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Convenient method for synthesis of thiazolo[3,2-*a*]pyrimidine derivatives in a one-pot procedure

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ABSTRACT

An efficient one-pot method to synthesize thiazolo[3,2-*a*]pyrimidine derivatives has been developed. The method involves the temperature controlled functionalization-annulation of 5-ethoxycarbonyl-6-methyl-4-aryl-3,4-dihydro-2(1*H*)-pyrimidin-2-thione (DHPM) derivatives with in-situ generated bromo-ketones received by reaction of different α-H carbonyl compounds with bromine.

1. Introduction

The concept of so-called 'privileged structures' for positioning functional groups to receptor sites has attracted considerable interest during the last decades. It has been successfully exploited across and within different target families and promises to be an effective approach for the discovery and optimization of novel bioactive molecules. Privileged structures with inherent affinity for diverse biological receptors represent an ideal source for core scaffolds and capping fragments for the design and synthesis of combinatorial libraries targeted at various receptors on a reasonable time scale.[1] The exploration of such structures in drug discovery is a perpetually ongoing challenge in medicinal chemistry. Dihydropyrimidinones **1** (DHPMs) appear to be a class of privileged organic compounds with medicinal significance due to their different biological and therapeutic activities.[2] These types of non-planar heterocycles are interesting structural units that are found in a vast number of biologically active natural compounds[3] and pharmaceuticals.[2] Hence, several methods for their production and purification have been developed in the recent past.[4] Moreover, they are important intermediates in organic synthesis providing access to other highly desirable structures.[5] A myriad of methodologies and protocols have been developed to synthesize DHPM derivatives.[6] A large number of the known synthetic methods are limited to particular substitution patterns. Thus it is necessary to develop novel methods to obtain advanced modifications[7] of these types of heterocycles in order to prove the possible privilege properties of the DHPM scaffolds.

DHPM derivatives are known to possess diverse pharmacological properties such as calcium channel modulators,[2b] hepatitis B virus replication inhibitors[8] and mitotic kinesin inhibitors.[9] In addition, due to the presence of several reactive centers much attention has been focused on the modification of their core by template decoration strategies. These nucleophilic centers allow a variety of mono and dialkylation, acylation[10] as well as the very prospective cyclization reactions.[11] One such possibility is to convert the dihydropyrimidine-thione **1** (DHPM, Biginelli compounds) into thiazolo[3,2-*a*]pyrimidine derivatives **3**, which are known to possess potential for: calcium channel antagonistic activity,[12] antifungal properties,[13] anti-inflammatory properties,[14] CDC25 phosphatase inhibitor activity,[15] mGluRs antagonist properties[16] and acetylcholinesterase inhibitor activity.[17]

Traditional methods for the preparation of thiazolo[3,2-*a*]pyrimidine from DHPM precursors include the reaction of Biginelli compounds with 2-Bromo-ketones,[12,18] methyl chloro acetate,[19] chloroacetyl chloride,[20] 1,2-dichloroethane,[13] chloroacetic acid[13] etc. to yield C2-N3 linked thiazolo[3,2-*a*]pyrimidine derivatives of type **3**. In this Letter, we describe a convenient and selective method to synthesize multifunctionalized thiazolopyrimidine derivatives (**3**), including an in-situ formation of the necessary bromoketones[21] from enolizable ketones in a single-pot reaction (Scheme 1).

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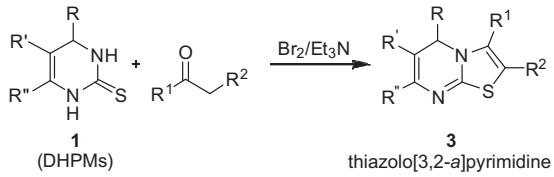
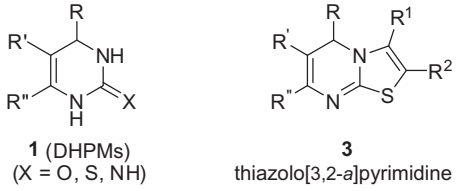


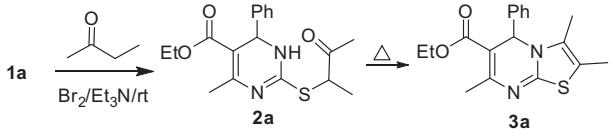
Scheme 1. Model reaction of DHPM **1** with enolizable ketones.



2. Results and discussion

In order to optimize the reaction conditions, 5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydro-2(1*H*)-pyrimidin-2-thione **1a** was used as the precursor for the synthesis of ethyl 2,3-dimethyl-5-phenyl-7-methyl-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylate **3a**. Initially we examined the in-situ generation of the bromoketone precursor by reacting 2-butanone (0.72 mmol) with molecular bromine (0.72 mmol) at ambient temperature. In order to find suitable reaction conditions, various solvents (2 ml) were investigated (Table 1). Complete consumption of the bromine was indicated by the disappearance of the yellow-brown color from the reaction mixture, which takes about 5–10 min depending upon the solvent used. Only in the case of DMF (Table 1; Entry 5) warming up of the reaction to 40 °C for at least 45 min was necessary to assure the complete consumption of bromine. To each clear reaction solution, 0.36 mmol of DHPM **1a** was introduced in the presence of 100 μL Et_3N. The reaction performance under different solvent conditions at room temperature has been investigated by LC–MS analysis. It was found that in case of chloroform as solvent the required *S*-alkylated intermediate **2a** was furnished in quantitative yield within 30 min. In all other solvents the reactions were not completed within this time. Additionally it was observed that prolonged reaction time at room temperature did not yield the desired cyclized thiazolopyrimidine **3a**. The reaction temperature was therefore elevated. It was observed that open chain intermediate **2a** gets converted into the desired thiazolopyrimidine **3a** at 80 °C. After heating the reactions for 2 hours the best yields were obtained in case of DCE (83%), THF (81%), DMF (82%) and methanol (76%) (Table 1; entry 3–5, 8). In the case of chloroform, where the first step yield was quantitative, the conversion to **3a** was incomplete. From all experiments 1,2-dichloroethane (DCE, Table 1; entry 3) was chosen as the optimal reaction solvent. Further optimization of the present reaction conditions revealed that after complete consumption of bromine at ambient temperature, DHPM and Et_3N can be introduced simultaneously and the reaction mixture can be immediately heated to 80 °C.[22] A basic extraction of the crude reaction solution with saturated aqueous $NaHCO_3$ was carried out prior to chromatographic purification. Prolonged processing of the reaction and larger quantities of the additives did not increase the overall reaction yield significantly. During the optimization experiments no side product due to ester cleavage, dialkylation or reaction with DCE were observed in LC–MS.

Table 1
Optimization conditions for the synthesis of thiazolopyrimidine **3a**



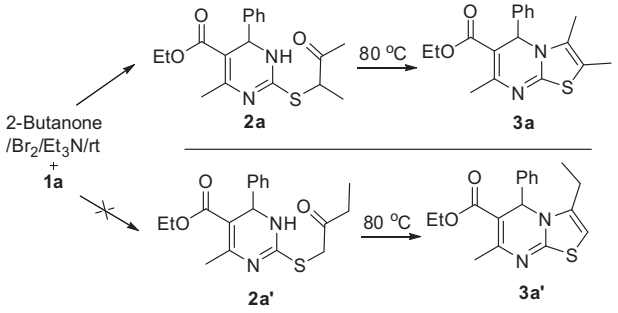
Entry	Solvent	Yield[a] **2** (%)	Yield[b] **3** (%)
1	DCM	56	57
2	Chloroform	82	62
3	DCE	43	83
4	THF	23	81
5	DMF	28	82
6	Ethyl acetate	21	46
7	Ether	34	23
8	Methanol	62	76
9	Hexane	<10	<10

[a] Isolated yield after 30 min shaking at rt.
[b] Isolated yield after 2 h heating at 80 °C.

The optimized reaction sequence includes the nucleophilic addition of DHPM sulfur (**1a**) to the α-position of the in-situ obtained aliphatic bromoketone and the subsequent condensation of the keto-group of **2a** to provide the desired thiazolopyrimidine **3a**. The *N*3-regioselectivity of the cyclization step was assumed to be due to the difference in the electron density at the *N*3 and *N*1 position of 3,4-dihydropyrimidine-thione **1a**. The higher basicity of the *N*3 resulted in the exclusive cyclization at this position. Moreover the selective C2-*N*3 annulation has been proven by single crystal X-ray crystallographic studies elsewhere.[18] Additionally, in order to rule out the alternative reaction route, which may lead to the isomeric **3a′** as shown in Scheme 2, a detailed ^1H NMR analysis was performed. The obtained ^1H NMR spectra of the purified product show resonance signals corresponding to the structure **3a** due to the lack of an olefinic proton and the presence of three methyl (-CH_3, singlets) protons at δ 1.98, 2.10 and 2.39. To compare the NMR spectra of both proposed structures, **3a′** was synthesized independently by using commercially available 1-bromo-2-butanone, instead of the 2-butanone/Br_2/Et_3N mixture, in the presence of K_2CO_3 as the base and acetone as solvent (Table 2; entry 2). The ^1H NMR spectrum of thus obtained product (67%) has shown distinctive signals corresponding to product **3a′** (see Supplementary data). Hence, **3a** could obviously be elucidated as the right structure for the obtained product in Scheme 2 and Table 1.

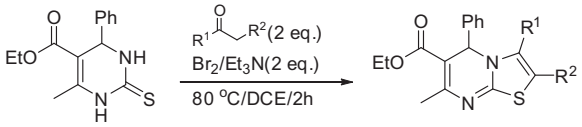
Various α-H bearing ketones were used to increase the chemical diversity on the thiazolo[3,2-*a*]pyrimidines **3** (see Table 2). The use of 2-hexanone gave mixture of unreacted **1a**, open chain **2b** and desired cyclic products **3b**, out of which **3b** was isolated in a yield of 30%. Reaction of acetone as ketone was carried out in excess of acetone as the solvent in the presence of 2 equivalents of both molecular bromine and Et_3N. The reaction mixture furnished a desired product **3c** exclusively in 82% yield after heating for 30 min.

The use of rather reactive acetylacetone furnished **3d** in 65% yield. Brominated ethylacetoacetate in DCE provides **3e** in 72% yield. Similarly benzyl acetoacetate under the same conditions furnished the desired product **3f** in 70% yield. Reaction of



Scheme 2. Comparison of **3a** with **3a′**.

Table 2
Reactions of 5-ethoxycorbonyl-6-methyl-4-phenyl-3,4-dihydro-2(1*H*)-pyrimidin-2-thione **1a** with Br_2/enolizable ketones



1a **3a-h**

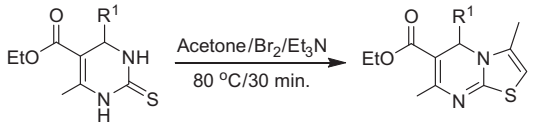
Entry	Ketone	Product	R^1	R^2	Isolated yield (%)
1	2-Butanone	**3a**	Me	Me	83
2	1-Bromo-2-butanone[a]	**3a′**	Et	H	67
3	2-Hexanone	**3b**	Me	Pr	30
4	Acetone[b]	**3c**	Me	H	82
5	Acetylacetone	**3d**	Me	–COMe	65
6	Ethylacetoacetate	**3e**	Me	–COOEt	72
7	Benzylacetoacetate	**3f**	Me	–COOBn	70
8	2,5-Hexadinone	**3g**	Me	$-CH_2COMe$	75
9	Cyclohexanone	**3h**	$-CH_2CH_2CH_2CH_2-$		69

[a] Reaction was performed in acetone using K_2CO_3 as the base.
[b] Reaction was performed in acetone as the solvent and the reactant.

2,5-hexadione was executed and the corresponding product **3g** was obtained in 75% isolated yield. When cyclohexanone was used the tricyclic product **3h** was isolated in 69% yield.

The scope of the optimized method was further extended by implementing it on various C4-substituted DHPMs with electron releasing and withdrawing substituents (Table 3). In this case acetone was used as the ketone of choice and reaction was performed in acetone as the solvent as well. This method is efficient for most of the substances used and furnishes the desired product in good yields. However in the case of *ortho*-NO_2 (**1h**) and 2,4-Cl_2Ph (**1k**) substituted DHPM-C4 phenyl, the desired product could not be obtained. While other ortho substituted DHPM-C4 phenyl, such as 2,4-$(OMe)_2$Ph (**1c**); 2,6-Cl_2Ph (**1j**); could yield the corresponding product **3j** and **3q** in 78% and 79% isolated yields, respectively. Therefore the reaction failure seems not to be due to the steric hindrance at the ortho position. In another example (Table 3; entry 11) where 2-thiophene substituted DHPM (**1l**) was used as the precursor, the desired product **3s** was obtained in high yield (82%). In order to check the scope of this method for a large scale production, an independent experiment in a 50 mL volume vial under stirring conditions was performed. A reaction of 1 g DHPM (**1a**) with acetone under a similar set of conditions (Table 2; entry 4) furnishes the required **3c** (984 mg) in 86% yield.

Table 3
Conversion of C4-substituent DHPM derivatives



1b-m **3i-r**

Entry	DHPM **1**	R^1	Product **3**	Isolated yield (%)
1	**1b**	4-OMe-C_6H_4	**3i**	84
2	**1c**	2,4-$(OMe)_2$-C_6H_3	**3j**	78
3	**1d**	3,4,5-$(OMe)_3$-C_6H_2	**3k**	72
4	**1e**	2,3-$(OMe)_2$-C_6H_3	**3l**	70
5	**1f**	3-OMe-C_6H_4	**3m**	77
6	**1g**	4-NO_2-C_6H_4	**3n**	67
7	**1h**	2-NO_2-C_6H_4	-	-
8	**1i**	4-Br-C_6H_4	**3o**	71
9	**1j**	2,6-Cl_2-C_6H_3	**3p**	79
10	**1k**	2,4-Cl_2-C_6H_3	-	-
11	**1l**	2-Thiophene	**3q**	82
12	**1m**	4-NMe_2-C_6H_4	**3r**	69

The corresponding thiazolo[3,2-*a*]pyrimidine derivatives **3** were obtained in a synthetically useful manner using the one-pot reaction strategy (Table 2 and 3). All received products were purified by flash chromatography using silica columns with ethyl acetate/hexane 20:80) eluent. All purified compounds were carefully characterized by IR, ^{1}H NMR, ^{13}C NMR, LC–MS and HR-MS analyses (see Supplementary data for details).

3. Summary

In summary, we developed a convenient and selective one-pot method for the synthesis of 5*H*-thiazolo[3,2-*a*]pyrimidine derivatives by exploiting the reaction of in-situ formed α-brominated ketones with dihydropyrimidine-2-thiones of type **1**. Moreover, the possibility of introducing a variety of substituents at different positions of the thiazolo[3,2-*a*]pyrimidine ring system was achieved by this method. The presented method delivers new screening candidates in an easy way and is well suited for robotic synthesis. The achievable 5*H*-thiazolo[3,2-*a*]pyrimidine derivatives may help in the understanding of the privileged nature of the DHPM core.

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Supplementary data

Supplementary data (experimental procedures, analytical characterization data and copy of ^{1}H/^{13}C NMR spectra) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.05.067.

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22. *General procedure for the synthesis of ethyl 2,3-disubsituted-5-aryl-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate* (**3**). To a solution of the ketone (0.72 mmol, 2 equiv) in 2 ml of 1,2-dichloroethane, molecular bromine (37 μL, 0.72 mmol, 2 equiv) was added slowly at ambient temperature. The resulting wine red solution was subjected to shaking until the disappearance of the color. To the clear reaction solution thus obtained, 5-ethoxycorbonyl-6-methyl-4-Aryl-3,4-dihydro-2(1*H*)-pyrimidin-2-thione (**1**) (0.36 mmol, 1 equiv) was added in a single portion followed by Et_3N (100 μL, 0.72 mmol, 2 equiv) addition. The reaction mixture was heated to 80 °C with vigorous shaking and the heating was continued for 2 hours. For work-up, the solvent was evaporated under reduced pressure and the residue was treated with aqueous solution of saturated $NaHCO_3$ followed by extraction with 10 ml ethyl acetate/water (1:1) mixture. The organic extracts were dried over anhydrous Na_2SO_4. After filtration the solvent was evaporated under reduced pressure and the crude product was subjected to flash chromatography (Silica-60, 0.06–0.20 mm, ethyl acetate/hexane mixtures) to obtain pure product **3**.