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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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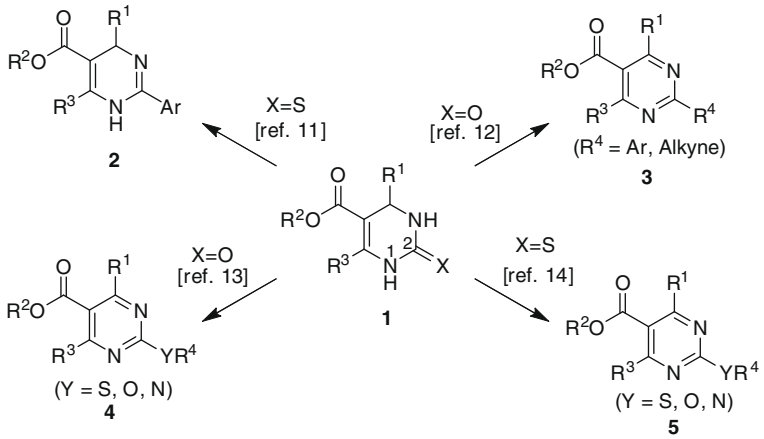
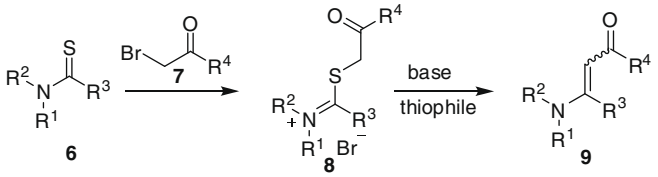


Figure 1. Reported methods to derive Biginelli DHPMs **1** at C-2 position.

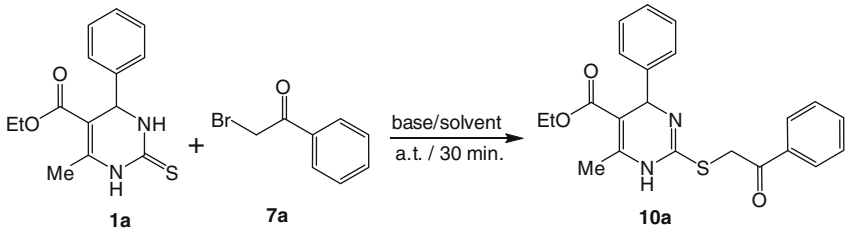


Scheme 1. Eschenmoser coupling reaction (Sulfide contraction).

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