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# Iron(II) Triflate Catalyzed Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones via the Biginelli Reaction

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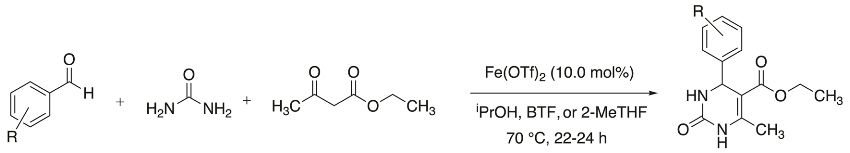
## Abstract

The synthesis of dihydropyrimidinones is of interest due to their biological activities. A common method for their synthesis is the Biginelli reaction, which is a one-pot multicomponent reaction of an aldehyde, urea and a *β*-ketoester. The Biginelli reaction is typically catalyzed by a Brønsted or Lewis acid. However, many of these catalysts, such as $BF_3 \cdot Et_2O$ and $AlCl_3$ are corrosive and/or toxic. Herein, we report the iron(II) triflate-catalyzed (10.0 mol%, 22 - 24 h) synthesis of dihydropyrimidinones via the Biginelli reaction in isopropanol as a solvent. The reaction is also reported in two other solvents, benzotrifluoride (a useful replacement for $CH_2Cl_2$) and 2-methyltetrahydrofuran, a bio-derived solvent. Iron(II) salts are attractive catalysts because of their low cost, low toxicity, and ease of handling.



## Keywords

Aldehydes, Biginelli Reaction, 3,4-Dihydropyrimidin-2(1*H*)-ones, Green Chemistry, Iron(II) Triflate, Multicomponent Reactions

## 1. Introduction

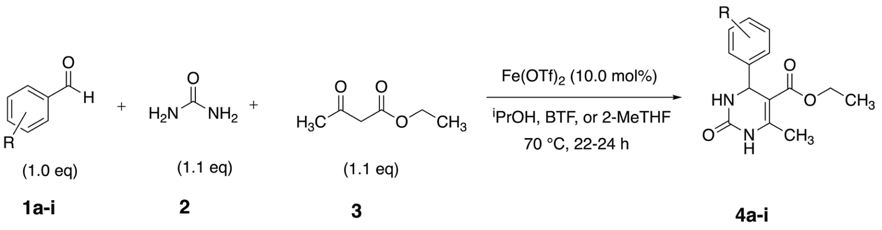
Dihydropyrimidinone scaffolds are of considerable interest in medicinal chemistry because of their relative ease of construction and the range of biological activities they exhibit. They have been reported to show anti-hypertensive and calcium-channel blocking activities [1], anti-mitotic properties [2], antioxidant properties [3], and antibiotic properties [4]. Although Biginelli reported the first synthesis of dihydropyrimidinones in 1893 [5], it is only since the 1990's that several other methods for their synthesis have been reported. The Biginelli reaction is a classic example of a multicomponent reaction (MCR) that allows rapid assembly of a complex structure in a single step [6] [7]. The mechanism of the Biginelli reaction has been extensively studied [8] [9]. In the last couple of decades, several catalysts have been reported for the Biginelli reaction, which include Lewis acids and bases. A few representative examples of Lewis acid/acidic catalysts used for the Biginelli reaction include *tetra*-butyl ammonium bromide [10], $CaF_2$ [11], $Y(NO_3)_3{\cdot}6H_2O$ [12], $Bi(OTf)_3$ [13], $Cu(OTf)_2$ [14], and $InCl_3$ [15]. The Biginelli reaction has also been done under solvent-free conditions using montmorillonite KSF [16]. There are fewer reports of the Biginelli reaction catalyzed under basic conditions, and these include $(NH_4)_2CO_3$ [17], $PPh_3$ [18], and *t*-BuOK [19]. Organocatalysts, such as L-proline [20], have also been used to catalyze the Biginelli reaction. A few examples of the asymmetric Biginelli reaction have been reported as well [21]. Iron compounds have attracted attention as catalysts in recent years due to their ready availability and relative non-toxicity compared to precious metal-based catalysts [22]. Iron(III) salts such as $FeCl_3{\cdot}6H_2O$ [23], $FeF_3$ [24], $Fe(CF_3CO_2)_3$ [25], $Fe(CF_3SO_3)_3$ [25], and $Fe(OTs)_3$ [26] have been successfully employed as catalysts for the Biginelli reaction. Iron(III) chloride worked well as a catalyst, but the reaction required 1.5 equivalents of urea for optimal results, and the isolation protocol generates considerable aqueous waste. Iron(III) fluoride also works well as a catalyst, but the product isolation protocol requires an aqueous work-up, thus resulting in a considerable aqueous waste stream that can contain HF. In addition, $FeF_3$ itself is quite toxic [27]. Iron(III) acetate and iron(III) triflate catalyzed reactions have been reported under solvent-free conditions, but again, the product isolation protocol generates a lot of aqueous waste stream. A solvent-free protocol has been reported using $Fe(NO_3)_3{\cdot}9H_2O$ [28]. However, caution must be exercised in grinding metal nitrates, especially on a large scale. Sustainable approaches to the Biginelli reaction have been summarized in the literature [29].

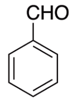
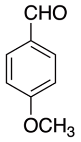
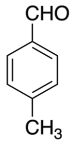
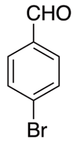
## 2. Results and Discussion

Due to our continued interest in developing environmentally friendly synthetic methodology, we investigated the utility of iron(II) trifluoromethanesulfonate (triflate) as a catalyst for the Biginelli reaction. Iron(II) salts are generally inexpensive, not very corrosive, and easy to handle. There are fewer reports of the utility of iron(II) triflate in organic synthesis [30]-[33]. Herein, we report the utility of iron(II) triflate as a catalyst for the Biginelli reaction that minimizes the generation of an aqueous waste stream.

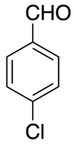
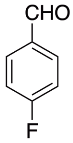
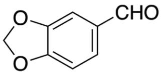
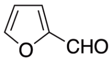
The results of this study are summarized in **Table 1**. As can be seen from **Table 1**, iron(II) triflate (10.0 mol%) is an efficient catalyst for the synthesis of dihydropyrimidinones from a variety of aldehydes. Although the reaction worked with lower catalyst loading (5.0 mol%), optimal reaction times and yields were seen with the use of 10.0 mol% catalyst. Several solvents were examined for the reaction, and the best results were obtained in isopropanol, which is a relatively environmentally benign solvent [34]. This methodology avoids an aqueous work-up and hence large aqueous waste streams are avoided. The yields were lower with furfural (entry 1h) and decanal (entry 1i). The results with aldehydes containing an electron-withdrawing group, such as 3-nitrobenzaldehyde and 3-hydroxybenzaldehyde, were less promising, and the crude product was a mixture of desired product and several intermediates. We also explored the utility of an aprotic solvent, benzotrifluoride (BTF) [35] [36]. BTF is an attractive and safer alternative to the highly toxic $CH_2Cl_2$, which is now banned by the US EPA. In addition, the reaction was also attempted in 2-methyltetrahydrofuran (2-MeTHF), which is a bio-derived solvent readily available from furfural and levulinic acid, and is considered an environmentally friendly alternative to THF [37]. The use of 2-MeTHF as a solvent gave better yields than BTF.

**Table 1.** Iron(II) triflate catalyzed synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones via the Biginelli reaction.



| Entry[a] | Aldehyde[b] | Solvent[c,d] | Yield[e] (%)<br>4a - i |
|---|---|---|---|
| 1a [38] |  | $^{i}$PrOH<br>BTF<br>2-MeTHF | 72<br>61<br>74 |
| 1b [38] |  | $^{i}$PrOH<br>BTF<br>2-MeTHF | 93<br>59<br>74 |
| 1c [38] |  | $^{i}$PrOH | 73 |
| 1d [39] |  | $^{i}$PrOH | 85[f] |

**Continued**

| | | | |
|---|---|---|---|
| 1e [38] |  | $^i$PrOH<br>BTF<br>2-MeTHF | 90<br>73<br>86 |
| 1f [40] |  | $^i$PrOH | 73 |
| 1g [41] |  | $^i$PrOH | 73 |
| 1h [38] |  | $^i$PrOH | 40 |
| 1i [41] | $CH_3(CH_2)_8CHO$ | $^i$PrOH | 56 |

[a]Superscript against entry number refers to literature reference for product. [b]All aldehydes are commercially available and were purified before use. [c]Reaction mixtures were heated using a temperature-controlled hot plate. [d]The progress of the reaction was followed by TLC (disappearance of aldehyde, 2,4-DNP stain). [e]Refers to yield of the isolated product that was determined to be ≥98% pure by $^1H$ & $^{13}C$ NMR. All products have been reported previously and were characterized by $^1H$ & $^{13}C$ NMR spectroscopy. Reactions were run at least two times and yields were found to be reproducible. [f]Reaction was run with 1.3 equivalents of ethyl acetoacetate and 1.3 equivalents of urea.

## 3. Experimental Section

*Three representative procedures are given here.*

*Reaction in isopropanol (entry 1b)*:

A solution of *p*-anisaldehyde (0.212 g, 1.56 mmol, 1.0 eq), urea (0.103 g, 1.72 mmol, 1.1 eq) and ethyl acetoacetate (0.223 g, 0.218 mL, 1.72 mmol, 1.1 eq) in isopropanol (4.0 mL) was stirred at room temperature as iron(II) triflate (0.055 g, 0.156 mmol, 10.0 mol%) was added. The reaction mixture was heated at 70˚C (temperature-controlled hot plate). After 22.5 h, the mixture was cooled to room temperature. The solvent was removed on a rotary evaporator, and the residue was triturated with $CH_3OH/H_2O$ (1:1, v/v, 5.0 mL) once to yield 0.42 g (93%) of **4b** as a light tan colored solid. $^1H$ NMR ($CDCl_3$, 400 MHz) (9 peaks) $\delta$ 1.1 (t, 3H, $J = 7.0$ Hz), 2.3 (s, 3H), 3.8 (s, 3H), 4.1 (q, 2H, $J = 7.0$ Hz), 5.3 (d, 1H), 5.8 (d, 1H), 6.8 (d, 2H, $J = 8.2$ Hz), 7.2 (d, 2H, $J = 8.2$ Hz), 8.3 (s, 1H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) (13 peaks) $\delta$ 14.1, 18.6, 55.1, 55.2, 60.0, 101.5, 113.9, 127.8, 136.0, 146.0, 153.4, 159.1, 165.7.

*Reaction in BTF (entry 1b)*:

A mixture of *p*-anisaldehyde (0.501 g, 3.68 mmol), urea (0.243 g, 4.05 mmol, 1.1 equiv.) and ethyl acetoacetate (0.527 g, 0.512 mL, 4.05 mmol, 1.1 equiv.) in BTF (5.0 mL) was stirred at room temperature as iron(II) triflate (0.130 g, 0.368 mmol, 10.0 mol%) was added. The reaction mixture was heated at 70˚C (temperature-controlled hot plate). After 24 h, the mixture was cooled to room temperature. The solvent was then removed by suction filtration and the resulting crude solid was triturated with $CH_3OH/H_2O$ (1:1, v/v, 10.0 mL) twice to yield 0.632 g (59%) of **4b** as a light tan colored solid.

*Reaction in* 2-*MeTHF* (*entry 1b*):

A solution of *p*-anisaldehyde (0.504 g, 3.70 mmol, 1.0 eq), urea (0.244 g, 4.07 mmol, 1.1 eq) and ethyl acetoacetate (0.530 g, 0.519 mL, 4.07 mmol, 1.1 eq) in 2-MeTHF (6.0 mL) was stirred at room temperature as iron(II) triflate (0.131 g, 0.37 mmol, 10.0 mol%) was added. The reaction mixture was heated at 70˚C (temperature-controlled hot plate). After 24 h, the mixture was cooled to room temperature. The solvent was removed on a rotary evaporator, and the residue was triturated with $CH_3OH/H_2O$ (1:1, v/v, 10.0 mL) twice to yield 0.787 g (74%) of **4b** as a light tan colored solid.

## 4. Conclusion

In summary, a new method for the Biginelli reaction that works in several different environmentally benign solvents, viz. isopropanol, benzotrifluoride, and 2-methyltetrahydrofuran, has been developed using an inexpensive and commercially available catalyst, iron(II) triflate. The best results were obtained in isopropanol, while 2-methyltetrahydrofuran is a viable option as it is a bio-derived solvent.

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## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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