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Regioselective and Sequential Mono- and Diamination of 5,7-Dichloro-pyrido[2,3-d]pyrimidine-2,4-diones

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Contents:

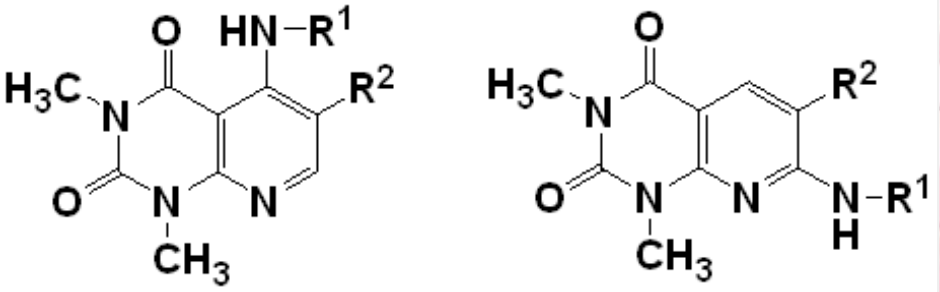
Abstract

5-Amino- and 5,7-diamino-pyrido[2,3-d]pyrimidine-2,4-diones were prepared easily from the corresponding 5,7-dichloro-pyrido[2,3-d]pyrimidine-2,4-diones with aliphatic and aromatic amines. The 7-monoazides, obtained by azidation of the chlorides, were converted to iminophosphoranes by reaction with triphenylphosphane via Staudinger reaction. Hydrolysis produced in one step 7-amino-pyrido[2,3-d]pyrimidine-2,4-diones.

Introduction

Pyrido[2,3-d]pyrimidinedione derivatives form a class of fused heterocyclic compounds which reveal interesting pharmacological and biological properties. Thus, they have been used

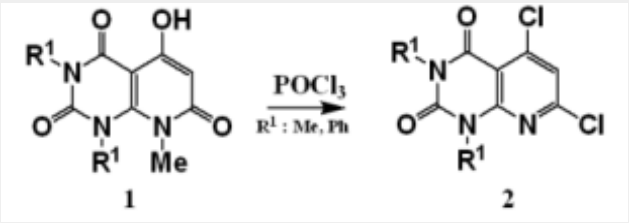
as effective antitumor agents, as antibacterials, anticonvulsant or enzyme inhibitor agents [1].
Amino-substituted pyrido[2,3-d]pyrimidinediones such as structures **A** and **B** [2] have been found to bind to adenosine A_1 and A_{2A} receptor in micromolar concentration. The structure-activity relationship for pyrido[2,3-d]pyrimidinediones as ligands of adenosine receptors have been studied recently [2].
These findings prompted us to study the synthesis of 5-amino- and 5,7-diamino-pyrido[2,3-d]pyrimidinediones having similar structural elements as a continuation of earlier studies on pyrido[2,3-d]pyrimidinediones [3].
Some results in the synthesis of azido hetarenes [4] raised the question of regioselectivity during reactions of the azide anion with 2,4-dichloroquinolines, which are known to give nucleophilic substitution both in 2 and 4 position [5].
In the reaction with amines, 2,4-diaminoquinolines, 2-amino-4-chloroquinolines or 4-amino-2-chloroquinolines were obtained [6].
Kinetic studies indicate that the chloro atom in position 4 of 2,4-dichloroquinolines is about two times more reactive towards nucleophiles [5, 7] and predominantly an addition-elimination mechanism is observed [8].
By kinetic control and suitable reaction conditions the regioselective azidation of 2,4-dichloroquinolines could be performed [9].
So we intended to study this reaction sequence with 5,7-dichloro-pyrido[2,3-d]pyrimidinediones and amines or azides to obtain 5-amino- and 5,7-diamino-pyrido[2,3-d]pyrimidinediones.



A B

R^2 : H, CN, $CO_2C_2H_5$

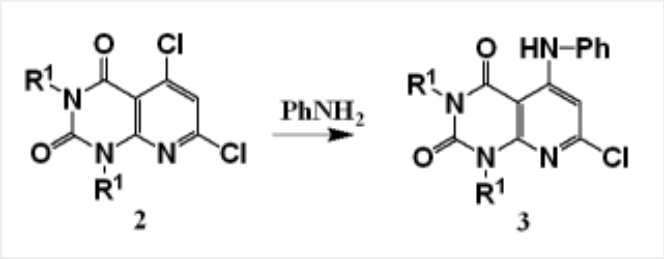
Amination of 5,7-dichloro-pyrido[2,3-d]pyrimidinediones with primary amines

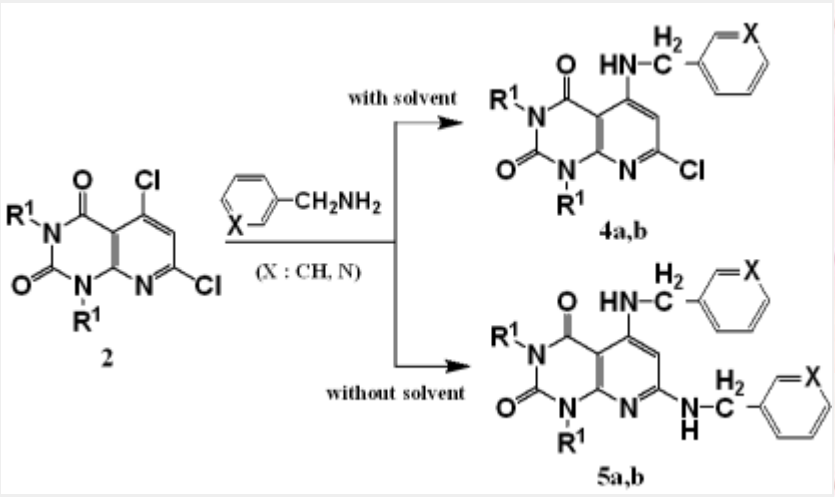


1 2

For the conversion into reactive intermediates, 5-hydroxy-8-methyl-pyrido[2,3-d]pyrimidine-2,4,7-triones **1** were reacted with phosphoryl chloride in order to exchange the 5-hydroxy group to a 5-chloro substituent. Although the reaction temperature were rather mild, surprisingly the 8-methyl group was cleaved during this reaction as it is known from 4-hydroxypyridones and the only reaction products which could be obtained were the 5,7-dichloro-pyrido[2,3-d]pyrimidine-2,4-diones **2**.

Aromatic amines such as aniline and alkylamines such as benzylamine and 3-picolyamine were used as the reaction agents to study regioselective amination of 5,7-dichloro-

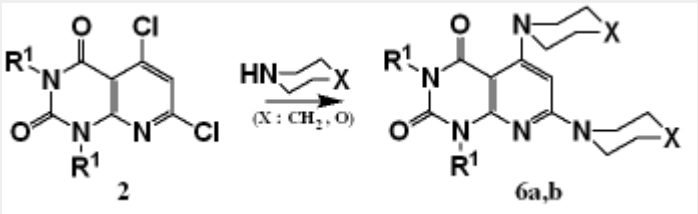




pyrido[2,3-d]pyrimidinediones **2**. When 5,7-dichloro compounds **2** were heated with aniline in protic solvents (e.g. alcohols), a regioselective monosubstitution took place at position 5, and in a very good yield 7-chloro-5-phenylamino-pyrido[2,3-d]pyrimidinediones **3** were isolated.

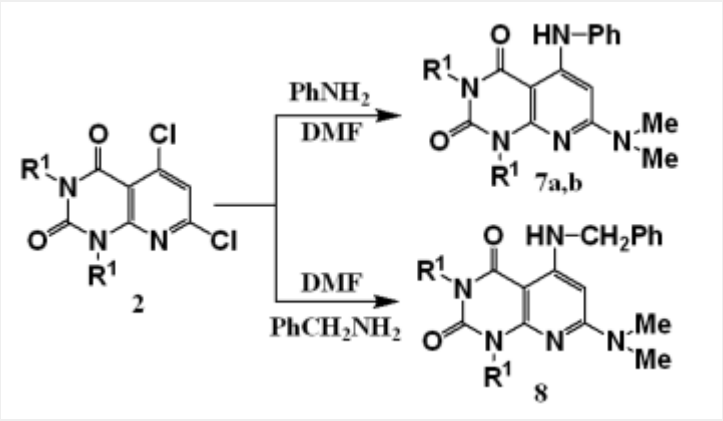
The reaction of 5,7-dichloro-pyrido[2,3-d]pyrimidinediones **2** with alkylamines such as benzylamine and 3-picolylamine in a molar ratio in protic solvents gave similar results as obtained with aniline. In this way 5-benzylamino-7-chloro-pyrido[2,3-d]pyrimidinediones **4a** and 7-chloro-5-(3-picolyl amino)-pyrido[2,3-d]pyrimidinediones **4b** were obtained.
When the reaction of **2** and excess of alkylamines was carried out without solvent at higher temperatures, both chloro atoms of **2** were exchanged and the 5,7-diamino products **5a,b** were obtained in good yields.
A similar bis-amination of **2** with excess of aniline as aromatic amine was not observed.

Amination of 5,7-dichloro-pyrido[2,3-d]pyrimidinediones with secondary amines



Reaction of 5,7-dichloro compounds **2** with secondary alkyl amines such as morpholine and piperidine, using the amines as solvent, showed an exchange of both chloro atoms leading to 5,7-dipiperidino-pyrido[2,3-d]pyrimidinediones **6a** and 5,7-dimorpholino-pyrido[2,3-d]pyrimidinediones **6b**.
Efforts to afford a mono-alkylation failed: Both using protic solvents, lower temperatures and other molar ratios led in any case to a mixture of mono- and diaminated products, probably because of the higher reactivity of alkylamines compared with aniline.

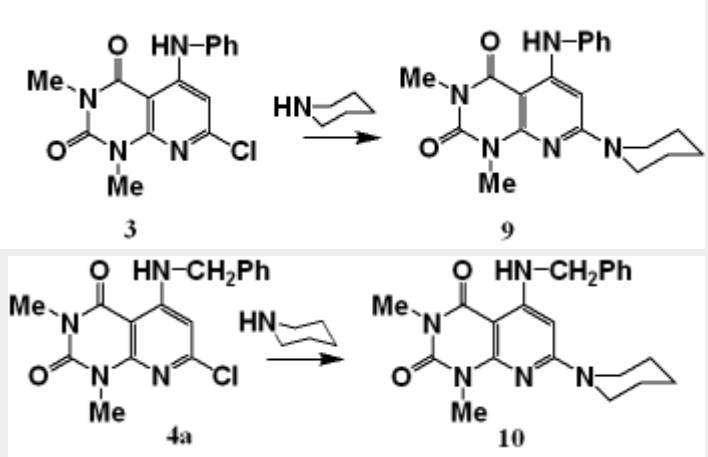
Amination of 5,7-dichloro-pyrido[2,3-d]pyrimidinediones with DMF as the solvent



Whereas the reaction of 5,7-dichloro compounds **2** with aniline in protic solvents showed an exchange of only one chloro atom at the position 5, surprisingly, the use of dimethylformamide as the solvent for this reaction gave an exchange of both chloro atoms, at position 5 and 7. However structural assignment showed that not the aniline was introduced in position 7, but the dimethylamino group, deriving from a decomposition of the solvent, DMF.
Thus, the reaction of 5,7-dichloro compounds **2** with aniline in dimethylformamide gave 7-dimethylamino-5-phenylamino-pyrido[2,3-d]pyrimidinediones **7**.
Similar, the reaction of 5,7-dichloro compounds **2** with benzylamine in dimethylformamide as the solvent gave 5-benzylamino-7-dimethylamino-pyrido[2,3-

d]pyrimidinediones **8**.

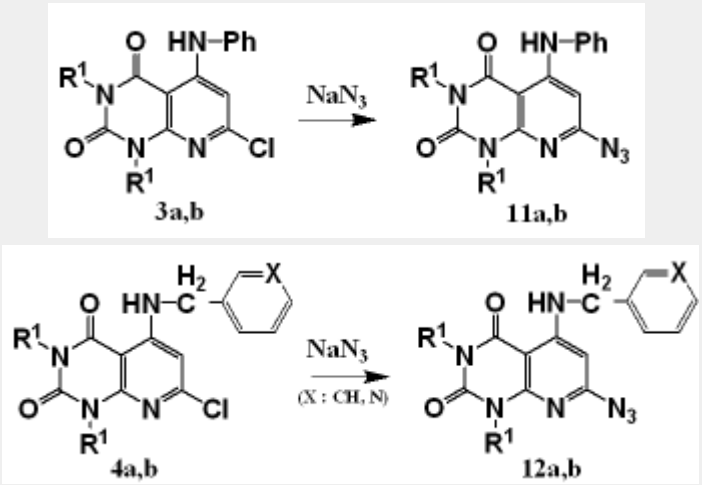
Sequential bisamination of 5,7-dichloro-pyrido[2,3-d]pyrimidinediones



Reaction of 7-chloro-1,3,-dimethyl-5-phenylamino-pyrido[2,3-d]pyrimidinedione (**3**) with piperidine in protic solvents gave 5-phenylamino-7-piperidino-pyrido[2,3-d]pyrimidinedione (**9**), the chloro atom at the position C-7 was exchanged against the piperidino group. Reaction of 5-benzylamino-7-chloro-1,3-dimethyl-pyrido[2,3-d]pyrimidinedione (**4a**) with piperidine in protic solvents gave similar results as obtained with **3**: 5-benzylamino-1,3-dimethyl-7-piperidino-pyrido[2,3-d]pyrimidinedione (**10**) was obtained.
Using these regioselective amination reactions it could be shown that the chloro atom in position 5 of 5,7-dichloro-pyrido[2,3-d]pyrimidinediones **2** is - similar as found in 2,4-dichloroquinolines [6, 9] - much more reactive towards nucleophiles than the chloro atom in position 7.

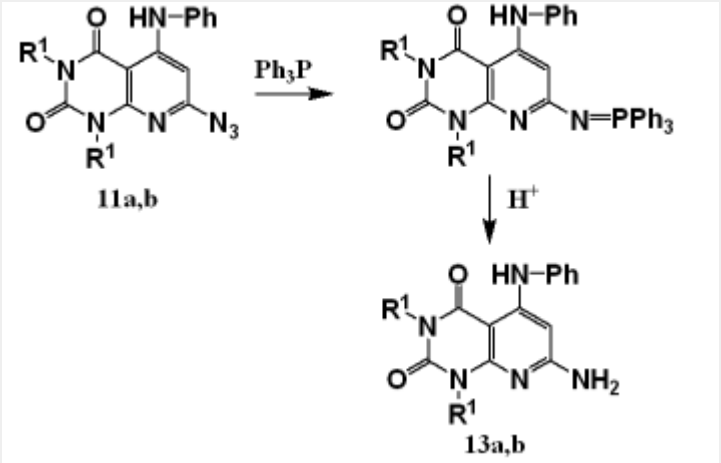
Sequential amination of 5,7-dichloro-pyrido[2,3-d]pyrimidinediones via azides

(1) Azidation

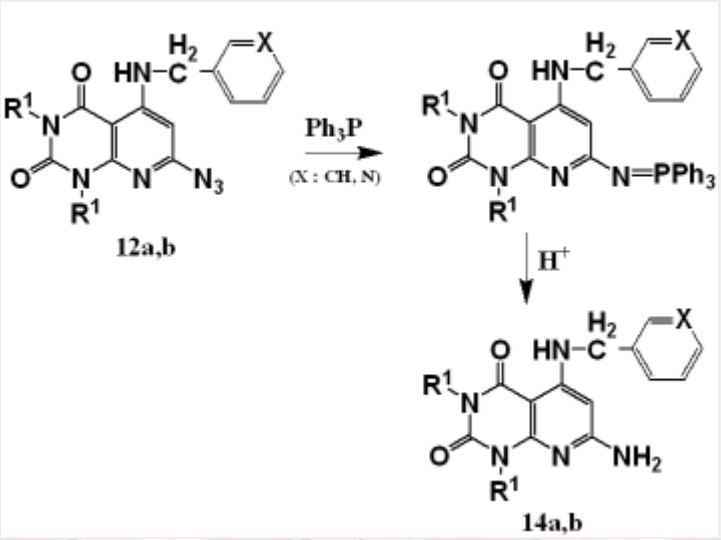


Because a direct introduction of an unsubstituted amino group (e.g. by exchange with ammonia) was not successful, we selected the 2-step reaction which involved in the first step the azidation by halogen exchange. The aim was again to obtain mixed 5,7-bisamination.
Reaction of 7-chloro-5-amino-substituted compounds **3** and **4** with excess sodium azide in dry dimethylformamide gave 7-azido-5-amino-substituted compounds **11** and **12** in a pure form and good yield. 2-Azidoheterocycles are known to exist in an tautomeric equilibrium of azide and tetrazol [10]. In contrast to the findings of the quinoline series [9], which exist predominantly in the tetrazolo form, the 7-monoazides **11**, **12** show strong azide signals in the IR spectra which reveal that in this case the equilibrium is shifted to the azide and not to the tetrazole form.

(2) Staudinger and Aza-Wittig reaction



The reduction of azides to amines can be performed in several ways. Most of these reactions involve a reduction step, which can affect sensitive substituents. The mildest way which does not interfere with other parts of the molecule, is known as subsequent Staudinger reaction with phosphanes to iminophospühoranes, followed by an Aza-Wittig reaction by hydrolysis of the iminophosphoranes to azides. This reaction sequence was chosen for the transformation of azides to amines. The 7-monoazido-pyrido[2,3-d]pyrimidinediones **11**, **12** were converted to intermediate iminophosphoranes by reaction with triphenylphosphane. A subsequent



hydrolysis of the intermediate iminophosphoranes without isolation produced with aqueous acetic acid in a one-pot reaction the desired 5,7-diamino-pyrido[2,3-d]pyrimidinediones **13**,**14**.

Comparison of ^{1}H-NMR spectra of 7-amino-pyrido[2,3-d]pyrimidinediones **13**, **14** with similar 5-amino-pyrido[2,3-d]pyrimidinetriones [3] revealed that the proton signal of the 7-NH_2 group in **13**, **14** was observed at delta = 4.50-6.70 ppm, which can be distinguished clearly from the proton signal of 5-NH_2 of the 5-amino-pyrido[2,3-d]pyrimidinetriones at 9.10-11.40 ppm.

Conclusion

We have developed a regioselective amination on 5,7-dichloro-pyrido[2,3-d]pyrimidinediones. The chloro atom in position 5 of 5,7-dichloro-pyrido[2,3-d]pyrimidinediones is more reactive towards nucleophiles. Reaction of 5-amino-substituted-7-chloro-pyrido[2,3-d]pyrimidinediones with excess sodium azide gave 7-monoazido-5-amino-substituted-pyrido[2,3-d]pyrimidinediones in a pure form and good yield. 7-Amino-5-amino-substituted-pyrido[2,3-d]pyrimidinediones compounds were obtained from the corresponding 7-azido- compounds by Staudinger / Aza-Wittig reaction.

Experimental

7-Chloro-5-amino-substituted-1,3-disubstituted-pyrido[2,3-d]pyrimidine-2,4-diones (3, 4): A 1:1 mixture of the appropriate substituted of 5,7-dichloro-1,3-disubstituted-pyrido[2,3-d]pyrimidine-2,4-dione (**2**) and suitable primary amine was dissolved in sec-alcohols and heated under reflux with stirring. After cooling, the solvent was removed under reduced pressure, the residue digested with water and the formed precipitate collected by suction filtration.
5,7-Diamino-substituted-1,3-disubstituted-pyrido[2,3-d]pyrimidine-2,4-diones (5, 6): A solution of 5,7-dichloro-1,3-disubstituted-pyrido[2,3-d]pyrimidine-2,4-dione (**2**) in excess of primary amine was heated under reflux. The solution was removed under reduced pressure, the residue digested with water, acidified and extracted with the appropriate solvent, dried and taken to dryness. The residue was digested with ethanol and the formed precipitate was collected by suction filtration.
5-Amino-substituted-7-dimethylamino-1,3-disubstituted-pyrido[2,3-d]pyrimidine-2,4-diones (7, 8): A 1:1 mixture of 5,7-dichloro-1,3-disubstituted-pyrido[2,3-d]pyrimidine-2,4-dione (**2**) and amines (aniline, benzylamine) in dimethylformamide as the solvent was heated under reflux with intensive stirring. After cooling, the solvent was removed under reduced pressure, and the residue was digested with water. The formed precipitate was collected by suction, washed with water and dried.
5,7-diamino-substituted-1,3-dimethyl-pyrido[2,3-d]pyrimidine-2,4-diones (9, 10): A 1:1 mixture of 7-chloro-5-amino-substituted-1,3-dimethyl-pyrido[2,3-d]pyrimidine-2,4-diones **3 or 4** and piperidine in sec-alcohols as the solvent was heated under reflux with intensive stirring. After cooling, the solvent was removed under reduced pressure, the residue was digested with water and the formed precipitate collected by suction filtration.
7-Azido-5-amino-substituted-1,3-disubstituted-pyrido[2,3-d]pyrimidine-2,4-diones (11, 12): A suspension of 7-chloro-5-amino-substituted-1,3-disubstituted-pyrido[2,3-d]pyrimidine-2,4-diones **2** and sodium azide in dry dimethylformamide was stirred for several hours, then the reaction mixture was poured into of ice/water and the precipitate filtered.
7-Amino-5-amino-substituted-1,3-disubstituted-pyrido[2,3-d]pyrimidine-2,4-diones (13, 14): 1) A solution of triphenylphosphane in dry toluene was added to 7-azido-5-amino-substituted-1,3-substituted-pyrido[2,3-d]pyrimidine-2,4-diones **11** or **12** to start the slightly exothermic reaction. The starting material dissolved, followed immediately by precipitation of the product. The reaction mixture was allowed to cool and the precipitate was filtered and washed with cyclohexane. 2) A mixture of 5-amino-substituted-1,3-disubstituted-7-triphenylphosphoranylideneamino-pyrido[2,3-d]pyrimidine-2,4-dione, glacial acetic acid and water was refluxed for several hours. After cooling, to the reaction mixture water was added, and the precipitate was filtered by suction.

Acknowledgement

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