



One-step aldehyde group transformation by using guanidine and aminoguanidine: Synthetic, structural and computational studies



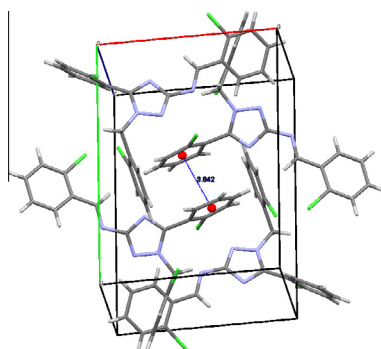
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HIGHLIGHTS

- We report new synthetic methodologies of triazine derivatives.
- Structure of 1-(2-chlorobenzyl)-5-(2-chlorophenyl)-N-[(1E)-(2-chlorophenyl)methylene]-1,2,4-triazolidin-3-amine.
- 2,4-Diamino-3,6-dihydro-6-(2-chlorophenyl)-1,3,5-triazine was synthesized.
- Multinuclear NMR, X-ray and DFT characterization.
- High yield from low cost starting materials.

GRAPHICAL ABSTRACT



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ABSTRACT

New triazine derivatives 2,4-diamino-3,6-dihydro-6-(2-chlorophenyl)-1,3,5-triazine (**1**) and 1-(2-chlorobenzyl)-5-(2-chlorophenyl)-N-[(1E)-(2-chlorophenyl)methylene]-1,2,4-triazolidin-3-amine (**2**) were synthesized by a one-pot synthesis using 2-chlorobenzaldehyde, guanidine and aminoguanidine, respectively. The FTIR, multinuclear NMR, and single crystal X-ray characteristics of these compounds have been determined experimentally and rationalized on the basis of DFT calculation method.

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1. Introduction

Aldehydes are a class of compounds of great interest from the synthetic, theoretical and application point of view. They can be transformed into a wide range of structures through applying a variety of reactions. Like ketones, aldehydes are sp^2 hybridized and could exist in the form of keto or enol tautomer. The

equilibrium is strongly thermodynamically driven, and at room temperature the keto form is favored. The conversion between the two forms can be catalyzed by either acids or bases. As electrophiles, they are subject to be attacked by nucleophiles, and participate in many nucleophilic addition reactions.

In this paper, we reported the transformation of aldehyde group by guanidine and aminoguanidine to new triazine derivatives. Despite its potential value there are many papers describing this conversion. In most cases products are Schiff bases [1–13]. However, there are only few works showing the ring closure reaction

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similar to ours, all without NMR and X-ray characteristics [14]. The presented discussion is particularized by computational and spectroscopic studies. The triazines have been found broad applications in pharmaceutical and agrochemical industries [15–19]. They have also attracted considerable attentions due to their biological and medicinal activities, such as antileukemic, against resistant malarial strains, antitumor, diuretic, herbicides or in cancer therapy [20–26]. Triazine derivatives are cytotoxic to parasites since they offer excellent selectivity between parasites and host cells [27–29].

2. Experimental

2.1. General

NMR spectra were obtained with Bruker Avance 400 and 500 operating at 500.18 or 400.13 MHz (^1H), 125.78 or 100.5 MHz (^{13}C) at 21 °C. Chemical shifts referenced to ext. TMS (^1H , ^{13}C). Coupling constants are given in Hz. Mass spectra were obtained with a Varian 500 MS with applied ESI technique. Melting points were determined on MPA100 OptiMelt melting point apparatus and uncorrected. 2-Chlorobenzaldehyde, guanidine sulfate and aminoguanidine bicarbonate were purchased from Sigma–Aldrich, and were used without further purification.

2.1.1. Synthesis of compounds

2.1.1.1. Synthesis of 2,4-diamino-3,6-dihydro-6-(2-chlorophenyl)-1,3,5-triazine (1). Guanidine sulfate (30.3 g, 0.28 mol) was partially dissolved in a mixture of methanol (300 mL) and DMSO (5 mL). Subsequently, K_2CO_3 (38.7 g, 0.28 mol) was added, and the reagents were heated under reflux for an hour, then 2-chlorobenzaldehyde (39.2 g, 0.28 mol) in a solution of methanol (50 mL) was added. After the addition, the reaction mixture was stirred under reflux overnight, followed by filtration. The solvent was evaporated from the resulting solution. The crude product was purified by extraction at Soxhlet apparatus using EtOH:

1; 32.47 g (0.146 mol; 52%); (white); m.p._{dec.} = 177–178 °C; ^1H NMR (DMSO- d_6 ; 400.2 MHz; 75 °C) δ = 5.44 (bs, 4H, NH), 5.99 (s, 1H, CH), 7.29 (d, J = 7.6 Hz, 1H, aromatic), 7.34 (t, J = 7.5 Hz, 1H, aromatic), 7.38 (d, J = 7.8 Hz, 1H, aromatic), 7.49 (d, J = 7.5 Hz, 1H, aromatic); $^{13}\text{C}\{^1\text{H}\}$ NMR (DMSO- d_6 ; 100.5 MHz; 60 °C) δ = 65.32, 126.87, 128.38, 128.60, 128.86, 131.01, 142.13 (bs), 158.15; MS (MeOH + AcOH): (ESI) (M + H) $^+$ = 224 (100% ^{35}Cl) and 226 (32% ^{37}Cl).

2.1.1.2. Synthesis of 1-(2-chlorobenzyl)-N-(2-chlorobenzylidene)-5-(2-chlorophenyl)-1H-1,2,4-triazol-3-amine (2). Aminoguanidine bicarbonate (38.1 g, 0.28 mol) was partially dissolved in water (100 mL). Subsequently, K_2CO_3 (38.7 g, 0.28 mol) was added, and the reagents were heated under reflux for an hour. Then the water was evaporated and 2-chlorobenzaldehyde (78.7 g, 0.56 mol) in solution of methanol (100 mL) was added. After the addition, the reaction mixture was stirred overnight (16 h), followed by filtration. The solvent was evaporated from the resulting solution. The crude product was purified by crystallization from MeOH:

2; 21.4 g (48.5 mmol; 26%); (beig); m.p. = 124–125 °C; ^1H NMR (DMSO- d_6 ; 500.18 MHz) δ = 3.34 (s, 2H, CH_2), 7.28–7.33 (m, 2H, aromatic), 7.34 (dd, J = 5.9, 2.9 Hz, 1H, aromatic), 7.41 (dd, J = 6.0, 2.9 Hz, 1H, aromatic), 7.48–7.55 (m, 2H, aromatic), 7.58–7.62 (m, 2H, aromatic), 7.65 (td, J = 7.2, 1.8 Hz, 2H, aromatic), 7.68 (dd, J = 8.0, 0.7 Hz, 1H, aromatic), 8.23 (d, J = 7.7 Hz, 1H, aromatic), 9.58 (s, 1H, CHN); $^{13}\text{C}\{^1\text{H}\}$ NMR (DMSO- d_6 ; 125.78 MHz) δ = 50.09, 126.83, 127.43, 127.60, 127.81, 128.35, 129.37, 129.86, 130.04, 130.22, 130.94, 131.89, 132.05, 132.45, 132.50, 132.53, 132.92, 133.85, 135.79, 152.66, 159.75, 164.72; MS: (ESI)

(M) $^+$ = 441 (100%), 443 (100%), 442 (25%), 444 (25%) 445 (43%); CCDC 921074.

2.2. Crystallization

The crystal of **2** suitable for X-ray analysis was obtained from hot MeOH solution.

2.3. DFT calculations

The calculations were carried out by using Gaussian 09 [30] program. The DFT/B3LYP [31,32] method was used for the geometry optimization and electronic structure determination. The geometry optimization was made for gas phase molecule and a frequency calculation was carried out, verifying that the optimized molecular structure obtained corresponds to energy minimum, thus only positive frequencies were expected. The absence of the imaginary frequencies, as well as of negative eigenvalues of the second derivative matrix has been obtained in geometry optimization of all compounds. The calculations were performed using the polarization functions for all atoms: 6-31G ** – carbon, nitrogen, oxygen, chloride and hydrogen. Natural charges were calculated with use of the NBO 5.0 package included in Gaussian 09.

2.4. Crystal structure determination and refinement

The crystal of **2** was mounted in turn on a Gemini A Ultra, Oxford Diffraction automatic diffractometer equipped with a CCD detector for data collection. X-ray intensity data were collected with graphite monochromated Mo K_α radiation (λ = 0.71073 Å) at temperature of 295.0(2) K **2**, with ω scan mode. Ewald sphere reflections were collected up to 2θ = 50.10. Details of crystal data and refinement are gathered in Table 1, and selected bond lengths and angles for compounds are listed in Table 2. During the data

Table 1
Crystal data and structure refinement details for **2**.

	2
Empirical formula	$\text{C}_{22}\text{H}_{15}\text{Cl}_3\text{N}_4$
Formula weight	441.73
Temperature (K)	295.0(2) K
Radiation	Mo K_α λ = 0.71073 Å
Color, habit	Colorless, plate
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell dimensions	
a (Å)	10.8119(9)
b (Å)	13.4154(9)
c (Å)	15.4186(13)
β (°)	110.016(9)
Volume (Å 3)	2101.3(3)
Z	4
Calculated density (Mg/m 3)	1.396
Absorption coefficient (mm $^{-1}$)	0.452
$F(000)$	904
Crystal dimensions (mm)	0.27 × 0.19 × 0.06
θ range for data collection (°)	3.35–25.05
Index ranges	–8 ≤ h ≤ 12 –15 ≤ k ≤ 13 –18 ≤ l ≤ 15
Reflections collected	7993
Independent reflections	3714 [R_{int}] = 0.0326]
Data/restraints/parameters	3714/0/262
Goodness-of-fit on F^2	1.073
Final R indices [$I > 2\sigma(I)$]	R_1 = 0.0528 wR_2 = 0.1190
R indices (all data)	R_1 = 0.0944 wR_2 = 0.1524
Largest diff. Peak and hole (e Å $^{-3}$)	0.765 and –0.501
CCDC number	921074

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