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Highly Diastereoselective Synthesis of C(6)-Functionalized Dihydroimidazotriazines

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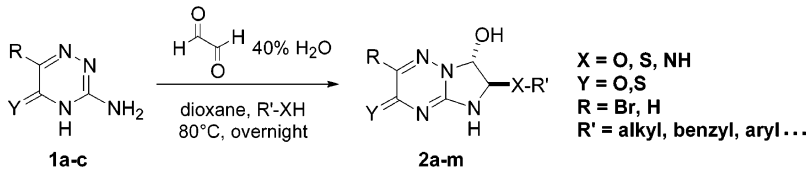
ABSTRACT



The first examples of C(6)-substituted 7-hydroxy-6,7-dihydro-*5H*-imidazo[1,2-*b*][1,2,4]triazines have been prepared by ring closure of different 5(*2H*)-1,2,4-triazin-3-ones 1a–c with 40% aqueous glyoxal and various nucleophiles (alcohols, thiols, or amines). The structure and exact stereochemistry of 2a was established by a single X-ray diffraction study and ^{1}H and ^{13}C NMR spectra analysis. The process was shown to be totally regio- and diastereoselective. A mechanism involving an imine intermediate was proposed.

1,2,4-Triazines are a well-known class of heterocyclic compounds[1] and have been studied for a long time.[2] The increasing interest in 1,2,4-triazines is mainly due to their interesting properties as precursors of aza analogues of pyrimidine nucleic bases, antibiotics, herbicides,[3] etc. In the course of our studies on selective functionalization of 1,2,4-triazines to generate polycyclic rings, we first examined the nucleophilic character of the amino group in position 3 on 5(*2H*)-1,2,4-triazin-3-one. Diazotation reactions, followed by addition on ethyl nitroacetate or nitroacetonitrile[4] or by condensation reactions with β-diketones such as malonaldehyde, were unsuccessful. The nonreactive amine was completely recovered. However, we discovered that, in the presence of aqueous glyoxal in hot ethanol, **1a** led to dihydroimidazotriazine derivative **2a**.

The present paper describes the condensation of 3-amino-1,2,4-triazine derivatives **1a**−**c**[5−7] with 40% aqueous glyoxal in the presence of various nucleophiles such as alcohols, amines, or thiols. In addition, mechanistic considerations on the formation of the resulting C(6)-substituted 7-hydroxy-6,7-dihydro-*5H*-imidazo[1,2-*b*][1,2,4]triazines **2a**−**m** have been examined.

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(1) Neunhoffer, H. *Comprehensive Heterocyclic Chemistry II*; Katritsky, A. R., Rees, C. W., Scriven, E. F. W., Eds.; Pergamon Press: Oxford, UK, 1996; Vol. 6, p 507.
(2) Neunhoffer, H.; Wiley, P. F. *The Chemistry of Heterocyclic Compounds*; John Wiley: New York, 1974.
(3) Pozharskii, A. F.; Soldatenkov, A. T.; Katritsky, A. R. *Heterocycles in Life and Society*; Wiley: Chichester, UK, 1997.
(4) Rusinov, V. L.; Petrov, A. Y.; Chupakhin, O. N.; Klyuev, N. A.; Aleksandrov, G. G. *Khim. Geterotsikl. Soedin.* **1985**, *5*, 682−688.
(5) Oxidation of 3-amino-1,2,4-triazine (**1b**): Sasaki, T.; Minamoto, K. *Chem. Pharm. Bull.* **1964**, *12*, 1329−1338.
(6) Bromination of **1b** (**1a**): Lovelette, C. A. *J. Heterocycl. Chem.* **1979**, *16*, 555−560.
(7) Thiation of **1b** (**1c**): Wei, D.-C.; Hwang, L.-C.; Han, C.-H.; Lee, K.-H.; Tzeng, C.-C. *Heterocycles* **1993**, *36*, 2733−2743.

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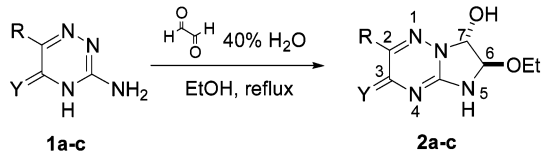
As mentioned before, reacting 3-amino-6-bromo-5(*2H*)-1,2,4-triazinone **1a** with glyoxal (5 equiv) in ethanol (ca. 300 equiv) under neutral conditions gave the unexpected compound **2a** in 89% yield. This process was generalized to other aminotriazine derivatives **1b**,**c** with satisfactory yields, as reported in Scheme 1. Preliminary studies had

Scheme 1



shown that the presence of the alcohol was essential for the success of the reaction. Indeed, when the reaction was performed without alcohol, only starting material was recovered.

Both ^{1}H and ^{13}C NMR spectra led us to think that only one of the two possible diastereoisomers was formed. ^{1}H NMR spectra analysis in DMSO-d_6 revealed a coupling corresponding to H(5) and H(6) (J = 7.3 Hz). This observation was confirmed by the disappearance of both the doublet assigned to NH and the constant coupling, when D_2O was added. On the other hand, no coupling was found between H(6) and H(7) in DMSO-d_6 while with MeOD, a coupling constant of J = 1.1 Hz was observed.

The structure and exact stereochemistry of **2a** was established by a single X-ray diffraction study (an ORTEP view of a single molecule of **2a** is given in Figure 1).

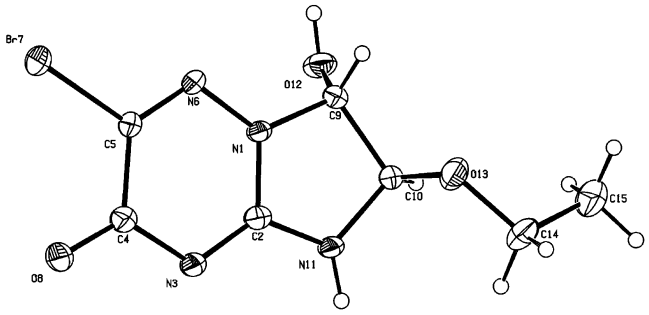
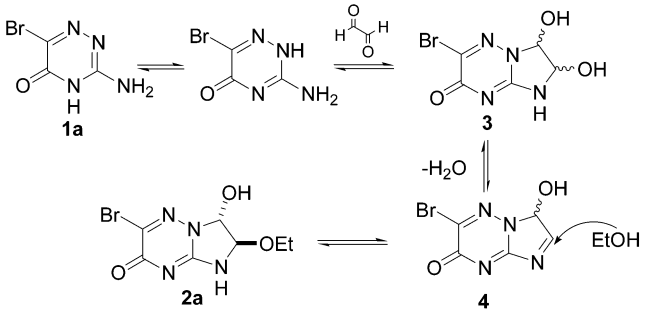


Figure 1. ORTEP view of compound **2a**.[8]

In particular, it confirmed the formation of the predictably most stable trans adduct and the positions of both NH(11) and OH(12) were unambiguously determined by Fourier synthesis.[9] Moreover, the O(12)−C(9)−C(10)−O(13) dihedral angle (θ = −136.0(3)°) confirmed the trans diastereoisomerism of **2a**. On the other hand, the "imidazole" moiety is almost planar. The maximum deviation of N(11) and C(9) atoms from the least-squares plane is 0.08 Å. Finally, the space group $P4_2/n$ is centrosymmetric, indicating that **2a** is isolated as a racemate.

As shown above, the condensation reaction leading to **2a** is a completely regio- and diastereoselective process. Here, only the (6-OEt,7-OH) isomer is observed, with a trans stereochemistry. In an attempt to understand the mode of ring closure and the observed stereochemistry, we postulated for the following possible mechanism. On the basis of mechanistic considerations described on 5,6-diamino-1,2,4-triazines,[10,11] we anticipated the mechanism outlined in Scheme 2.

Scheme 2



We suggested a double addition of amino groups on each aldehyde moiety of glyoxal, with formation of the diol intermediate **3**. This diol would be in equilibrium with imine **4**, onto which ethanol could add.[12] This mechanism is in accordance with the formation of only one diastereoisomer: the regiospecificity of the reaction would be directly linked to the formation of the imine intermediate, whereas the diastereoselectivity could be explained by the steric hindrance, the alcohol attacking opposite to the remaining hydroxyl group (particularly bulky in this coplanar cyclic system), thus giving rise to the trans adduct. Nevertheless, we cannot completely exclude that compound **2a** could be the thermodynamic product, resulting from an equilibrium between the cis and the trans isomers.[11] The isolation of the diol intermediate **3** would have significantly proved this mechanism, but we were never able to achieve this goal using the procedures described for 5,6-diamino-1,2,4-triazines.[10,11]

Looking at this mechanism, we thought that not only ethanol but any nucleophile could add to imine **4**, thus raising prospects for a much more general reaction than initially intended.

(8) There is no correspondence between IUPAC and ORTEP numbering.

(9) Sheldrick, G. M., Kröger, C., Goddard, R. *SHELX 86 in Crystallographic Computing 3*; Oxford University Press: New York, 1985; p 175−189.

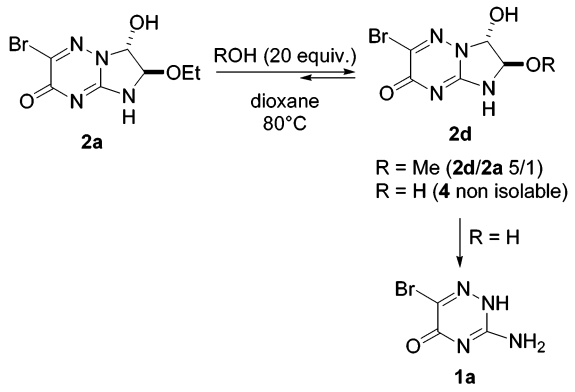
(10) Lee, K. H.; Huang, B.-R.; Chen, Y.-L.; Tzeng, C.-C. *Heterocycles* **1993**, *36*, 2577−2589.

(11) Tzeng, C.-C.; Rychlewska, U.; Hodgson, D. J.; Panzica, R. P. *J. Heterocycl. Chem.* **1986**, *23*, 33−42.

(12) The formation of an epoxide intermediate could be considered. In this case the reaction would be diastereoselective but the regioselectivity would be hard to explain.

First, we anticipated that it might be possible to carry out an exchange of substituent at the C(6) position by any nucleophile. To address to this question, we heated the solution of ethoxy adduct **2a** in dioxane (vide infra) in the presence of 20 equiv of methanol or water (Scheme 3). The

Scheme 3



formation of the methoxy adduct **2d** with methanol and the isolation of 3-amino-5(*2H*)-1,2,4-triazin-3-one **1a** with water were in absolute concordance respectively with the equilibrium of the reaction and with the hypothesis of an unstable intermediate **4**.

Furthermore, aiming to generalize this reaction to nucleophiles which are not useful solvents (e.g. solid, expensive, or toxic products), we optimized the reaction conditions with ethanol as reagent only.

The condensation of 3-amino-6-bromo-5(*2H*)-1,2,4-triazinone **1a** with glyoxal in the presence of ethanol was chosen as the model reaction (Scheme 1). After a brief study, we found that the cyclization could be performed by using dioxane as solvent without decreasing the yield, while curiously, using THF, no cyclization occurred. Thus, the optimized conditions were determined in dioxane. The amount of ethanol and the concentration of the medium were both crucial parameters (Table 1).

Table 1. Influence of the Concentration and of the Amount of Ethanol

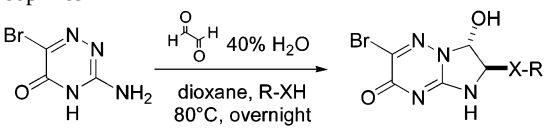
entry[a]	ethanol equivalent	conc. of **1a** (mol·L^{-1})	yield[b] (%)
1	20	0.20	13
2	20	0.10	45
3	**20**	**0.05**	**87**
4	10	0.05	19
5	5	0.05	15

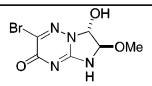
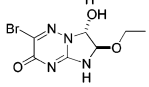
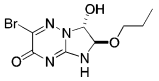
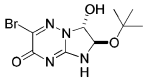
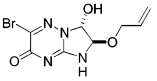
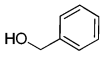
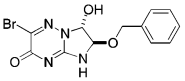
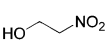
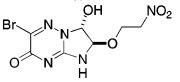
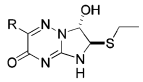
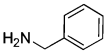
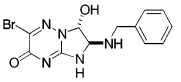
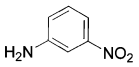
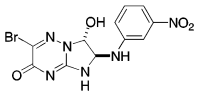
[a] The quantity of glyoxal was set up to 5 equiv. [b] Yield of pure, isolated **2a**.

We found that a diluted mixture (0.05 M) was required to obtain the same yield as when ethanol was used as solvent. Finally, only 20 equiv of ethanol, but not less, was required to reach maximum yields.

Using a solvent and reducing substantially the amount of ethanol, we were then able to study the behavior of 3-amino-6-bromo-5(*2H*)-1,2,4-triazinone **1a** toward elaborated or solid nucleophiles. Thus, the process was generalized through the use of various alcohols, thiols, or amines (Table 2).

Table 2. Functionalization at C(6) Position by Various Nucleophiles



run	nucleophile (R-XH)	products	n°	yield[a] (%)
1	MeOH		**2d**	78%
2	EtOH		**2a**	87%
3	PrOH		**2e**	75%
4	*t*BuOH		**2f**	[b] —
5			**2g**	22%[c]
6			**2h**	79%
7			**2i**	80%
8	EtSH		**2j** (R=Br) **2k** (R=EtS)	60% 36%
9			**2l**	84%
10			**2m**	76%

[a] Yield of pure, isolated products. [b] Only starting material was recovered. [c] Complete conversion but degradation during purification by column chromatography.

Concerning alcohols, we noticed that the length of the alkyl chain or the presence of a benzyl group had almost no influence on the reaction (Table 2, entries 1, 2, 3, and 6). Moreover, the functionalized alcohol 2-nitroethan-1-ol gave the expected C(6)-substituted products **2i** in very satisfactory yields. Allyl alcohol was also found to be an efficient nucleophile (complete conversion), but unfortunately the corresponding adduct **2g** was prone to degradation during

silica gel column chromatography. Moreover, compound **2f** resulting from the addition of *tert*-butyl alcohol had never been formed, probably due to steric reasons.

The synthetic utility of this reaction was further demonstrated by the successful addition of other types of nucleophiles. Thus, adduct **2j**, arising from the reaction with ethanethiol, was isolated in 60% yield, with competition of the substitution of bromine (**2k**, 36%). When 40 equiv of EtSH was used, only **2k** was isolated in 70% yield. Finally, benzylamine led to 2-bromo-6-benzylamino-7-hydroxy-(6,7)-dihydro-*5H*-imidazo[1,2-*b*][1,2,4]triazin-3-one **2*l*** in 84% yield. Remarkably, good yields were even obtained with a deactivated aniline (Table 2, entry 10).

In conclusion, we have described in this paper the unexpected reaction of 3-amino-6-bromo-5(*2H*)-1,2,4-triazinone **1a** with glyoxal in ethanol. The condensation with glyoxal is followed by addition of ethanol to yield compound **2a**. The process was shown to be totally regio- and diastereoselective, and a mechanism involving an imine intermediate **4** was proposed.

Interestingly, other aminotriazines could be used as substrates, and ethanol could be replaced by various nucleophiles (other alcohols, thiols, or amines) with total diastereocontrol of the isolated compounds **2a**−**m**. This general reaction leading to previously unknown, functionalized compounds may find interesting applications in different fields of chemistry.

Acknowledgment. The Orleans group thanks CEA/Le Ripault for financial support.

Supporting Information Available: Experimental procedures and spectroscopic data for **2a**−**m** and experimental crystallographic details for **2a** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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