Tetrahedron Letters 54 (2013) 5537–5540

Contents lists available at ScienceDirect

Tetrahedron Letters

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

A one-pot, three-component, microwave-promoted synthesis of 2-amino-substituted 7-amino-1,2,4-triazolo[1,5-*a*]-[1,3,5]triazines ☆

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ARTICLE INFO

Article history:
Received 1 July 2013
Revised 18 July 2013
Accepted 31 July 2013
Available online 7 August 2013

Keywords:
Multicomponent reaction
Microwave-assisted synthesis
Triazoles
Triazines
Purine isosters

ABSTRACT

A new, efficient, catalyst-free, one-pot, three-component method for the synthesis of 2-amino-substituted 7-amino-1,2,4-triazolo[1,5-*a*][1,3,5]triazines using 3,5-diamino-1,2,4-triazoles, cyanamide, and triethyl orthoformate is developed. The reaction proceeds smoothly under microwave-assisted heating. Advantages of the method include using easily available reagents, short reaction times, and operational simplicity.

The 1,2,4-triazolo[1,5-*a*][1,3,5]triazine ring system represents a 5-aza-isoster of purine, which is the most ubiquitous natural N-heterocycle.[2] In humans, purines are involved in functioning of more than 3250 proteins, which utilize them either as substrates or cofactors.[3] These proteins are estimated to include more than half of the most drugable targets, mainly enzymes and receptors. Using purine isosters provides an efficient strategy for the discovery of agents targeting selectively the purine-dependent enzymes and receptors. Notable examples of such isosteric molecules include 8-azaguanine, which was developed as a drug for the treatment of acute leukemia (Fig. 1).[4] Isosteric to hypoxanthine, allopurinol, being the first specific drug for chronic gout treatment, has remained the 'gold standard' for more than half century.[5] More functionalized isosters of hypoxanthine were applied effectively to the development of the PDE 5 inhibitors, sildenafil and vardenafil, which have become 'blockbuster' drugs since their development.[6] The current standard used in A_{2a} adenosine receptor research, ZM 241385 is a derivative of 5-azapurine.[7]

A number of methods for the synthesis of 5-azapurines (1,2,4-triazolo[1,5-*a*][1,3,5]triazines) have been developed.[8,9] In our

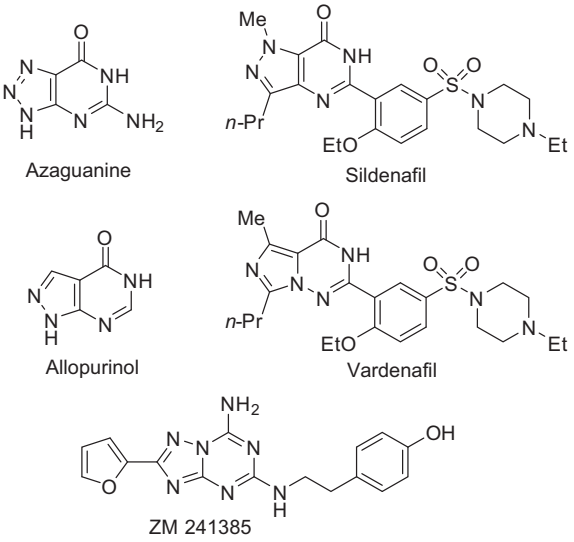

Figure 1. Therapeutic agents based on isosteric purine skeletons.

☆ Part 24 in the series 'Fused heterocyclic systems with *s*-triazine ring', for part 23, see Ref. 1.

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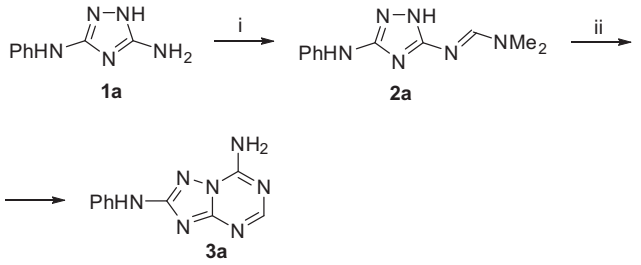
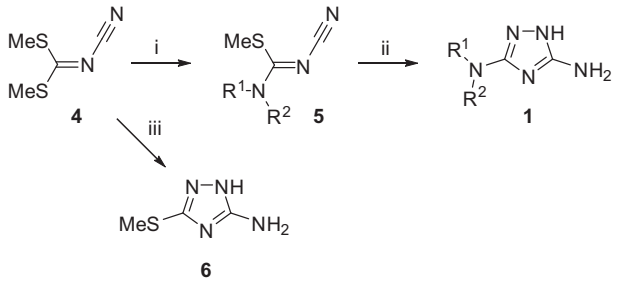
0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.07.158



Scheme 1. Reagents and conditions: (i) DMF-DMA (1.5 equiv), toluene, reflux, 10 min; (ii) $NCNH_2$ (2 equiv), MeONa (2 equiv), MeOH, reflux, 24 h.



Scheme 2. Reagents and conditions: (i) R^1R^2NH (1 equiv), MeOH, reflux, 3 h; (ii) N_2H_4 (1.1 equiv), EtOH, reflux, 3 h; (iii) N_2H_4 (1.1 equiv), MeOH, 40 °C, 5 h.

ongoing program on the exploration of 5-azapurine derivatives, we have developed effective methods for the synthesis of 1,2,4-triazolo[1,5-*a*][1,3,5]triazines with 7-amino-,[1,9d] 5,7-diamino-,[9j] and 2,5,7-triamino-[9h] substitution types. The synthesis of substituted 2,7-diamino-1,2,4-triazolo[1,5-*a*][1,3,5]triazines can be achieved using a previously reported method,[9d] as was demonstrated by the preparation of 7-amino-2-phenylamino-1,2,4-triazolo[1,5-*a*][1,3,5]triazine (**3a**). Condensation of 5-amino-3-phenylamino-1,2,4-triazole (**1a**) with *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) followed by the base-catalyzed reaction of the resulting product **2a** with cyanamide successfully afforded **3a** (Scheme 1). Other methods for the annelation of aminotriazine rings to give 1,2,4-triazolo[1,5-*a*][1,3,5]triazines involve various combinations of stepwise sequential reactions of 5-amino-1,2,4-triazoles, triethyl orthoformate, and cyanamide or their synthetic equivalents.[9d,10] Considering the fact that the outcome of all these reactions was independent of the reagent introduction order, we assumed that the synthesis of 2,7-diamino-1,2,4-triazolo[1,5-*a*][1,3,5]triazines could be carried out using these reagents in a one-pot, three-component process.

One-pot multicomponent reactions play an important role in medicinal chemistry providing diverse small drug-like molecules in a single step.[11] Multicomponent syntheses have been exploited for the preparation of many heterocyclic scaffolds. In general, the multicomponent approach relies on channeling all pre-equilibrated reactions into a convergent manner leading to exclusive formation of the desired products. This challenge required careful selection of the reagents and reaction conditions. Using 5-amino-1,2,4-triazoles in multicomponent reactions as a 1,3-binucleophilic reagent has been well documented;[12] triethyl orthoformate has also been applied for various multicomponent heterocyclic syntheses.[13] Therefore we expected that these reagents would be suitable for the preparation of 2,7-diamino-1,2,4-triazolo[1,5-*a*][1,3,5]triazines in a multicomponent fashion. In this Letter, we report a new, one-pot, multicomponent method for the synthesis of 2-amino-substituted 7-amino-1,2,4-triazolo[1,5-*a*][1,3,5]triazines (**3**).

For the preparation of the starting 3,5-diamino-1,2,4-triazoles (**1**), we employed a previously reported method[9h] using the reaction of dimethyl *N*-cyanodithiocarbonimidate (**4**) with different amines, followed by treatment of *N*-substituted *N*′-cyano-*S*-methylisothioureas **5** with hydrazine in ethanol (Scheme 2). The reaction of **4** with hydrazine afforded triazole **6**, which was also used as a substrate for our three-component reaction.

We started optimization of the conditions for our planned multicomponent reaction by attempting the preparation of already known[9d] 7-amino-2-phenylamino-1,2,4-triazolo[1,5-*a*][1,3,5]triazine (**3a**) as a model case. Our attempt to carry out the reaction of **1a**, triethyl orthoformate, and cyanamide by heating in methanol overnight resulted in the formation of a complex mixture of compounds with only 6% of the desired product **3a**, as identified by HPLC analysis. Exploring the reaction further, we were pleased to find that heating (150 °C, 20 min) in methanol under microwave irradiation resulted in the formation of **3a**, which could be easily isolated in 75% yield by simple filtration.[14] An attempt to substitute triethyl orthoformate with DMF-DMA in the microwave reaction was not successful and resulted in a mixture containing 16% of **3a**, as determined by HPLC. However, triethyl orthoformate could be replaced by trimethyl orthoformate without substantial change in the yield of **3a** (72%).

To study the substrate scope, a series of 3,5-diamino-1,2,4-triazoles (**1**) were subjected to the reaction with triethyl orthoformate and cyanamide under the optimized conditions (Table 1). The presence of electron-donating and electron-withdrawing groups on the phenyl ring was well tolerated and afforded products **3b–h** in good yields (70–75%). Moreover, the reaction was also successful for the preparation of 7-amino-1,2,4-triazolo[1,5-*a*][1,3,5]triazines with phenylalkylamino substituents at position 2 of the heterocyclic ring (**3i**, **j**). Overall, the reaction demonstrated high selectivity. No products of side reactions at the substituted amino group of the triazoles **1** were isolated. Morpholine- and methylthio-substituted products **3k** and **3l** were synthesized via this method from the corresponding triazoles **1k** and **1l** without any complications.

Similar to the stepwise sequential aminotriazine annelation, our one-pot procedure was regioselective, with triazine ring closure at N-1 of the aminotriazoles **1** and introduction of the amino group at position 7. Theoretically possible side products of the cyclization at N-4 of **1** as well as a regioisomer with the amino group at position 5 were not isolated.

Structure assignments were made on the basis of spectral analysis[15] and by comparison with isomeric [4,3-*a*]-fused structures,[16] as well as known **3a**, and related 7-amino-,[1,9d] 5,7-diamino-,[9j] and 2,5,7-triamino-[9h] substituted 1,2,4-triazolo[1,5-*a*][1,3,5]triazines. Similar to the observations for these structures, the lone pair of electrons on the 7-amino group of **3** were highly delocalized over the π-electron system of the 1,2,4-triazolo[1,5-*a*][1,3,5]triazine skeleton. This led to an increased rotational barrier at the 7-amino group, which was coplanar with the heterocyclic ring. As a result, the signals of the 7-amino group in the ^{1}H NMR spectra were split and shifted downfield (7.86–8.38 ppm and 8.51–9.01 ppm). In the ^{1}H NMR spectra, the triazine ring proton gave a signal at 8.11–8.29 ppm. The characteristic signals of the 1,2,4-triazolo[1,5-*a*][1,3,5]triazine core in the ^{13}C NMR spectra of **3** appeared at 150.0–150.6 ppm (C-7), 155.8–157.4 ppm (C-3a), 157.9–159.1 ppm (C-5), and 161.6–166.6 ppm (C-2).

In conclusion, we have developed a new, efficient, one-pot, three-component method for the synthesis of 2-amino-substituted 7-amino-1,2,4-triazolo[1,5-*a*][1,3,5]triazines (**3**) from 3,5-diamino-1,2,4-triazoles (**1**), cyanamide, and triethyl orthoformate. The reaction was enabled by heating under microwave irradiation. Advantages of the reported method for the construction of drug-like molecules with a 5-azapurine core include the use of easily available reagents, short reaction times, and operational simplicity.