Tetrahedron xxx (2015) 1–5

Contents lists available at ScienceDirect

Tetrahedron

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

A facile synthesis of new coumarin-3,4-dihydropyrimidin-2(1*H*)-ones/thiones dyads

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ARTICLE INFO

Article history:
Received 21 March 2015
Accepted 10 April 2015
Available online xxx

Keywords:
Nitrogen heterocycles
3-(Acetoacetyl)coumarins
3,4-Dihydropyrimidinone
3,4-Dihydropyrimidinethione
Biginelli reaction

ABSTRACT

A new series of 4-aryl-6-methyl-5-(2-oxo-2*H*-chromene-3-carbonyl)-3,4-dihydropyrimidin-2(1*H*)-ones/thiones (DHPMs) have been synthesized through multicomponent Biginelli reactions, involving 3-(acetoacetyl)coumarin derivatives, *para*-substituted benzaldehydes, and urea/thiourea in refluxing acetonitrile, in the presence of a catalytic amount of sulfuric acid. The structure of all newly synthesized compounds has been established by 2D NMR spectroscopic spectra (HSQC, HMBC, and NOESY), elemental analysis, and mass spectrometry.

1. Introduction

Nitrogen heterocycles are a very important class of compounds and an interesting field for research with great opportunities for the synthesis of novel drugs. For instance, pyrimidinone derivatives are widely distributed in nature and exhibit various biological properties, such as antimalarial,[1–3] antibacterial,[4] antifungal,[5] anti-HIV,[6] antiviral,[7] anticancer,[8] and anti-inflammatory[9,10] activities. Therefore, the corresponding dihydropyrimidinones (DHPMs) have exhibited important therapeutic and pharmacological properties, namely as the integral backbone of several calcium channel blockers,[11] antihypertensive agents,[12] and α1a-antagonists.[13] A broad range of biological effects including antiviral, antitumor, antibacterial, and anti-inflammatory activities have been described for these compounds.[13–15] Functionalized DHPMs have shown significant antibacterial,[16] antiviral,[17] and antitumor[18] activities. The synthesis of DHPMs has been the focus of great interest for organic and medicinal chemists.[13,15] The most common method for the synthesis of DHPMs and the corresponding dihydropyrimidinethiones (DHPMTs) involves the multicomponent Biginelli reaction.[19] The original Biginelli protocol for the preparation of DHPMs consisted of heating a mixture of three components, a β-ketoester, an aldehyde, and urea, in ethanol containing a catalytic amount of HCl.[20] Multicomponent reactions (MCRs) are convergent reactions, in which three or more starting materials react to form a product. In an MCR, a product is assembled according to a cascade of elementary chemical reactions. In contrast to classical multistep linear synthetic protocols, MCRs enable expedient and efficient assembly of molecules of structural complexity and diversity in one-pot operations with facile execution, high atom economy, and selectivity. Multicomponent reactions (MCRs) have facilitated many fascinating and challenging transformations in organic synthesis. These reactions obviate the isolation and purification of intermediates and diminish waste generation, thereby enhancing the greenness of transformations. MCRs are emerging as powerful tools in the synthesis of complex biologically important compounds.[21]

Several reports on the synthesis and biological evaluation of pyrimido-fused heterocycles such as pyrimido[4,5-*d*]pyridazin-8(7*H*)-ones,[22] pyrano[2,3-*d*]pyrimidines, pyrido[2,3-*d*]pyrimidines,[23] and 2,4-diaminopyrido[2,3-*d*]pyrimidines[24] are available in the literature.

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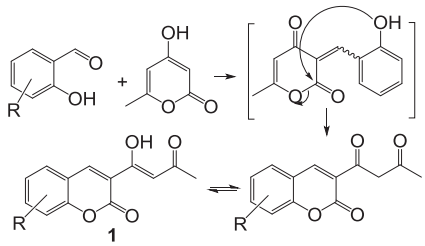
http://dx.doi.org/10.1016/j.tet.2015.04.028
0040-4020/

In continuation of our interest on the synthesis of fused heterocycles,[25] herein we describe a simple and efficient strategy for the synthesis of a new series of 4-aryl-6-methyl-5-(2-oxo-2*H*-chromene-3-carbonyl)-3,4-dihydropyrimidin-2(1*H*)-ones/thiones (**4a**–**e**, **5a**–**d**, **6a**–**d**, **7**, and **8**) under mild conditions using 3-(acetoacetyl)coumarin derivatives **1a**–**e** as key synthons.

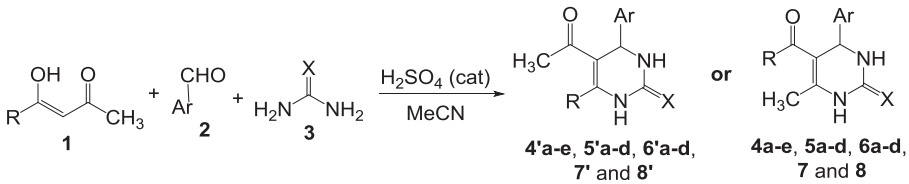
2. Results and discussion

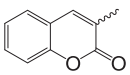
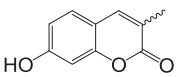
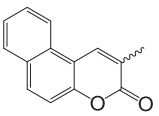
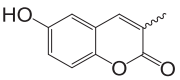
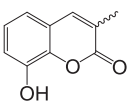
A 3-acetoacetylcoumarin derivatives **1a**–**e** have recently been synthesized in our laboratory from substituted salicylaldehydes and 4-hydroxy-6-methyl-2*H*-pyran-2-one (triacetic acid lactone=TAL) through a tandem microwave-assisted Knoevenagel condensation and intramolecular trans-lactonization process in an organobasic medium (Scheme 1).[26] These compounds are key building blocks, as they contain a coumarin nucleus as well as the active methylene group of the acetoacetyl moiety, which is prone to undergo further useful chemical transformations. Following our studies on the establishment of new synthetic routes to biologically active heterocyclic compounds, we developed an efficient one-pot synthesis of 4-aryl-6-methyl-5-(2-oxo-2*H*-chromene-3-carbonyl)-3,4-dihydropyrimidin-2(1*H*)-ones/thiones (**4a**–**e**, **5a**–**d**, **6a**–**d**, **7**, and **8**). After several experiments, we found that these new compounds could be obtained via a one-pot multicomponent reaction of the 1,3-dicarbonyl branch of 3-(acetoacetyl)coumarins/3-(acetoacetyl)benzo[*f*]coumarins **1a**–**e**, *para*-substituted benzaldehydes **2** and urea/thiourea **3**, in the presence of sulfuric acid under refluxing acetonitrile (Table 1).



Scheme 1. Synthesis of 3-(acetoacetyl)coumarins **1**.

Table 1
Synthesis of 4-aryl-6-methyl-5-(2-oxo-2*H*-chromene-3-carbonyl)-3,4-dihydropyrimidin-2(1*H*)-ones/thiones **4a**–**e**, **5a**–**d**, **6a**–**d**, **7**, and **8**



Entry	Product	R	Ar	X	Yield (%)	Mp (°C)
1	**4a**		C_6H_5	O	72	130–133
2	**4b**		4-$NO_2C_6H_5$	O	50	260
3	**4c**		4-ClC_6H_5	O	42	134
4	**4d**		C_6H_5	S	56	140–145
5	**4e**		4-ClC_6H_5	S	52	180–185
6	**5a**		C_6H_5	O	82	240
7	**5b**		4-$NO_2C_6H_5$	O	42	235
8	**5c**		4-ClC_6H_5	O	50	135
9	**5d**		C_6H_5	S	60	168–170
10	**6a**		C_6H_5	O	83	206
11	**6b**		4-$NO_2C_6H_5$	O	70	225
12	**6c**		4-ClC_6H_5	O	42	180–186
13	**6d**		C_6H_5	S	70	160
14	**7**		C_6H_5	O	94	225
15	**8**		C_6H_5	O	65	203

The mechanism of the Biginelli reaction together with the structure of the used synthons suggested the possible formation of two dihydropyrimidinones/thiones-type compounds **4a**–**e**, **5a**–**d**, **6a**–**d**, **7**, **8** or **4′a**–**e**, **5′a**–**d**, **6′a**–**d**, **7′**, **8′** (Scheme 2, Table 1). This process starts with the formation of an imine **9**, by condensation of the benzaldehyde **2** with urea/thiourea **3**, which then reacts with the 1,3-dicarbonyl **1** after protonation the imines' nitrogen **10**. In the last step of the mechanism there are two possible cyclization sites, which can lead after dehydration to DHPM(T)s **4a**–**e**, **5a**–**d**, **6a**–**d**, **7**, **8** or **4′a**–**e**, **5′a**–**d**, **6′a**–**d**, **7′**, **8′**. However, the cyclization occurred only at the most electrophilic carbonyl carbon of the intermediate **11** (Scheme 2).

Please cite this article in press as: Benazzouz, A.; et al., Tetrahedron (2015), http://dx.doi.org/10.1016/j.tet.2015.04.028