Tetrahedron 70 (2014) 7900–7905

Contents lists available at ScienceDirect

Tetrahedron

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

Synthesis of novel *peri*-fused heterocyclic systems—pyrimido[4,5,6-*de*][1,8]naphthyridines, based on interaction of 4,6-dichloro-2-methylthiopyrimidine-5-carbaldehyde with geminal enediamines

Olga Yu. Bakulina, Alexander Yu. Ivanov, Pavel S. Lobanov, Dmitrii V. Dar'in *

St. Petersburg State University, 198504 St. Petersburg, Russian Federation

ARTICLE INFO

Article history:
Received 3 July 2014
Received in revised form 11 August 2014
Accepted 27 August 2014
Available online 6 September 2014

Keywords:
Enediamines
Pyrimidonaphthyridines
Pyrido[4,3-*d*]pyrimidines
Cyclization
Aromatic nucleophilic substitution

ABSTRACT

The synthetic approach to novel *peri*-fused heterocyclic systems—pyrimido[4,5,6-*de*][1,8]naphthyridines, has been developed. It consists of successive treatment of 4,6-dichloro-2-methylthiopyrimidine-5-carbaldehyde with 2 mol of geminal β-(acyl)enediamines and includes substitution of a chlorine atom with the nucleophilic carbon atom of the enediamine and cyclization of the corresponding intermediate.

1. Introduction

Push–pull type geminal enediamines have proved to be very convenient and efficient building blocks in synthesis of various α-aminoazaheterocycles including the fused ones.[1] In one of our previous works we have shown that the interaction between 3,3-diaminoacrylate (**1a**) and 5-acetyl-4,6-dichloropyrimidine results in novel *peri*-fused heterocyclic system—dihydropyrimido[4,5,6-*de*][1,8]naphthyridine.[2]

In this work we focused our efforts on developing the method to synthesize new *peri*-fused heterocycles—pyrimido[4,5,6-*de*][1,8]naphthyridines, based on the interaction of aldehyde **4** with enediamines **1**. The key stage of the synthesis is the cyclization of compounds **3** (Scheme 1). It proceeds by means of intramolecular nucleophilic substitution of hydrogen, and includes the addition of an amino group to a pyridine ring followed by further oxidation of the formed intermediate. Recently, the utility of this kind of reaction in the synthesis of fused azaheterocycles has already been demonstrated by Charushin and Chupakhin et al.[3] This approach has two advantages: first—the presence of a leaving group (halogen usually) is not necessary, and second—the ring functionalization proceeds without the use of transition-metal catalysis.

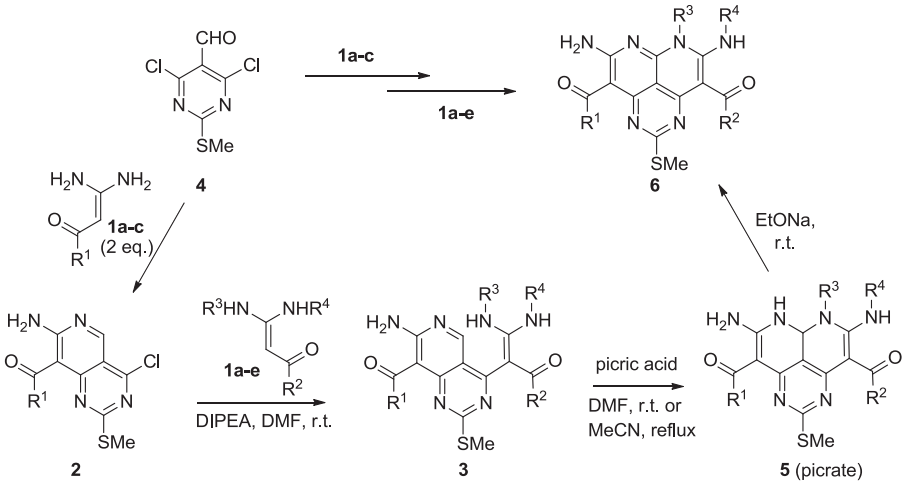
The synthesis of new heterocyclic systems with a wide range of functional groups and high potential for further functionalization is of obvious interest for both organic synthesis and pharmacology. Nowadays the process of searching and creating drugs based on fused azaheterocycles actively goes on and stimulates continuous interest of chemists and pharmacologists in producing heterocyclic systems with new relative locations of heterorings and heteroatoms. In the literature, the syntheses of *peri*-fused azaheterocycles are represented rather sparingly. At the same time the members of this class of heterocycles are of practical as well as theoretical interest, some of them are structural parts of natural compounds.[4]

2. Results and discussion

4-Chloropyridopyrimidines **2** are easily available due to the reaction of enediamines **1a**–**c** with aldehyde **4**. The synthesis of compounds **2a**,**b** was described by us earlier,[5] and compound **2c** was isolated for the first time. The reaction of pyridopyrimidines **2** with diaminoacrylic esters **1a**,**d**,**e** and anilide **1c** proceeds smoothly giving compounds **3** in high yields (Table 1). It is highly chemoselective: the chlorine atom is substituted by the carbon nucleophilic atom of the enediamine. This enediamine was introduced into the reaction either as the free base or hydrochloride. *N*,*N*-Diisopropylethylamine (DIPEA) was used as a base, however, the reaction with cyclic enediamine **1d** proceeds much more purely and with higher yield when a twofold excess of enediamine is used

* Corresponding author. Tel.: +7 981 787 1252; fax: +7 812 428 6733; e-mail address: d.dariin@spbu.ru (D.V. Dar'in).

http://dx.doi.org/10.1016/j.tet.2014.08.066
0040-4020/



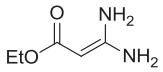
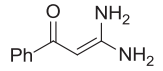
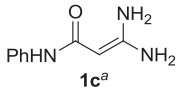
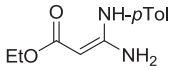
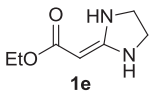
Scheme 1.

(Table 1, entry 7). Compound **3e** proved to be not stable enough to be isolated as an individual substance. Therefore in this case, further transformations were carried out in situ.

The low reactive enediamine **1b** failed to react with pyridopyrimidine **2a**. No conversion was observed at room temperature, and heating (60 °C) only resulted in an unidentified complex mixture (Table 1, entry 4). However, compound **3b** bearing both benzoyl and ethoxycarbonyl groups can be obtained if the sequence of introducing of enediamines **1a** and **1b** into the synthesis is changed. The pyridopyrimidine **3b** was isolated in high yield under mild conditions by successive treatment of highly reactive aldehyde **4** with enediamine **1b** and then with **1a** (Table 1, entry 2). Thus, while planning synthesis including two enediamines with different reactivity one should use the lower reactive enediamine on the first stage when pyridopyrimidine **2** is obtained.

Compounds **3** undergo cyclization into dihydropyrimidonaphthyridines **5** when treated with picric acid in refluxing MeCN or in DMF at room temperature (Scheme 1). Picric acid was chosen due to the ability of picrates to crystallize finely. The starting compounds **3** are readily soluble in small amounts of MeCN or DMF, while picrates of dihydropyrimidonaphthyridines **5** are substantially insoluble in the same volume of solvent and they precipitate off from the reaction mixture. Compounds **5** were isolated in high yields as monopicrates (Table 2). The picrates **5b** and **5c** gradually decompose while being kept at room temperature in solution (for several days) or in solid state (during 2–4 weeks). The *N*-monosubstituted compound **3f** reacts selectively by its unsubstituted amino group (Table 2, entry 5). However, compound **3g** with both nitrogen atoms of enediamine moiety bearing substituents also undergoes cyclization easily. The picrate **5g** degrades

Table 1
Reaction of enediamines **1** with pyridopyrimidies **2**. Synthesis of compounds **3**

Entry	1	2	Time	3	Yield/%
1	 **1a**	**2a** R^1=OEt	4 days	**3a** R^1=R^2=OEt, R^3=R^4=H	79
2	**1a**	**2b** R^1=Ph	4 days	**3b** R^1=Ph, R^2=OEt, R^3=R^4=H	95
3	**1a**[a]	**2c** R^1=NHPh	20 h	**3c** R^1=NHPh, R^2=OEt, R^3=R^4=H	94
4	 **1b**	**2a**		**3d** R^1=OEt, R^2=Ph, R^3=R^4=H	0
5	 **1c**[a]	**2c**	3 h	**3e** R^1=R^2=NHPh, R^3=R^4=H	—
6	 **1d**[a]	**2a**	20 h	**3f** R^1=R^2=OEt, R^3=*p*-Tol, R^4=H	91
7	 **1e**	**2a**	6 days	**3g** R^1=R^2=OEt, R^3+R^4=CH_2CH_2	80[b]

[a] Enediamine was used as hydrochloride.
[b] Twofold excess of enediamine was used.