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SYNTHESIS, STRUCTURE, PROPERTIES OF 1,2,4,5-TETRAZINES

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Keywords:
1,2,4,5-tetrazines, aromatic nitriles, hydrazine hydrate, dihydrotetrazines, oxidation reactions

Abstract. *The paper discusses the synthesis of 3,6-diaryl-1,2,4,5-tetrazines by the reaction of aromatic nitriles with hydrazine hydrate in the presence of elemental sulphur. We study the structure of synthesised dihydro-1,2,4,5-tetrazines by ^{1}H NMR spectroscopy, quantum chemical modelling, and the density functional method with a basis set of 6-31G (d,p) basis set. As a result, 1,4-dihydro- are similar to 1,2-dihydrotetrazines in terms of their total energy values. Additionally, the equilibrium in a mixture is in approximately equal amounts for most their substrates. The corresponding 3,6-diaryl-1,2,4,5-tetrazines were synthesised by oxidising the obtained dihydro-1,2,4,5-tetrazines with sodium nitrite in glacial acetic acid. Their structure was confirmed by ^{1}H NMR spectroscopy. The authors forecast effective binding to receptors and enzymes for all synthesised target compounds.*

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Introduction

Azaheterocycles are of particular interest among the wide variety of heterocyclic compounds [1]. They draw attention primarily because of their broad spectrum of biological activity. The 1,2,4,5-tetrazines are the most widespread compounds. The presence of four nitrogen acceptor atoms in their structure determines the uniqueness of the physicochemical properties of this class of heterocyclic compounds. Indeed, they are high-energy compounds [7-11], and have fluorescent properties [2], ability to interact with various nucleophiles and dienophiles [3-6]. Tetrazines have a large number of heteroatoms in their structure and possess additional capabilities for non-covalent binding with various biological targets. The highly electrophilic nature of the heterocycle can enable chemical binding with pathogenic objects, thereby disrupting their functions. Therefore, 1,2,4,5-tetrazine derivatives show various types of biological activity, such as herbicidal [12], antimalarial [13], anti-inflammatory [14], antibacterial [15], and antitumour [16-18].

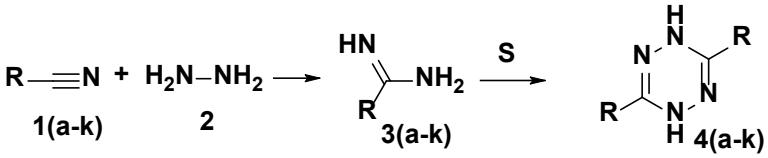
In this regard, the development of methods for obtaining and transforming 1,2,4,5-tetrazines is a crucial task for medical chemistry and the chemistry of heterocyclic compounds.

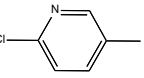
Main body

We synthesised the target products in two stages. At the first stage, we obtained 3,6-diaryl-1,2,4,5-tetrazines by reacting aromatic nitriles with hydrazine hydrate; at the second stage, we oxidised them with sodium nitrite in acetic acid to 1,2,4,5-tetrazines (Scheme 1).

Upon heating aromatic nitriles in a significant excess (15-fold in moles) of hydrazine monohydrate, the yields of 3,6-diaryl-1,2,4,5-tetrazines did not exceed 50%. It was not possible to isolate individual reaction products for some substrates. Many of the mixtures were resinous. This is due to the presence of intermediate (amidrazones), starting and by-products. Some literary sources [19] mention the use of sulphur for the production of dihydro-1,2,4,5-tetrazines.

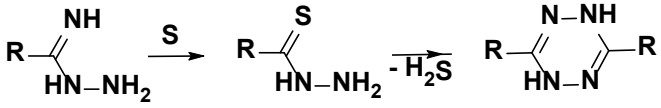
The addition of sulphur to the synthesis reaction of dihydro-1,2,4,5-tetrazines allowed us to increase the yield of 3,6-diphenyl-dihydro-1,2,4,5-tetrazine **4a** from 32% to 70%, and also to obtain dihydro-1,2,4,5-tetrazines **4**(**b**-**k**), which could not be obtained without the use of sulfur.



R = Ph (**a**), $PhCH_2$ (**b**), 4-BrC_6H_4 (**c**), 4-FC_6H_4 (**d**), 4-$CH_3OC_6H_4$ (**e**), 4-$NO_2C_6H_4$ (**f**), 2,4-$(CH_3O)_2C_6H_3$ (**g**), Py (**h**),  (**i**), 3-Tp (**j**), 4-$CF_3C_6H_4$ (**k**)

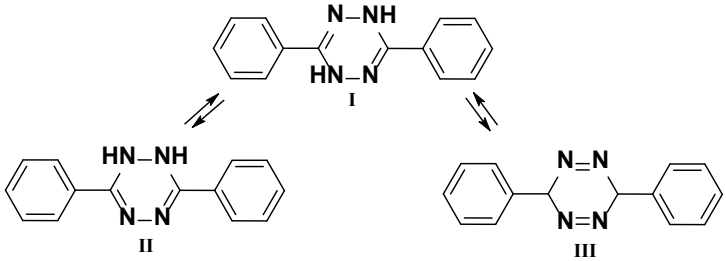
Scheme 1

The mechanism of the reaction in the presence of sulphur has not been studied. However, based on the fact that hydrogen sulphide is released during the reaction, it can be assumed that the imino group (=NH) is first replaced by sulphur, which is then cleaved off during the reaction (Scheme 2).



Scheme 2

3,6-Diaryl-1,2,4,5-tetrazines can be formed and exist in the form of three isomers (Scheme 3).

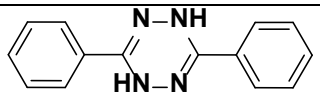
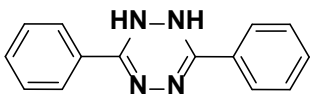
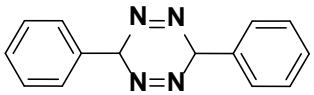


Scheme 3

According to the literature, some authors propose the structure of 1,2-dihydro-1,2,4,5-tetrazines, which are unstable and prone to oxidation; others suggest 1,4-dihydro-1,2,4,5-tetrazines, while the others – 3,6-dihydro-1,2,4,5-tetrazines. However, none of the authors provide spectral data for this group of compounds. All researchers used them further to obtain 1,2,4,5-tetrazines. We studied the structure of synthesised 3,6-diaryl-1,2,4,5-tetrazines using ^{1}H NMR spectroscopy and quantum chemical modelling. The data from the ^{1}H NMR spectra indicate that most dihydro-1,2,4,5-tetrazines are formed as mixtures of isomers with one of them predominating. The ^{1}H NMR spectrum shows proton signals from one isomer for 3,6-dibenzyldihydro-1,2,4,5-tetrazine **4b** and 3,6-di(pyridin-4-yl)-dihydro-1,2,4,5-tetrazine **4h.** It couldn't be clearly linked to a specific structure.

We performed quantum chemical modelling of all three possible isomers to determine the most stable isomers of 3,6-diphenyldihydro-1,2,4,5-tetrazine **4a**. These will therefore be present in greater quantities in the isomeric mixture. We performed calculations using the PC GAMESS/*FireFly8.2* software package [20]; for the gas phase using the density functional method with a 6-31G (d,p) basis set. Table 1 presents the results.

Table 1. Energy characteristics of isomeric 3,6-diphenyldihydro-1,2,4,5-tetrazines

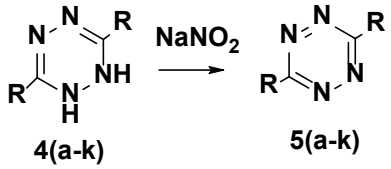
Isomer	Total energy, atomic units (ΔE^*, kJ/mol)
 **I**	-759.6677 (ΔE = 0)
 **II**	-759.6573 (ΔE =27.31)
 **III**	-759.6141 (ΔE =140.75)

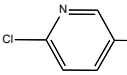
* – calculated relative to the energy of the most thermodynamically stable isomer

According to the calculations (Table 1), the most stable isomer is 3,6-diphenyl-1,4-dihydro-1,2,4,5-tetrazine **I**; the least stable is 3,6-diphenyl-3,6-dihydro-1,2,4,5-tetrazine **III**. Consequently, the formation and presence of the latter isomer in the isolated product is unlikely. The 1,4-dihydrotetrazine **I** and 1,2-dihydrotetrazine **II** are pretty close in terms of total energy (ΔE = 27.31 kJ/mol). This allows us to assume they can turn into each other and be found in a mixture in roughly equal amounts. It explains the complex proton signal system in the ^{1}H NMR spectrum of 3,6-diphenyldihydro-1,2,4,5-tetrazine **4a**.

We performed the oxidation of 3,6-diaryl-1,2,4,5-tetrazines with sodium nitrite in glacial acetic acid to obtain 3,6-diaryl-1,2,4,5-tetrazines using a well-known method described in [21] (Scheme 4).

The structure and purity of the obtained substances **5(a-k)** were confirmed by TLC, elemental analysis, and ^{1}H NMR spectroscopy.



R = Ph (**a**), $PhCH_2$ (**b**), 4-BrC_6H_4 (**c**), 4-FC_6H_4 (**d**), 4-$CH_3OC_6H_4$ (**e**), 4-$NO_2C_6H_4$ (**f**), 2,4-$(CH_3O)_2C_6H_3$ (**g**), Py (**h**),  (**i**), 3-Tp (**j**), 4-$CF_3C_6H_4$ (**k**)

Scheme 4

The predicted biological activities of the synthesised compounds were calculated using the PASS (Prediction of Activity Spectra for Substances) Online programme [22]. The compounds studied **5(a-k)** are forecasted to bind effectively to receptors and enzymes (inhibition of arylmalonate decarboxylase, nicotinic alpha-6-beta-3-beta-4-alpha-5 receptors, etc.).

Experimental part

We recorded NMR spectra on a Varian XL-400 instrument for solutions in DMSO-d_6 at 25 °C. The signals of the residual solvent protons (δ_H 2.50 ppm) were selected as the reference for chemical shift counting; the tetramethylsilane signal was used as a marker. We performed elemental analysis on a PerkinElmer 2400 unit. We determined the melting temperature using a Büchi M-560 melting point and boiling point apparatus.

General method for synthesising compounds 4(a-k). We placed 30 mmol of nitrile, 209 mmol of hydrazine hydrate and 30 mmol of sulphur dissolved in 15 ml of ethanol into a flat-bottomed flask equipped with a reflux condenser. The reaction mixture solidified and turned into a yellow crystalline 'cake' when stirred at 100 °C for 3 hours (hydrogen sulphide was released). We cooled the resulting mass, filtered out the precipitate, and washed it on a filter with ethanol. We purified the product by recrystallisation from ethanol.

3,6-Diphenyldihydro-1,2,4,5-tetrazine **(4a)**. Yield is 2.49 g (70%), crystalline substance, melting point is 195-197 °C. Found, %: C 71.24, H 4.95, N 23.81. $C_{14}H_{12}N_4$. Calculated, %: C 71.17, H 5.12, N 23.71.

3,6-Dibenzyldihydro-1,2,4,5-tetrazine **(4b)**. Yield is 1.11 g (28%), white crystalline substance, melting point is 170-172 °C. NMR ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 4.08 (s, 2H, CH_2), 5.81 (s, 1H, NH), 7.08-7.32 (m, 5H, Ph). Found, %: 72.67, H 6.21, N 21.12. $C_{16}H_{16}N_4$. Calculated, %: C 72.70, H 6.10, N 21.20.

3,6-Di(4-bromophenyl)dihydro-1,2,4,5-tetrazine **(4c)** Yield is 5.50 g (93%), a pink crystalline substance, melting point is 194-197 °C. Found, %: C 42.56, H 2.67, N 14.03. $C_{14}H_{10}Br_2N_4$. Calculated, %: C 42.67, H 2.56, N 14.22.

3,6-Di(4-fluorphenyl)dihydro-1,2,4,5-tetrazine **(4d)** Yield is 3.88 g (95%), an orange crystalline substance, melting point is 182-185 °C. Found, %: C 61.53, H 3.77, N 21.01. $C_{14}H_{10}F_2N_4$. Calculated, %: C 61.76, H 3.70, N 20.58.

3,6-Di(4-methoxyphenyl)dihydro-1,2,4,5-tetrazine **(4e)** Yield is 1.07 g (24%), a yellow crystalline substance, melting point is 194-197 °C. Found, %: C 64.71, H 5.53, N 18.88. $C_{16}H_{16}N_4O_2$. Calculated, %: C 64.85, H 5.44, N 18.91.

3,6-Di(4-nitrophenyl)dihydro-1,2,4,5-tetrazine **(4f)** Yield is 0.99 g (25%), a red crystalline substance, melting point is 195-198 °C. Found, %: C 51.66, H 3.11, N 25.65. $C_{14}H_{10}N_6O_4$. Calculated, %: C 51.54, H 3.09, N 25.76.

3,6-Di(2,4-dimethoxyphenyl)dihydro-1,2,4,5-tetrazine **(4g)**. Yield is 1.92 g (36%), a red crystalline substance, melting point is 97-100 °C. Found, %: C 60.46, H 5.75, N 15.62. $C_{18}H_{20}N_4O_4$. Calculated, %: C, 60.66; H, 5.66; N, 15.72.

3,6-Di(pyridin-4-yl)dihydro-1,2,4,5-tetrazine **(4h).** Yield is 0.42 g (12%), a white crystalline substance, melting point is 186-189 °C. NMR ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 6.51 (s, 1H, NH), 8.12 (d, 2H, H-3,5, *J*=7.5), 8.76 (d, 2H, H-2,6, *J*=7.5). Found, %: C 60.55, H 4.14, N 35.31. $C_{12}H_{10}N_6$. Calculated, %: C 60.50, H 4.23, N 35.27.

3,6-Di(chlorpyridin-4-yl)dihydro-1,2,4,5-tetrazine **(4i).** Yield is 2.03 g (44%), an orange-coloured crystalline substance, melting point is 187-190 °C. Found, %: C 46.80, H 2.65, N 27.19. $C_{12}H_8Cl_2N_6$. Calculated, %: C 46.93, H 2.63, N 27.36.

3,6-Di(thiophen-3-yl)dihydro-1,2,4,5-tetrazine **(4j).** Yield is 1.49 g (40%), a brick-coloured crystalline substance, melting point is 203-207 °C. Found, %: C 48.43, H 3.29, N 22.35. $C_{10}H_8N_4S_2$. Calculated, %: C 48.37, H 3.25, N 22.56.

3,6-Di(4-(trifluoromethyl)phenyl)dihydro-1,2,4,5-tetrazine **(4k)**. Yield is 2.73 g (49%), a pinkish crystalline substance, melting point is 180-183 °C. Found, %: C 51.74, H 2.66, N 14.92. $C_{16}H_{10}F_6N_4$. Calculated, %: C 51.62, H 2.71, N 15.05.

General method for the synthesis of 3,6-diaryl-1,2,4,5-tetrazines 5(a-k). We dissolved 12 mmol of dihydro-1,2,3,5-tetrazine in 10 ml of glacial acetic acid in a flat-bottomed flask equipped with a reflux condenser. While cooling and stirring vigorously, a solution of sodium nitrite (20 mmol) was added to 5 ml of water. The mixture was stirred for 20 minutes; the precipitate was filtered off and recrystallised from ethanol.

3,6-Diphenyl-1,2,4,5-tetrazine **(5a)**. Yield is 1.26 g (45%), a bright pink crystalline substance, melting point is 193-195 °C. NMR ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 7.68-7.75 (m, 3H, Ph), 8.54-8.58 (m, 2H, Ph). Found, %: C 71.66, H 4.32, N 23.82. $C_{14}H_{10}N_4$. Calculated, %: C 71.78, H 4.30, N 23.92.

3,6-Dibenzyl-1,2,4,5-tetrazine **(5b)**. Yield is 1.07 g (34%), a pink crystalline substance, melting point is 63-64 °C. NMR ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 4.58 (s, 2H, CH_2), 7.22-7.32 (m, 5H, Ph). Found, %: C 73.37, H 5.45, N 21.18. $C_{16}H_{14}N_4$. Calculated, %: C 73.26, H 5.38, N 21.36.

3,6-Di(4-bromophenyl)-1,2,4,5-tetrazine **(5c)** Yield is 1.41 g (30%), a light pink crystalline substance with a melting point of 195-197 °C. NMR ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 7.69 (d, 2H, H-3,5, *J*=8.5), 8.00 (d, 2H, H-2,6, *J*=8.5). Found, %: C 43.04, H 2.16, N 14.19. $C_{14}H_8Br_2N_4$. Calculated, %: C 42.89, H 2.06, N 14.29.

3,6-Di(4-fluorphenyl)-1,2,4,5-tetrazine **(5d)** Yield is 0.91 g (28%), a pink crystalline substance, melting point is 183-185 °C. NMR ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 7.28-7.34 (m, 2H, H-3,5), 8.65-8.69 (m, 2H, H-2,6). Found, %: C 62.01, H 3.08, N 20.88. $C_{14}H_8F_2N_4$. Calculated, %: C 62.22, H 2.98, N 20.73.

3,6-Di(4-methoxyphenyl)-1,2,4,5-tetrazine **(5e)** Yield is 0.76 g (24%), a purple crystalline substance, melting point is 220-223 °C. NMR ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 4.00 (s, 3H, CH_3), 7.10-7.30 (m, 2H, H-3,5), 8.45-8.55 (m, 2H, H-2,6). Found, %: C 65.42, H 4.68, N 19.08. $C_{16}H_{14}N_4O_2$. Calculated, %: C 65.30, H 4.79, N 19.04.

3,6-Di(4-nitrophenyl)-1,2,4,5-tetrazine **(5f)** Yield is 1.87 g (48%), a purple crystalline substance, melting point is 231-234 °C. NMR ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 8.51 (d, 2H, H-2,6, *J*=8.6), 8.91 (d, 2H, H-3,5, *J*= 8.6). Found, %: C 51.76, H 2.51, N 25.85. $C_{14}H_8N_6O_4$. Calculated, %: C 51.86, H 2.49, N 25.92.

3,6-Di(pyridin-4-yl)-1,2,4,5-tetrazine **(5h).** Yield is 0.42 g (15%), a purple crystalline substance, melting point is > 250 °C (with decomposition). NMR ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 8.46-8.53 (m, 2H, H-3,5), 8.93-8.90 (m, 2H, H-2,6). Found, %: C 61.09, H 3.44, N 35.51. $C_{12}H_8N_6$. Calculated, %: C 61.01, H 3.41, N 35.58.

3,6-Di(2-chlorpyridin-4-yl)-1,2,4,5-tetrazine **(5i).** Yield is 2.82 g (77%), a brick-coloured crystalline substance, melting point is 186-188 °C. Found, %: C 47.09, H 2.07, N 27.31. $C_{12}H_6Cl_2N_6$. Calculated, %: C 47.24, H 1.98, N 27.54.

3,6-Di(thiophen-3-yl)-1,2,4,5-tetrazine **(5j).** Yield is 1.56 g (53%), a pink neon-coloured crystalline substance, melting point is 208-210 °C. NMR ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 7.87 (d, 1H, H-5, *J*= 5.1), 7.99 (d, 1H, H-4, *J*= 5.1), 8.76 (s, 1H, H-2). Found, %: C 48.60, H 2.40, N 22.56. $C_{10}H_6N_4S_2$. Calculated, %: C 48.76, H 2.46, N 22.75.

3,6-Di(4-(trifluoromethyl)phenyl)-1,2,4,5-tetrazine **(5k)**. Yield is 1.29 g (29%), a purple crystalline substance, melting point is > 220 °C (with decomposition). NMR ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 7.88-7.92 (m, 2H, H-2,6), 8.75-8.79 (m, 2H, H-3,5). Found, %: C 51.79, H 2.26, N 15.19. $C_{16}H_8F_6N_4$. Calculated, %: C 51.90, H 2.18, N 15.13.

Conclusions

During this study, the reactivity of aromatic nitriles in reactions with hydrazine hydrate was investigated. The sulphur is necessary for the effective synthesis of dihydro-1,2,4,5-tetrazines. As a result of studying the structure of synthesised dihydro-1, 2,4,5-tetrazines using ^{1}H NMR spectroscopy and quantum chemical modelling, we established 1,4-dihydro- and 1,2-dihydrotetrazines are similar in terms of total energy values and approximately equal in quantity in the mixture at equilibrium. Based on the obtained dihydro-1,2,4,5-tetrazines, 1,2,4,5-tetrazine structures were synthesised. All synthesised compounds are prospective to bind receptors and enzymes effectively.

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