

Metal triflimide as a Lewis acid catalyst for Biginelli reactions in water

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Abstract—Metal triflimides such as Ni(NTf₂)₂, Cu(NTf₂)₂ and Yb(NTf₂)₃ catalyzed the Biginelli reaction to afford 3,4-dihydropyrimidin-2(1H)-ones more efficiently in pure water at room temperature than did corresponding metal triflate salts.
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Lewis acids-promoted reactions have attracted much attention in modern organic chemistry.¹ Generally, typical Lewis acids, such as BF₃, TiCl₄ and SnCl₄, are immediately hydrolyzed by atmospheric moisture, and they should therefore be treated in strictly dry conditions to prevent the loss of their catalytic activities. Due to the increasing awareness of environmental problems in chemical research and industry, efforts have been made to develop environmentally sustainable processes. Water-accessible Lewis acid catalysts have attracted much attention and have been extensively studied since Kobayashi et al. reported that rare earth metal triflates, such as Sc(OTf)₃, Y(OTf)₃ and Yb(OTf)₃, can be used as Lewis acid catalysts in water-containing (so-called aqueous) solvents.² It is obvious that water is the most inexpensive and environmentally sustainable solvent. In addition, water as a solvent often not only accelerates organic reactions but also improves reaction selectivity due to hydrophobic effects or ‘on-water’ effects, even when the reactants are insoluble in water.³ In the course of our studies to develop a new synthetic methodology based on the feature of water as a solvent, we have become interested in a Lewis acid catalyst that can be used *in pure water, not in aqueous media*. In this letter, we report that metal triflimides,⁴ such as Ni(NTf₂)₂, Cu(NTf₂)₂ and Yb(NTf₂)₃, exhibited superior catalytic activity for the Biginelli reaction to the corresponding metal triflates in pure water.⁵ The Biginelli reaction is one of the widely used multi-component reactions and was first reported by Biginelli in 1893 (Fig. 1).⁶ This

reaction is a condensation reaction between a β-ketoester, an aldehyde and urea under strongly acidic conditions. This condensation reaction has been used for the synthesis of dihydropyrimidin-2-ones, which have attracted considerable interest because of their pharmaceutical and therapeutic properties.⁷ Despite the usefulness of the Biginelli reaction, the efficiency of this method is considerably limited due to the strongly acidic and harsh reaction conditions. To overcome these problems, several Lewis acids, such as Sr(OTf)₂,^{8a} MgBr₂,^{8b} ZnCl₂,^{8c} In(OTf)₃,^{8d} LiBr,^{8e} CeCl₃,^{8f} Cu(OTf)₂,^{8g} ZrCl₄,^{8h} FeCl₃–NiCl₂,⁸ⁱ BiCl₃,^{8j} Mn(OAc)₂,^{8k} FeCl₃,^{8l} Ln(OTf)₃,^{8m} LaCl₃,⁸ⁿ InCl₃^{8o} and BF₃,^{8p} have been used to facilitate the reactions and an enantioselective Biginelli reaction catalyzed by Yb(OTf)₃ has also recently been reported.⁹ In addition, significant improvements in the reaction rate and yield for the Biginelli reaction carried out under microwave irradiation have been reported.¹⁰

Mechanisms of the Biginelli reaction are shown in Figure 2. This multi-component reaction consists of two steps: (1) the formation of an acyliminium ion and (2) addition of β-ketoester to an acyliminium ion followed by cyclization–dehydration steps, and the

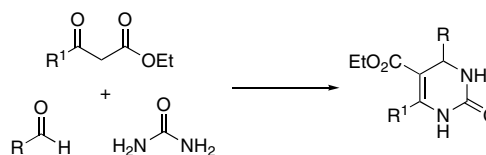


Figure 1. Biginelli reaction.

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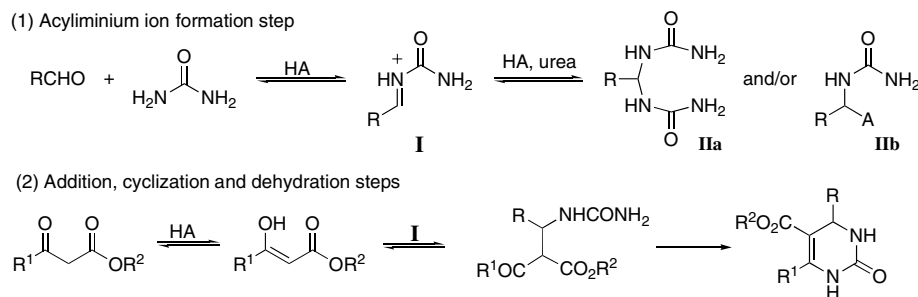


Figure 2. Mechanisms of the Brønsted acid-mediated classical Biginelli reaction.

formation of an acyliminium ion has been reported to be a rate-determining step.^{5b} In the presence of a Lewis acid catalyst, Lewis acids are thought to accelerate the acyliminium ion formation and addition reaction through a metal enolate formation and/or coordination to an acyliminium ion as shown in Figure 3.

We first investigated the catalytic activities of metal triflimides for the Biginelli reactions, and we also performed metal triflates-catalyzed Biginelli reaction in water for comparison. Metal triflimide salts were prepared from the corresponding metal hydroxides, carbonates or oxides with HNTf₂, in water according to the procedure reported in the literature.^{4a} In a typical procedure for the Biginelli reaction, urea (1.5 mmol), *p*-anisaldehyde (1.0 mmol), ethyl acetoacetate (1.0 mmol) and a metal triflimide or a metal triflate (5 mol %) were mixed in water and stirred for 24 h at ambient temperature. The Biginelli compound was obtained by simple filtration of the reaction mixture, and the results are summarized in Table 1. Metal triflimides, except for Zn(NTf₂)₂, were shown to catalyze the Biginelli reaction more efficiently to give the dihydropyrimidinone in water without heating than the corresponding metal triflates, which showed weak catalytic activities. In addition, although metal triflates-catalyzed reactions afforded the desired product together with considerable amounts of polymeric materials, by using metal triflimides the formation of undesired by-products was suppressed considerably to give the Biginelli product and recovered materials. In metal triflimide-catalyzed reactions, prolonged reaction time (72 h) improved the yields to some extent and elevated reaction temperature (70 °C), rather, lowered the yields.

With the aim of improving the reaction yields, we attempted to add catalytic amounts of Brønsted acid to the reaction mixture in order to facilitate the formation of an acyliminium ion. The results are shown in Table 2. Addition of CH₃CO₂H (entry 1), CF₃CO₂H (entries 2 and 6), HCl (entries 4 and 7) or CH₃SO₃H (entries 5

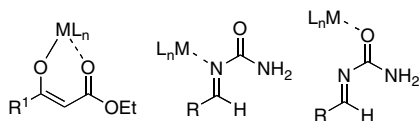


Figure 3.

Table 1. Biginelli reactions of *p*-anisaldehyde, ethyl acetoacetate and urea catalyzed by metal triflimides and metal triflates^a

Entry	Lewis acids	Yields (%)
1	Ni(NTf ₂) ₂	59, 65, ^c 40 ^d
2	Ni(OTf) ₂	Complex mixture
3	Cu(NTf ₂) ₂	65, 70, ^c 62 ^d
4	Cu(OTf) ₂	<10 ^b
5	Zn(NTf ₂) ₂	8
6	Yb(NTf ₂) ₃	88, 90 ^c
7	Yb(OTf) ₃	<5 ^b

^a The reactions were carried out in the presence of *p*-anisaldehyde (1.0 mmol), ethyl acetoacetate (1.0 mmol), urea (1.5 mmol) and a Lewis acid catalyst (5 mol %) in water (1 mL) at ambient temperature for 24 h.

^b Considerable amounts of inseparable by-products were accompanied by the Biginelli product.

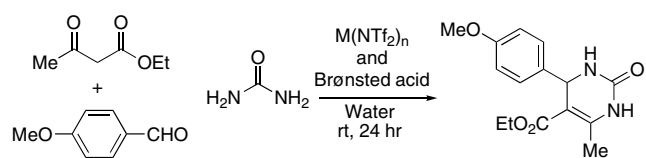
^c The reaction was carried out for 72 h.

^d The reaction was carried out at 70 °C.

and 9) considerably improved the yields of the Ni(NTf₂)₂- and Cu(NTf₂)₂-catalyzed reactions, and HNTf₂ (entries 3 and 8) was not necessarily effective, though no improvement was observed with the combination of Yb(NTf₂)₃ and HCl (entry 10).

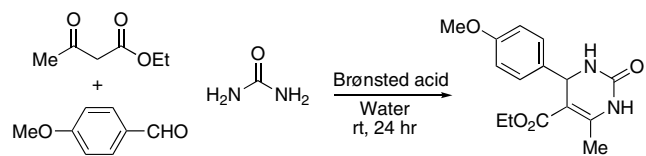
To confirm that a metal triflimide catalyst is needed to obtain high yields in the Biginelli reaction, we also examined the catalytic activity of Brønsted acid in the absence of metal triflimides. The results are shown in Table 3. CH₃CO₂H, HCl and CH₃SO₃H did not catalyze the reaction (entries 1, 3 and 5), but CF₃CO₂H and HNTf₂ showed moderate catalytic activities (entries 2 and 4). Bose reported that *p*-TsOH was a good catalyst for the Biginelli reaction,^{5a} but in our conditions *p*-TsOH was not effective, probably due to a relatively mild and diluted reaction condition compared to Bose's conditions (entry 6).

Considering that Biginelli reactions catalyzed by conventional Brønsted acid are generally performed in water or alcoholic solvents under reflux conditions,^{6b} low yields of the reaction indicated in entries 1, 3, 5 and 6 of Table 3 are reasonable because our experiments

Table 2. Biginelli reactions of *p*-anisaldehyde, ethyl acetoacetate and urea catalyzed by metal triflimides in the presence of Brønsted acids^a

Entry	Lewis acids	Additives	Yields (%)
1	Ni(NTf ₂) ₂	CH ₃ CO ₂ H	84
2	Ni(NTf ₂) ₂	CF ₃ CO ₂ H	90
3	Ni(NTf ₂) ₂	HNTf ₂	71
4	Ni(NTf ₂) ₂	HCl	71
5	Ni(NTf ₂) ₂	CH ₃ SO ₃ H	92
6	Cu(NTf ₂) ₂	CF ₃ CO ₂ H	>95
7	Cu(NTf ₂) ₂	HCl	>95
8	Cu(NTf ₂) ₂	HNTf ₂	65
9	Cu(NTf ₂) ₂	CH ₃ SO ₃ H	>95
10	Yb(NTf ₂) ₃	HCl	85

^a The reactions were carried out in the presence of *p*-anisaldehyde (1.0 mmol), ethyl acetoacetate (1.0 mmol), urea (1.5 mmol) and a Brønsted acid (5 mol %) in water (1 mL) with a Lewis acid catalyst (5 mol %) at ambient temperature for 24 h.

Table 3. Biginelli reactions of *p*-anisaldehyde, ethyl acetoacetate and urea catalyzed by Brønsted acids^a

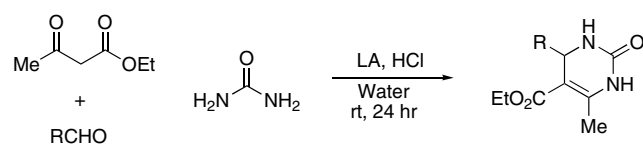
Entry	Brønsted acid ^b	Yields (%)
1	CH ₃ CO ₂ H (4.7)	<5
2	CF ₃ CO ₂ H (0.23)	56
3	HCl (-2.2)	<5
4	HNTf ₂ (1.2)	33
5	CH ₃ SO ₃ H (-1.2)	<5
6	<i>p</i> -TsOH	<5

^a The reactions were carried out in the presence of *p*-anisaldehyde (1.0 mmol), ethyl acetoacetate (1.0 mmol), urea (1.5 mmol) and a Brønsted acid (5 mol %) in water (1 mL) at ambient temperature for 24 h.

^b Values in parentheses indicate p*K*_a values of acids in water.

were performed at room temperature, and it is noteworthy that CF₃CO₂H and HNTf₂ could catalyze the Biginelli reaction in moderate efficiency despite the fact that their acidities are lower than those of HCl and CH₃SO₃H, which showed only a weak activity. In reactions promoted by metal triflimides, p*K*_a values of Brønsted acids were also not reflected in the efficiency of the reactions. We cannot explain this ambiguity clearly; however, considering that the rate-determining step of the Biginelli reaction is an acyliminium ion formation step, the difference in Brønsted acids may affect the equilibrium points among aldehydes, **I**, **IIa** and **IIb** (Fig. 2).^{5b}

We also examined the Biginelli reaction using other aldehydes in the presence of Cu(NTf₂)₂ and Brønsted

Table 4. Biginelli reaction between urea, ethyl acetoacetate and various aldehydes^a

Entry	R	Lewis acids	Yields (%)
1	Ph	Cu(NTf ₂) ₂	88
2	4-HO-Ph	Cu(NTf ₂) ₂	71
3	4-Cl-Ph	Cu(NTf ₂) ₂	74
4	2-Me-Ph	Cu(NTf ₂) ₂	77
5	2-Cl-Ph	Cu(NTf ₂) ₂	34
6	2-Cl-Ph	Yb(NTf ₂) ₃	38 ^b
7	2-Cl-Ph	Ni(NTf ₂) ₂	25
8	<i>n</i> -C ₅ H ₁₁	Cu(NTf ₂) ₂	80
9	<i>n</i> -C ₅ H ₁₁	Yb(NTf ₂) ₃	55 ^c

^a The reactions were carried out in the presence of *p*-anisaldehyde (1.0 mmol), ethyl acetoacetate (1.0 mmol), urea (1.5 mmol), HCl (10 mol %) and Lewis acid (10 mol %) in water (1 mL) at ambient temperature for 24 h. The crude products were purified with SiO₂ column chromatography.

^b Considerable amounts of inseparable impurities were accompanied.

^c The reaction was carried out within 71 h.

acids (Table 4). Ni(NTf₂)₂ and Yb(NTf₂)₃ can also be used as catalysts, but they catalyzed the reaction less effectively than Cu(NTf₂)₂-HCl did as shown in Table 2. Since Cu(NTf₂)₂ was adsorbed onto the precipitation of the Biginelli products during the reaction, resulting in lowering of the reaction efficiency in some cases, we used 10 mol % of the catalyst. The Biginelli reaction using benzaldehyde, other aromatic aldehydes and an aliphatic aldehyde proceeded smoothly to give the dihydropyrimidinones in good yields (entries 1, 2, 3 and 8), and sterically hindered *o*-tolaldehyde also reacted efficiently (entry 4), though electron-deficient *o*-chlorobenzaldehyde gave the product in a low yield (entries 5–7). We also examined the Biginelli reaction of *p*- and *o*-nitrobenzaldehyde using Cu(NTf₂)₂, Ni(NTf₂)₂ and Yb(NTf₂)₃ with acid additives, but they did not react to give the Biginelli products probably due to the insolubility of these aldehydes in water.

In conclusion, we have first demonstrated that *metal triflimide salts can work as Lewis acids in pure water* and these Lewis acids, such as Ni(NTf₂)₂, Cu(NTf₂)₂ and Yb(NTf₂)₃, catalyze the Biginelli reaction more efficiently in pure water under mild conditions than do conventional metal triflates. The addition of a Brønsted acid considerably improved the yields of the reactions.

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