enamine routes precisely, however, the initial formation of a large amount of **15** strongly suggested that the imine route appears as the major pathway to the final DHPM. To our surprise, the Knoevenagel adduct **17** was not observed on TLC throughout the entire process, indicating that the Knoevenagel route is completely prohibited in competition with the other two routes (Figure 1b).

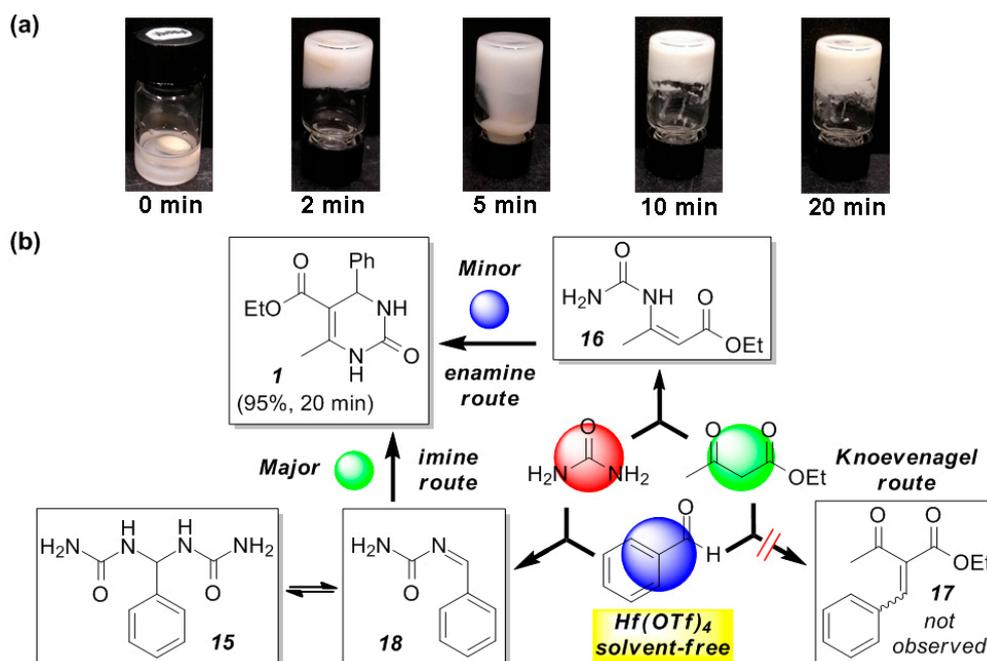


Figure 1. The photos (a) and proposed mechanism (b) for the $\text{Hf}(\text{OTf})_4$ -catalyzed Biginelli reaction under solvent-free conditions.

In contrast, analysis of the “one-pot, three-component” Biginelli reaction without $\text{Hf}(\text{OTf})_4$ showed that Knoevenagel adduct **17** was observed due to the catalysis by urea as reported by Puripat and coworkers [48]. This result suggested that the imine and enamine routes are less competitive without $\text{Hf}(\text{OTf})_4$. However, based on the ‘sequential bimolecular condensations’ (Scheme 1C, step 2), **17** could not further react with urea to yield **1** without $\text{Hf}(\text{OTf})_4$. It was observed that as the amount of **17** decreased between 3 and 8 h, an unexpected byproduct **19**, the adduct of **17** and ethyl acetoacetate, began to accumulate and was isolated in 14% yield at the end. This result indicated that solvent-free conditions alone is not sufficient for the fast and high-yielding formation of **1**. The synergistic effect of both solvent-free conditions and $\text{Hf}(\text{OTf})_4$ catalysis not only drastically accelerated the Biginelli reaction via imine and enamine routes but also avoided the formation of Knoevenagel adduct, which may lead to an undesired byproduct.

Interestingly, when N,N' -dimethylurea, instead of urea, was applied as a substrate (Figure 2), the corresponding $\text{Hf}(\text{OTf})_4$ -catalyzed reaction took much longer even under solvent-free conditions and afforded DHPM **20** in only moderate yield (68%, 24 h). Knoevenagel adduct **17** was the only intermediate observed on TLC. The simplified bimolecular condensation reactions showed that while N,N' -dimethylurea did not react with benzaldehyde at all, it could slowly react with ethyl acetoacetate to form a very small amount of pyrimidine **21** (10%, 24 h). However, in the three-component reaction, byproducts **19** and **21** were totally absent. These results showed that when both of the imine and

enamine routes are blocked due to a certain specific substrate, the Knoevenagel route could dominate the reaction and eventually afford the DHPM product.

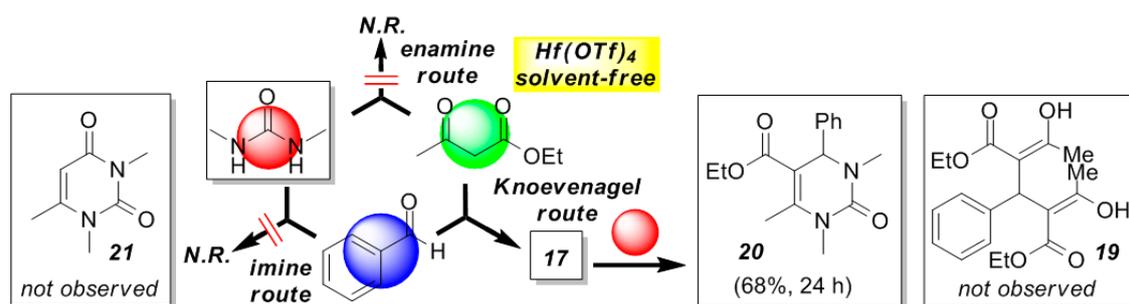


Figure 2. Mechanism variation for N,N' -dimethylurea-based Biginelli reaction.

2.4. Activation Effect of $\text{Hf}(\text{OTf})_4$ on β -Ketoester

In our previous research, we have revealed Hf(IV) cation's strong capability on activating benzaldehyde [50]. Many previous reports [13,14,20,24,29] had proposed that the interactions of metal cations with β -ketoester are also involved in the catalysis of Biginelli reaction. However, not much evidence has been provided to support this point. In current research, we utilized $^1\text{H-NMR}$ to examine the activation effects of Hf(IV) on β -ketoester (Supplementary Materials, Figure S43–S44). Interestingly, when 5 mol% of $\text{Hf}(\text{OTf})_4$ was added to methyl acetoacetate in $\text{MeOH-}d_4$, the rate of H-D exchange was remarkably promoted. As shown in Figure 3b, 93% of the proton at active methylene position was exchanged to deuterium in only 2 h. In the control experiment, it took 8 h for the H-D exchange to reach the equilibrium at 93% without $\text{Hf}(\text{OTf})_4$ (Figure 3a). Similar to the promoted tautomerization of dimethylphosphite in Kabachnik reaction [50], Hf(IV) accelerated the tautomerization of methylacetoacetate between the ketone and enol forms, thereby increasing overall reaction rate. More importantly, it was observed that Hf(IV) also activated the β -ketone moiety and induced the formation of ketal, which accounted for ~55% of the total β -ketoester used. This result is in good agreement with our observations that all steps involving benzaldehyde and ethyl acetoacetate (Scheme 1) are largely promoted.

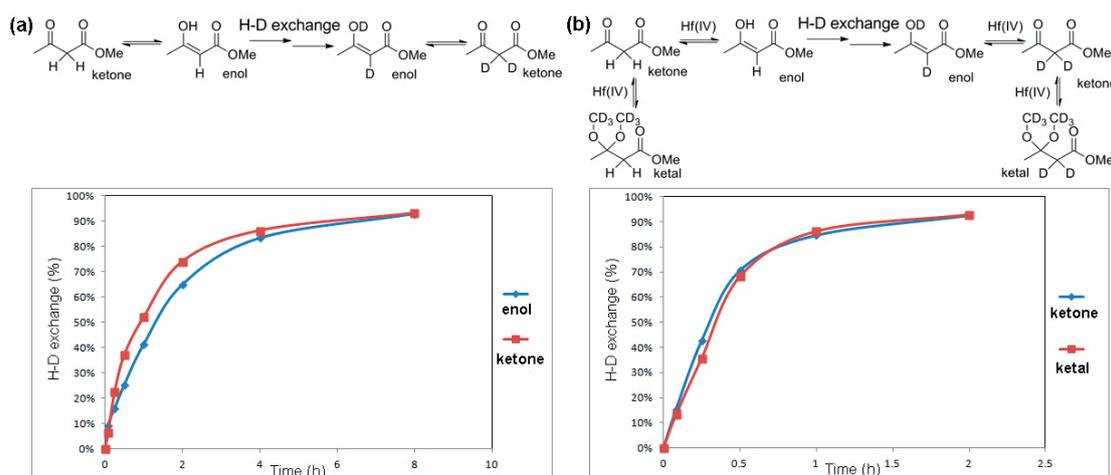


Figure 3. The H-D exchange reactions of methyl acetoacetate in $\text{MeOH-}d_4$ in the absence (a) or presence (b) of $\text{Hf}(\text{OTf})_4$.

3. Materials and Methods

3.1. General Methods

General chemical reagents and solvents were obtained from commercial suppliers. All reactions were monitored by thin layer chromatography on plates coated with 0.25 mm silica gel 60 F254 (Qingdao Haiyang Chemicals, Qingdao, China). TLC plates were visualized by UV irradiation (254 nm, Shanghai Peiqing Sci & Tech, Shanghai, China). Flash column chromatography employed silica gel (particle size 32–63 μm , Qingdao Haiyang Chemicals, Qingdao, China). Melting points were determined with a Thomas-Hoover melting point apparatus and uncorrected (Thomas Scientific, Swedesboro, NJ, USA). NMR spectra were obtained with a Bruker AV-400 instrument (Bruker BioSpin, Faellanden, Switzerland) with chemical shifts reported in parts per million (ppm, δ) and referenced to CDCl_3 or $\text{DMSO-}d_6$. The NMR spectra of compounds **1–17** and **19–21** were provided in Supplementary Materials (Figures S1–S42). IR spectra were recorded on a Bruker Vertex-70 spectrometer (Bruker Optics, Billerica, MA, USA). Low-resolution mass spectra were reported as m/z and obtained with a Bruker amaZon SL mass spectrometer (Bruker Daltonics, Billerica, MA, USA).

3.2. General Synthetic Procedure and Characterization of DHPMs **1–14** and **20**

To a mixture of aldehyde (1.0 mmol), β -ketoester/diketone (1.0 mmol), and urea/thiourea (1.2 mmol) was added $\text{Hf}(\text{OTf})_4$ (0.01 mmol). The reaction was stirred at 80 $^\circ\text{C}$ for 20–30 min. Then ethanol (2 mL) was added to the reaction to dissolve the solid residue completely. Upon cooling, the solid precipitate was filtered, washed, and dried to afford pure DHPM product. For compounds **9**, **10**, **13**, **14**, and **20**, the crude product was directly dissolved in CH_2Cl_2 and purified by flash column chromatography.

5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (1). The reaction of benzaldehyde (106 mg, 1 mmol), ethyl acetoacetate (130 mg, 1 mmol), urea (72 mg, 1.2 mmol), and $\text{Hf}(\text{OTf})_4$ (8 mg, 0.01 mmol) afforded **1** (247 mg, 95%) as a white solid; mp 209–210 $^\circ\text{C}$. $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ 9.18 (s, 1H), 7.73 (s, 1H), 7.32–7.25 (m, 5H), 5.14 (s, 1H), 3.98 (q, $J = 6.8$ Hz, 2H), 2.25 (s, 3H), 1.09 (t, $J = 6.8$ Hz, 3H) ppm; $^{13}\text{C-NMR}$ (100 MHz, $\text{DMSO-}d_6$): δ 165.3, 152.1, 148.3, 144.8, 128.3 ($\times 2$), 127.2, 126.2 ($\times 2$), 99.2, 59.1, 53.9, 17.7, 14.0 ppm; IR (KBr): ν_{max} 3248, 3121, 1725, 1699, 1648, 1420, 1314, 1221, 1090, 698 cm^{-1} ; LRMS (ESI+): m/z calcd for $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_3$ [$\text{M} + \text{H}$] $^+$ 261.1; found 261.2.

5-Ethoxycarbonyl-6-methyl-4-(4-methylphenyl)-3,4-dihydropyrimidin-2(1H)-one (2). The reaction of 4-methylbenzaldehyde (120 mg, 1 mmol), ethyl acetoacetate (130 mg, 1 mmol), urea (72 mg, 1.2 mmol), and $\text{Hf}(\text{OTf})_4$ (8 mg, 0.01 mmol) afforded **2** (252 mg, 92%) as a white solid; mp 218–219 $^\circ\text{C}$. $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ 9.15 (s, 1H), 7.67 (s, 1H), 7.15 (d, $J = 8.4$ Hz, 2H), 6.87 (d, $J = 8.4$ Hz, 2H), 5.10 (d, $J = 2.6$ Hz, 1H), 3.98 (q, $J = 7.1$ Hz, 2H), 3.71 (s, 3H), 2.24 (s, 3H), 1.10 (t, $J = 7.1$ Hz, 3H) ppm; $^{13}\text{C-NMR}$ (100 MHz, $\text{DMSO-}d_6$): δ 165.4, 158.4, 152.1, 147.9, 137.0, 127.4 ($\times 2$), 113.7 ($\times 2$), 99.6, 59.1, 55.0, 53.3, 17.7, 14.1 ppm; IR (KBr): ν_{max} 3244, 3113, 2937, 1723, 1704, 1650, 1460, 1309, 1286, 1222, 1088, 783 cm^{-1} ; LRMS (ESI+): m/z calcd for $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_3$ [$\text{M} + \text{H}$] $^+$ 275.1; found 275.2.

5-Ethoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (3). The reaction of 4-methoxybenzaldehyde (136 mg, 1 mmol), ethyl acetoacetate (130 mg, 1 mmol), urea (72 mg, 1.2 mmol), and $\text{Hf}(\text{OTf})_4$ (8 mg, 0.01 mmol) afforded **3** (270 mg, 93%) as a white solid; mp 201–202 $^\circ\text{C}$. $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ 9.17 (s, 1H), 7.70 (s, 1H), 7.12 (s, 4H), 5.12 (s, 1H), 3.98 (q, $J = 7.0$ Hz, 2H), 2.25 (s, 6H), 1.10 (t, $J = 7.0$ Hz, 3H) ppm; $^{13}\text{C-NMR}$ (100 MHz, $\text{DMSO-}d_6$): δ 165.4, 158.4, 152.1, 147.9, 137.0, 127.4 ($\times 2$), 113.7 ($\times 2$), 99.6, 59.1, 55.0, 53.3, 17.7, 14.1 ppm; IR (KBr): ν_{max} 3250, 3113, 2940, 1714, 1695, 1652, 1440, 1306, 1279, 1220, 1085, 769 cm^{-1} ; LRMS (ESI+): m/z calcd for $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_4$ [$\text{M} + \text{H}$] $^+$ 291.1; found 291.0.

4-(4-Chlorophenyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one (4). The reaction of 4-chlorobenzaldehyde (140 mg, 1 mmol), ethyl acetoacetate (130 mg, 1 mmol), urea (72 mg, 1.2 mmol),

and Hf(OTf)₄ (8 mg, 0.01 mmol) afforded **4** (259 mg, 88%) as a yellow solid; mp 215–216 °C. ¹H-NMR(400 MHz, DMSO-*d*₆): δ 9.26 (s, 1H), 7.78 (s, 1H), 7.39 (d, *J* = 8.1 Hz, 2H), 7.26 (d, *J* = 8.1 Hz, 2H), 5.16 (s, 1H), 3.98 (q, *J* = 7.0 Hz, 2H), 2.26 (s, 3H), 1.09 (t, *J* = 7.0 Hz, 3H) ppm; ¹³C-NMR (100 MHz, DMSO-*d*₆): δ 165.2, 151.9, 148.6, 143.7, 131.8, 128.3 (×2), 128.1 (×2), 98.9, 59.2, 53.4, 17.7, 14.0 ppm; IR (KBr): ν_{max} 3248, 3113, 2933, 1725, 1707, 1649, 1313, 1290, 1222, 1091, 698 cm⁻¹; LRMS (ESI+): *m/z* calcd for C₁₄H₁₅ClN₂O₃ [M + H]⁺ 295.1; found 295.1.

5-Ethoxycarbonyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one (**5**). The reaction of 4-nitrobenzaldehyde (151 mg, 1 mmol), ethyl acetoacetate (130 mg, 1 mmol), urea (72 mg, 1.2 mmol), and Hf(OTf)₄ (8 mg, 0.01 mmol) afforded **5** (259 mg, 85%) as a yellow solid; mp 212–213 °C. ¹H-NMR(400 MHz, DMSO-*d*₆): δ 9.36 (s, 1H), 8.21 (d, *J* = 8.4 Hz, 2H), 7.90 (s, 1H), 7.51 (d, *J* = 8.4 Hz, 2H), 5.29 (s, 1H), 3.98 (q, *J* = 7.0 Hz, 2H), 2.27 (s, 3H), 1.09 (t, *J* = 7.0 Hz, 3H) ppm; ¹³C-NMR (100 MHz, DMSO-*d*₆): δ 165.0, 152.0, 151.7, 149.3, 146.7, 127.6 (×2), 123.7 (×2), 98.2, 59.3, 53.7, 17.8, 14.0 ppm; IR (KBr): ν_{max} 3240, 3116, 2964, 1729, 1707, 1646, 1520, 1348, 1216, 1008, 782, 697 cm⁻¹; LRMS (ESI+): *m/z* calcd for C₁₄H₁₅N₃O₅[M + H]⁺ 306.1; found 306.1.

5-Ethoxycarbonyl-4-(2-furanyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**6**). The reaction of furfural (96 mg, 1 mmol), ethyl acetoacetate (130 mg, 1 mmol), urea (72 mg, 1.2 mmol), and Hf(OTf)₄ (8 mg, 0.01 mmol) afforded **6** (228 mg, 91%) as a white solid; mp 209–210 °C. ¹H-NMR(400 MHz, DMSO-*d*₆): δ 9.25 (s, 1H), 7.76 (s, 1H), 7.55 (s, 1H), 6.36–6.35 (m, 1H), 6.09 (d, *J* = 3.0 Hz, 1H), 5.20 (d, *J* = 3.3 Hz, 1H), 4.05–4.00 (m, 2H), 2.23 (s, 3H), 1.13 (t, *J* = 7.1 Hz, 3H) ppm; ¹³C-NMR (100 MHz, DMSO-*d*₆): δ 165.0, 156.0, 152.4, 149.3, 142.1, 110.3, 105.2, 96.8, 59.2, 47.7, 17.7, 14.1 ppm; IR (KBr): ν_{max} 3244, 3102, 1701, 1649, 1318, 1234, 1100, 740 cm⁻¹; LRMS (ESI+): *m/z* calcd for C₁₂H₁₄N₂O₄ [M + H]⁺ 251.1; found 251.1.

5-Ethoxycarbonyl-4-(2-thienyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**7**). The reaction of 2-thenaldehyde (112 mg, 1 mmol), ethyl acetoacetate (130 mg, 1 mmol), urea (72 mg, 1.2 mmol), and Hf(OTf)₄ (8 mg, 0.01 mmol) afforded **7** (253 mg, 95%) as a white solid; mp 216–217 °C. ¹H-NMR(400 MHz, DMSO-*d*₆): δ 9.33 (s, 1H), 7.92 (s, 1H), 7.34 (d, *J* = 5.0 Hz, 1H), 6.95–6.90 (m, 2H), 5.42 (d, *J* = 3.3 Hz, 1H), 4.06 (q, *J* = 7.0 Hz, 2H), 2.22 (s, 3H), 1.16 (t, *J* = 7.0 Hz, 3H) ppm; ¹³C-NMR (100 MHz, DMSO-*d*₆): δ 165.0, 152.2, 148.8, 148.6, 126.6, 124.5, 123.4, 99.8, 59.3, 49.3, 17.6, 14.1 ppm; IR (KBr): ν_{max} 3334, 3237, 3120, 1703, 1650, 1317, 1225, 1096, 789 cm⁻¹; LRMS (ESI+): *m/z* calcd for C₁₂H₁₄N₂O₃S [M + H]⁺ 267.1; found 267.0.

5-Methoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (**8**). The reaction of benzaldehyde (106 mg, 1 mmol), methyl acetoacetate (116 mg, 1 mmol), urea (72 mg, 1.2 mmol), and Hf(OTf)₄ (8 mg, 0.01 mmol) afforded **8** (236 mg, 96%) as a white solid; mp 216–217 °C. ¹H-NMR(400 MHz, DMSO-*d*₆): δ 9.25 (s, 1H), 7.78 (s, 1H), 7.34–7.23 (m, 5H), 5.15 (d, *J* = 3.3 Hz, 1H), 3.53 (s, 3H), 2.26 (s, 3H) ppm; ¹³C-NMR (100 MHz, DMSO-*d*₆): δ 165.8, 152.2, 148.6, 144.6, 128.4 (×2), 127.2, 126.1 (×2), 99.0, 53.8, 50.7, 17.8 ppm; IR (KBr): ν_{max} 3338, 2950, 1713, 1680, 1661, 1642, 1431, 1380, 1346, 1280, 1237, 1088, 755, 700 cm⁻¹; LRMS (ESI+): *m/z* calcd for C₁₃H₁₄N₂O₃ [M + H]⁺ 247.1; found 247.1.

5-Ethoxycarbonyl-4-(4-methylphenyl)-6-propyl-3,4-dihydropyrimidin-2(1H)-one (**9**). The reaction of 4-methylbenzaldehyde (120 mg, 1 mmol), ethyl butyrylacetate (158 mg, 1 mmol), urea (72 mg, 1.2 mmol), and Hf(OTf)₄ (8 mg, 0.01 mmol) afforded (**9**) (269 mg, 89%) as a glassy solid; mp 146–147 °C. ¹H-NMR(400 MHz, DMSO-*d*₆): δ 9.13 (s, 1H), 7.67 (s, 1H), 7.11 (s, 4H), 5.10 (d, *J* = 2.6 Hz, 1H), 3.97 (q, *J* = 7.0 Hz, 2H), 2.62 (t, *J* = 7.3 Hz, 2H), 2.25 (s, 3H), 1.55 (q, *J* = 7.3 Hz, 2H), 1.10 (t, *J* = 7.0 Hz, 3H), 0.90 (t, *J* = 7.3 Hz, 3H) ppm; ¹³C-NMR (100 MHz, DMSO-*d*₆): δ 165.1, 152.3, 152.1, 142.0, 136.3, 128.8 (×2), 126.1 (×2), 99.2, 59.1, 53.6, 32.3, 21.6, 20.6, 14.0, 13.6 ppm; IR (KBr): ν_{max} 3252, 3121, 1702, 1643, 1308, 1210, 1084, 796 cm⁻¹; LRMS (ESI+): *m/z* calcd for C₁₇H₂₂N₂O₃ [M + H]⁺ 303.2; found 303.2.

5-Ethoxycarbonyl-6-ethyl-4-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (**10**). The reaction of 4-methoxybenzaldehyde (136 mg, 1 mmol), ethyl propionylacetate (144 mg, 1 mmol), urea (72 mg, 1.2 mmol), and Hf(OTf)₄ (8 mg, 0.01 mmol) afforded (**10**) (252 mg, 83%) as a glassy solid; mp 151–152 °C. ¹H-NMR(400 MHz, CDCl₃): δ 8.61 (s, 1H), 7.22–6.80 (m, 4H), 6.25 (s, 1H), 5.31 (s, 1H),

4.05 (q, $J = 6.9$ Hz, 2H), 3.76 (s, 3H), 2.74–2.64 (m, 2H), 1.25–1.14 (m, 6H) ppm; $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 165.4, 159.1, 154.2, 151.8, 136.3, 127.7 ($\times 2$), 113.9 ($\times 2$), 100.6, 59.9, 55.2, 54.8, 25.2, 14.1, 12.6 ppm; IR (KBr): ν_{max} 3386, 3241, 3103, 2978, 1702, 1646, 1511, 1460, 1302, 1220, 1173, 797 cm^{-1} ; LRMS (ESI+): m/z calcd for $\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}_4$ $[\text{M} + \text{H}]^+$ 305.1; found 305.2.

5-Acetyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (11). The reaction of benzaldehyde (106 mg, 1 mmol), 2,4-pentanedione (100 mg, 1 mmol), urea (72 mg, 1.2 mmol), and $\text{Hf}(\text{OTf})_4$ (8 mg, 0.01 mmol) afforded **11** (253 mg, 95%) as a white solid; mp 239–240 °C. $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ 9.21 (s, 1H), 7.85 (s, 1H), 7.34–7.24 (m, 5H), 5.26 (d, $J = 2.6$ Hz, 1H), 2.29 (s, 3H), 2.10 (s, 3H) ppm; $^{13}\text{C-NMR}$ (100 MHz, $\text{DMSO-}d_6$): δ 194.2, 152.1, 148.0, 144.2, 128.5 ($\times 2$), 127.3, 126.4 ($\times 2$), 109.6, 53.8, 30.2, 18.8 ppm; IR (KBr): ν_{max} 3258, 1712, 1702, 1675, 1455, 1366, 1330, 1236, 769 cm^{-1} ; LRMS (ESI+): m/z calcd for $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_2$ $[\text{M} + \text{H}]^+$ 231.1; found 231.1.

5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-thione (12). The reaction of benzaldehyde (106 mg, 1 mmol), ethyl acetoacetate (130 mg, 1 mmol), thiourea (91 mg, 1.2 mmol), and $\text{Hf}(\text{OTf})_4$ (8 mg, 0.01 mmol) afforded **12** (226 mg, 82%) as a yellow solid; mp 208–209 °C. $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ 10.34 (s, 1H), 9.66 (s, 1H), 7.36–7.21 (m, 5H), 5.18 (d, $J = 2.6$ Hz, 1H), 4.00 (q, $J = 7.0$ Hz, 2H), 2.29 (s, 3H), 1.10 (t, $J = 7.0$ Hz, 3H) ppm; $^{13}\text{C-NMR}$ (100 MHz, $\text{DMSO-}d_6$): δ 174.3, 165.1, 145.0, 143.5, 128.5 ($\times 2$), 127.7, 126.4 ($\times 2$), 100.7, 59.6, 54.0, 17.1, 14.0 ppm; IR (KBr): ν_{max} 3327, 3172, 3099, 1982, 1669, 1574, 1465, 1327, 1283, 1176, 1118, 760, 693 cm^{-1} ; LRMS (ESI+): m/z calcd for $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_2\text{S}$ $[\text{M} + \text{H}]^+$ 277.1; found 277.1.

5-Ethoxycarbonyl-6-ethyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-thione (13). The reaction of benzaldehyde (106 mg, 1 mmol), ethyl propionylacetate (144 mg, 1 mmol), thiourea (91 mg, 1.2 mmol), and $\text{Hf}(\text{OTf})_4$ (8 mg, 0.01 mmol) afforded (PE/EA = 5:3) **13** (232 mg, 80%) as a glassy solid; mp 156–157 °C. $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 8.57 (s, 1H), 7.97 (s, 1H), 7.31–7.24 (m, 5H), 5.35 (d, $J = 3.1$ Hz, 1H), 4.09–4.01 (m, 2H), 2.73 (q, $J = 7.5$ Hz, 2H), 1.21–1.11 (m, 6H) ppm; $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 174.6, 164.9, 148.5, 142.5, 128.9, 128.5, 128.3, 127.0, 126.8, 102.0, 60.4, 56.0, 24.8, 14.0, 12.0 ppm; IR (KBr): ν_{max} 3179, 2982, 1705, 1649, 1474, 1185, 1099, 762, 696 cm^{-1} ; LRMS (ESI+): m/z calcd for $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_2\text{S}$ $[\text{M} + \text{H}]^+$ 291.1; found 291.1.

5-Ethoxycarbonyl-6-methyl-4-pentyl-3,4-dihydropyrimidin-2(1H)-one (14). The reaction of *n*-hexaldehyde (100 mg, 1 mmol), ethyl acetoacetate (130 mg, 1 mmol), urea (72 mg, 1.2 mmol), and $\text{Hf}(\text{OTf})_4$ (8 mg, 0.01 mmol) afforded (PE/EA = 2:1) **14** (209 mg, 82%) as a white solid; mp 151–152 °C. $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 8.21 (s, 1H), 5.85 (s, 1H), 4.30–4.13 (m, 3H), 2.28 (s, 3H), 1.52 (m, 2H), 1.42–1.25 (m, 9H), 0.86 (t, $J = 6.6$ Hz, 3H) ppm; $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 166.0, 154.6, 146.7, 101.8, 60.0, 51.7, 36.9, 31.5, 24.1, 22.6, 18.6, 14.4, 14.1 ppm; IR (KBr): ν_{max} 3245, 3121, 2954, 1725, 1420, 1314, 1221, 1090, 698 cm^{-1} ; LRMS (ESI+): m/z calcd for $\text{C}_{13}\text{H}_{22}\text{N}_2\text{O}_3$ $[\text{M} + \text{H}]^+$ 255.3; found 255.3.

5-Ethoxycarbonyl-1,3,6-trimethyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (20). The reaction of benzaldehyde (106 mg, 1 mmol), ethyl acetoacetate (130 mg, 1 mmol), *N,N'*-dimethyl urea (106 mg, 1.2 mmol), and $\text{Hf}(\text{OTf})_4$ (8 mg, 0.01 mmol) afforded **20** (199 mg, 68%) as colorless oil. $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 7.30–7.21 (m, 5H), 5.24 (s, 1H), 4.16–4.11 (m, 2H), 3.26 (s, 3H), 2.91 (s, 3H), 2.48 (s, 3H), 1.24 (t, $J = 7.1$ Hz, 3H) ppm; $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 166.0, 153.9, 149.2, 141.1, 128.6 ($\times 2$), 127.9, 126.6 ($\times 2$), 103.7, 60.9, 60.1, 34.4, 31.0, 16.6, 14.2 ppm; IR (KBr): ν_{max} 3240, 3110, 2980, 1710, 1665, 1316, 1220, 1097, 780 cm^{-1} ; LRMS (ESI+): m/z calcd for $\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}_3$ $[\text{M} + \text{H}]^+$ 289.1; found 289.1.

3.3. Synthetic Procedures and Characterization of 15–17, 19, and 21

1,1'-Phenylmethanediyl-bis-urea (15). To the mixture of benzaldehyde (106 mg, 1 mmol) and urea (72 mg, 1.2 mmol) was added $\text{Hf}(\text{OTf})_4$ (8 mg, 0.01 mmol). The reaction was stirred at 80 °C for 10 min. Upon cooling, the white solid residue was washed with CH_2Cl_2 ($\times 3$) and EtOH ($\times 3$) to afford **15** (111 mg, 80%) as a white solid; mp 216–218 °C. $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ 7.33 (s, 5H), 7.26

(s, 1H), 6.94 (ds, 1H), 6.77 (ds, 1H), 6.18 (ds, 2H), 5.66 (s, 2H) ppm; $^{13}\text{C-NMR}$ (100 MHz, $\text{DMSO-}d_6$): δ 157.6, 157.5, 142.5, 128.0 ($\times 2$), 127.0, 125.9 ($\times 2$), 59.1 ppm; LRMS (ESI+): m/z calcd for $\text{C}_9\text{H}_{12}\text{N}_4\text{O}_2$ [$\text{M} + \text{H}$] $^+$ 209.1; found 209.1.

3-Ureido-crotonic acid ethyl ester (16). To the mixture of ethyl acetoacetate (130 mg, 1 mmol) and urea (72 mg, 1.2 mmol) was added $\text{Hf}(\text{OTf})_4$ (8 mg, 0.01 mmol). The reaction was stirred at 80 °C for 10 min. (The yield of **16** in the reaction mixture was determined to be 24% by $^1\text{H-NMR}$ in $\text{DMSO-}d_6$ when reaction reached equilibrium.) Flash column chromatography afforded (PE/EA = 4:1) **16** (9 mg, 5%) as a white solid (due to partial decomposition during purification); mp 165–166 °C. $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 10.15 (s, 1H), 6.80 (bs, 2H), 4.76 (s, 1H), 4.06 (q, $J = 7.0$ Hz, 2H), 2.24 (s, 3H), 1.18 (t, $J = 7.1$ Hz, 3H) ppm; $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 168.2, 156.7, 154.1, 91.7, 58.7, 21.5, 14.2 ppm; LRMS (ESI+): m/z calcd for $\text{C}_7\text{H}_{12}\text{N}_2\text{O}_3$ [$\text{M} + \text{H}$] $^+$ 173.1; found 173.1.

(E)-2-Acetyl-3-phenylacrylic acid ethyl ester (17a). To the mixture of benzaldehyde (106 mg, 1 mmol) and ethyl acetoacetate (130 mg, 1 mmol) was added $\text{Hf}(\text{OTf})_4$ (8 mg, 0.01 mmol). The reaction was stirred at 80 °C for 30 min. Flash column chromatography afforded (PE/DCM = 5:4) **17a** (89 mg, 20%) as yellow oil. $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 7.66 (s, 1H), 7.37 (s, 5H), 4.29 (q, $J = 7.1$ Hz, 2H), 2.34 (s, 3H), 1.32 (t, $J = 7.1$ Hz, 3H) ppm; $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 203.2, 164.5, 140.5, 134.3, 133.0, 130.4, 129.7 ($\times 2$), 129.0 ($\times 2$), 61.6, 31.2, 14.2 ppm; LRMS (ESI+): m/z calcd for $\text{C}_{13}\text{H}_{14}\text{O}_3$ [$\text{M} + \text{H}$] $^+$ 219.1; found 219.2.

(Z)-2-Acetyl-3-phenylacrylic acid ethyl ester (17b). After **17a** was eluted from the column, more polar eluent afforded (PE/EA = 10:1) **17b** (89 mg, 21%) as yellow oil. $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 7.57 (s, 1H), 7.46–7.37 (m, 5H), 4.33 (q, $J = 7.2$ Hz, 2H), 2.42 (s, 3H), 1.27 (t, $J = 7.2$ Hz, 3H) ppm; $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 194.6, 167.7, 141.2, 134.7, 133.0, 130.7, 129.5 ($\times 2$), 128.8 ($\times 2$), 61.7, 26.5, 13.8 ppm; LRMS (ESI+): m/z calcd for $\text{C}_{13}\text{H}_{14}\text{O}_3$ [$\text{M} + \text{H}$] $^+$ 219.1; found 219.2.

(2Z,4Z)-Diethyl 2,4-bis(1-hydroxyethylidene)-3-phenylpentanedioate (19). The mixture of benzaldehyde (106 mg, 1 mmol), ethyl acetoacetate (130 mg, 1 mmol), and urea (72 mg, 1.2 mmol) was stirred at 80 °C for 24 h. Flash column chromatography afforded (PE/EA = 5:2) **19** (24 mg, 14%) as a white solid; mp 160–161 °C. $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 7.29–7.10 (m, 5H), 5.89 (s, 1H), 4.89 (s, 1H), 4.12–4.04 (m, 4H), 2.31 (s, 6H), 1.22 (t, $J = 7.1$ Hz, 6H) ppm; $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 167.7 ($\times 2$), 147.8, 144.0 ($\times 2$), 128.0 ($\times 2$), 127.9 ($\times 2$), 126.1, 104.2 ($\times 2$), 59.8 ($\times 2$), 39.7, 19.5 ($\times 2$), 14.3 ($\times 2$) ppm; LRMS (ESI+): m/z calcd for $\text{C}_{19}\text{H}_{24}\text{O}_6$ [$\text{M} + \text{H}$] $^+$ 349.2; found 349.2.

1,3,6-Trimethyluracil (21). To the mixture of ethyl acetoacetate (130 mg, 1 mmol) and urea (72 mg, 1.2 mmol) was added $\text{Hf}(\text{OTf})_4$ (8 mg, 0.01 mmol). The reaction was stirred at 80 °C for 24 h. Flash column chromatography afforded (DCM/EA = 5:2) **21** (15 mg, 10%) as a white solid; mp 115–116 °C. $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 5.16 (s, 1H), 3.39 (s, 3H), 3.32 (s, 3H), 2.22 (s, 3H) ppm; $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 162.4, 152.6, 151.4, 101.2, 31.7, 27.9, 20.2 ppm; LRMS (ESI+): m/z calcd for $\text{C}_7\text{H}_{10}\text{N}_2\text{O}_2$ [$\text{M} + \text{H}$] $^+$ 155.1; found 155.1.

4. Conclusions

In summary, $\text{Hf}(\text{OTf})_4$ was identified as a highly efficient catalyst for Biginelli reaction. Under solvent-free conditions, as low as 1 mol% $\text{Hf}(\text{OTf})_4$ could catalyze efficient formation of a diversity of 2-oxo/thio DHPMs in only 20–30 min. The mechanistic investigation based on ‘sequential bimolecular condensations’ showed that the enhancement of imine route and unexpected activation of enamine route are responsible for the dramatically improved catalytic activity of $\text{Hf}(\text{OTf})_4$ under solvent-free conditions over that under solvent-based conditions. The tracing of ‘one-pot, three-component’ Biginelli reaction not only confirmed our observations on individual routes but also revealed the formation of bisureide **15** as a transient intermediate and total inhibition of Knoevenagel route under $\text{Hf}(\text{OTf})_4$ catalysis and solvent-free conditions. However, in the case of an N,N' -dimethylurea-based Biginelli reaction, the corresponding DHPM **20** was obtained almost solely via Knoevenagel route rather than the prohibited imine and enamine routes in a much slower rate.

These results strongly suggest that the mechanism for Biginelli reaction may vary depending on both reaction conditions and reactivity of substrates, and should not be simply interpreted as the same as the classic Biginelli reaction. In addition, the $^1\text{H-NMR}$ tracing of the H-D exchange reaction of methyl acetoacetate in $\text{MeOH-}d_4$ illustrated that $\text{Hf}(\text{OTf})_4$ not only accelerated the tautomerization of methylacetoacetate but also activated the β -ketone moiety, thereby contributing to the overall promotion of Biginelli reaction.

Supplementary Materials: The following are available online, Figures S1–S42: The NMR spectra of compounds 1–17 and 19–21; Figures S43–S44: The $^1\text{H-NMR}$ tracing of the H-D exchange reactions of methyl acetoacetate in $\text{MeOH-}d_4$.

Author Contributions: Contributions: R.K., S.-S.G., and Q.S. conceived and designed the experiments; R.K., S.-B.H., J.-Y.W., X.-C.P., and Z.-B.X. performed the experiments and analyzed the data; S.-S.G. and Q.S. wrote the paper.

Funding: This research was funded by National Natural Science Foundation of China (21562021), Fellowship for Young Scientists (2015BCB23009), and Sci & Tech Project from Dept of Education (GJJ160763) of Jiangxi Province.

Conflicts of Interest: The authors declare no conflict of interest.

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Sample Availability: Samples of the compounds are available from the authors.



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