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A simple and convenient synthesis of 5-amino-substituted tetrazolo[1,5-*a*]-1,3,5-triazin-7-one salts

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ABSTRACT

A simple and convenient three-step synthesis of 5-amino-substituted tetrazolo[1,5-*a*]-1,3,5-triazin-7-one sodium salts based on a fairly simple sequence of nucleophilic substitution of chlorine atoms in cyanuric chloride has been developed. The corresponding tetrabutylammonium salts were synthesized by cation-exchange with tetrabutylammonium chloride. The structures of the products were characterized by IR, ^{1}H NMR and ^{13}C NMR spectroscopy, and by elemental and X-ray analysis.

The family of condensed azolo-1,3,5-triazines is of considerable interest as its members exhibit a wide spectrum of biological activities. Among these compounds, particular attention has been paid to heterocyclic ring systems that are isosteric to purine. There have been many studies on the chemistry and bioactivity of pyrazolo[1,5-*a*]-1,3,5-triazines (5-aza-9-deazapurines)[1] and 1,2,4-triazolo[1,5-*a*]-1,3,5-triazines (5-azapurines).[2]

The tetrazolo[1,5-*a*]-1,3,5-triazine heterocyclic system is an isostere of purine (5,8-diazapurine), and 5-amino-substituted tetrazolo[1,5-*a*]-1,3,5-triazin-7-ones are 5,8-diaza analogues of guanine (Fig. 1). This close structural similarity of tetrazolo[1,5-*a*]-1,3,5-triazine to purine makes this heterocyclic system an attractive and promising core structure for the development of new bioactive compounds, for example, isosteres of cyclic and acyclic nucleosides.

However, the synthesis of tetrazolo-1,3,5-triazine heterocyclic system derivatives has been an ongoing problem until recently. There were no convenient methods for their preparation, and with one exception,[3] there was a lack of studies on the bioactivity in the tetrazolo[1,5-*a*]-1,3,5-triazine series.

Azido-1,3,5-triazines, the precursors for tetrazolo-1,3,5-triazines, have been known for a long time. However, the existence of condensed tetrazolo-1,3,5-triazines had only been suggested on the basis of theoretical considerations by analogy with other azines.[4–7] The presence of tetrazolo-1,3,5-triazines in equilibrium with azido-1,3,5-triazines was registered by ^{13}C NMR spectroscopy in 1988,[7] but the equilibrium was strongly shifted to the azido form, and tetrazolo-1,3,5-triazines were not preparatively separated. Nevertheless, the first representative of tetrazolo-1,3,5-triazines was obtained and characterized a year earlier in 1987.[8] Therefore, this indicates that there should be appropriate conditions available for the formation and stabilization of the tetrazolo-1,3,5-triazine system.

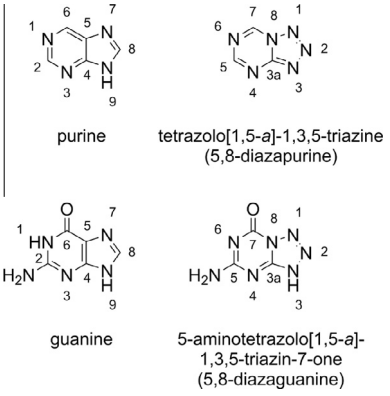

Figure 1. Purine, guanine, and their 5,8-diaza analogues.

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It is known[4] that the azine part of the molecule is responsible for the magnitude of the charge on the bridgehead nitrogen atom in condensed tetrazoloazines, and the higher negative charge on the nitrogen atoms of the azine ring provides a greater possibility for tetrazole ring closure. Delocalization of the negative charge on other N-atoms at the *meta*-position of the azine ring enhances the stability of the azido form. Therefore, an increase in the number of nitrogen atoms relative to a six-membered ring causes destabilization of the condensed tetrazole ring and an increase of the stability of the azide form. The relative position of the nitrogen atoms in the ring is equally important. This can be amply illustrated by the azido derivatives of pyridazine, pyrazine, and pyrimidine.[4] The azido-1,3,5-triazines are an extreme case, as they exist predominantly in the azido form.[4,7]

The presence of electron-donating substituents increases the electron density on the nitrogen atoms of the six-membered ring, promoting stabilization of the tetrazole form and shifting the azide-tetrazole equilibrium to the tetrazole form. The effect of electron-withdrawing substituents is opposite to that of electron-donating substituents, and increases the stability of the azido form.[9–13] However, even the presence of strong electron-donating groups (amino, dimethylamino, and alkoxy groups) on the 1,3,5-triazine ring does not lead to tetrazole ring closure.[7] Calculations show that the introduction of an electron-donating amino group to azido-1,3,5-triazines favors the tetrazole form.[14] In contrast, the introduction of an electron-withdrawing nitro group favors the azido form.[14]

A number of studies[12,15–25] on the effect of the nature of solvents both on the azide-tetrazole equilibrium, and the stabilization of one or another tautomeric form, show that increasing the solvent polarity stabilizes the tetrazole form (in some cases, the only registered tautomer). In contrast, in weakly polar or non-polar solvents, the azide form is predominant.[15–17] According to calculations on the azido-1,3,5-triazines (cyanuric azide, amino and nitrodiazido-1,3,5-triazine), the azido form prevails in CCl_4, whereas the tetrazole form is favored in DMSO and water.[14]

The first preparative synthesis of tetrazolo-1,3,5-triazine was described[8] in 1987 which involved the reaction of 5-aminotetrazole with 3-phenyl-2-propenoyl isothiocyanate to give 7-styryltetrazolo[1,5-*a*]-1,3,5-triazine-5-thione. Since then, there have been only a few papers[3,8,26–29] reporting the synthesis of tetrazolo-1,3,5-triazine derivatives. Kessenich et al. obtained triphenylphosphanimino derivatives of tetrazolo[1,5-*a*]-1,3,5-triazine by reaction of cyanuric azide with triphenylphosphine.[26,27] Bekircan et al. showed[3] that 5,7-diphenyl-tetrazolo[1,5-*a*]-1,3,5-triazine could be obtained by treatment of 5-aminotetrazole with N-acyl imidates. The reaction of the tetramethylammonium salt of 2-hydroxy-4,6-bis(trinitromethyl)-1,3,5-triazine with sodium azide was reported[28] to lead to the tetramethylammonium salt of 5-trinitromethyltetrazolo[1,5-*a*]-1,3,5-triazin-7-one.

The synthesis of 5-dimethylamino(diethylamino)-tetrazolo[1,5-*a*]-1,3,5-triazin-7-one sodium salts was described earlier[29] on the basis of successive substitution of the trinitromethyl groups in 2-amino-substituted 4,6-bis(trinitromethyl)-1,3,5-triazines under the action of sodium nitrite and sodium azide. One of the drawbacks of this approach is an inability to involve weakly basic amines in the trinitromethylation-amination reaction of cyanuric chloride to obtain the starting 2-amino-substituted 4,6-bis(trinitromethyl)-1,3,5-triazines.[30] Moreover, the starting bis(trinitromethyl) compounds and the intermediate monotrinitromethyl compounds require great care in handling and storage due to both fire and explosion hazards. Furthermore, there is no trinitromethyl group in the final structures of the 5-(amino or substituted amino)tetrazolo[1,5-*a*]-triazin-7-ones.

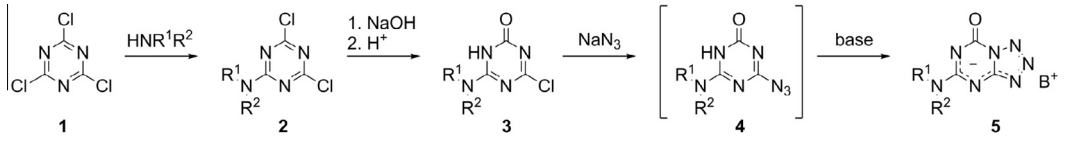
2-Amino-substituted 4,6-dichloro-1,3,5-triazines (**2**), bearing two labile chlorine atoms, would appear to be more suitable as starting materials. They can easily be prepared in high yields from commercially available 2,4,6-trichloro-1,3,5-triazine (**1**) via known procedures,[31–33] with no limitations on the basicity of the amines used.

Previously, we showed[34] that 4-(amino or substituted amino)-6-chloro-1,3,5-triazin-2(1*H*)-ones (**3**) could be obtained in moderate to high yields (up to 93%) via selective substitution of one chlorine atom with a hydroxy group in **2**.

To form the condensed tetrazolo[1,5-*a*]-1,3,5-triazine system we intended to replace the remaining chlorine atom in **3** with an azido group to obtain the key 4-amino-substituted 6-azido-1,3,5-triazine-2(1*H*)-ones (**4**). Subsequent cyclization of the key azide to the annelated tetrazole under the action of base should give 5-(amino or substituted amino)tetrazolo[1,5-*a*]-1,3,5-triazine salts (**5**) (Scheme 1).

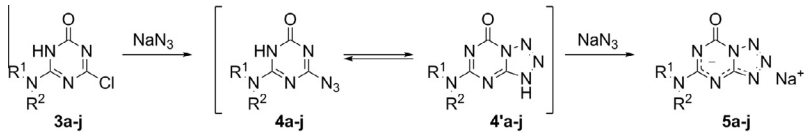
The reactions of compounds **3a–j** with sodium azide were carried out in DMF/acetone (1:2, v/v). Two moles of sodium azide were needed to complete the reaction (the extent of conversion of **3a–j** was monitored by TLC). However, the expected azides **4a–j** were not obtained, instead the reaction gave 5-aminotetrazolo[1,5-*a*]-1,3,5-triazin-7-one sodium salts **5a–j** (Scheme 2). The yields of the products **5a–j** are given in Table 1.

Attempts to replace the second mole of sodium azide with one mole of a particular base always led to the corresponding salts of the starting compound **3**, and azidation did not occur. While the presence of the second mole of sodium azide in the mixture did



NR^1R^2 = NH_2 (**a**); NMe_2 (**b**); NHPr-*n* (**c**); NHPr-*i* (**d**); NHCy (**e**); NHPh (**f**); $NH(C_6H_4Me\text{-}p)$ (**g**); $N(CH_2)_4$ (**h**); $N(CH_2)_5$ (**i**); $N(CH_2CH_2)_2O$ (**j**)

Scheme 1. General synthetic strategy to 5-amino-substituted tetrazolo[1,5-*a*]-1,3,5-triazin-7-one salts.



Scheme 2. The azidation reaction of 4-amino-substituted 6-chloro-1,3,5-triazin-2-ones **3a–j**.