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Chiral ionic liquid-catalyzed Biginelli reaction: stereoselective synthesis of polyfunctionalized perhydropyrimidines

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Abstract

A chiral ionic liquid-catalyzed, efficient and unprecedented version of the Biginelli reaction using new variants of its active methylene component, viz. 2-phenyl-1,3-oxazol-5-one/2-methyl-2-phenyl-1,3-oxathiolan-5-one, with aromatic aldehydes and urea/thiourea enantio- and diastereoselectively, yields 5-amino-/mercaptoperhydropyrimidines. This three-component domino cyclocondensation reaction is effected via ring transformation of an isolable intermediate in a one-pot procedure.
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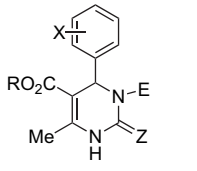
Keywords: Ionic liquids; Perhydropyrimidines; Stereoselective synthesis; Biginelli reaction; Oxazolone; Oxathiolanone

1. Introduction

FDA approved dihydropyridine (DHP) derivatives Nifedipine, Nicardipine and Amlodipine have become almost indispensable for the treatment of cardiovascular diseases such as hypertension, cardiac arrhythmias, or angina.[1] Consequently, interest has also been focused on their aza-analogues such as dihydropyrimidine (DHPM) derivatives (Fig. 1), which are superior in potency and duration of antihypertensive activity to classical calcium channel modulator DHP drugs and compare favourably with second-generation drugs Nicardipine and Amlodipine.[2,3] Furthermore, monastrol and various marine natural products incorporating DHPM scaffolds are valuable new leads for the development of anticancer and AIDS therapy.[4,5]



R = alkyl, Z = O, S
X = 2-/3-NO_2, 2-CF_3
E = ester, acyl, amide

Figure 1.

The amino and mercapto functions are synthetically and pharmacologically readily manipulable. Perhydropyrimidine scaffolds incorporating the $-NH_2$ and $-SH$ functions are hitherto unreported and are not accessible through any one of the known synthetic routes although they appear as attractive scaffolds to be utilized for exploiting chemical diversity and generating a drug-like library to screen for lead candidates.

The Biginelli reaction[6] is one of the fundamental one-pot three-component cyclocondensation strategies for the synthesis of DHPM scaffolds. In the last two decades, more efficient conditions have been found for the Biginelli reaction using soft Lewis acids as catalyst.[7] Microwave irradiation[8] as well as solid-phase and fluoro-phase techniques[9] facilitating this synthesis have also become increasingly widespread. In over 110 years of study of the Biginelli reaction, only minor structural variations in all the three building blocks have been reported[10,11] apart from a very recently reported major structural variation where the urea component was replaced by a guanidine system.[12] However, to the best of our knowledge,

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there has been no such major variation in the active methylene building block, this could be a significant and useful extension of the Biginelli reaction for the synthesis of polyfunctionalized perhydropyrimidines.

Ionic liquids (ILs) have attracted increasing interest in the context of green chemistry owing to their great potential as environmentally benign reaction media.[13–16] Now ILs have marched far beyond the border of solvent showing their significant roles in controlling the reaction as new catalysts[16–18] and reagents.[19,20] A recent review[21] presents studies on the application of chiral ionic liquids (CILs) not only as an opportunity but also as a challenge for researchers. Although a few examples of the application of achiral ILs in the Biginelli reaction are available in the literature,[22,23] we are unaware of the use of a chiral IL in this reaction. The chiral ionic liquids L-prolinium sulfate (Pro_2SO_4), L-alaninium hexafluorophosphate ($AlaPF_6$) and L-threoninium nitrate ($ThrNO_3$), which we have used in the present study, are directly obtainable from a natural α-amino acid.[24] The present work is of particular importance in the context of green chemistry whose principles include the utilization of biorenewable resources. The reason for which we have been spurred to use chiral ionic liquids in the Biginelli reaction stems from the desire to achieve a degree of asymmetric induction and thus obtain enantio- and diastereomerically pure perhydropyrimidines as the biological activity of DHPMs is strictly dependent on the absolute configuration at the C-4 stereocentre.[10,25]

Prompted by the above valid points and as part of our continuous drive to devise new stereoselective cyclization processes,[26–30] we decided to investigate the potential of chiral ionic liquids to accelerate the Biginelli reaction for the enantio- and diastereoselective synthesis of polyfunctionalized perhydropyrimidines employing 2-phenyl-1,3-oxazol-5-one and a recently reported[29] mercaptoacetyl transfer agent, 2-methyl-2-phenyl-1,3-oxathiolan-5-one (Fig. 2), as new variants of the active methylene building block in this venerable reaction (Schemes 1 and 2).

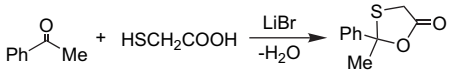
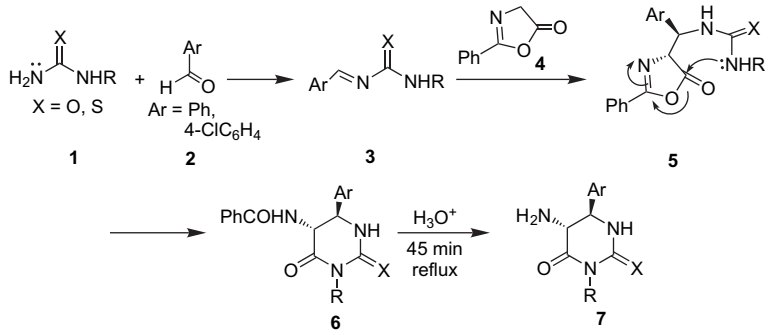


Figure 2. Preparation of mercaptoacetyl transfer agent 2-methyl-2-phenyl-1,3-oxathiolan-5-one.

Interestingly, the unprecedented variants of the Biginelli reaction reported herein yielding polyfunctionalized perhydropyrimidines with high enantio- and diastereoselectivity represent the first example of this venerable reaction catalyzed by a chiral ionic liquid.

2. Results and discussion

The envisaged strategy for the major variation in the active methylene building block of the Biginelli reaction was successful by stirring a mixture of either 2-phenyl-1,3-oxazol-5-one **4** (Scheme 1) or 2-methyl-2-phenyl-1,3-oxathiolan-5-one **8** (Scheme 2) with urea/thiourea **1**, an aromatic aldehyde **2** and Pro_2SO_4 in THF at room temperature for 21–30 h. Isolation and purification by column chromatography afforded perhydropyrimidines as a single diastereomer **6** in 80–92% yields with 81–94% enantiomeric excess (ee), and **10** in 82–93% yields with 78–95% ee. Under conventional reaction conditions[31] and using other CILs ($AlaPF_6$ and $ThrNO_3$) these new reagents **4** and **8** afforded the same perhydropyrimidines in relatively lower yields (41–53%), with significantly lower stereoselectivity (ee 48–57%) and slightly lower trans diastereoselectivity (89–93%). The diastereomeric ratios in the crude isolates were checked by ^{1}H NMR spectroscopy to note any inadvertent alteration of these ratios during subsequent purification. The crude isolates of **6** and **10** were found to be a diastereomeric mixture containing 91–95% and 92–97% of the trans isomer, respectively. The diastereoselectivity was determined by ^{1}H NMR spectroscopy and ee by chiral HPLC. In the trans isomers **6** and **10**, 5-H and 6-H are axial as indicated by their coupling constant ($J_{5,6}$=9.2 Hz, J_{trans}; the cis coupling constant $J_{5,6}$=3.9 Hz). The absence of any measurable NOE between 5-H and 6-H also supports the trans stereochemistry of the compounds **6** and **10**.



3,5-7	R	Ar	X	3,5-7	R	Ar	X
a	H	Ph	O	**e**	2-MeC$_6$H$_4$	Ph	O
b	H	Ph	S	**f**	Et	Ph	O
c	Ph	Ph	O	**g**	H	4-ClC$_6$H$_4$	O
d	Ph	Ph	S	**h**	H	4-ClC$_6$H$_4$	S

Scheme 1. Tentative mechanism for the formation of 5-aminoperhydropyridines **7**.

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