Tetrahedron Letters 59 (2018) 2759–2762

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

# Versatility of the Biginelli reaction: Synthesis of new biphenyl dihydropyrimidin-2-thiones using different ketones as building blocks

Itamar Luís Gonçalves [a], Leonardo Davi [a], Liliana Rockenbach [a], Gustavo Machado das Neves [a], Luciano Porto Kagami [a], Rômulo Faria Santos Canto [c], Fabrício Figueiró [b], Ana Maria Oliveira Battastini [b], Vera Lucia Eifler-Lima [a,*]

[a] Laboratório de Síntese Orgânica Medicinal (LaSOM), Faculdade de Farmácia, Universidade Federal do Rio Grande do Sul. Avenida Ipiranga, 2752, Porto Alegre, RS, Brazil
[b] Laboratório 22, Departamento de Bioquímica, Universidade Federal do Rio Grande do Sul. Rua Ramiro Barcelos, 2600, Porto Alegre, RS, Brazil
[c] Laboratório de Química Medicinal de Compostos de Selênio (QMCSe), Programa de Pós-Graduação em Ciências da Saúde, Universidade Federal de Ciências da Saúde de Porto Alegre, Rua Sarmento Leite, 245 - Centro Histórico, Porto Alegre, RS, Brazil

ARTICLE INFO

*Article history:*
Received 6 May 2018
Revised 30 May 2018
Accepted 2 June 2018
Available online 2 June 2018

*Keywords:*
Biginelli reaction
Structural diversity
Multicomponent reaction

ABSTRACT

A multi-component synthesis of biphenyl dihydropyrimidin-2-thiones from 1-phenylthiourea, aldehydes and ketones or di-ketones has been demonstrated. The reaction proceeded well for aldehydes with electron donor or acceptor substituents under mild conditions.



## Introduction

Biginelli reaction involves the acid-catalyzed multicomponent synthesis of 3,4-dihydropyrimidin-2(1H)-ones(thiones) (DHPMs), employing easily accessible starting materials, such as aldehydes, urea or analogue and compounds with methylene active hydrogens. Thus, this reaction is a powerful tool for the fast and easy generation of libraries with great structural diversity.[1,2] However, the structural diversity of N-1 aryl substituted DHPMs has been poorly explored. In fact, only a few investigations have reported direct N1 alkylation of DHPMs[3,4], and the arylation in the N1 position has not been reported at all. The literature relates that the reactions to obtain N1-substituted DHPMs using substituted thio (ureas)[5] have only been performed with ethyl acetoacetate as a methylene active hydrogen compound.[6,7]

As the pharmacologic effect of these molecules has been extensively investigated in the last few years, it is very important to obtain structural diversity in DHPMs.[8] This heterocycle class is defined as a privileged structure, a term that refers to scaffolds with versatility for interacting with different biological targets, giving rise to important pharmacological effects.[9] In this context, the synthesis of N1-substituted DHPMs with a replacement of the ester moiety by ketones is a very useful strategy for pharmacological *in vivo* investigation, as the ester group may undergo hydrolysis to carboxylic acids and inactivation by *in vivo* metabolism.[10] Recent *in silico* ADMET prediction indicated the hydrolysis of the ester group of DHPMs as reactions of metabolism catalyzed by CYP enzymes.[11]

## Results and discussion

In a previous study, a focused library of two sets of N1-aryl substituted DHPMs was synthesized, using eleven different substituted phenylthiourea, ethyl acetoacetate and two aromatic aldehydes.[12] In continuation of the projects of our group, with the aim of obtaining structural diversity in DHPM scaffolds, chemical diversity in the library was achieved by using the versatility of the Biginelli reaction through exploration of variations at the C-5 position of the biphenyl dihydropyrimidin-2-thione core, using ketones as building blocks instead of a β-ketoester. Thus, using four different ketones **1**–**4** and three aldehydes **6**–**8** in the Biginelli reaction, with 1-phenylthiourea **5,** under mild conditions, it was possible to create a small focused library of 12 DHPMs **9**–**20** with a good chemical and structural variety and purity. For this purpose, diketones (2,4-pentanedione **1** and 1,3-cyclohexanodione **2**) and simple ketones were chosen as building blocks (cyclohexanone **3** and 3,4-dihydro-1(2H) naphthalenone **4**) (See Fig. 1.).

* Corresponding author.
*E-mail address:* itamar3141@yahoo.com.br (V.L. Eifler-Lima).

https://doi.org/10.1016/j.tetlet.2018.06.006
0040-4039/

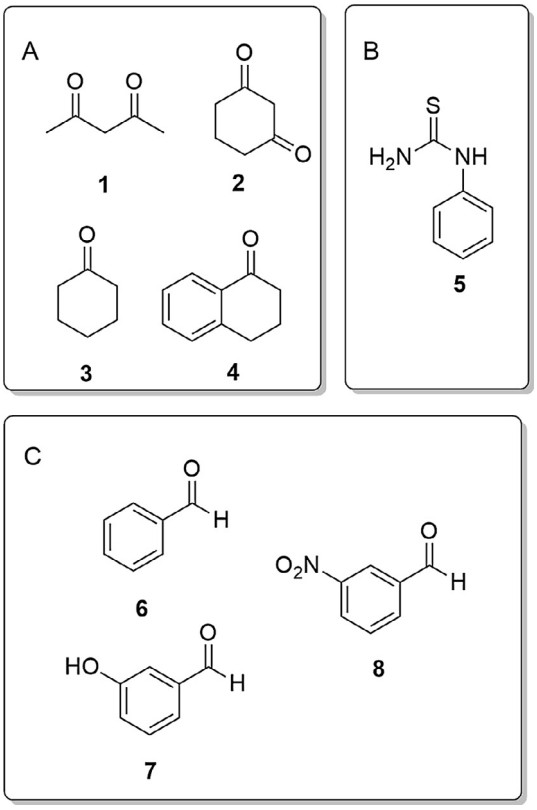
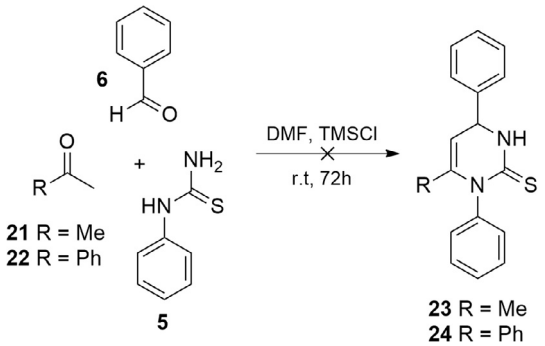



**Fig. 1.** The methylene active compound (A), 1-phenylthiourea (B), and aldehyde (C) building blocks used in the Biginelli reaction.

**Table 1**
Synthesis of biphenyl dihydropyrimidin-2-thiones by the Biginelli reaction using four different ketones (**1**–**4**) and three aldehydes (**6**–**8**) with 1-phenylthiourea (5).[a]

| Methylene active | Aldehyde | Product | Yield |
|---|---|---|---|
| 1 | 6 | 9 | 56% |
| 1 | 7 | 10 | 61% |
| 1 | 8 | 11 | 76% |
| 2 | 6 | 12 | 81% |
| 2 | 7 | 13 | 67% |
| 2 | 8 | 14 | 69% |
| 3 | 6 | 15 | 65% |
| 3 | 7 | 16 | 58% |
| 3 | 8 | 17 | 52% |
| 4 | 6 | 18 | 42% |
| 4 | 7 | 19 | 49% |
| 4 | 8 | 20 | 65% |

[a] Reaction conditions: ketone or di-ketone (1 mmol), aromatic aldehyde (1 mmol), phenylthiourea (1 mmol) in DMF (~1.0 mL) and TMSCl (6 mmol) at room temperature.




**Scheme 1.** Propanone **21** and methyl phenyl ketone **22** did not allow to DHPMs **23** and **24**.