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A convenient method for the synthesis of 7-amino-substituted 1,2,4-triazolo[1,5-*a*][1,3,5]triazin-5-amines ☆

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ABSTRACT

A new practical synthesis of 7-amino-substituted 1,2,4-triazolo[1,5-*a*][1,3,5]triazin-5-amines is developed. The triazine ring closure of 5-guanidino-3-phenyl-1,2,4-triazole with trichloroacetonitrile proceeds chemo- and regioselectively depending on the nature of the solvent. Conducting the reaction in toluene provided 7-trichloromethyl-1,2,4-triazolo[1,5-*a*][1,3,5]triazin-5-amine as the product, which can be further aminated efficiently with replacement of the trichloromethyl group.

The 5-aza-analogues of purines, 1,2,4-triazolo[1,5-*a*][1,3,5]triazines have attracted significant attention in recent years as potential bioactive molecules. They are known to modulate the processes that involve regulatory biogenic purines.[2] Research in this area has led to the development of 5,7-diamino-1,2,4-triazolo[1,5-*a*][1,3,5]triazines which demonstrate high affinity and selectivity towards adenosine receptors, especially antagonistic activity against A_1 and A_{2A} adenosine receptors.[3] Among them, ZM 241385 (N^5-[2-(4-hydroxyphenyl)ethyl]-2-(2-furyl)-1,2,4-triazolo[1,5-*a*][1,3,5]triazine-5,7-diamine) has found application as a standard reference compound and a useful tool for investigation of A_{2A} adenosine receptors.[4] A number of ligands for various types of adenosine receptors, which were developed using the purine scaffold, have an alkyl, aralkyl or aryl substituted amino group located at the carbon atom corresponding to position 7 of the 1,2,4-triazolo[1,5-*a*][1,3,5]triazine nucleus.[5] However, these types of 1,2,4-triazolo[1,5-*a*][1,3,5]triazines have not yet been explored extensively.

Methods for the preparation of unsymmetrically substituted 5,7-diamino-1,2,4-triazolo[1,5-*a*][1,3,5]triazines typically involve two general synthetic pathways. Both of the routes are similar and utilize the same reagents, namely 5-amino-1,2,4-triazoles **1**, *N*-cyanocarbonimidates **2** and substituted amines **4**, but react with each other via different sequences as shown in Scheme 1.

The reaction of 5-amino-1,2,4-triazoles **1** with **2**, using the method initially developed by Caulkett et al.,[6] provided a mixture of products **5–7**, the type and ratio of which depended on the reaction conditions. The yields were usually poor and separation of the products by chromatography was required. The compounds **5** and **6** were further converted into the desired 5,7-diamino-1,2,4-triazolo[1,5-*a*][1,3,5]triazines **8** and **9** via reaction with amines **4**. An alternative synthesis of 5,7-diamino-1,2,4-triazolo[1,5-*a*][1,3,5]triazines using the reaction of 5-amino-1,2,4-triazoles **1** with **3**, initially prepared from *N*-cyanocarbonimidates **2** and amines **4** required, as a rule, long reaction times, harsh conditions and also provided mixtures of the compounds **8** and **9** separable by chromatography.[7]

Due to the disadvantages of these methods, the practical and regioselective synthesis of unsymmetrically substituted 5,7-diamino-1,2,4-triazolo[1,5-*a*][1,3,5]triazines remains a challenging problem. Therefore, a new simple synthetic approach to the preparation of 7-amino-substituted 1,2,4-triazolo[1,5-*a*][1,3,5]triazin-5-amines **9** would be a valuable contribution to the chemistry and pharmacology of 1,2,4-triazolo[1,5-*a*][1,3,5]triazines.

Recently, we reported the synthesis of 1,2,4-triazolo[1,5-*a*][1,3,5]triazines using a regioselective ring closing reaction of 5-guanidino-1,2,4-triazoles.[8] These synthons are readily available which makes them attractive building blocks for the construction of the 1,2,4-triazolo[1,5-*a*][1,3,5]triazine system. In this Letter, we reveal some new aspects of their chemistry, and in particular, we describe the reactions of 5-guanidino-1,2,4-triazole **13** with another versatile reagent, trichloroacetonitrile.[9]

5-Guanidino-3-phenyl-1,2,4-triazole (**13**) was prepared via the reaction of benzhydrazide (**10**) with cyanoguanidine (**11**) in the presence of hydrochloric acid followed by treatment of the resulting *N*-benzamidobiguanide (**12**) with aqueous alkali (Scheme 2).[8] The synthetic utility of trichloroacetonitrile in heterocyclic chemistry has been well recognized,[9] particularly in ring closing reactions as a one-carbon inserting reagent. We found that trichloroacetonitrile reacted with 5-guanidino-3-phenyl-1,2,4-triazole (**13**) affording different products in different solvents (Scheme 2). Treatment of **13** with trichloroacetonitrile with heating in toluene proceeded with elimination of ammonia and provided 5-amino-2-phenyl-7-trichloromethyl-1,2,4-triazolo[1,5-*a*][1,3,5]triazine (**14**),[10] exclusively, in high yield. Analogous reaction in ethanol resulted in

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☆ Part 12 in the series 'Fused heterocyclic systems with *s*-triazine ring', for part 11 see Ref. 1.

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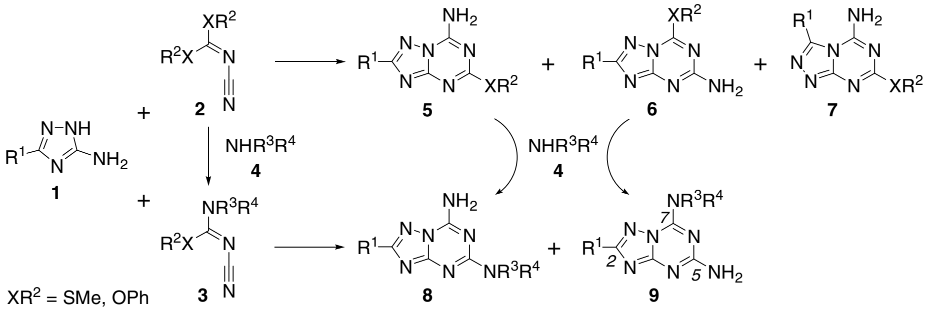
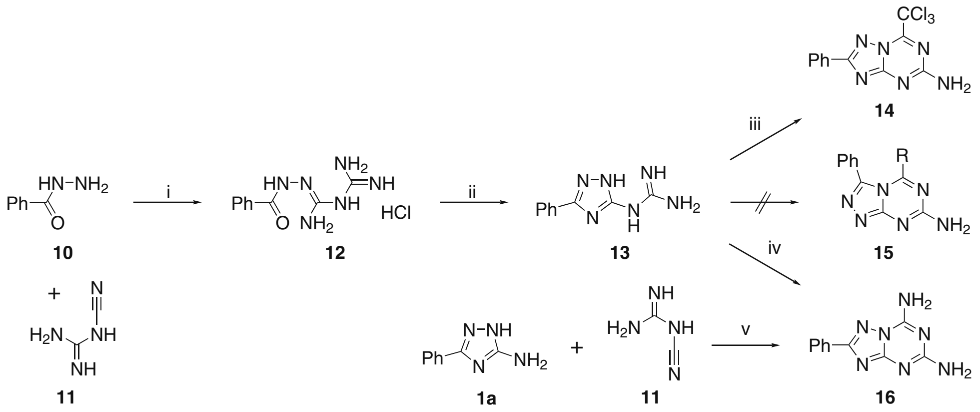


Scheme 1. General synthetic approach to unsymmetrically substituted 5,7-diamino-1,2,4-triazolo[1,5-*a*][1,3,5]triazines.



Scheme 2. Reagents and conditions: (i) cyanoguanidine (1.1 equiv), HCl (1 equiv), EtOH, reflux, 4 h (80%); (ii) 10% NaOH, 80 °C, 6 h (68%); (iii) $NCCCl_3$ (2.0 equiv), PhMe, reflux, 7 h (94%); (iv) $NCCCl_3$ (1.5 equiv), EtOH, reflux, 8 h (85%); (v) HCl (1.0 equiv), water, reflux, 12 h (64%).

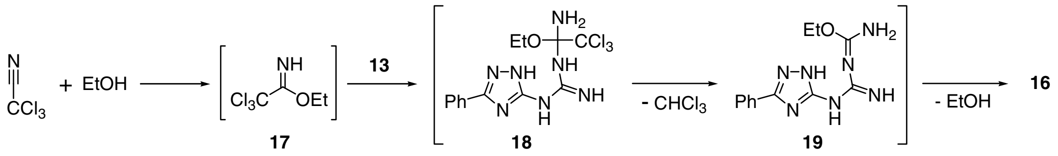
the elimination of chloroform and formation of 5,7-diamino-2-phenyl-1,2,4-triazolo[1,5-*a*][1,3,5]triazine (**16**), which was identical with the sample prepared via an alternative synthetic pathway from 5-amino-1,2,4-triazole **1a** and cyanoguanidine (**11**).[11] Both these reactions of **13** with trichloroacetonitrile were regioselective and afforded only the products of ring closure at nitrogen atom N-1 of the triazole **13**; the products of ring closure at N-4 (compound **15**) were not isolated in any of the cases. This fact was confirmed by ^{13}C NMR data.[10,11] In the [4,3-*a*] ring junction product, the signal of the triazole ring carbon atom bearing the phenyl group would appear at considerably higher field.[6]

The structure of product **14** was supported by NMR spectroscopy. The singlet due to the amino group protons at 8.24 ppm together with the signals of the phenyl ring protons in the ^1H NMR spectrum and the signal of the trichloromethyl group at 89.2 ppm in the ^{13}C NMR spectrum were diagnostic.

The role of ethanol in the synthesis of 5,7-diamino-1,2,4-triazolo[1,5-*a*][1,3,5]triazine (**16**) from **13** and trichloroacetonitrile can be explained by initial formation of imidate **17** as illustrated in Scheme 3. The addition of **17** to the guanidine group of **13** and subsequent elimination of chloroform from adduct **18** would afford intermediate **19**, which upon intramolecular cyclocondensation would provide **16**.

It was found that the trichloromethyl group of **14** readily underwent nucleophilic substitution with amines affording 7-amino-substituted 1,2,4-triazolo[1,5-*a*][1,3,5]triazin-5-amines **9** in good yields (Table 1).[12] This reaction was found to be general, and proceeded smoothly with a variety of primary and secondary amines with alkyl, aryl and aralkyl substituents under heating at 100 °C in dry DMF. The reaction of **14** with aliphatic amines (e.g., methylamine and ethylamine) was also carried out conveniently with excellent chemoselectivity affording **9** even in aqueous solutions of excess amine.[13]

Both of the amino groups of compounds **9** were found to be located in the plane of the 1,2,4-triazolo[1,5-*a*][1,3,5]triazine nucleus and were strongly involved in π electron delocalization with the heterocycle as were shown by NMR spectroscopy data and by an X-ray crystallography study (Fig. 1).[1] Rotation around the C-7–NR^1R^2 bond was hindered leading to the broadening of the signals of the NR^1R^2 group in the NMR spectra, particularly for compounds



Scheme 3. Proposed mechanism for the formation of 5,7-diamino-1,2,4-triazolo[1,5-*a*][1,3,5]triazine (**16**), and the role of ethanol.