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Studies on the Biginelli reaction: a mild and selective route to 3,4-dihydropyrimidin-2(1*H*)-ones via enamine intermediates

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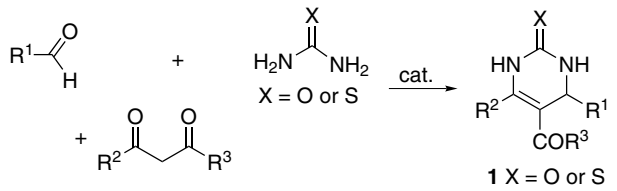
Abstract—L-Proline methyl ester hydrochloride was found to be an effective catalyst for assembling (±)-dihydropyrimidinones under mild conditions. Mechanistic insights into the useful selectivity elements of this amine-catalyzed process are also reported.

The synthesis of functionalized 3,4-dihydropyrimidin-2-(1*H*)-ones (DHPMs, **1**, Scheme 1) represents an excellent example of the utility of one-pot multiple component condensation reactions. Readily assembled as racemates by the Biginelli reaction, DHPMs display a range of useful pharmacological activity.[1] The reaction has traditionally been catalyzed by strong mineral acids, but more recently has been performed using numerous milder Lewis acid and heteropolyacid catalysts.[2]

The currently-accepted mechanism of the Biginelli reaction involves nucleophilic attack of the dicarbonyl compound on a reactive *N*-acyliminium ion intermediate. Recent mechanistic studies on L-proline catalysis[3] led us to test this amino acid in making DHPMs enantioselectively. While our work was in progress, another group developed a solvent-free synthesis of DHPMs in the presence of L-proline, but observed no enantioselectivity.[4] We investigated several additional chiral amines as catalysts, and here report the usefulness of proline methyl ester hydrochloride in promoting Biginelli condensations.

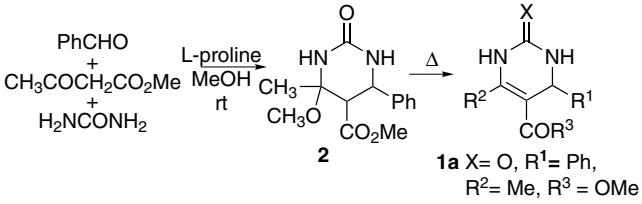


Scheme 1.

Condensation of PhCHO, methyl acetoacetate, and urea in the presence of L-proline (10 mol %, EtOH, reflux) afforded DHPM **1a** (Scheme 2), but as in the solvent-free process,[4] the product was racemic (30% yield). Interestingly, condensations in MeOH as solvent formed a previously-undetected heterocycle **2** at rt (30%, mixture of racemic diastereomers).[5] Intermediate **2** could be converted to racemic **1a** upon warming.

Several other enantiomerically pure secondary amines capable of forming enamines were investigated as Biginelli catalysts, including L-proline methyl ester, *trans*-4-hydroxy-L-proline, L-prolinols **3**–**5**, pyrrolidine **6**, aminoquinuclidine **7**, and imidazolidinone **8**[6] (Fig. 1). However, in each case, **1a** was obtained in low-to-modest yield with no enantioselectivity.

Interestingly, the HCl salt of L-proline methyl ester (10 mol %) afforded (±)-**1a** in nearly quantitative yield. The requirement for secondary amine as its HCl salt suggested a mechanism involving acid-promoted



Scheme 2.

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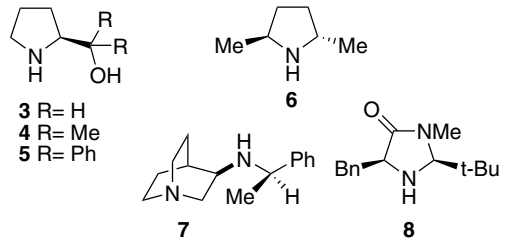
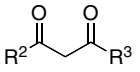


Figure 1.

Table 1. Biginelli condensations leading to DHPMs **1** catalyzed by L-Pro-OMe·HCl[a]

R^1CHO		Urea X =	Product (% yield)
Ph	R^2 = Me, R^3 = OMe	O	**1a** (99)
3-$OMeC_6H_5$	R^2 = Me, R^3 = OMe	O	**1b** (82)
4-$OMeC_6H_5$	R^2 = Me, R^3 = OMe	O	**1c** (86)
4-$NO_2C_6H_5$	R^2 = Me, R^3 = OMe	O	**1d** (68)
4-BrC_6H_5	R^2 = Me, R^3 = OMe	O	**1e** (69)
3-OMe-4-OH-C_6H_4	R^2 = Me, R^3 = OMe	O	**1f** (70)
n-C_3H_7	R^2 = Me, R^3 = OMe	O	**1g** (63)
Ph	R^2, R^3 = Me	O	**1h** (66)
4-$OMeC_6H_5$	R^2, R^3 = Me	O	**1i** (33)
Ph	R^2 = Ph, R^3 = OEt	O	**1j** (10)[b]
Ph	R^2 = Me, R^3 = OMe	S	**4k** (30)
Ph	R^2 = Me, R^3 = OMe	*N*-Me-urea	**4l** (58)

[a] An ethanol solution of aldehyde (2.0 M) containing dicarbonyl compound (1.0 equiv), urea (1.1–1.5 equiv) and L-Pro-OMe·HCl (10 mol %) was heated at reflux for 18 h. Crystalline product was obtained either by crystallization upon cooling, or by removing the ethanol in vacuo and triturating the residue with EtOH.

[b] This reaction required 3 d at reflux; no **1j** was formed after 18 h.

enamine addition. Consistent with that hypothesis, the pre-formed L-Pro-OMe enamine of methyl acetoacetate[7] afforded (±)-**1a** in only 9% yield. However, upon addition of HCl (0.9 equiv), **1a** was formed in 54% yield. In further support of an enamine mechanism, triethylamine hydrochloride, which cannot form enamines, afforded **1a** in 24% yield.[8]

While HCl salts of **2**–**8** were also more active catalysts than the corresponding free bases, results were consistently superior with L-Pro-OMe·HCl (10 mol %), and afforded access to a range of DHPMs (Table 1) under significantly milder conditions than the standard Biginelli process.

Both aromatic and aliphatic aldehydes were transformed into DHPMs using L-Pro-OMe·HCl as catalyst. Thioureas and N-substituted ureas also underwent successful condensation. DHPMs could be synthesized using pentane-2,4-dione as the β-dicarbonyl nucleophile. Consistent with the proposed mechanism, condensation leading to **1j** was very slow with ethyl benzoylacetate, which is known to form enamines only sluggishly.[9]

The formation of racemic DHPMs seems surprising in retrospect, given the likely involvement of a chiral enamine in the condensation. Interestingly, Biginelli reactions involving chiral Ce and In acetoacetates were recently reported to form DHPMs with only low ee's.[10] Taken together, these data suggest that a highly enantioselective DHPM synthesis may also require asymmetric activation of the electrophilic acylimine component. Nevertheless, the ability to differentiate dicarbonyl nucleophiles using L-Pro-OMe·HCl is a novel hallmark of enamine-promoted Biginelli condensations, and might serve as a useful selectivity element in complex synthesis.[11]

Acknowledgements

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