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Synthesis of new 5-aza-isosteres of guanine containing aryl and hetaryl substituents on the 1,2,4-triazole ring

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ABSTRACT

The oxidative cyclization of 4-amino-substituted 6-arylidene(hetarylmethylidene)hydrazinyl-1,3,5-triazin-2-ones with lead(IV) tetraacetate proceeds via a Dimroth-type rearrangement to give 5-amino-substituted 2-aryl(hetaryl)-1,2,4-triazolo[1,5-*a*]-1,3,5-triazin-7-ones. IR, NMR, and X-ray studies have shown that the only products of the reactions were the [1,5-*a*]-isomers.

The 1,2,4-triazolo-1,3,5-triazine heterocyclic system is an aza-analogue of purine, and is of interest as a promising basic structure to design new bioactive compounds.[1] Since the first report appeared in 1991,[2] there have been numerous studies on 1,2,4-triazolo[1,5-*a*]-1,3,5-triazines as selective nonxanthine inhibitors of A_{2a}-type adenosine receptors.[2,3] Compound ZM241385 (7-amino-2-(furan-2-yl)-5-[2-(4-hydroxyphenyl)-ethyl]amino-1,2,4-triazolo[1,5-*a*]-1,3,5-triazine), which possesses the highest inhibitory activity,[3a,b] has been widely used as a standard reference compound.

Variation of the substituents at positions 2, 5, and 7 of the 1,2,4-triazolo[1,5-*a*]-1,3,5-triazine system allows the preparation of compounds with a wide spectrum of biological activity, for example, antidepressants,[4] treatments for Parkinson's disease,[5] immunosupressors,[6] and anti-inflammatory[7] and antitumor agents,[8] as well as compounds with antithymidine phosphorylase activity.[9]

Increased numbers of reports on the synthesis and biological activity of 1,2,4-triazolo-1,3,5-triazine derivatives in the last few years reinforces the 1,2,4-triazolo[1,5-*a*]-1,3,5-trizaine system as a promising scaffold for the development of new bioactive compounds.

In continuation of our studies[10] on the synthesis of 5-aza-isosteres of guanine, we describe herein efforts to obtain 1,2,4-triazolo [1,5-*a*]-1,3,5-triazine derivatives, containing aryl or hetaryl substituents at position 2 (Fig. 1).

These heterocyclic bases, or their cyclic and acyclic nucleosides are of interest as antiviral and antitumor compounds.

There are three general approaches described for the synthesis of the 1,2,4-triazolo-1,3,5-triazine heterocyclic system:[11] (i) formation of the 1,3,5-triazine ring on the basis of amino-1,2,4-triazoles; (ii) formation of the 1,2,4-triazole ring on the basis of 1,3,5-triazine derivatives; and (iii) concurrent formation of both the 1,3,5-triazine and 1,2,4-triazole rings by cyclization of linear molecules. Analysis of the literature shows that the main attention of

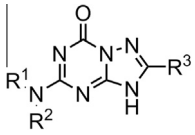

Figure 1. Desired 2-aryl(hetaryl) 1,2,4-triazolo-1,3,5-triazines. NR^1R^2—mono-, disubstituted amino groups or pyrrolidino, piperidino, morpholino groups; R^3—phenyl, 4-bromophenyl, 5-nitrofuran-2-yl.

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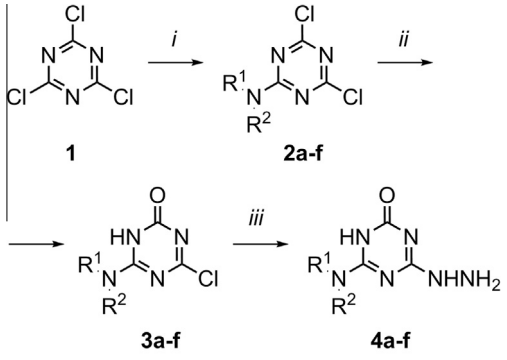
research has been focused on the first approach on the basis of 1,2,4-triazole derivatives.[3c,6a,9a,12] Thus little attention has been paid to the second approach on the basis of 1,3,5-triazine derivatives.[10,12a,13] In our opinion, this approach is very promising and offers several advantages. 2,4,6-Trichloro-1,3,5-triazine is a useful starting material, which allows the synthesis of a wide variety of 2,4-disubstituted 6-hydrazinyl-1,3,5-triazines in a relatively simple three-step manner. Following cyclization with one-carbon synthetic equivalents (carbonic acids, esters, orthoethers, aldehydes, anhydrides, chloroanhydrides, etc.) makes it possible to obtain various 1,2,4-triazolo[4,3-*a*]- and 1,2,4-triazolo[1,5-*a*]-1,3,5-triazines with a wide variety of substituents on the 1,3,5-triazine and 1,2,4-triazole rings.[10,12a,13a–h,14]

The oxidative cyclization of arylidenhydrazinyl-1,3,5-triazines is one of the methods for the formation of the 1,2,4-triazolo-1,3,5-triazine system. There are several examples of the application of this method for the synthesis of 1,2,4-triazolo-1,3,5-triazines.[12a,13a–d] However, all these examples are limited to derivatives bearing two amino substituents or one amino substituent, and phenoxy- or methylthio groups on the 1,3,5-triazine ring.

To synthesize new aza-isosteres of guanine, bearing aryl or hetaryl substituents on the 1,2,4-triazole ring, 4-amino-substituted 6-hydrazinyl-1,3,5-triazin-2-ones **4a**–**f** were used as the starting materials. These were obtained by successive substitution of the chlorine atoms in 2,4,6-trichloro-1,3,5-triazine (**1**) using amines, sodium hydroxide, and hydrazine-hydrate (Scheme 1).[10]

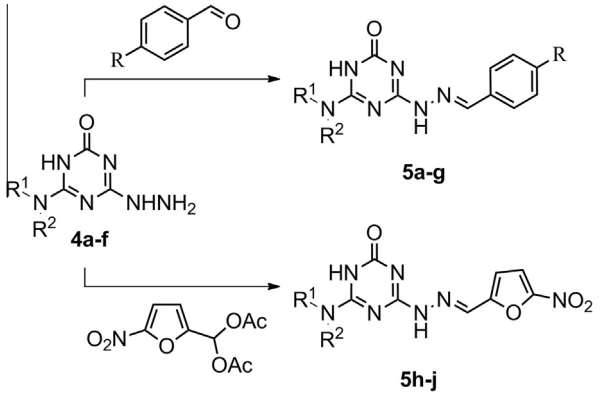
Benzylidene derivatives **5a**–**g** were obtained by the reaction of **4a**–**f** with the corresponding benzaldehyde in ethanol. The reaction with benzaldehyde proceeded smoothly at room temperature, whereas in the case of *p*-bromobenzaldehyde, the reaction required a higher reaction temperature (75 °C). 5-Nitrofurylidene derivatives **5h**–**j** were obtained by reflux of the starting hydrazinyl-1,3,5-triazines with 5-nitrofurfural diacetate in ethanol, and the reactions required longer times (Table 1).

The desired 2-aryl(hetaryl)-5-amino-1,2,4-triazolo[1,5-*a*]-1,3,5-triazin-7-ones **6a**–**j** were obtained *via* oxidative cyclization of the corresponding arylidene(hetarylmethylidene)hydrazinyl-1,3,5-triazinones **5a**–**j** with lead(IV) tetraacetate in acetic acid (Scheme 2, Table 2). Acetic acid was used as the reaction medium to increase the solubility of compounds **5a**–**j**, which were virtually insoluble in low polar dichloromethane and benzene, as commonly used solvents for the oxidative cyclization with lead tetraacetate.[12a,13a–d] The completion of the reaction was achieved after maintaining the reaction mixture at 80–85 °C for 10–14 h.

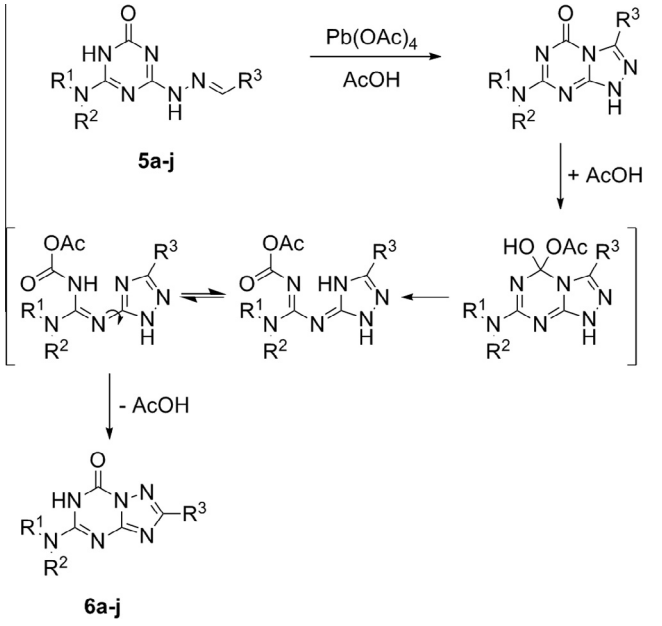


Scheme 1. Synthesis of 4-amino-substituted 6-hydrazinyl-1,3,5-triazine-2-ones **4a**–**f**: (i) HNR^1R^2, Et_2O; (ii) (1) NaOH, MeCN–H_2O, (2) HCl; (iii) hydrazine hydrate, H_2O.

Table 1
Reaction time, reaction temperature, yields, and melting points of arylidene(hetarylmethylidene)hydrazines **5a**–**j**



Product	NR^1R^2	R	*T* (°C) (Time (h))	Yield (%)	Mp (°C)
5a	$N(CH_3)_2$	H	20 (8.5)	97	280–282
5b	NHPr	H	20 (10.5)	91	264–266
5c	NHPr-*i*	H	20 (10)	94	213–215
5d	$N(CH_2)_4$	H	20 (9)	96	295–296
5e	$N(CH_2)_5$	H	20 (8)	87	253–255
5f	$N(CH_2)_2O$	H	20 (9.5)	94	275–276
5g	$N(CH_2)_2O$	Br	75 (5.5)	67	287–289
5h	$N(CH_3)_2$	—	75 (42)	78	285–287
5i	$N(CH_2)_4$	—	75 (34)	80	271–273
5j	$N(CH_2)_5$	—	75 (41)	69	254–256



Scheme 2. Oxidative cyclization of arylidene(hetarylmethylidene) hydrazines **5a**–**j**.

The oxidative cyclization gave only [1,5-*a*]-isomers, and no [4,3-*a*]-isomers were obtained. The ease of the Dimroth-type rearrangement is apparently due to the following factors: the presence of the carbonyl function in the starting triazinones **5a**–**j**, and the use of highly polar acetic acid as the solvent. The first factor facilitates the 1,3,5-triazine ring opening, probably, via intermediate attachment of acetic acid (Scheme 2). The adduct rearranges via 1,3,5-triazine ring opening, rotation of the linear moiety (mixed acetic-carbamic anhydride) around the exocyclic C–N bond, and