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Facile conversion of Biginelli 3,4-dihydropyrimidin-2(1*H*)-thiones to 2-(2-hydroxy-2-arylvinyl) dihydropyrimidines via Eschenmoser coupling

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ABSTRACT

A one-pot, two-step synthesis protocol for the conversion of Biginelli 3,4-dihydropyrimidin-2(1*H*)-thiones to 2-(2-hydroxy-2-arylvinyl) dihydropyrimidine (DHPM) derivatives via Eschenmoser sulfide contraction coupling is described. Solution phase as well as solid-supported protocol was carried out for the decoration of the Biginelli DHMP scaffold at the C-2 position. The scope of the optimized protocol is demonstrated for different DHMP precursors.

1. Introduction

The search for new valuable drug candidates demands on the diversity, which can be created by combinatorial methods on a particular template and on the accessibility of appropriate scaffolds. One such template class is the 3,4-dihydropyrimidin-2(1*H*)ones/thione core **1**, which represents a class of heterocyclic molecules that have attracted a considerable interest to medicinal chemists.[1] The one-pot three-component Biginelli reaction[2] has been known for more than a century for the preparation of 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs). In the past decades, the scope of this cyclocondensation reaction was gradually extended by variation of the three building blocks, which developed an access to a large number of structurally diverse DHPMs.[3] Various diversification methods for Biginelli products can be found in the literature.[4]

The nonplanar DHPM derivatives are attractive molecules for drug research because of their known multifaceted pharmacological profiles. Introduction of DHPMs resulted in the discovery of new kind of calcium channel modulators,[1] hepatitis B virus replication inhibitors,[5] mitotic kinesin inhibitors[6] and α1a-adrenergic receptor antagonists.[7] Several natural marine polycyclic guanidine alkaloids such as crambine, batzelladine B (potent HIV gp-120CD4 inhibitors) and ptilomycalin alkaloids also consist DHPM-derived structures in their skeleton, and the Biginelli route was chosen for their total synthesis.[8] It seems to be reasonable that DHPMs are privileged structures for drug research.

Due to the ongoing search for small molecular stem cell modulators, we looked for suitable scaffolds with known multiple drug effects. Despite the fact that pyrimidine derivatives are found in a wide range of biologically active molecules,[9] there are only some derivatization methodologies known for the Biginelli DHPMs **1** at the C-2 positions. Whereas alkylation and acylation protocols were found in the literature,[10] and only a few examples make use of a C-2 O/S substitution strategy (Fig. 1). An appropriate synthetic method would be very useful to prepare new chemical entities.

In 2004, Lengar and Kappe described a microwave-assisted Pd(0)-catalyzed/Cu(I)-mediated carbon–carbon cross coupling of 3,4-dihydropyrimidine-2-thiones **1** with boronic acids which yields 2-aryl-1,4-dihydropyrimidines **2**.[11] A similar kind of palladium-catalyzed C–C Suzuki/Sonogashira coupling of 2-chloropyrimidine with boronic acids or alkynes for the synthesis of C-2

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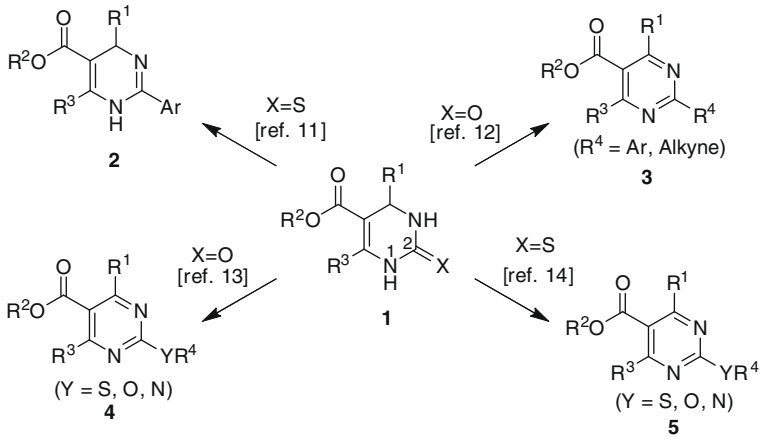
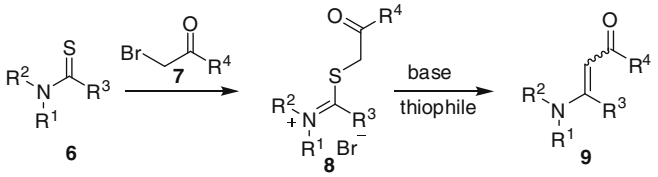


Figure 1. Reported methods to derive Biginelli DHPMs **1** at C-2 position.

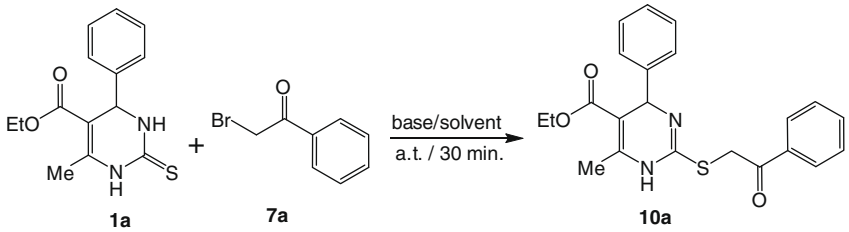


Scheme 1. Eschenmoser coupling reaction (Sulfide contraction).

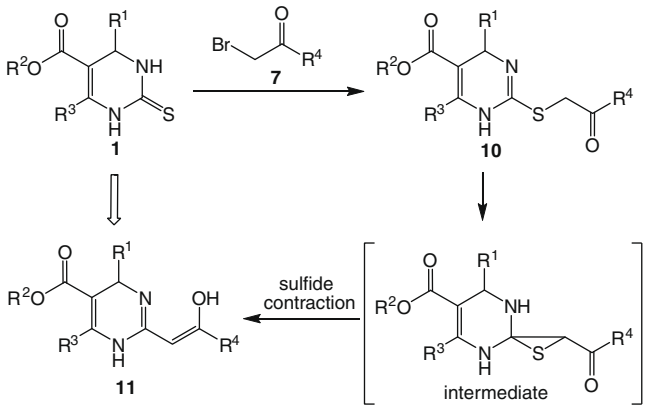
functionalized pyrimidines **3** was recently described by Srinivasan and co-workers[12] Kang et al. described a two-step procedure to convert Biginelli DHPMs to the C-2 functionalized pyrimidines **4** via a tautomerization–activation-coupling (TAC) process by employing conventional peptide coupling agents.[13] Matloobi and Kappe have reported a microwave-assisted nucleophilic displacement of C-2 sulfones of DHPM derivatives with a variety of nucleophiles to furnish C-2 decorated pyrimidines **5**.[14] However, in the latter two cases mostly hetero-S, N and O nucleophiles were used, except of malononitrile which led to the formation of a C–C bond at C-2 position.

We envisaged the Eschenmoser sulfide contraction method to receive a new C–C bond at the C-2 position of **1**. In general, classical Eschenmoser sulfide contraction conditions[15] yield vinylogous amides of type **9**. The reaction sequences involve the alkylation of secondary or tertiary thioamide moieties **6** with α-bromoketones **7**. The sulfur extraction from the received intermediate **8** forms product **9** with a new carbon–carbon bond (Scheme 1).

Table 1
Screening of alkylation conditions for selective functionalization of C-2 sulfur



Entry	Base (1.5 equiv)	Solvent	Product	Isolated yield (%)
1	Et_3N	DCM	**10a**	88
2	Et_3N	DMF	**10a**	78
3	Et_3N	Dioxane	**10a**	69
4	Et_3N	THF	**10a**	82
5	Et_3N	MeCN	**10a**	64
6	DBU	DCM	**10a**	87
7	DBU	DMF	**10a**	74
8	DBU	Dioxane	**10a**	60
9	DBU	THF	**10a**	76
10	Pyridine	THF	**10a**	67
11	Pyridine	DMF	**10a**	81
12	K_2CO_3	Acetone	**10a**	**92**
13	K_2CO_3	DCM	**10a**	45
14	K_2CO_3	DMF	**10a**	71



Scheme 2. Eschenmoser coupling route to C-2 functionalized 1,4-dihydropyrimidines **11**.

2. Experimental and results

We made use of this route for the formation of C-2 modified DHPM derivatives of type **11**. Initially, we optimized the alkylation of 5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-thione **1a** with phenacyl bromide **7a** under basic conditions. Various base/solvent combinations were investigated (Table 1). It was found that 1.5 equiv of K_2CO_3 in acetone furnished the desired product **10a** within 30 min in 92% yield at room temperature. The use of other organic bases such as Et_3N, DBU and pyridine led to lower yields (Table 1). No side reaction products such as ester cleavage or di-alkylation were detected in the LC–MS analysis. Even, the generally possible thiazolopyrimidine formation was also not detected at any stage of the reaction.[16] But prolonged reaction times or increased reaction temperatures led to lower yields of the desired product **10a**.

To develop a useful one-pot protocol, the selective alkylation of the C-2 sulfur of **1** with α-bromoketones **7** has to be followed by the subsequential elimination of the bridged sulfur by addition of a thiophilic agent (Scheme 2). To furnish the desired C–C coupled product **11a** as depicted in Scheme 2, triphenylphosphine was added as the thiophilic agent. It was found that **10a** get slowly converted into the desired product **11a** if the reaction was heated to 80 °C. After 10 h, 78% overall yield of **11a** was obtained. Further increase in temperature, reaction time or quantity of phosphine did not increase the yield significantly. A chromatographic work-up was necessary to isolate the desired product **11a** from the phosphine sulfide. Additionally, the reaction was carried out with trioctylphosphine. But in both cases, an excessive chromatographic work-up was necessary to separate the desired product **11a** from the phosphine and phosphine sulfides. Hence, this one-pot method using dissolved thiophilic phosphines suffers from poor purity and hard work-up. To overcome this problem, we made use of polymer-supported triphenylphosphine, which acts as thiophilic agent as well as scavenger for unreacted α-bromoketones **7**. Therefore, commercially available polymer bound triphenylphosphine (polystyrene, 2% DVD, 3 mmol/g, Fluka) was used. Upon comparing the products obtained with PPh_3 (1.5 equiv) and trioctylphosphine (1.5 equiv) with polymer bound PPh_3 (1.5 equiv), it was found that in the latter case the desired product **11a** was obtained exclusively. In order to study the role of base in sulfide contraction step, we did an independent experiment in which a purified **10a** was treated with polymer bound PPh_3 in acetone at 80 °C. It was found that instead of sulfide contraction the deprotection of the C-2 sulfur took place, and the starting DHPM **1a** was observed.

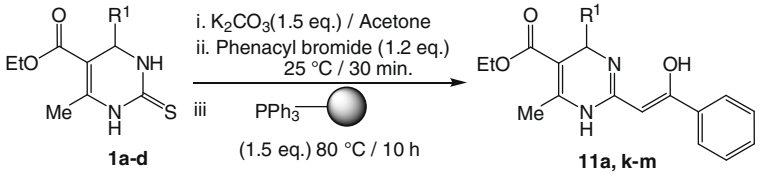
After optimizing the one-pot two-step reaction, we studied different C-4 substituted Biginelli substrates with phenacyl bromide **7a** (Table 2). To further explore the scope of this one-pot reaction, we used a variety of α-bromoketones **7a–j** with DHPM **1a** under current conditions (Table 3). It was found that α-bromoketones **7a–j** bearing different substituents on the phenyl ring underwent the Eschenmoser coupling very well within 10 h.[17]

In each case, the corresponding C-2-substituted products were obtained in a synthetically useful manner (Tables 2 and 3). All received products were purified by a chromatographic work-up (usual conditions: Silica 60, ethyl acetate/hexane 20:80). It was observed that the ^{1}H NMR spectra of all the products **11** (Table 2) show a duplicate set of some signals (approximately 3:1 ratio) due to different tautomers of **11** in solution. But all products shown in Table 2 were well characterized by ^{1}H NMR, ^{13}C NMR, IR and HRMS.

3. Summary

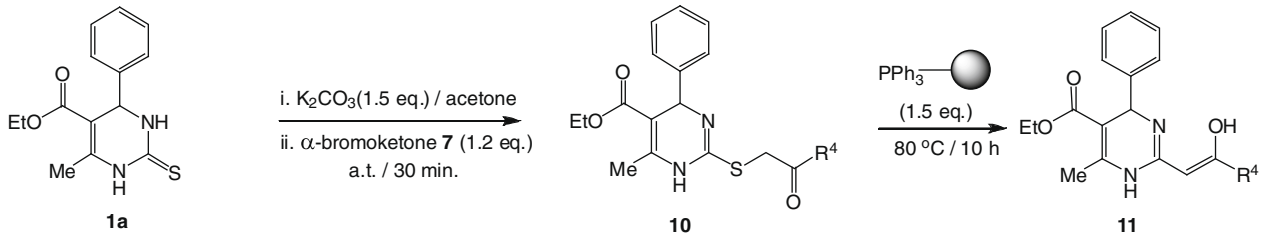
In summary, thiono derivatives of DHPM derivatives **1** readily undergo Eschenmoser sulfide contraction in a one-pot two-step procedure and furnish dihydropyrimidines of type **11**. The one-pot procedure includes the selective alkylation of DHPMs **1** at C-2 position with α-bromoketones **7** and the subsequent elimination of the bridged sulfur assisted by solid-supported triphenylphosphine.

Table 2
Eschenmoser coupling for different Biginelli substrates

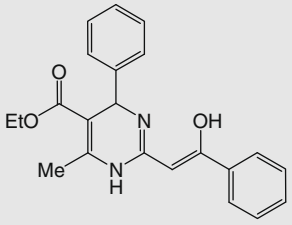
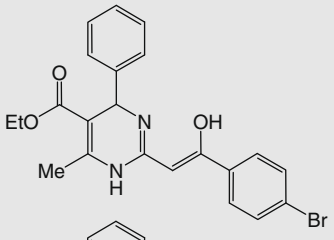
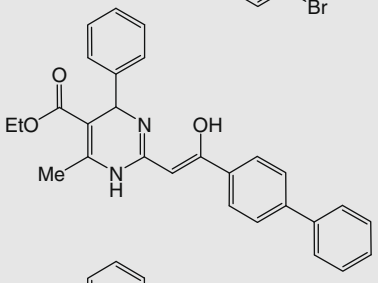
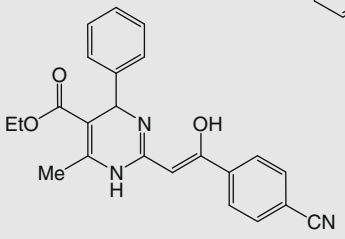
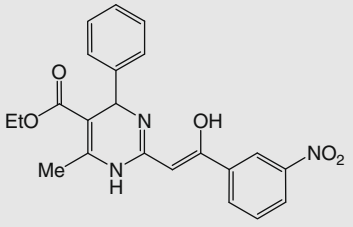
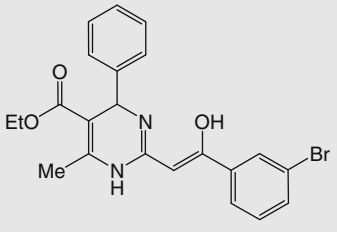


Entry	DHPM **1**	R^1	Product **11**	Isolated yield (%)
1	**1a**	Ph	**11a**	80
2	**1b**	4-OMe–C_6H_4	**11k**	82
3	**1c**	2,4-$(OMe)_2$–C_6H_3	**11l**	78
4	**1d**	3,4,5-$(OMe)_3$–C_6H_2	**11m**	75

Table 3
Conversion of 3,4dihydropyrimidin-2(1*H*)-thione **1a** to 2-(2-hydroxy-2-arylvinyl)dihydropyrimidines **11a–j**

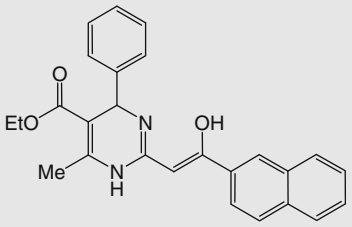
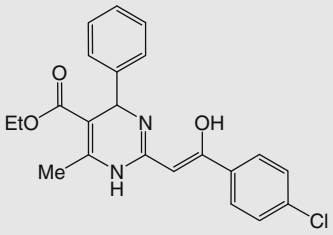
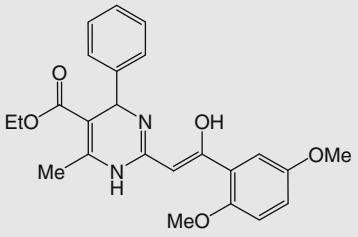
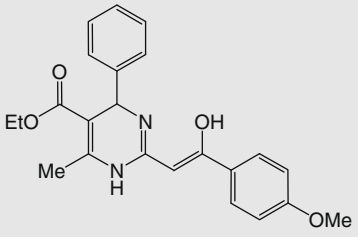


1a **10** **11**

Entry	α-Bromoketone **7**	Product **11**	Isolated yield (%)
a	$PhCOCH_2Br$		80
b	$4\text{-}BrC_6H_4COCH_2Br$		82
c	$4\text{-}PhC_6H_4COCH_2Br$		78
d	$4\text{-}CNC_6H_4COCH_2Br$		88
e	$3\text{-}NO_2C_6H_4COCH_2Br$		90
f	$3\text{-}BrC_6H_4COCH_2Br$		83

(*continued on next page*)

Table 3 (*continued*)

Entry	α-Bromoketone **7**	Product **11**	Isolated yield (%)
g	β-$C_{10}H_7COCH_2Br$		77
h	4-$ClC_6H_4COCH_2Br$		91
i	2,5-$(OMe)_2C_6H_3COCH_2Br$		86
j	4-$OMeC_6H_3COCH_2Br$		84

Acknowledgments

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Supplementary data

Available experimental procedures and analytical characterization data for compounds are provided. Characteristic data of selected compounds **11** are presented. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.027.

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17. *General procedure*: Conversion of 3,4-dihydropyrimidin-2(1*H*)-thione to 2-(2-hydroxy-2-arylvinyl)-dihydropyrimidine. To a stirred solution of 5-ethoxycarbonyl-6-methyl-4-aryl-3,4-dihydro-pyrimidin-2(1*H*)-thione (**1a**)

(0.36 mmol, 1 equiv) in acetone (2 mL), subsequently K_2CO_3 (75 mg, 0.54 mmol, 1.5 equiv) and the α-bromoketone **7** (0.43 mmol, 1.2 equiv) were added at ambient temperature. After stirring for ca. 30 min at ambient temperature (TLC monitoring, until all DHPM get consumed), polymer bound triphenylphosphine (0.54 mmol) (polystyrene, 2% DVB, 3 mmol/g, Fluka 93093) was added in one portion, and the reaction temperature was shifted to 80 °C. Stirring was continued for additional 10 h to complete the reaction (TLC monitoring). For work-up, 1 mL EtOAc was added to the reaction mixture, and the polymer was filtered. The filtrate was concentrated under reduced pressure and subjected to a flash chromatography system (Intelli-Flash 310, Varian; Silica 60) using 30% ethyl acetate in hexane to obtain pure samples of **11**. The ^{1}H NMR spectra of all products **11** show two sets of signals with approximate 3:1 intensity. This is due to different conformations of the C2–C bond as well as the possible tautomerism of the dihydropyrimidin core **11**.