# Three-Component One-Pot Synthesis of Pyrimidinone Derivatives in Fluorous Media: Ytterbium Bis(perfluorooctanesulfonyl)imide Complex Catalyzed Biginelli-Type Reaction



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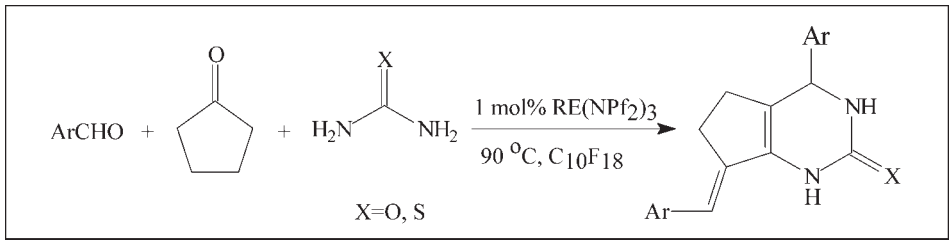


The condensation of aromatic aldehyde, cyclopentanone, and urea or thiourea in the presence of Ytterbium bis(perfluorooctanesulfonyl)imide complex in perfluorodecalin was used to synthesize a variety of benzylidene heterobicyclic pyrimidinones in excellent yields.

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## INTRODUCTION

Multicomponent reactions (MCRs) are powerful tools in modern medicinal chemistry, enabling straightforward access to large libraries of structurally related, drug-like compounds and thereby facilitating the generation of precursor candidates compounds. Hence, combined with the use of combinatorial chemistry and high throughput parallel synthesis, such reactions have constituted an increasingly valuable approach to drug discovery efforts in recent years [1,2].

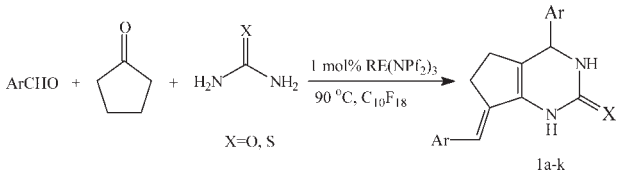
Over the past decade, pyrimidinone derivatives have attracted strong interest because of their useful biological activities, pharmaceutical, and therapeutic properties, such as antiviral, antitumor, antibacterial, and anti-inflammatory activities [3–6]. Classical Biginelli reactions involve one-pot condensations of an aldehyde, α,β-ketoester, and urea under strongly acidic conditions. In recent decades, the Biginelli reaction was extended the scope [7]. Especially, some fused pyrimidinones carrying an arylidene moiety exit not only the broad-spectrum antitumor activity but also a distinctive pattern of selectivity toward individual cell line such as that of leukemia. Thus, synthesis of these heterocycles is of much current importance for both organic synthesis and medicinal chemistry. Conventional methods for synthesis of this type of pyrimidinones involve condensation of α, α′-bis(substituted benzylidene)cycloalkanones with urea or thiourea using strong Bronsted acid [8] or base [9] as catalysts. Recently Pan and coworkers [7b] and Xu and coworkers [10] described efficiently alternative synthesis of these fused pyrimidinones by a three-component condensation with aromatic aldehyde, cyclopentanone, and urea or thiourea as starting materials. Each of the aforementioned methods has its own merits, while some of these methods are plagued with the limitation of poor yields, difficult workup, effluent pollution, and unrecyclability of catalysts.

Metal complexes with bis(perfluorooctanesulfonyl)-imide ligands are active and recyclable catalysts in the fluorous immobilized phase for Baeyer-Villiger oxidation [11], Diels-Alder reaction [12], esterification [13], and Friedel-Crafts acylation [14]. A key factor to accomplish the catalytic processes was ascribed to the use of long-enough perfluorinated—$N(SO_2C_8F_{17})_2$, whose structural characteristic can coordinate with a variety of metal cations to obtain the desired Lewis acid catalysts with appropriate catalytic activity, and the selective immobilization in the fluorous. Herein, this letter attempts to describe the catalytic activity of rare earth (III) bis-(perfluorooctanesulfonyl)imide complexes $RE[N(SO_2—C_8F_{17})_2]_3$, ($RE(NPf_2)_3$) in the one-pot synthesis of pyri-midinone from aromatic aldehyde, cyclopentanone, and urea or thiourea (Scheme 1), the so-called Biginelli-type three-component reaction.

## RESULTS AND DISCUSSION

At first, we began to study the catalytic activities of a series of rare earth bis(perfluorooctanesulfonyl)imide complexes to optimize the reaction condition of benzaldehyde, cyclopentanone, and urea (Scheme 2), which was chosen as a model reaction. The results are

**Scheme 1**




summarized in Table 1. It was obviously that rare earth bis(perfluorooctanesulfonyl)imide complexes catalyzed the Bigineli-type reaction efficiently and $Yb(NPf_2)_3$ showed the best catalytic activity among these complexes.

By using $Yb(NPf_2)_3$ as catalyst, we examined the effect of the amount of the catalyst on the model reaction mentioned earlier. When the amount of $Yb(NPf_2)_3$ was increased from 0.4 to 1.2 mol%, the yield was increased until to a maximum and then gradually decreased, and the highest yield was obtained at 1 mol% catalyst loading (Table 2, Entries 1–5).

Based on the earlier optimized results, with 1 mol% $Yb(NPf_2)_3$ as catalyst, we also investigated the effect of the reaction temperature ranging from 80 to 100°C, and the best results were obtained at 90°C (Table 2, Entries 4, 6 and 7). Meanwhile, further studies showed that the molar ratio of benzaldehyde, cyclopentanone, and urea at 1:1:1.2 was preferred.

Under the optimized conditions, the reactions of different aldehydes with cyclopentanone and urea or thiourea were examined. As listed in Table 3, aromatic aldehydes carrying different functional groups, such as methyl, methoxy, chloro, bromo, and nitro, were subjected to the reactions, and in all cases, the desired products were obtained in high yields (81–93%). All reactions were clean and free from any by-products. It is important to note that aldehydes with electron-withdrawing group were more reactive, and the reactions with cyclopentanone and urea were faster. The reason may be that the carbonyl carbon in aldehydes containing electron-withdrawing group are more electrophilic. Thiourea exhibited behavior similar to that urea.

The possibility of recycling $Yb(NPf_2)_3$ catalyst for the synthesis of 1a was also investigated. When the reaction was finished, the reaction mixture was cooled to room temperature. The fluorous phase containing catalysts was separated from reaction mixture by decantation and reused for the next cycle. The condensations of benzaldehyde, cyclopentanone, and urea under the conditions as mentioned earlier were run for five consecutive cycles, respectively, furnishing the corresponding pyrimidinones with 91%, 89%, 88%, 87%, and 87% isolated yields.

**Scheme 2**

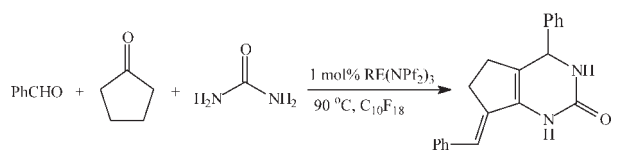



**Table 1**

$RE(NPf_2)_3$-catalyzed one-pot synthesis of benzylidene heterobicyclic pyrimidinones.[a]

| Entry | Catalyst | Yield[b] (%) |
|---|---|---|
| 1 | $Y(NPf_2)_3$ | 73 |
| 2 | $La(NPf_2)_3$ | 64 |
| 3 | $Ce(NPf_2)_3$ | 83 |
| 4 | $Nd(NPf_2)_3$ | 68 |
| 5 | $Sm(NPf_2)_3$ | 71 |
| 6 | $Eu(NPf_2)_3$ | 72 |
| 7 | $Tb(NPf_2)_3$ | 77 |
| 8 | $Dy(NPf_2)_3$ | 79 |
| 9 | $Er(NPf_2)_3$ | 85 |
| 10 | $Yb(NPf_2)_3$ | 91 |

[a] Reaction conditions: benzaldehyde (0.212 g, 2 mmol), cyclopentanone (0.168 g, 2 mmol), urea (0.146 g, 2.4 mmol), $C_{10}F_{18}$ (2 mL), $RE(NPf_2)_3$ (0.02 mmol), 90°C, 2.5 h.
[b] Isolated yield.

The mechanism for formation of benzylidene heterobicyclic pyrimidinones products is assumed to take place *via* coordination of $Yb(NPf_2)_3$ with an aldehyde, which then activates the attack of keto compound in its enol form and subsequent removal of OH group gives enone. Similar reaction further proceeds on this enone to give bis-benzylidene derivatives. The next are the Michael addition of urea, elimination of water, and cyclization to form pyrimidione.

In conclusion, we report a one-pot synthesis of fused pyrimidinone by $Yb(NPf_2)_3$-catalyzed Biginelli-type reaction of aromatic aldehyde, cyclopentanone, and urea or thiourea in fluorous media. The easy workup procedure, recyclable catalyst, short reaction times, and very good yields are the main advantages of this method.

**Table 2**

Reaction of benzaldehyde, cyclopentanone, and urea in the presence of $Yb(Npf_2)_3$ under different reaction conditions.[a]

| Entry | Amount of $Yb(NPf_2)_3$ (mol%) | Temperature (°C) | Yield[b] (%) |
|---|---|---|---|
| 1 | 0.4 | 90 | 42 |
| 2 | 0.6 | 90 | 67 |
| 3 | 0.8 | 90 | 83 |
| 4 | 1.0 | 90 | 91 |
| 5 | 1.2 | 90 | 89 |
| 6 | 1.0 | 80 | 68 |
| 7 | 1.0 | 100 | 85 |

[a] Reaction conditions: benzaldehyde (0.212 g, 2 mmol), cyclopentanone (0.168 g, 2 mmol), urea (0.146 g, 2.4 mmol), $C_{10}F_{18}$ (2 mL), 2.5 h.
[b] Isolated yield.

**Table 3**

Synthesis of benzylidene heterobicyclic pyrimidinones in the presence of $Yb(Npf_2)_3$ in $C_{10}F_{18}$.[a]

| Entry | Ar | X | Time (h) | Product | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | Ph | O | 2 | 1a | 91 |
| 2 | 4-$CH_3C_6H_4$ | O | 3 | 1b | 93 |
| 3 | 2-$CH_3C_6H_4$ | O | 3 | 1c | 81 |
| 4 | 4-$OCH_3C_6H_4$ | O | 3 | 1d | 85 |
| 5 | 4-$ClC_6H_4$ | O | 2 | 1e | 89 |
| 6 | 2-$ClC_6H_4$ | O | 2 | 1f | 84 |
| 7 | 4-$BrC_6H_4$ | O | 2 | 1g | 83 |
| 8 | 4-$NO_2C_6H_4$ | O | 2 | 1h | 92 |
| 9 | Ph | S | 6 | 1i | 94 |
| 10 | 4-$CH_3C_6H_4$ | S | 6 | 1j | 86 |
| 11 | 4-$ClC_6H_4$ | S | 5 | 1k | 92 |

[a] Reaction conditions: aldehyde (2 mmol), cyclopentanone (2 mmol), thiourea or urea (2.4 mmol), $C_{10}F_{18}$(2 mL), 90°C.
[b] Isolated yield.

## EXPERIMENTAL

Chemicals used were obtained from commercial suppliers and used without further purifications. $^1$H NMR, $^{13}$C, and $^{19}$F NMR spectra were recorded with a Bruker Advance RX500 spectrometer. Mass spectra were recorded on a Saturn 2000GC/MS instrument. Inductively coupled plasma (ICP) spectra were measured on an Ultima2C apparatus. Elemental analyses were performed on a Yanagimoto MT3CHN recorder.

**Typical procedure for preparation of $(C_8F_{17}SO_2)_2NH$.** $(C_8F_{17}SO_2)_2NH$ was prepared according to the literature [15,16]. Ammonia (300 mmol) was transferred with stirring perfluorooctanesulfonyl fluoride (50 g, 99.6 mmol) at −20°C for about 1 h, it was then continued at room temperature for 1 h. The solid product was acidified with HCl followed by addition of $Et_2O$. The organic layer was dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure, dried in vacuum at 80°C for 16 h to give $C_8F_{17}SO_2NH_2$ (87% yield). Then the mixture of perfluorooctanesulfonyl fluoride (45.4 g, 91 mmol), perfluorooctanesulfonamide (43.4 g, 87 mmol), and $Et_3N$ (76 mL) was heated at reflux for 23 h. The lower brown fluorous layer was washed with 10% HCl and dried in vacuum at 70°C for 6 h to afford $(C_8F_{17}SO_2)_2N$ $HNEt_3$. Finally, through acidic ion exchange resin column, $(C_8F_{17}SO_2)_2N$ $HNEt_3$ changed to afford $(C_8F_{17}SO_2)_2NH$ in 50% yield. Anal. Calcd. for $(C_8F_{17}SO_2)_2NH$: C,19.57; N: 1.43 H: 0.10. Found: C, 19.61; N: 1.45, H, 0.16. $^{19}$F NMR: δ-126.2, -121.8, -114.0, -81.2.

**Typical procedure for preparation of $Yb(NPf_2)_3$.** Ytterbium bis(perfluorooctanesulfonyl)imide complex, $Yb(NPf_2)_3$ was prepared according to the reported procedure [17]. The mixture of $Yb_2O_3$ (0.118 g, 0.3 mmol) and bis (perfluorooctanesulfonyl)imide (0.883 g, 0.9 mmol) in $H_2O$ (10 mL) at 110°C for 1 h. The resulting mixture was filtered through a membrane filter. The remaining water was removed under reduced pressure at 80°C for 16 h. The Ytterbium bis (perfluorooctanesulfonyl)imide complex was obtained in 98% yield. ICP: Calcd for $C_{48}O_{12}N_3F_{102}S_6Yb$: Yb, 5.56. Found: 5.60 Anal. Calcd. For $Yb[N(SO_2C_8F_{17})_2]_3$: C, 18.50; N, 1.35. Found: C: 18.45; N, 1.41. $^{19}$F NMR: δ −126.1, −121.2, −114.2, −81.4.

**Typical procedure for the preparation of 7-benzylidene-4-phenyl-3,4,6,7-tetrahydro-1*H*- cyclopenta[d] pyrimidin-2(5H)-one.** A mixture of benzaldehyde (0.212 g, 2 mmol), cyclopentanone (0.168 g, 2 mmol), urea (0.146 g, 2.4 mmol), and $Yb(NPf_2)_3$ (0.062 g, 0.02mmol) in perfluo-rodecalin ($C_{10}F_{18}$, cis and trans-mixture, 2mL) was well stirred at 90°C for appropriate time. After the reaction was completed, the system was cooled to room temperature. Then, the perfluorodecalin on the bottom was separated for the next cycle. Water was added to the reaction mixture, and the pure product was obtained by filtration followed by washing with acetone, ethyl acetate, and alcohol. Selected data: 7-benzylidene-4-phenyl-3,4,6,7-tetrahydro-1*H*-cyclopenta[d]pyrimidin-2(5*H*)-one, pale yellow solid; mp 236–239°C; $^1$H NMR (500 MHz, DMSO): δ = 1.97–2.01 (m, 1H), 2.49 (m, 1H), 2.71–2.82 (m, 2H), 5.15 (s, 1H), 6.63 (s, 1H), 7.21–7.38 (m, 11H), 8.78 (s, 1H). $^{13}$ C NMR: δ = 29.5, 29.8, 58.7, 117.8, 119.6, 127.2, 127.4, 128.6, 129.0, 129.5, 129.6, 137.1, 138.8, 140.3, 144.3, 154.4 ppm. MS (EI) *m/z* 303 $[M+H]^+$.

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