# New Ytterbium Complex-catalyzed Multicomponent Reactions for Synthesis of Dihydropyrimidines: [4 + 2] Cycloaddition vs. Biginelli Type Reaction

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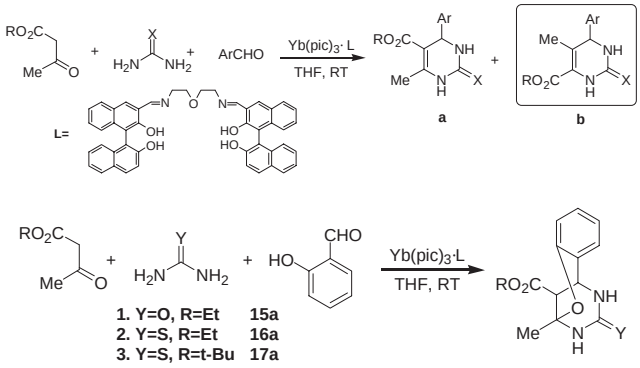
A new schiff base ytterbium complex was synthesized and used as catalyst for a three-component, one-pot reaction involving 1,3-keto ester with urea or thiourea and aldehyde. The reactions resulted in the formation of two different dihydropyrimidines, the Biginelli type 3,4-dihydropyrimidin-2-(1*H*)-ones and non-Biginelli type. A new mechanism based on [4 + 2] cycloaddition was proposed which serves as a reasonable explanation for the two different products.

Multicomponent reactions (MCRs) have received increasing interest in organic and medicinal chemistry[1] during the past two decades mainly owing to the high demands of drug discovery.[2] The venerable Biginelli reaction, one-pot cyclocondensation of aldehyde, $\beta$-keto ester, and urea or thiourea, is a classical way to produce multifunctionalized 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs).[3] DHPMs show a wide scope of important pharmacological properties and make up a large family of medicinally relevant compounds. The present attention on Biginelli type DHPMs is mainly due to their close structural relationship to the pharmacologically important as calcium channel modulators of the nifedipine type, and several marine natural products containing the dihydropyrimidine-5-carboxylate core exhibit anticancer properties.[4,5]

Pharmacological studies concerning the absolute configuration have demonstrated individual enantiomers perform opposing biological activities in most cases.[4] Nevertheless, only a few examples of asymmetric synthesis of this heterocyclic target have been reported.[6,7] Although the reaction was described over a century ago, and more and more attention are focused on Biginelli DHPMs, the mechanism of the classical three-component Biginelli condensation has not been elucidated with certainty and remains controversial.[8] The first so-called "ureidocrotonate mechanism" was proposed by Folkers and Johnson[9] in 1933. They suggested that the primary bimolecular condensation product *N*,*N*′-benzylidenebisurea is the first intermediate in this reaction. 40 years later in 1973, the "carbenium ion mechanism," proposed by Sweet and Fissekis,[10] suggested that an acid-catalyzed aldol condensation is the first and limiting step of the Biginelli reaction. The widely accepted mechanism proposed by Kappe[11] is the "N-acyliminium ion intermediate" path, which is a confirmation of Folkers and Johnson's. According to this mechanism, only a single product can be obtained. Herein, we proposed a new mechanism for the Biginelli reaction via [4 + 2] cycloaddition,[12] which serves as a reasonable explanation for the observation of two different dihydropyrimidine products during our experiment.

At the beginning, we focused on the asymmetric synthesis of DHPMs via the Biginelli reaction. A new BINOL-salen type chiral ligand was developed from the corresponding amine and BINOL-derived aldehyde in alcohol under ambient atmosphere.




**Scheme 1.** The reaction resulted in different products.

The Biginelli condensation of ethyl acetoacetate, benzaldehyde, and urea was catalyzed by ytterbium picrate [$Yb(pic)_3$] with the ligand (Scheme 1, Table 1, Entry 1). The result was not satisfactory for the reaction showing high conversion but the yield of expected product **1a** is very low (37%). After screening the reaction mixture carefully, we surprisingly found a new product **1b** yield in 54% which is also a dihydropyrimidine and is different in the methyl and ester group positions from the expected one. The differences are demonstrated by $^1$H NMR characterizations.

Because this intriguing finding, we proceeded to examine the scope of this side product with various substituted aromatic aldehydes, two 1,3-keto esters, and urea/thiourea.[13] Two different dihydropyrimidine products were found for most substrates (Table 1, Entries 1–14), and for salicylaldehyde (Table 1, Entries 15–17), because of the Biginelli type precursors were much easier to conduct intramolecular etherification, three sole diazatricyclic products were produced. The X-ray diffraction analysis of compound **4a**, **7a**, **11a**, and **16a** were then performed to confirm that the molecular structures are indeed as shown in Supporting Information.[15]

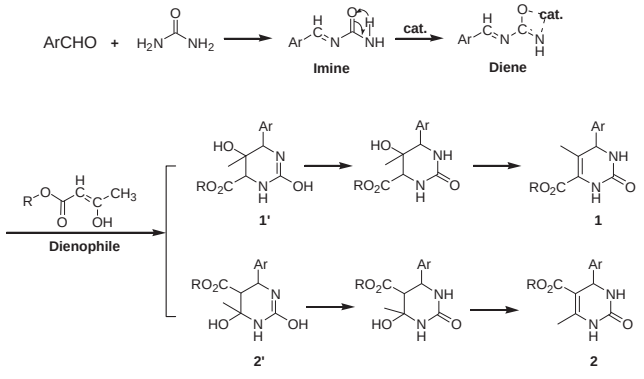
The non-Biginelli products could not be obtained according to the mechanism of Kappe's.[11] Thus, we proposed a new mechanism based on a [4 + 2] cycloaddition (Scheme 2). Condensation of urea and benzaldehyde affords imine, which is then enolized to form a diene, 1-benzylideneisourea. The $Yb(pic)_3$·L complex is assumed to contribute to the stabilization of diene intermediate. This is the key step which is different from the N-acyliminium intermediate. Subsequent cycloaddition with the enol generates the $\beta$-carbonyl compound and then gives the corresponding dihydropyrimidine **1a** and **1b** after elimination of a water molecule.

Methyl acrylate, instead of 1,3-keto ester, serving as a dienophile, was added to the mixture of benzaldehyde, urea and the ytterbium catalyst to validate the existence of diene intermediate. After 24 h stirring, two new compounds were observed (Scheme 3). The formation of A and B demonstrated generation

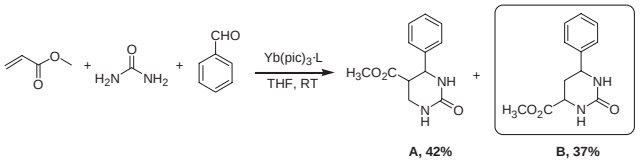
**Table 1.** Dihydropyrimidines synthesis catalyzed by $Yb(pic)_3{\cdot}L$[a]

| Entry | Ar | Y | R | Yield[b] a/% | Yield[b] b/% |
|---|---|---|---|---|---|
| 1 | $C_6H_5$ | O | Et | 37 | 54 |
| 2 | $C_6H_5$ | O | *t*-Bu | 54 | 38 |
| 3 | *p*-$CH_3$-$C_6H_4$ | O | Et | 31 | 21 |
| 4 | *p*-$CH_3$-$C_6H_4$ | O | *t*-Bu | 40 | 49 |
| 5 | *p*-OH-$C_6H_4$ | O | Et | 29 | 52 |
| 6 | *p*-OH-$C_6H_4$ | O | *t*-Bu | 62 | 27 |
| 7 | *o*-Cl-$C_6H_4$ | O | *t*-Bu | 46 | 45 |
| 8 | $C_6H_5$ | S | Et | 45 | 43 |
| 9 | $C_6H_5$ | S | *t*-Bu | 52 | 44 |
| 10 | *p*-$CH_3$-$C_6H_4$ | S | Et | 39 | 26 |
| 11 | *p*-OH-$C_6H_4$ | S | Et | 51 | 37 |
| 12 | *p*-OH-$C_6H_4$ | S | *t*-Bu | 47 | 46 |
| 13 | *o*-Cl-$C_6H_4$ | S | *t*-Bu | 46 | 45 |
| 14 | *p*-Cl-$C_6H_4$ | S | Et | 48 | 42 |
| 15 | *o*-OH-$C_6H_4$ | O | Et | 69 | 0 |
| 16 | *o*-OH-$C_6H_4$ | S | Et | 59 | 0 |
| 17 | *o*-OH-$C_6H_4$ | S | *t*-Bu | 82 | 0 |

[a]All reactions were carried out at room temperature with 10 mol % catalyst. [b]Isolated yields.




**Scheme 2.** The proposed mechanism.




**Scheme 3.** The indirect evidence.

of the diene, and then went through [4 + 2] cycloaddition with methyl acrylate. This is an indirect evidence for the existence of diene intermediate, and thus it is a reasonable assumption that the Biginelli reaction also proceeds via this path. Besides that, methyl acrylate is demonstrated to be a potential substrate for the Biginelli reaction.

In conclusion, we developed a new method for synthesis of two kinds of dihydropyrimidine (Biginelli type and non-Biginelli type), and a new mechanism for the Biginelli reaction based on [4 + 2] cycloaddition was proposed, which serves as a good explanation for the observed two products. The formation of diene intermediate, 1-benzylideneisourea was proven indirectly and the structures of **4a**, **7a**, **11a**, and **16a** were determined by single X-ray diffraction analysis.[14] Further work is undergoing to investigate the precise and specific role of $Yb(pic)_3{\cdot}L$ and improve selectivity of two DHPMs.

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13 General procedure for the catalytic Biginelli reaction: In a 10-mL Schlenk flask, a solution of 2 mL of THF, $Yb(pic)_3$ (0.05 mmol) and ligand (0.05 mmol) was stirred at room temperature. After 10 min, $\beta$-keto ester compound (0.5 mmol), aldehyde (0.5 mmol), and urea or thiourea (0.5 mmol) were introduced. After approximately 60 h, 5 mL of water was added, and the product was extracted with ethyl acetate (5 mL × 3). After the organic layer was dried (anhydrous $Na_2SO_4$) and evaporated, the residue was purified by column chromatography (petroleum ether (60–90 °C)/ethyl acetate, 6:1–4:1) to afford the corresponding product.

14 Crystallographic data reported in this manuscript have been deposited with Cambridge Crystallographic data centre as supplementary publication no. CCDC 685708 **4a**, 685709 **7a**. Copies of the data can be obtained, free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic data centre, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: +44-1223-336033; or e-mail: deposit@ccdc.cam.ac.uk).

15 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.


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