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Aromatic Nucleophilic Substitution in 1,2,4-Triazine 4-Oxides with Grignard Reagents

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Addition of the Grignard reagents to 1,2,4-triazine 4-oxides followed by aromatization of the intermediate σ^H-adducts by dehydrogenation or dehydration was used for synthesis of 5-alkyl- or 5-aryl-substituted 1,2,4-triazines and their 4-oxides.

Key words: 1,2,4-triazines, Grignard reagents, σ-adducts, aromatization, dehydrogenation, regioselectivity, heterocycles

An interest in 1,2,4-triazines is connected not only with their biological activity [1], but with application of 1,2,4-triazines in coordination and metallosupramolecular chemistry [2]. Easy functionalization of the 1,2,4-triazine ring followed by inverse electron demand Diels-Alder reaction is a versatile route to functionalized pyridines, including bi- and terpyridines – widely used as ligands [3]. 2,6-Bis(dialkyl-1,2,4-triazinyl)-pyridines are the most effective agents for extraction and separation of lanthanides and actinides in the management of nuclear wastes [4]. It is noteworthy that nature of the substituents in position 5 and 6 of the 1,2,4-triazine ring have a considerable influence on the separation factor [5]. In this paper we describe a new synthetic approach to alkyl and/or aryl substituted 1,2,4-triazines involving aromatic nucleophilic substitution of hydrogen in 1,2,4-triazine 4-oxides with Grignard reagents [6]. At the same time presence of the N-oxide group allows not only typical for such reactions oxidative but also deoxygenative aromatization of the intermediate σ^H-adducts extending variability of the suggested approach [7].

RESULTS AND DISCUSSION

Literature data about reactions of azine *N*-oxides with Grignard reagents are scarce. Usually not azine *N*-oxides themselves but products of their *O*-acylation – *N*-acyloxyazinium salts are used in such reactions at low temperature (–70°C) yielding 2-substituted pyridines [8] and quinolines [9].

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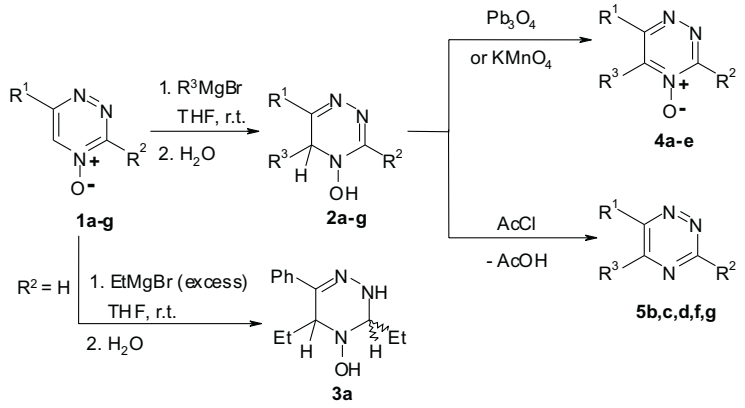
Contrary that 5-unsubstituted 1,2,4-triazine 4-oxides **1** were found to react with ethyl-, propyl- or phenylmagnesium bromide in dry THF at room temperature without any additional activation of the substrate to give after treatment with water 5-ethyl-, 5-propyl- or 5-phenyl-4-hydroxy-4,5-dihydro-1,2,4-triazines **2** (Scheme 1). Structure of the dihydrotriazines **2** were clearly established by ^{1}H NMR spectroscopy. Characteristic signal in this case except signals of substituents in the 1,2,4-triazine ring and protons of the nucleophile residue is the signal at 5.0–5.4 ppm corresponding to the proton attached to sp^3-carbon in the position 5 of the heterocycle. Mass-spectrometry and elemental analysis also confirmed the proposed composition.

When both positions 3 and 5 in the 1,2,4-triazine 4-oxide **1** were unsubstituted, the nucleophile attacked also position 5. Regioselectivity of the reaction was proved by comparison of ^{1}H NMR spectra of the products **2** and 3-ethyl-4-hydroxy-3,4-dihydrotriazines obtained from isonitrosoacetophenone hydrazone and acetaldehyde by the alternative method [10]. It confirmed the previous suggestions about kinetic control of the nucleophilic attack at the position 5 of the 1,2,4-triazine 4-oxides **1** contrary to the position 3, which was proved to be under thermodynamic control [11]. With an excess of Grignard reagent occurred addition of the second molecule of nucleophile in the position 3 of the 1,2,4-triazine ring. Thus, reaction of 6-phenyl-1,2,4-triazine 4-oxide **1a** with at least double excess of ethylmagnesium bromide resulted in the diadduct **3a**.

Scheme 1



Aromatization of the σ-adducts **2** can be performed out by two alternative paths: dehydrogenation and dehydration. For dehydrogenation of the intermediates **2** two oxidizing systems were found to be appropriate: Pb_3O_4 in acetic acid or $KMnO_4$ in acetone. The reactions proceeded very easily to give corresponding 5-substituted 1,2,4-triazine 4-oxides **4** in good yields (Scheme 1). To obtain 5-substituted 1,2,4-triazines **5** the intermediate σ-adducts **2** were treated with acetyl chloride in chloroform. In this case aromatization of the adducts **2** was achieved by elimination of acetic

acid molecule after *O*-acylation of **2**. ^{1}H NMR spectra of the corresponding triazines **4** and triazine-4-oxides **5** are very closed and in both cases result of the reaction is disappearing of the signal at 5.0–5.4 ppm. Presence or absence of the *N*-oxide group was defined only by mass-spectrometric and elemental analysis. However, indirect evidence of that is color of the product. Thus, triazines **5** are yellow, while triazine 4-oxides are colorless crystals.

Table 1. Compounds obtained by reactions depicted in Scheme 1.

1–5	R^1	R^2	R^3	Yields, %		
				2	**4**	**5**
a	Ph	H	Et	35	25	–
b	Ph	Ph	Et	83	40	35
c	Ph	2-Furyl	Pr	73	68	75
d	Tol	2-4-$Cl_2C_6H_3$	Et	85	69	40
e	4-$MeOC_6H_4$	H	Et	50	52	–
f	Ph	2-Pyridyl	Ph	Not isolated		60
g	4-ClC_6H_4	4-ClC_6H_4	Ph	Not isolated		40

In conclusion, it was shown that suggested method for synthesis of wide series of substituted 1,2,4-triazines is convenient from two points of view: the first, starting triazine 4-oxides are rather available; the second, Grignard reagents can be various. Moreover, possible management of the reaction pathways allows to obtain both triazines and their 4-oxides.

EXPERIMENTAL

General. The melting points are uncorrected. Spectra ^{1}H NMR were measured on a Bruker WM-250 spectrometer (250.1 MHz), the solvent was DMSO-d_6 (if not specially marked), δ, ppm. Mass-spectra were measured on a Varian MAT-311 and AMD 604 spectrometers (electron impact 70 eV).

Reaction of 1,2,4-triazine-4-oxides with ethylmagnesium bromide. Solution of ethylmagnesium bromide in THF, prepared by dissolving magnesium (2 mmol) in ethyl bromide (2.5 mmol) and in THF (10 ml), was added with stirring to the 6-aryltriazine-4-oxide **1** (1 mmol). The mixture was evaporated, the residue was treated with water (~20 ml), this water mixture was heated under reflux 5–10 min, cooled down to room temperature, and crystals were filtered off and recrystallized from 2-propanol. The following compounds were obtained:

5-Ethyl-4-hydroxy-6-phenyl-4,5-dihydro-1,2,4-triazine (2a). M.p. 195°C, ^{1}H NMR, δ: 0.97 (3H, dd, J_1 = 6.1 Hz, J_2 = 6.4 Hz, CH_3CH_2), 1.65 and 2.05 (both 1H, m, CH_3CH_2), 5.23 (1H, dd, J_1 = 4.8 Hz, J_2 = 2.2 Hz, H-5), 7.43 (3H, m), 7.79 (2H, m), 8.35 (1H, s, H-3). Anal. Calc. for $C_{11}H_{13}N_3O$ (203.25): C, 65.01; H, 6.45; N, 20.67. Found: C, 64.89; H, 6.49; N, 20.54.

5-Ethyl-4-hydroxy-3,6-diphenyl-4,5-dihydro-1,2,4-triazine (2b). M.p. 230°C, ^{1}H NMR (DMSO-d_6), δ: 0.97 (3H, dd, J_1 = 2.5 Hz, J_2 = 6.3 Hz, CH_3CH_2), 1.72 and 2.10 (both 1H, m, CH_3CH_2), 5.09 (1H, dd, J_1 = 4.9 Hz, J_2 = 5.0 Hz, H-5), 7.50 (6H, m), 8.00 (4H, m), 11.09 (1H, br.s., OH). Mass spectrum (EI)(M^+) 279. Anal. Calc. for $C_{17}H_{17}N_3O$ (279.35): C, 73.36; H, 5.79; N, 15.10. Found: C, 73.52; H, 5.82; N, 14.81.

5-Propyl-4-hydroxy-3-(2-furyl)-6-phenyl-4,5-dihydro-1,2,4-triazine (2c). M.p. 190°C, ^{1}H NMR (DMSO-d_6), δ: 0.89 (3H, dd, J_1 = 7.3 Hz, J_2 = 7.3 Hz, $CH_3CH_2CH_2$), 1.40 (2H, m, $CH_3CH_2CH_2$), 1.69, 1.88 (both 1H, m, $CH_3CH_2CH_2$), 5.08 (1H, dd, J_1 = 6.0 Hz, J_2 = 5.6 Hz, H-5), 6.66 (1H, m), 7.41 (3H, m), 7.78 (4H, m), 11.10 (1H, br.s, OH). Anal. Calc. for $C_{16}H_{17}N_3O_2$ (283.33): C, 67.83; H, 6.05; N, 11.29. Found: C, 67.73; H, 6.14; N, 11.01.

5-Ethyl-4-hydroxy-3-(2,4-dichlorphenyl)-6-tolyl-4,5-dihydro-1,2,4-triazine (2d). M.p. > 250°C, ^{1}H NMR (DMSO-d_6), δ: 0.99 (3H, dd, J_1 = 7.0 Hz, J_2 = 7.0 Hz, CH_3CH_2), 1.82, 2.18 (both 1H, m, CH_3CH_2), 2.37 (3H, s, CH_3), 5.31 (1H, dd, J_1 = 5.3 Hz, J_2 = 5.3 Hz, H-5), 7.23 (2H, m), 7.53 (2H, m), 7.66 (3H, m). Anal. Calc. for $C_{18}H_{17}C_{12}N_3O$ (362.26): C, 59.68; H, 4.73; N, 11.60. Found: C, 59.63; H, 4.70; N, 11.50.

5-Ethyl-4-hydroxy-6-(4-methoxyphenyl)-4,5-dihydro-1,2,4-triazine (2e). M.p. 215°C, ^{1}H NMR (DMSO-d_6), δ: 0.88 (3H, dd, J_1 = 7.7 Hz, J_2 = 7.9 Hz, CH_3CH_2), 1.65 and 2.05 (both 1H, m, CH_3CH_2), 3.80 (3H, s, CH_3) 4.98 (1H, dd, J_1 = 6.6 Hz, J_2 = 6.6 Hz, H-5), 6.93 (2H, d, J = 8.7 Hz), 7.70 (2H, d, J = 8.7 Hz), 8.12 (1H, s, H-3). Anal. Calc. for $C_{12}H_{15}N_3O_2$ (233.27): C, 61.79; H, 6.48; N, 18.01. Found: C, 61.73; H, 6.48; N, 18.20.

3,5-Diethyl-4-hydroxy-6-phenyl-2,3,4,5-tetrahydro-1,2,4-triazine (3a). Yield 7%. M.p. 155°C, ^{1}H NMR (DMSO-d_6), δ: 0.90–1.15 (6H, m, $2CH_3CH_2$), 1.20–1.80 (4H, m, $2CH_3CH_2$), 3.70–3.76 (2H, m, H-5, H-3), 7.19–7.37 (4H, m), 7.54 (2H, m), 7.83 (1H, s, OH). Mass spectrum (EI)(M^+): 233. Anal. Calc. for $C_{13}H_{19}N_3O$ (233.32): C, 66.92; H, 8.21; N, 18.01. Found: C, 66.89; H, 8.39; N, 18.24.

Oxidation of 4-hydroxy-4,5-dihydro-1,2,4-triazines. Procedure A: The 4-hydroxy-4,5-dihydro-1,2,4-triazine (1 mmol) was suspended in acetone (20 ml) . Solution of $KMnO_4$ (0.66 mmol) was added with stirring and cooling at 5°C. After 30 min mixture was filtered. After removing of the solvent, residue was treated with boiling hexane that then was evaporated off. Obtained crystals were recrystallized from hexane.

Procedure B. The 4-hydroxy-4,5-dihydro-1,2,4-triazine (1 mmol) was dissolved in acetic acid (5 ml), the solution of $Pb(CH_3COO)_2$ prepared by dissolving of Pb_3O_4 (1 mmol) in acetic acid (5 ml) was added with cooling at 5°C. After 15 min. water (10 ml) was added to the solution, this mixture was extracted with chloroform. The chloroform fraction was washed with carbonate sodium solution, dried with sodium sulphate. After removing of the solvent, crystals were recrystallized from hexane. The following compounds were obtained:

5-Ethyl-6-phenyl-1,2,4-triazine-4-oxide (4a). M.p. 70°C, ^{1}H NMR (DMSO-d_6), δ: 1.21 (3H, t, J = 7.4 Hz, CH_3CH_2), 2.79 (2H, q, J = 7.4 Hz, CH_3CH_2), 7.56 (5H, s), 9.49 (1H, s, H-3). Anal. Calc. for $C_{11}H_{11}N_3O$ (201.23): C, 65.66; H, 5.51; N, 20.88. Found: C, 65.56; H, 5.48; N, 20.89.

5-Ethyl-3,6-diphenyl-1,2,4-triazine-4-oxide (4b). M.p. 97°C, ^{1}H NMR (DMSO-d_6), δ: 1.25 (3H, t, J = 7.5 Hz, CH_3CH_2), 2.89 (2H, q, J = 7.5 Hz, CH_3CH_2), 7.58 (8H, m), 8.27 (2H, m). Mass spectrum (EI)(M^+) 277. Anal. Calc. for $C_{17}H_{15}N_3O$ (277.33): C, 73.63; H, 5.45; N, 15.15. Found: C, 73.65; H, 5.46; N, 15.09.

5-Ethyl-3-furyl-6-phenyl-1,2,4-triazine-4-oxide (4c). M.p. 130°C, ^{1}H NMR (DMSO-d_6), δ: 1.24 (3H, t, J = 7.0 Hz, CH_3CH_2), 2.87 (2H, q, J = 7.0 Hz, CH_3CH_2), 6.77 (1H, m), 7.57 (5H, m), 8.05 (2H, m). Anal. Calc. for $C_{15}H_{13}N_3O_2$ (267.29): C, 67.41; H, 4.90; N, 15.72. Found: C, 67.54; H, 5.00; N, 15.81.

5-Ethyl-3-(2,4-dichlorphenyl)-6-tolyl-1,2,4-triazine-4-oxide (4d). M.p. 167°C, ^{1}H NMR (DMSO-d_6), δ: 1.22 (3H, t, J = 7.4 Hz, CH_3CH_2), 2.47 (3H, s, CH_3), 2.85 (2H, q, J = 7.4 Hz, CH_3CH_2), 7.38 (2H, m), 7.55 (3H, m), 7.69 (2H, m). Anal. Calc. for $C_{18}H_{15}Cl_2N_3O$ (360.25): C, 60.01; H, 4.20; N, 11.66. Found: C, 60.11; H, 4.13; N, 11.50.

5-Ethyl-6-(4-methoxyphenyl)-1,2,4-triazine-4-oxide (4e). M.p. 85°C, ^{1}H NMR (DMSO-d_6), δ: 1.18 (3H, t, J = 7.3 Hz, CH_3CH_2), 2.77 (2H, q, J = 7.3 Hz, CH_3CH_2), 3.87 (3H, s, OCH_3), 7.06 (2H, d, J = 8.5 Hz), 7.52 (2H, d, J = 8.5 Hz), 9.45 (1H, s, H-3). Anal. Calc. for $C_{12}H_{13}N_3O_2$ (231.26): C, 62.33; H, 5.67; N, 18.17. Found: C, 62.23; H, 5.65; N, 18.17.

Dehydration of 4-hydroxy-4,5-dihydro-1,2,4-triazines. The 4-hydroxy-4,5-dihydro-1,2,4-triazine (1 mmol) was suspended in chloroform with cooling at 5°C, then acetyl chloride (1 mmol) was added. The obtained solution was washed with water concentrate solution of potassium carbonate, dried over sodium sulphate. After removing of the solvent, crystals were recrystallized from hexane. The following compounds were obtained:

5-Ethyl-3,6-diphenyl-1,2,4-triazine (5b). M.p. 65°C, ^{1}H NMR (DMSO-d_6), δ: 1.33 (3H, t, J = 7.4 Hz, C<u>H</u>$_3$CH$_2$), 2.95 (2H, q, J = 7.4 Hz, CH$_3$C<u>H</u>$_2$), 7.80 (8H, m), 8.54 (2H, m). Mass spectrum (EI)(M^+) 261. Anal. Calc. for $C_{17}H_{15}N_3$ (261.33): C, 78.13; H, 5.79; N, 16.08. Found: C, 78.41; H, 5.71; N, 15.94.

5-Ethyl-3-furyl-6-phenyl-1,2,4-triazine (5c). M.p. 87°C, ^{1}H NMR (DMSO-d_6), δ: 1.27 (3H, t, J = 7.0 Hz, C<u>H</u>$_3$CH$_2$), 2.87 (2H, q, J = 7.0 Hz, CH$_3$C<u>H</u>$_2$), 6.72 (1H, m), 7.55 (6H, m), 7.93 (1H, m). Anal. Calc. for $C_{15}H_{13}N_3O$ (267.29): C, 71.70; H, 5.21; N, 16.72. Found: C, 71.38; H, 5.18; N, 16.63.

5-Ethyl-3-(2,4-dichlorphenyl)-6-tolyl-1,2,4-triazine (5d). M.p. 121°C, ^{1}H NMR (DMSO-d_6), δ: 1.26 (3H, t, J = 7.3 Hz, C<u>H</u>$_3$CH$_2$), 2.46 (3H, s, C<u>H</u>$_3$), 2.96 (2H, q, J = 7.3 Hz, CH$_3$C<u>H</u>$_2$), 7.39 (2H, m), 7.60 (4H, m), 7.93 (1H, m). Anal. Calc. for $C_{18}H_{15}Cl_2N_3$ (344.25): C, 62.80; H, 4.39; N, 12.21. Found: C, 62.68; H, 4.56; N, 12.01.

5,6-Diphenyl-3-pyridyl-1,2,4-triazine (5f). M.p. 193°C, ^{1}H NMR (DMSO-d_6), δ: 7.41–7.67 (11H, m), 7.55 (5H, m), 8.09 (1H, m), 8.57 (1H, m), 8.88 (1H, m). Mass spectrum (EI)(M^+): 310. Anal. Calc. for $C_{20}H_{14}N_4$ (310.36): C, 77.40; H, 4.55; N, 18.05. Found: C, 77.42; H, 4.60; N, 18.00.

3,6-Di(4-chlorophenyl)-5-phenyl-1,2,4-triazine (5g). M.p. 179°C, ^{1}H NMR (DMSO-d_6), δ: 7.38–7.73 (11H, m), 8.56 (2H, m). Anal. Calc. for $C_{21}H_{13}N_3Cl_2$ (378.26): C, 66.68; H, 3.46; N, 11.11. Found: C, 66.61; H, 3.14; N, 11.28.

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