Addition of Hydrazine to 4,7-Dihydro[1,2,4]triazolo[1,5-*a*]pyrimidines: Hydrazine Derivatives of 4,5,6,7-Tetrahydro[1,2,4]triazolo[1,5-*a*]pyrimidine

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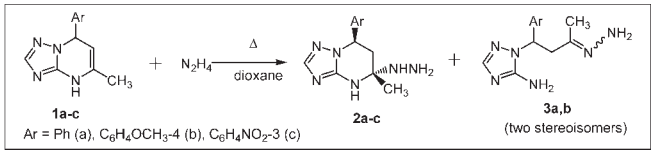

The 7-aryl-4,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidines **1a-c** can undergo addition of hydrazine to the enamine double bond leading to hydrazine derivatives of tetrahydrotriazolopyrimidines **2a-c**; the process is usually accompanied by partial opening of pyrimidine ring leading to **3a,b**.

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INTRODUCTION

1,4-Dihydroazines are compounds which are very important in biological processes. According to the available data about the structure–activity relationship for 1,4-dihydropyridines [1], the phenyl substituent at position 4 of dihydropyrimidine ring is the most suitable for showing physiological activity. However, the stereochemistry of addition processes for 4-aryl-1,4-dihydroazines was not widely investigated, in spite of their simplicity and their similarity to chemical processes in nature [2]. It is also known that dihydroazines fused with azole ring possess a relatively stable dihydro structure (in comparison with nonfused 1,4-dihydroazines, such as 1,4-dihydropyridine and 1,6-dihydropyrimidine). This makes them convenient models for studying many theoretical problems of organic chemistry, e.g. tautomerization, stereochemistry, and chemical reactivity [3]. In addition, there are many compounds with various types of physiological activity exactly among dihydroazolopyrimidines [4].

Only several adducts of dihydroazolopyrimidines (namely hydrates) are described; they were formed either by attempt of preparation of corresponding dihydroazolopyrimidine [5], or directly from previously prepared dihydroazolopyrimidine in attempts of its salt formation with HCl (as side product without isolation) [6].

The aim of this work was to investigate the ability of the enamine fragment of the 7-aryl-5-methyl-4,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidine to react with nucleophile and to study the stereochemistry of nucleophilic addition to dihydroazine ring which should be influenced by aryl ring. The investigated dihydroazolopyrimidine contains supposedly only one reaction center for nucleophile attack, namely the C-5 carbon. The most appropriate nucleophilic reagent for this case, in our opinion, could be hydrazine. The earlier described reactions of analogous acetyl derivatives with hydrazine or hydroxylamine [2] (Scheme 1) were accompanied by heterocyclizations leading to only one stereoisomer (a pair of enantiomers) in both cases; the stereochemistry of heterocyclization products was consistent with nucleophilic attack of the enamine double bond from the sterically less hindered side of the dihydroazolopyrimidine system.

RESULTS AND DISCUSSION

We studied the reaction of dihydroazolopyrimidines **1a-c** with hydrazine by heating in dioxane. The products obtained from **1a,b** were showed in the NMR ^{1}H spectrum in the presence of two groups of signals (compounds **2a,b** and **3a,b**, respectively). In case of 3-nitrophenyl derivative (**1c**), the presence of only one compound was observed (**2c**). Pure compound **3b** was isolated by fractional crystallisation of the obtained mixture **2b** and **3b**; the attempts to isolate either **2a** or **3a** in analogous way were fully unsuccessful.

The elemental analysis for pure **3b** and **2c** and for obtained mixtures showed that compounds **2** and **3** are isomers, and their composition corresponded to addition of one molecule of hydrazine to azolopyrimidine **1**.

The ^{1}H NMR spectra of **2a–c**, **3a,b** in DMSO-d_6 (Table 1) were similar and showed signals of ABX systems

Table 1

The ^{1}H NMR data for **2a-c, 3a,b** (δ/ ppm).

Compound	Substituent	NH	ArH	Aliphatic protons				Coupling constants / Hz		
				H_X (7-H)	H_B (2-H)	H_A (2-H)	CH_3	$^3J_{BX}$	$^3J_{AX}$	$^2J_{AB}$
2a (in mixture with **3a**)	Ph	–	7.14–7.57	5.25	2.43	1.85	1.30	4.6	11.3	15.0
2b (in mixture with **3b**)	4-$CH_3OC_6H_4$	–	6.80–7.35	5.14	2.36	1.83	1.28	4.9	11.6	13.8
2c	3- $O_2NC_6H_4$	7.37 (1H, s)	8.16 (1H, m), 8.09 (1H, s), 7.60–7.72 (2H, m), 7.42 (1H, m)	5.40	2.49	1.87	1.30	5.0	11.6	11.8
3a (in mixture with **2a**)	Ph	6.10, 5.53	7.14–7.57	5.55	3.11	2.84	1.50	8.8	5.8	15.0
3b	4-$CH_3OC_6H_4$	6.10, 5.51	7.29–7.31 (2H, m), 7.29 (1H, s), 6.81–6.85 (2H, m)	5.51	3.03	2.79	1.55	8.6	6.1	14.7

(the signals of **3** were shifted downfield in comparison with **2**), singlets of CH_3 groups, and multiplets of aromatic rings. Compound **3b** also showed broad signals of two NH_2 groups, but in the spectrum of **2c** only one signal of NH protons was observed in the aromatic region.

The ^{13}C NMR spectra of **2c** and **3b** were allowed to make the structure assignment. Both compounds showed signals of aliphatic CH and CH_2 carbons, but compound **2c** showed signal of quaternary carbon in the aliphatic region, at 69.2 ppm, which was consistent with the proposed structure of cyclic adduct. In contrast, the spectrum of **3b** contained an additional signal downfields, at ~159.0 ppm, which was assigned to imine carbon. Thus, compound **3b** has the opened, noncyclic structure, as shown in Scheme 2. Two series of signals were observed in the spectrum of **3b**. The minor signals had low intensity and probably represented the stereoisomers of **3b** which had different configuration of the C=N–NH_2 fragment. The assignment of signals in ^{13}C NMR spectrum of **3b** was based on HSQC experiment.

The reaction can be described by Scheme 2:

Two stereoisomers are possible for compounds **2**, but in their NMR spectra the signals of only one stereoisomer were observed. The stereochemistry of **2** was investigated by NOE measurements. The irradiation of CH_3 showed enhancement for *ortho* protons of aromatic ring which proved proximity of the protons and showed that methyl group and aryl substituent are both oriented in the same direction from the plane of the azolopyrimidine system. Thus, compounds **2** have the stereochemistry as shown in Scheme 2.

The ^3J values between H_X and H_A in **2a–c** were 11.3–11.6 Hz (Table 1) indicating that H_X and H_A are both axial. Such contradiction between coupling data and NOE results could be explained by equilibrium between conformers of **2a–c** (Scheme 3).

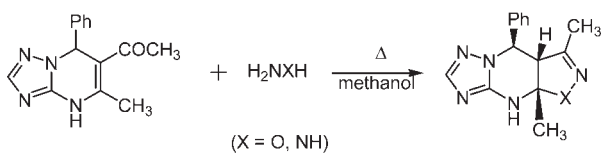
Thus, 7-aryl derivatives of 4,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidines can add nucleophiles directly, and their nucleophilic attack occurs from the side opposite to the orientation of aryl substituent. Compounds **2a–c**, **3a, b** were quite unstable in DMSO-d_6 solutions undergoing partial elimination of hydrazine (for **2**), partially full decomposition in about 0.5–1.0 h at room temperature.

EXPERIMENTAL

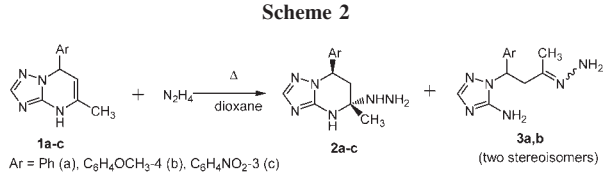
The melting points, determined on a Kofler apparatus, are uncorrected. The ^{1}H and ^{13}C NMR spectra were obtained on a Varian Mercury VX-200 or Bruker DMX 600 in DMSO-d_6 with TMS as a internal standard. The EI mass spectra were measured on a Varian 1200L at 70 eV.

4,7-Dihydro-5-methyl-7-aryl[1,2,4]triazolo[1,5-*a*]pyrimidines (1b,c). General procedure. Compounds 1b,c were prepared by the procedure described in ref. 7 for 1a. A mixture of commercially available 3-amino-1,2,4-triazole (0.84 g, 10 mmol) and the corresponding substituted benzylideneacetone (10.0 mmol)

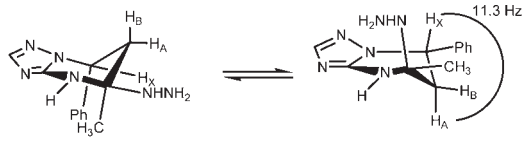
Scheme 1



Scheme 2



Scheme 3



2a

in DMF (1 mL) was refluxed for 30 min. The reaction mixture was cooled to 20°C, mixed with benzene (20 mL) and the precipitate formed was collected by filtration and crystallized from DMF-methanol mixture.

4,7-Dihydro-5-methyl-7-(4-methoxyphenyl)[1,2,4]triazolo[1,5-*a*]pyrimidine (1b). 4,7-Dihydro-5-methyl-7-(4-methoxyphenyl)[1,2,4]triazolo[1,5-*a*]pyrimidine (1b) was isolated with yield 58% and melted at 215–216°C (from mixture of DMF and methanol). The ^{1}H NMR signals were found in DMSO-d_6 at 1.85 s, 3H (4-CH_3), 3.70 s, 3H (OCH_3), 4.50 d, 1H (6-H), 5.09 d, 1H, ^3J = 2.0 (7-H), 6.86 m, 2H (*m*-ArH), 7.11 m, 2H (*o*-ArH), 7.51 s, 1H (2-H), 9.52 br.s, 1H (NH). The ^{13}C NMR signals were measured in DMSO-d_6 at δ, ppm: 18.9 (5-CH_3), 55.8 (OCH_3), 59.6 (C-7), 96.1 (C-6), 114.5 (*m*-C_{Ar}), 128.8 (o-C_{Ar}), 132.4 (*i*- C_{Ar}), 135.3 (C-5), 149.6 (C-3*a*), 149.8 (C-2), 159.5 (*p*-C_{Ar}). The ei ms spectrum showed peaks at *m*/*z* (%)242 (87) [M^+], 227 (57) [M^+-15], 214 (34) [M^+-28], 200 (40) [M^+-42], 135 (100) [M^+-107]. Anal. Calcd. for $C_{13}H_{14}N_4O$ (242.3): 64.45% C, 5.82% H, 23.13% N. Found: 64.39% C, 5.71% H, 23.05% N.

4,7-Dihydro-5-methyl-7-(3-nitrophenyl)[1,2,4]triazolo[1,5-*a*]pyrimidine (1c). Yield 52%; m.p. 249–250°C (ethanol). ^{1}H NMR (DMSO-d_6): 1.88 s, 3H (CH_3), 4.61 m, 1H (6-H), 6.23 m, 1H (7-H), 7.60 s, 1H (2-H), 7.62–7.67 m, 2H (5,6-ArH), 8.03 m, 1H (2-ArH), 8.12–8.18 m, 1H (4-ArH), 9.73 br.s, 1H (NH). ^{13}C NMR (DMSO-d_6): 19.0 (5-CH_3), 59.3 (C-7), 94.9 (C-6), 121.9 (2-C_{Ar}), 123.5 (4-C_{Ar}), 131.0 (5-C_{Ar}), 133.5 (6-C_{Ar}), 134.1 (C-5), 145.2 (1-C_{Ar}), 148.6 (3-C_{Ar}), 149.9 (C-3*a*), 150.4 (C-2). MS [EI, *m*/*z* (rel. %)]: 257 (78) [M^+], 242 (25) [M^+-15], 210 (14) [M^+-47], 135 (100) [M^+-122], 128 (13) [M^+-129]. Anal. Calcd. for $C_{12}H_{11}N_5O_2$ (257.3): 56.03% C, 4.31% H, 27.22% N. Found: 55.92% C, 4.24% H, 27.18% N.

5-Methyl-7-phenyl-4,5,6,7-tetrahydro[1,2,4]triazolo[1,5-*a*]pyrimidin-5-yl)hydrazine (2a) and 2-(3-hydrazono-1-phenylbutyl)[1,2,4]triazol-3-amine (3a). A solution of 1a [7] (1.40 g, 6.6 mmol) and 85% hydrazine hydrate (1.66 g, 30 mmol) in dioxane (7 mL) was heated for 60 min and the solvent was evaporated under reduced pressure. The residue was triturated with diethyl ether (10 mL) and allowed to stand for 2 days. The formed precipitate (1.51 g) was filtered off. It contained, according to the ^{1}H NMR data (Table 1) about 60% of 2a and 40% of 3a. Anal. Calcd. for $C_{12}H_{16}N_6$ (244.3): 59.00% C, 6.60% H, 34.40% N. Found: 58.87% C, 6.54% H, 34.35% N.

Compounds **2b,c** and **3b** were prepared in analogous way from **1b** and **1c**, respectively. In case of **1c**, the precipitate formed contained only pure **2c**.

A mixture of **2b** and **3b** was isolated in 96% yield and contained, according to the ^{1}H NMR data, 65% of **2b** and 35% of **3b**.

Pure compound **3b** was isolated by careful crystallization of the obtained mixture from dioxane-diethyl ether; m.p. 175–177°C. ^{13}C NMR (DMSO-d_6), for major stereoisomer: 14.5 (CH_3), 44.1 (CH_2), 55.6 (OCH_3), 56.4 (CH), 114.1, 129.0 (*m*- and *o*-C_{Ar}), 133.2 (*i*-C_{Ar}), 144.2 (C-5 of triazole), 148.6 (CH of triazole), 155.1 (—C=N—), 159.0 (*p*-C_{Ar}); for minor stereoisomer: 22.8 (CH_3), 34.8 (CH_2), 54.8 (OCH_3), 55.6 (CH), 114.2, 128.6 (*m*- and *o*-C_{Ar}), 133.1 (*i*-C_{Ar}), 145.3 (C-5 of triazole), 148.9 (CH of triazole), 155.4 (—C=N—), 159.2 (*p*-C_{Ar}). Anal. Calcd. for $C_{13}H_{18}N_6O$ (274.3): 56.92% C, 6.61% H, 30.64% N. Found: 56.83% C, 6.55% H, 30.71% N.

Compound **2c**, m.p. 153–154°C, was isolated in yield 73%. ^{13}C NMR (DMSO-d_6) δ, ppm: 24.2 (CH_3), 41.2 (C-6), 55.7 (C-7), 69.2 (C-5), 122.6 (*p*-C_{Ar}), 123.1 (*o*-C_{Ar}), 130.5 (*m*′-C_{Ar}), 134.6 (o′-C_{Ar}), 143.3 (*i*-C_{Ar}), 148.3 (*m*-C_{Ar}), 149.3 (C-2), 154.7 (C-3*a*). Anal. Calcd. for $C_{12}H_{15}N_7O_2$ (289.3): 49.82% C, 5.23% H, 33.89% N. Found: 49.69% C, 5.14% H, 33.97% N.

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