HETEROCYCLES, Vol. 55, No. 1, 2001, pp. 127 - 133, Received, 22nd September, 2000

^{1}H- AND ^{13}C-NMR INVESTIGATIONS ON σ–ADDUCT FORMATION OF 1,2,4-TRIAZINE 4-OXIDES AND 3-CHLORO-6-PHENYL-1,2,4-TRIAZINE WITH LIQUID AMMONIA AND ALKYLAMINES

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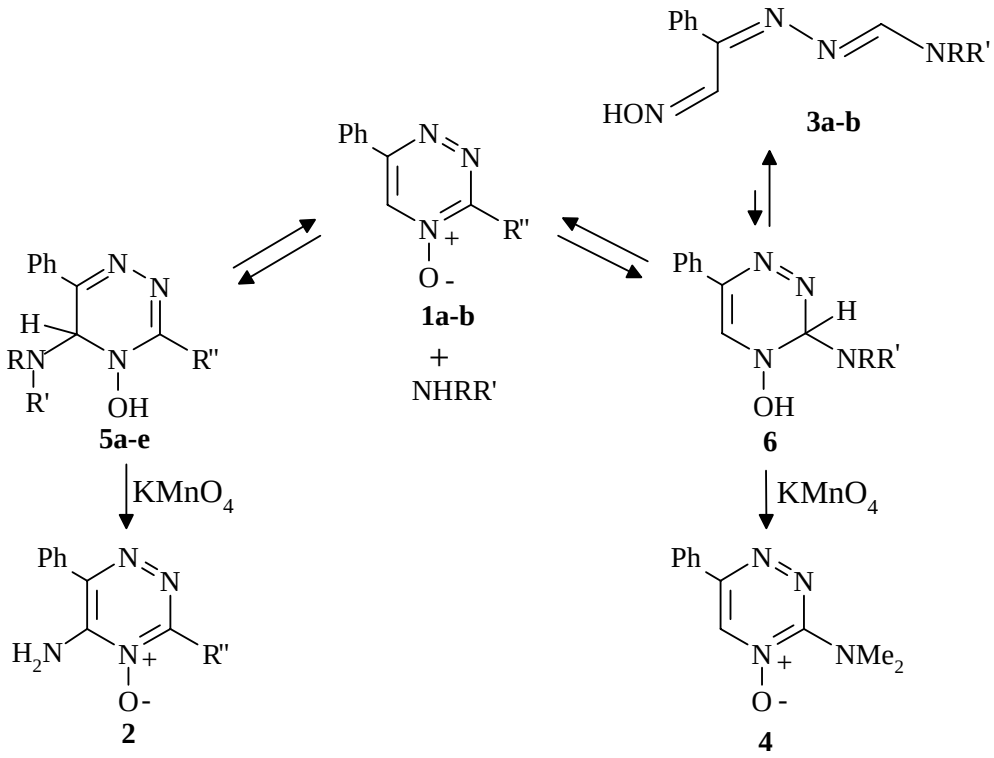
Abstract -^{1}H- and ^{13}C-NMR spectra of the σ-adducts formed between 6-phenyl-1,2,4-triazine 4-oxide (**1a**), 3-ethyl-6-phenyl-1,2,4-triazine 4-oxide (**1b**) and liquid ammonia, methylamine or dimethylamine are described, together with ^{1}H NMR spectra of 3-chloro-6-phenyl-1,2,4-triazine (**7)** in liquid ammonia. The results of the NMR study have shown that the carbon C-5 in **1a-b** and **7** is the preferred site for nucleophilic attack by liquid ammonia and alkylamines at low temperatures (from -75^{o} to -20^{o}C). The σ–adduct (**5e**) formed between **1a** and dimethylamine at -75^{o}C on heating to -20^{o}C irreversibly converts to open-chain product (**3a**), *via* intermediary C-3 σ–adduct (**6**). The amination of **7** into 3-amino-6-phenyl-1,2,4-triazine (**10**) occurs *via* S_N(AE) mechanism involving the isomerisation of the C-5 σ–adduct (**8**) into the C-3 σ–adduct (**9**) as confirmed by a ^{15}N study with labeled liquid ammonia.

Oxidative aminations are currently of great practical use for the direct introduction of the amino residue into nitroarenes and electrophilic heterocycles.[1] It has previously been reported that 6-phenyl-1,2,4-triazine 4-oxide (**1a)**, when reacted with liquid ammonia/ potassium permanganate at -33^{o}C, gives 5-amino-6-phenyl-1,2,4-triazine 4-oxide (**2**) in good yield.[2] The formation of **2** suggests the intermediacy of C-5 σ-adduct (**5a**), although no indication for its existence has been proved by spectroscopy. More recent studies have shown that reaction of **1a** with dimethylamine or methylamine at room temperature

leads to the open-chain products (**3a** and **3b**).[3,4] Compound (**3a**) can irreversibly be converted into 3-dimethylamino-6-phenyl-1,2,4-triazine (**4**) on treatment with potassium permanganate (see Scheme 1).



1a: R"=H; **1b:** R"=Et
3a: R=R'=Me; **3b:** R=H, R'=Me
5a: R=R'=R"=H; **5b:** R=R'=H, R"=Et; **5c:** R=R"=H, R'=Me
5d: R=H, R'=Me, R''=Et; **5e:** R=R'=Me, R"=H

Scheme 1

Both reactions leading to different substitution pattern seem to indicate that the site of nucleophilic attack in **1a** is strongly dependent on temperature. At low temperature (-33°C) the stable C-5 σ-adduct (**5a**) is formed, being the precursor of compound (**2**). At room temperature a short living intermediary C-3 σ-adduct (**6**) is obtained, that undergoes ring-opening and formation of the 1-hydroxy-1,4,5-triazahexa-1,3,5-trienes (**3a** and **3b**). In order to detect the occurrence of the intermediary C-5 σ-adducts we studied ^{1}H– and ^{13}C–NMR spectra of 6-phenyl-1,2,4-triazine 4-oxide (**1a**) and 3-ethyl-6-phenyl-1,2,4-triazine 4-oxide (**1b**) in liquid ammonia, methylamine and in dimethylamine at low temperatures. The change of hybridization from sp^2 to sp^3 of the carbon atom where addition of the amino group takes place can be easily established by these techniques.[5] Measurement of the ^{1}H-NMR spectrum of **1a** in liquid ammonia/ $CDCl_3$ at –50°C showed that both 1,2,4-triazine protons appeared at a much higher field than the resonance signals observed in the solution of compound (**1a)** in $CDCl_3$ (see Table 1). The upfield shift

was found to be the most pronounced for the H-5 proton (Δδ=3.2 ppm) compared to H-3 proton (Δδ=1.8 ppm) indicating that ammonia has been added selectively to C-5, resulting in **5a**. In order to substantiate further that adduct formation takes place at C-5 and not C-3 we have also measured the ^{1}H-NMR spectrum of **1b** in liquid ammonia at –50^{o}C. The spectrum showed the same upfield shift of 3.2 ppm for H-5 proving the presence of σ-adduct (**5b**). Measurements of the ^{1}H-NMR spectra of **1a** and **1b** in methylamine /$CDCl_3$ at –20^o C also support the occurrence of a covalent amination at position 5. Again, Δδ values of about 3 ppm are found for the H-5 protons, clearly indicating the presence of adducts (**5c** and **5d)** (see Table1).

Table 1. ^{1}H NMR spectra of 1,2,4-triazine 4-oxides (**1a-b**)**,** their adducts **(5a-e**) with liquid ammonia, methylamine, dimethylamine and open-chain products (**3a-b**)

Comp.	σ-Adduct	Solvent	t, ^{o}C	^{1}H NMR, δ, ppm; *J*, Hz		
				5-H(s,1H)	3-R	Ph
1a		$CDCl_3$	rt	8.53 (d, 1H, *J*=1.7)	9.28 (d, 1H, *J*=1.7)	7.6 (m, 3H), 8.0 (m, 2H)
1b		$CDCl_3$	rt	8.53	1.49 (t, 3H, *J*=7.4), 3.22 (q, 2H, *J*=7.4)	7.6 (m, 3H), 8.0 (m, 2 H)
1a	**5a**	$NH_3/CDCl_3$	-50	5.35	7.44 (s, 1H)	7.3 (m, 3H), 7.9 (m, 2H)
1b	**5b**	$NH_3/CDCl_3$	-50	5.36	2.71 (m, 2H)[a]	7.5 (m, 3H), 8.0 (m, 2H)
1a	**5c**	$MeNH_2/CDCl_3$	-20	5.42	7.61 (s, 1H)	7.3 (m, 3H), 7.9 (m, 2H)
1b	**5d**	$MeNH_2/CDCl_3$	-20	5.61	[a]	7.3 (m, 3H), 8.0 (m, 2H)
1a	**5e**	Me_2NH/ acetone-d_6	-70	5.40	7.92 (s, 1H)	7.3 (m, 3H), 8.0 (m, 2H)
3a		Me_2NH/ acetone-d_6	-70	8.91	8.10 (s, 1H)	7.2 (m, 3H), 7.8 (m, 2H)
3a[b]		DMSO-d_6	rt	8.76	8.08 (s, 1H)	7.3 (m, 3H), 7.7 (m, 2H)
3b		$MeNH_2/CDCl_3$	-20	9.04	8.13 (s, 1H)	7.2 (m, 3H), 7.7 (m, 2H)
3b[c]		DMSO-d_6	rt	8.82	8.11 (d, 1H, *J*=5)	7.3 (m, 3H), 7.7 (m, 2H)

[a] Signals of protons of the ethyl group are under signals of a solvent

[c] other signals: 3.00 (s, 6H, NMe_2), 11.2 (br s, 1H, OH)

[b] other signals: 2.84 (d, 3H, NMe *J*=5 Hz), 7.2 (br s, 1H), 11.4 (br s, 1H, OH)

Similarly, 6-phenyl-1,2,4-triazine 4-oxide (**1a**) gives σ-adduct (**5e**) with dimethylamine/acetone-d_6 at –75°C (see Table 1). These low temperature conditions are necessary in order to avoid transformation of **5e** into open-chain product (**3a**). Increasing temperature from -75°C to -40°C leads to slow transformation of **5e** into **3a** as observed by appearance and rise of two singlets in ^{1}H-NMR spectrum at δ=8.1 and δ=8.9, attributed to the H-3 and H-5 protons in **3a**, and fall of the corresponding signals of σ-adduct (**5e**). The gradual conversion of **5e** into **3a** at –40°C has been recorded by ^{1}H NMR spectra comparing integral intensity of both kind of signals. It allows to value the ratio of products of the nucleophilic addition of dimethylamine at C-3 and C-5 carbon atoms of 1,2,4-triazine ring (see Table 2 and Figure 1). On further heating of the solution of **1a** in dimethylamine from –40° to -20°C the mixture irreversibly converts to **3a** within a few minutes. Evaporation of the solvent gave a pure **3a** identical with an authentic sample.[3]

Table 2. Conversion of σ-adduct (**5e**) to open-chain product (**3a)** in time at -40° C in Me_2NH/acetone-d_6 (3:1)

Time, min	4	26	44	57	70	90
Conversion %	20	40	50	55	60	65

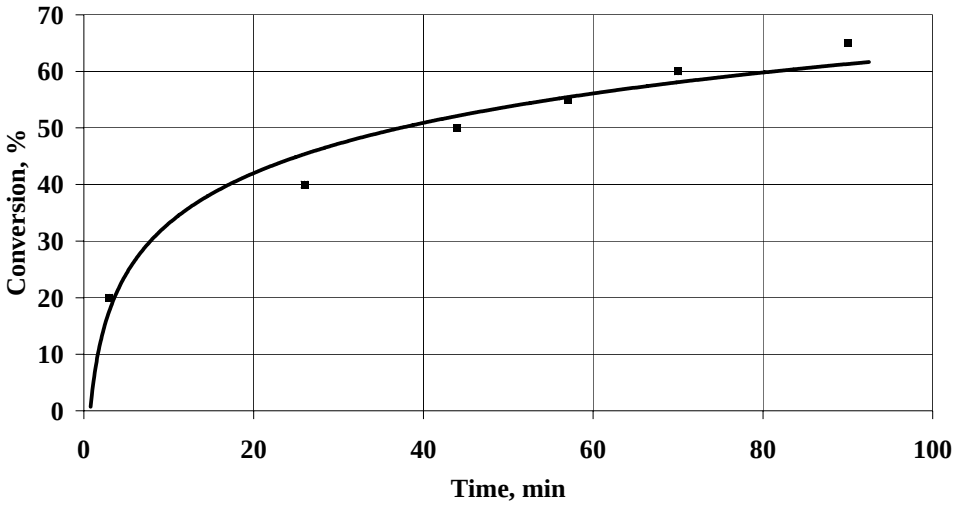


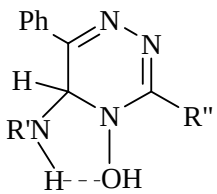
Figure 1. σ-Adduct's (**5e**) conversion (%) to open-chain isomer (**3a**) at -40°C in Me_2NH/acetone-d_6

These structural assignments of σ–adducts of 1,2,4-triazine 4-oxides were confirmed by measuring the ^{13}C-NMR spectra of the compounds (**1a**) and (**1b**) in liquid ammonia and methylamine under the condition as mentioned above. As expected, all carbon atoms are shifted upfield compared with the shieldings of corresponding carbon atoms of the parent compounds in $CDCl_3$. The greatest upfield shift we found for C-5 proving the formation of a covalent σ-adducts (**5a-d**) (see Table 3).

Table 3. ^{13}C NMR spectra of 1,2,4-triazine 4-oxides (**1a-b**) and their adducts (**5a-d**) with liquid ammonia and methylamine

Comp.	σ-Adduct	Solvent	^{13}C NMR, δ, ppm		
			C-5	C-3	other signals
1a		$CDCl_3$	132.0	149.8	127.6, 129.5, 131.8, 132.3, 157.5
1b		$CDCl_3$	132.5	155.9	9.2, 22.7, 126.9, 129.0, 131.0, 131.4, 161.5
1a	**5a**	$NH_3/CDCl_3$	65.2	143.7	126.0, 128.1, 128.7, 140.4, 141.4
1b	**5b**	$NH_3/CDCl_3$	67.0	147.6	10.7, 21.6, 126.1, 128.8, 129.1, 135.4, 140.8
1a	**5c**	$MeNH_2/CDCl_3$	70.5	143.3	126.2, 128.1, 128.7, 138.2, 139.4
1b	**5d**	$MeNH_2/CDCl_3$	71.1	152.7	126.1, 128.2, 128.5, 137.6, 138.9

That on heating from –75° to –20°C adduct (**5e**) irreversibly converts to open-chain product (**3a**), probably *via* adduct (**6**)**,** is apparently due to the fact that σ-adduct (**5e**) is kinetically favored one and the formation of adduct (**6**) is thermodynamically controlled process. Similar conversion of **1a** into open-chain product (**3b)** proceeds with ethanolic methylamine.[3] However, the reaction is much slower than in case of dimethylamine and requires a room temperature for completion. Such behavior has never been observed in the reaction of **1a** with liquid ammonia. Obviously in the C-5 adducts, formed with liquid ammonia or methylamine, a strong hydrogen bond stabilizes the adducts (**5a-d)** retarding or preventing the isomerisation of the latter into **6** (see Figure 2). In adduct (**5e)** stabilization by hydrogen bond formation can not take place.

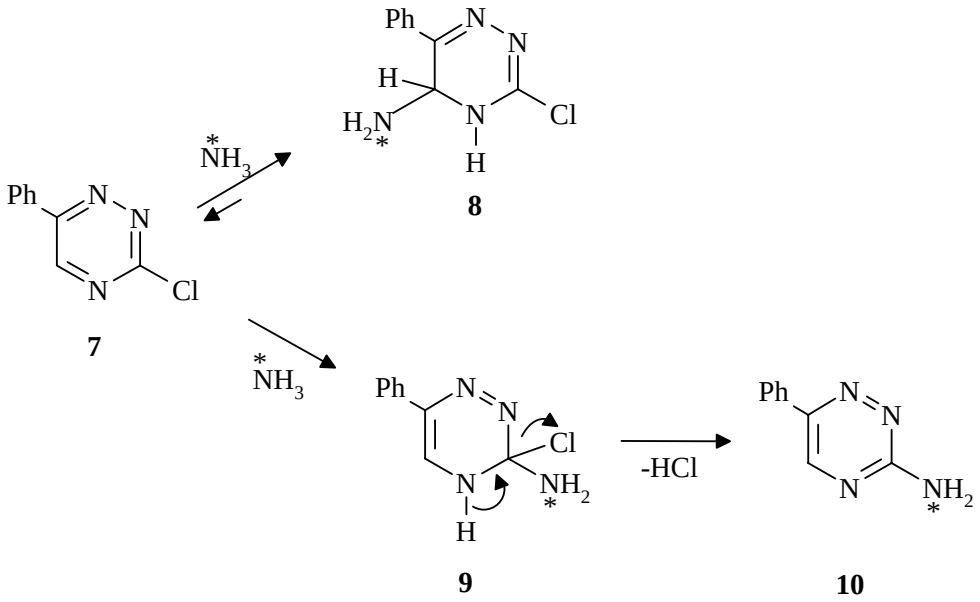


5a: R'=R"=H **5b**: R'=H, R"=Et
5c: R'=Me, R"=H **5d:** R'=Me, R"=Et

Figure 2

In this context it is of interest to mention that amination of 3-chloro-6-phenyl-1,2,4-triazine (**7**) into the

corresponding 3-amino-6-phenyl-1,2,4-triazine (**10**), using liquid ammonia free of amide ion at –33°C, involves the intermediacy of the C-5 σ–adduct (**8**) as unequivocally proved by the ^{1}H NMR spectrum, showing that proton at C-5 is shifted upfield ($\Delta\delta$= 3.4 ppm) as compared with chemical shift of H-5 in **8** in $CDCl_3$.[6]



Scheme 2

When the reaction was carried out with ^{15}N labeled liquid ammonia (containing 11% excess of ^{15}N), the 3-amino compound (**10**) was exclusively labeled in the amino group as confirmed by MS spectrometric determinations.[7] It proves that the substitution of the chlorine atom by the amino group does not occur according to S_N (ANRORC) mechanism, as is in the case with potassium amide,[8] but involves the isomerisation of the C-5 σ–adduct (**8**) into the C-3 σ–adduct (**9**), which aromatizes by loss of the chloride ion. In contrast to the C-5 σ–adducts (**5a-d**), the C-5 σ–adduct (**8**) is not stabilized by hydrogen bonding and can easily undergo isomerisation *via* **7** into **9** (see Scheme 2).

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded with Bruker WM-250 (250.1 MHz), Bruker WM-200 (operating at 200.1 MHz for protons and 50.3 MHz for carbons), Bruker DRX-500 (operating at 500.1 MHz for protons and 125.8 MHz for carbons) with TMS as internal standard. Spectra in $CDCl_3$ and DMSO-d_6 were recorded at ambient tempereture, in the mixture of liquid ammonia/$CDCl_3$ (3:1) at -50 °C, in liquid methylamine/$CDCl_3$ (3:1) at -20 °C, in liquid dimethylamine/acetone-d_6 (3:1) at -70, -40 and -20 °C. Field-frequency lock signal was obtained from $CDCl_3$ in case of liquid ammonia and methylamine and

acetone-d_6 in case of dimethylamine. The ^{15}N measurements were taken with an AE MS 902 spectrometer. The accuracy of these measurements is ±0.2.

3-Amino-6-phenyl-1,2,4-triazine (10). 3-Chloro-6-phenyl-1,2,4-triazine (**7**) (96 mg, 0.5 mmol) was added to a dry liquid ammonia (10 mL) with exclusion of moisture. After the mixture was stirred for 15 h at -33 ^{o}C the ammonia was evaporated off. Crude product was washed with water, purified by column chromatography (silica gel, chloroform - acetone 3:1) and recrystallised from ethanol-water. Yield 40 mg (46%), mp 196-197 (lit.[9] mp 197-198 ^{o}C).

3-[^{15}N]-Amino-6-phenyl-1,2,4-triazine (10*). Compound (**10**)* was obtained from **7** and ^{15}N-labelled liquid ammonia by the same procedure as that used for unlabelled compound (**10**).

ACKNOWLEDGEMENTS

This work was partly supported the Russian Foundation for Basic Research (project no. 99-03-32923)

We are grateful to Dr. A. van Veldhuizen for ^{1}H and ^{13}C NMR measurements in liquid methylamine.

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7. To establish which percentage of ^{15}N is present on the nitrogen of the amino group in **10***, we converted compound (**10**)* into 3-chloro-6-phenyl-1,2,4-triazine (**7**) according to reported method.[8] ^{15}N excess in compound (**10**)* and (**7**) was established by mass spectrometric determination of the intensities of the M+1 and M peaks.

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