Tetrahedron 67 (2011) 5156–5161

Contents lists available at ScienceDirect

Tetrahedron

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

Novel synthesis approach and antiplatelet activity evaluation of 6-alkylamino-2,4-dialkyl(aryl)thiopyrimidines

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ARTICLE INFO

Article history:
Received 7 March 2011
Received in revised form 4 May 2011
Accepted 13 May 2011
Available online 19 May 2011

Keywords:
Pyrimidine
Diazotization
Disulfide
Synthesis

ABSTRACT

A new and efficient procedure has been designed for the preparation of 6-alkylamino-2,4-dialkyl(aryl) thiopyrimidines. The first alkylthio group was introduced into the pyrimidine ring by S-alkylation. The introduction of the second one was successfully achieved using the diazotization–alkylthionation method to afford 2,4-dialkyl(aryl)thio-6-chloropyrimidines. Subsequent nucleophilic displacement by the corresponding amines conveniently gave a series of the target compounds. Thus, the two same or different alkylthio groups were easily introduced into the pyrimidine ring through the two different approaches. The human anti-platelet aggregation activity of the newly synthesized compounds is also described.

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1. Introduction

Pyrimidines play an essential role in several biological processes and have considerable chemical and pharmacological importance in terms that the pyrimidine ring can be found in nucleoside antibiotics, antibacterial and cardiovascular.[1–6] Pyrimidine derivatives, especially, alkylthio-substituted pyrimidines, such as 2-propylthio-triazolopyrimidines[7] and thienopyrimidines[8] have attracted much attention because of their quite high anti-platelet aggregation activity as inhibitors for P2-receptor family. As related works, there have been active attempts to develop the antagonist of P2Y receptors (which mediate platelet aggregation induced by adenosine diphosphate, ADP) by employing adenine nucleotide derivatives containing two phosphate groups, i.e., adenosine-3′,5′-bisphosphate analogues, as $P2Y_1$ receptor antagonists[9,10] and 4-alkoxyl-2-alkylthio-6-aminopyrimidine derivatives as $P2Y_{12}$ receptor antagonists.[11] The evaluated anti-platelet aggregation ability of a series of the synthesized pyrimidine derivatives proves their potential as lead compounds to develop a new series of $P2Y_{12}$ antagonists.[11] Furthermore, the results appear to suggest the importance of the chemical structure of alkylthio substituents and of the presence of a free amino group for the activity. As for adenine nucleotide analogues against P_{2T} receptor, the effective enhancement of the activity by N-monoalkylation at the 6-position of the adenine moiety has been found out by Ingall et al.[12] Considering such findings on the structure of the antagonist candidates, we achieved one hypothesis that N-monoalkylation of pyrimidine compounds might also increase anti-platelet aggregation activity. Furthermore, to date, there are few report on the synthesis and evaluation of dialkyl(aryl)thio-substituted pyrimidines as platelet aggregation inhibitors. Hence, we designed to introduce another alkylthio group into the pyrimidine ring (Fig. 1). As it is well known, the introduction of alkyl/arylthio groups into the pyrimidine ring is commonly achieved through either the alkylation of thiol groups or the nucleophilic substitution of halogens by alkylmercaptides. However, these

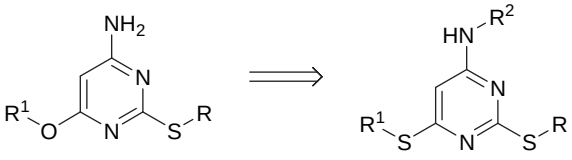

Fig. 1. Structures of 4-alkoxyl-2-alkylthio-6-aminopyrimidines and 6-alkylamino-2,4-dialkyl(aryl)thiopyrimidines.

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doi:10.1016/j.tet.2011.05.056

processes must be conducted under harsh conditions, especially in the absence of activating substituents. In the present study, we successfully introduced the two same or different alkyl(aryl)thio groups into the pyrimidine ring with two different approaches, S-alkylation and diazotization–alkylthionation, giving the key intermediate 2,4-dialkyl(aryl)thio-6-chloropyrimidines. Thus far, there has been no report on the application of the diazotization–alkylthionation reaction to aminopyrimidine derivatives. The subsequent nucleophilic displacement of the chloro groups by the corresponding amines affords a series of 6-alkylamino-2,4-dialkyl(aryl)thiopyrimidines. Herein, we describe the details of the convenient synthesis and the evaluation results of all the synthesized compounds as human platelet aggregation inhibitors.

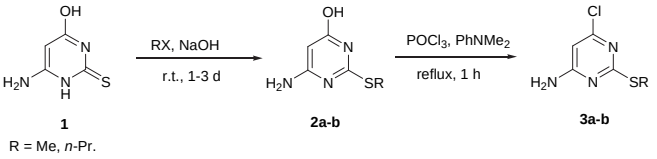
2. Results and discussion

2.1. Chemistry

6-Alkylamino-2,4-dialkyl(aryl)thiopyrimidines have been previously prepared by two methods. One was the treatment of 3-phenyl-l,2,3-triaxolo[4,5-*d*]pyrimidine-5,7-dithione with butyl lithium and an alkylating agent.[13] Though the route was short, the reaction was conducted at a low temperature (−70 °C), resulting in a low yield (30%). Another method was the conversion of 4,6-dihydroxyl-2-mercaptopyrimidine to 6-alkylamino-2,4-dialkylthiopyrimidines via S-alkylation, chlorination, and nucleophilic substitution.[14] However, it was likely to afford the byproduct of 2,4,6-trialkylthiopyrimidines.

During the last few years, our group has been working on the development of new platelet aggregation antagonists with the sulfur-substituted pyrimidine derivatives. In our method described below, 6-alkylamino-2,4-dialkyl(aryl)thiopyrimidines can be synthesized in good yields from a commercially available starting material, 4-amino-6-hydroxyl-2-mercaptopyrimidine **1**, under simple and mild reaction conditions.

We first synthesized 2-alkylthio-4-amino-6-chloropyrimidines (**3a**,**b**) from the starting compound **1** by a well-established procedure (Scheme 1).[15–17] The tautomerized thiol group was alkylated under basic conditions in the presence of the appropriate alkyl halide to obtain **2a**,**b**. Then, the hydroxyl group was chlorinated with phosphoryl chloride ($POCl_3$)[18] in combination with dimethylaniline to increase the yield. After the excess $POCl_3$ was removed in vacuo, the residue was poured into the mixture of the cooled concentrated ammonium hydroxide and chloroform. When the residue was dissolved completely, it was extracted with chloroform, concentrated, and then purified by column chromatography to afford 2-alkylthio-4-amino-6-chloropyrimidines (**3a**,**b**).



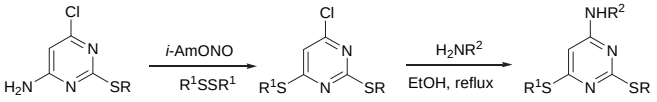
1 **2a-b** **3a-b**

R = Me, *n*-Pr.

Scheme 1. Synthesis of compounds **3** from **1** via S-alkylation and chlorination.

The introduction of dialkyl(aryl)thio groups into the pyrimidine rings was a key step. Initially, we attempted to prepare the designed compounds **5** from **3** via displacement of sodium alkylmercaptides and N-alkylation. However, the N-alkylation of 4-amino-2,6-dialkyl(aryl)thiopyrimidines would give a mixture of two products, monoalkyl and dialkyl products.[19] Thus, we took into account the need to employ an alternative method.

It is already known that primary aromatic amines,[20] such as aniline,[21] pyridine,[20] and guanosine derivatives,[12] can be directly converted into sulfides through diazotization under nonaqueous and neutral conditions. However, the diazotization–alkylthionation reaction of aminopyrimidine derivatives has not been reported in earlier studies. We have found the addition of isoamyl nitrite (*i*-AmONO) into the mixture of 2-alkylthio-4-amino-6-chloropyrimidine derivatives **3** and excess dialkyl(aryl) disulfide at 60 °C yields the corresponding alkyl(aryl)thio derivatives. In the reaction process, the mixed solution became deep brown with the immediate evolution of gas, which lasted until the completion of the reaction. As a result, we have succeeded in transforming the free amino groups of the compounds **3a**,**b** to alkyl(aryl)thio groups, whereby 2,4-dialkyl(aryl)thio-6-chloropyrimidines (**4a**–**e**) were obtained (Scheme 2). However, the mechanism of this reaction presently has not been identified.[21–24]



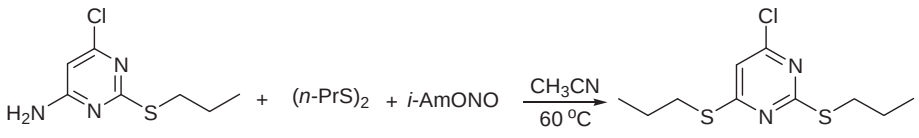
3a-b **4a-e** **5a-i**

R = Me, *n*-Pr; R^1 = *n*-Pr, *i*-Pr, Ph, Bn; R^2 = Bn, CH_2CH_2Ph.

Scheme 2. Preparation of compounds **5** from **3**.

To optimize the synthesis conditions, we selected 4-amino-6-chloro-2-propylthiopyrimidines **3b** and dipropyl disulfide as model substrates, and examined the effects of different amount of the dialkyl(aryl) disulfide in the presence of *i*-AmONO (6.2 equiv of **3b**) in anhydrous acetonitrile at 60 °C. The examination was initially commenced with 10 M equiv of dipropyl disulfide according to the previous literature. However, the yield at the molar ratio of 7:1 (Table 1,

Table 1
Optimizing reaction conditions for synthesis of **4b**



3b **4b**

Entry	Compound **3b** (equiv)	$(n\text{-PrS})_2$ (equiv)	*i*-AmONO (equiv)	Catalyst	Time (h)	Product **4b** (Yield, %)
1	1	10	6.2	No	2	76
2	1	7	6.2	No	2	75
3	1	5	6.2	No	2	65
4	1	1	6.2	No	2.5	46
5	1	7	6.2	CuCl	1	77
6	1	7	6.2	CuCl	2	78
7	1	7	6.2	No	1	55

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