On the Amination of 1,2,4-Triazines by Potassium Amide in Liquid Ammonia and by Phenyl Phosphorodiamidate. A ^{15}N-study (1)

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The amination of 5-R- and 6-R-3-X-1,2,4-triazines (R = C_6H_5, t-C_4H_9, X = SCH_3, SO_2CH_3, $N^+(CH_3)_3$, Cl) by potassium amide in liquid ammonia has been studied. In all reactions the formation of the corresponding 3-amino-1,2,4-triazines takes place; in some reactions by-products were found: from 5-phenyl- and 5-t-butyl-3-(methylthio)-1,2,4-triazine a ring contracted product *i.e.* 5-phenyl and 5-t-butyl-3-(methylthio)-1,2,4-triazole, from 6-phenyl-3-(methylthio)-1,2,4-triazine the dimer 3,3'-bis(methylthio)-6,6'-bisphenyl-5,5'-bi-1,2,4-triazine and from 5-t-butyl-3-(trimethylammonio)-1,2,4-triazine chloride compound bis-(5-t-butyl-1,2,4-triazin-3-yl)-amine. Furthermore the conversion of 5-phenyl- and 5-t-butyl-1,2,4-triazin-3-one into the corresponding 3-amino compound by treatment with phenyl phosphorodiamidate (PPDA) was studied. A ^{15}N study of these aminations showed that nearly all compounds undergo substitution according to both S_N(AE) and S_N(ANRORC) processes. The contribution of each of the competitive mechanisms to the amination is strongly influenced by the character of the leaving group.

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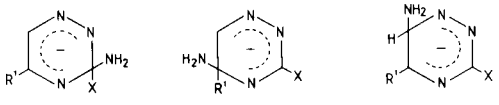
Introduction.

It has been reported (2) that 5-phenyl-3-X-1,2,4-triazines (X = Cl, Br, I) when reacted with potassium amide in liquid ammonia give a complex mixture of products containing *i.a.* 3-amino-5-phenyl-1,2,4-triazine, 3-X-5-phenyl-1,2,4-triazole and several 1,3,5-triazine derivatives. Their formation was explained by a series of reactions, involving as initial steps the formation of the three σ adducts *i.e.* 3-amino-(**1**, R^1 = C_6H_5), 5-amino-(**2**, R^1 = C_6H_5) and the 6-amino-3-X-5-phenyldihydro-1,2,4-triazinide (**3**, R^1 = C_6H_5). These adducts are not stable but react further. Both **1** and **2** are converted into the 3-amino-5-phenyl-1,2,4-triazine, however, **1** according to an S_N(AE) process, **2** according to an S_N(ANRORC) mechanism (for X = Cl, 96%; X = Br, 93%; for X = I, 63%). Adduct **3** is exclusively transformed into 3-X-5-phenyl-1,2,4-triazole. Since the formation of these three adducts is competitive we became interested in i) the influence of C-3 substituents, having a different leaving group character, on the adduct formation, ii) whether substituents being bulkier than the phenyl group are able to retard or even prevent addition at position 5. In the present paper we report on the amination of the 5- and 6-substituted 3-(methylthio)-, 3-(methanesulfonyl), 3-(trimethylammonio)- and 3-chloro-1,2,4-triazines (**4**, R = C_6H_5 or t-C_4H_9) by potassium amide in liquid ammonia. Moreover the preparation of 3-amino-1,2,4-triazines from the corresponding 1,2,4-triazin-3-ones, using phenyl phosphorodiamidate (PPDA) has been studied.

Scheme 1

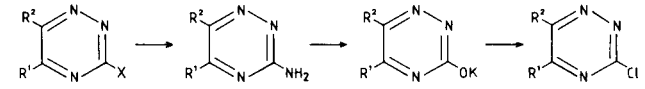


II. Amination by Potassium Amide in Liquid Ammonia.

II.a. Product Studies.

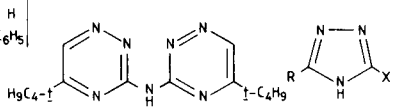
On treatment of 3-(methylthio)-5-phenyl-1,2,4-triazine (**4a**) with potassium amide in liquid ammonia in a very slow reaction (5 hours) 3-amino-5-phenyl-1,2,4-triazine (**5a**) was obtained, together with small amounts of 3-(methylthio)-5-phenyl-1,2,4-triazole (**8a**). For the reaction conditions and yields, see Table I. Reaction of **4a** with liquid ammonia (thus free of potassium amide) at -33° for 5 hours did not give **5a**. Only unchanged material could be retrieved. With potassium amide/liquid ammonia 3-(methylthio)-5-t-butyl-1,2,4-triazine (**4b**) is converted into **5b** and **8b**, respectively. Compounds **5a**, **5b** and **8a** were identified by comparison with authentic specimens (2,3,4). 1,2,4-Tri-

Scheme 2

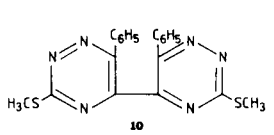


	R^1	R^2	X
a)	C_6H_5	H	SCH_3
b)	t-C_4H_9	H	SCH_3
c)	H	C_6H_5	SCH_3
d)	C_6H_5	H	SO_2CH_3
e)	t-C_4H_9	H	SO_2CH_3
f)	C_6H_5	H	$N^+(CH_3)_3$
g)	t-C_4H_9	H	$N^+(CH_3)_3$
h)	t-C_4H_9	H	Cl
i)	H	C_6H_5	Cl
j)	C_6H_5	H	OH
k)	t-C_4H_9	H	OH

	R^1	R^2
a)	C_6H_5	H
b)	t-C_4H_9	H
c)	H	C_6H_5



a) R = C_6H_5
b) R = t-C_4H_9



azole (**8b**) is unknown and its structure was proved by i) correct microanalysis, ii) mass spectrometry showing a parent peak at m/e = 171, iii) ^{1}H nmr spectrum featuring a singlet at 1.45 ppm (9H, t-C_4H_9) and a singlet at 2.6 ppm (3H, CH_3), iv) infrared spectrum, showing an absorption band at 3150 cm^{-1} (NH). The reaction of 3-(methanesulfonyl)-5-phenyl-1,2,4-triazine (**4d**) with 5-t-butyl-3-(methanesulfonyl)-1,2,4-triazine (**4e**) with potassium amide is very fast; already in 15 minutes the reaction was completed. The sole products which were isolated were the 3-amino compounds **5a** and **5b**, respectively (Table I). Also both 3-(trimethylammonio)-1,2,4-triazine chlorides **4f** and **4g** and 5-t-butyl-3-chloro-1,2,4-triazine (**4h**) were converted quickly into the corresponding 3-amino compounds **5a** and **5b**. In the reaction of **4g** an additional product, *i.e.* bis(5-t-butyl-1,2,4-triazin-3-yl)amine (**9**) was found (Table I). Compound **9** showed its ^{1}H nmr signals at 1.45 ppm (s, 18H) and at 9.05 ppm (s, 2H); infrared spectrum (potassium bromide) of **9** features an absorption band at 3250 cm^{-1} (NH). Since above-mentioned ring contractions of **4a** and **4b** into **8a** and **8b**, respectively, start by a series of reactions, involving as initial adduct the triazinide **3** (R^1 = C_6H_5 and t-C_4H_9, X = SCH_3), we became interested whether in 3-X-1,2,4-triazines, in which position 6 is occupied by a voluminous group, the ring contraction will still take place. For that reason we also investigated the reaction of 3-(methylthio)-6-phenyl-1,2,4-triazine (**4c**) and 3-chloro-6-phenyl-1,2,4-triazine (**4i**) with potassium amide. We observed in both reactions the formation of the 3-amino compound **5c**, but found in the reaction with **4c** in addition a small amount of 3,3′-bis(methylthio)-6,6′-bisphenyl-5,5′-bi-1,2,4-triazine (**10**). No indication for the formation of a triazole was found. The structure of **10** was proved by i) the correct microanalysis, ii) the mass spectrum, showing the parent peak at m/e = 404, iii) the ^{1}H nmr spectrum showing a sharp singlet at 2.65 ppm (6H, 2 × CH_3) and a multiplet between 6.8-7.4 (10H, 2 × C_6H_5).

Table I

Reaction Conditions, Products and Their Yields of the Reaction of the 1,2,4-Triazines (**4a-4i**) with Potassium Amide in Liquid Ammonia

Substrate	Reaction temperature (°C)	Reaction time (minutes)	Product(s)	Yield %
4a	-33	300	**5a**	71
			8a	4
4b	-33	300	**5b**	62
			8b	3.5
4c	-33	300	**5c**	51
			10	1
4d	-33	15	**5a**	65
4e	-33	15	**5b**	59
4f	-33	15	**5a**	42
4g	-33	15	**5b**	35
			9	25
4h	-33	30	**5b**	49
4i	-75	30	**5c**	52

Compound **10** could alternatively be obtained from **4c** by treatment with potassium cyanide in methanol-water, a method known (5) for dimerization of 1,2,4-triazines, which have an unoccupied C-5 position. The mechanism of formation of **10** can be discussed in terms of an addition-oxidation reaction (6).

II.b. Amination of ^{15}N-Labelled 1,2,4-Triazines.

In order to investigate in which reactions the 3-amino compounds are formed according to the S_N(ANRORC) mechanism and in which percentage, we reacted the [4-^{15}N]-1,2,4-triazines **4a***, **4b***, **4d***, **4f*** and **4h*** with unlabelled potassium amide (method A) and the unlabelled compounds **4c**, **4e**, **4g** and **4i** with ^{15}N-labelled potassium amide (method B).

To establish which percentage of the excess of ^{15}N is present on the ring nitrogen and which percentage on the nitrogen of the amino group in the 3-amino compound, we converted [x-^{15}N]-3-amino-1,2,4-triazine (**5***) into the potassium salt of [x-^{15}N]-1,2,4-triazin-3-one (**6***) by treatment with potassium hydroxide. Since **6** is not volatile enough

Table II

Results of Measurement of Excess of ^{15}N in the Compounds **4***, **5***, and **7***

Run	Substrate	% ^{15}N Excess	[x-^{15}N]-3-Amino-1,2,4-triazine (**5***)	% ^{15}N Excess	[x-^{15}N]-3-Chloro-1,2,4-triazine (**7***)	% ^{15}N Excess	% S_N(ANRORC)
1	**4a***	7.0	**5a***	7.0	**7a***	0.0	100
2	**4b***	4.6	**5b***	4.7	**7b***	0.2	95
3	**4c**	0.0	**5c***	4.8	**7c***	4.0	83
4	**4d***	4.8	**5a***	4.8	**7a***	3.2	33
5	**4e**	0.0	**5b***	4.6	**7b***	2.5	54
6	**4f***	4.8	**5a***	5.0	**7a***	3.3	34
7	**4g**	0.0	**5b***	11.9	**7b***	1.6	13
8	**4h***	4.8	**5b***	4.6	**7b***	0.2	95
9	**4i**	0.0	**5c***	4.8	**7c***	4.0	83
10	**4j***	4.8	**5a***	5.0	**7a***	4.5	10
11	**4k***	4.7	**5b***	4.7	**7b***	4.7	0

for mass spectrometric investigation, this salt was converted into the more volatile [x-^{15}N]-3-chloro-1,2,4-triazine (**7***). Mass spectrometric determination of the excess of ^{15}N - by measuring the M + 1 and M peak - in **5*** and **7*** gave the results as summarized in Table II. The percentage of excess of ^{15}N in **7*** also reflects the percentage of excess of ^{15}N, present in the triazine ring of **5***.

II.c. Discussion.

On comparison of the percentage of S_N(ANRORC) mechanism, which occurs in the amination of the 5-substituted 3-(methylthio)-1,2,4-triazines (**4a** and **4b**) (see runs 1 and 2) with that found previously (2) with 3-(methylthio)-1,2,4-triazine [93% S_N(ANRORC)] it is evident that the presence of a phenyl or *t*-butyl group has no considerable effect on changing the course of the amination. Apparently in the compounds **4a** and **4b** adduct formation at position 5 - the initial step in the ANRORC mechanism - is not prevented by these substituents. A remarkable conclusion especially for the *t*-butyl group since this group besides being bulky is also electron-donating and both effects would have been expected to disfavor addition at C-5 and make the direct nucleophilic displacement at C-3 according to the S_N(AE) process more effective. The phenyl and *t*-butyl group in position 5 are not different in influencing the course of the amination as was shown by the fact that the percentage of S_N(ANRORC) mechanism obtained for the 5-*t*-butyl-3-chloro-1,2,4-triazine (**4h** = 95%) is about the same as that previously reported (2) for 3-chloro-5-phenyl-1,2,4-triazine (= 87%). On comparing the percentage of S_N(ANRORC) mechanism in the series of 5-*t*-butyl-1,2,4-triazines, containing at position 3 the substituent X with different leaving group mobility *i.e.* **4b**, **4e**, **4g** and **4h**, the addition to C-5 follows quantitatively the order Cl, SCH_3 > SO_2CH_3 > $^+N(CH_3)_3$. This reactivity order has also been found in the pyrimidine series (7). Thus, the trimethylammonio compound is least inclined to addition to C-5 and favors addition to C-3, the initial step in the S_N(AE) reaction. It has been found that in this strong basic medium the SO_2CH_3 group is partly present as the anion SO_2 - $^-CH_2$ (7).

III. Amination of 1,2,4-Triazin-3-ones by Phenyl Phosphorodiamidate (PPDA).

It has been reported that PPDA is a useful reagent for the preparation of amino heterocycles from the corresponding oxo heterocycles (8,9). On applying this reagent the 5-phenyl- (**4j**) and 5-*t*-butyl-1,2,4-triazin-3-one (**4k**) are converted into the corresponding 3-amino compounds **5a** and **5b** in yields of 61 and 39%, respectively. Since it has been found that the conversion of quinazolin-4-one into 4-aminoquinazoline by PPDA partly involves a ring-opening process (10) we were interested to know whether also in the conversion of **4j**, **4k** into **5** an S_N(ANRORC) process would be involved. By applying the same technique and the same series of reactions as described in Section II.b., using as starting material 4-^{15}N-labelled **4j**, **4k** (**4j***, **4k***) we could establish that the conversion **4j** → **5a** occurs for only 10% according to an S_N(ANRORC) process, while in the conversion **4k** → **5b** no S_N(ANRORC) process was involved at all (see runs 10 and 11 in Table II).

EXPERIMENTAL

Melting points were determined on a Buchi SMP-20 apparatus. The pmr spectra were measured with a JEOL JNM C-60 H. TMS (= 0.00) was used as internal standard. The ^{15}N measurements were carried out with an AE MS 902 spectrometer.

Starting Materials.

The following compounds were prepared by procedures given in the literature: 3-(methylthio)-5-phenyl-1,2,4-triazine (**4a**) (11), 5-*t*-butyl-3-(methylthio)-1,2,4-triazine (**4b**) (12), 3-(methylthio)-6-phenyl-1,2,4-triazine (**4c**) (13), 3-(methanesulfonyl)-5-phenyl-1,2,4-triazine (**4d**) (13), 5-*t*-butyl-3-(methanesulfonyl)-1,2,4-triazine (**4e**) (13), 5-phenyl-3-(trimethylammonio)-1,2,4-triazine chloride (**4f**) (13), 5-*t*-butyl-3-(trimethylammonio)-1,2,4-triazine chloride (**4g**) (13), 5-*t*-butyl-3-chloro-1,2,4-triazine (**4h**) (13), 3-chloro-6-phenyl-1,2,4-triazine (**4i**) (13), 5-phenyl-1,2,4-triazin-3-one (**4j**) (14) and 5-*t*-butyl-1,2,4-triazin-3-one (**4k**) (13).

3-X-[4-^{15}N]-1,2,4-triazines (**4a***, **4b***, **4d***, **4f***, **4h***).

These compounds were prepared by the same procedure as described for the unlabelled compounds. The required [^{15}N]S-methylthiosemicarbazide was synthesized in a three-step synthesis from ^{15}N-labelled potassium thiocyanate and ^{15}N-labelled thiosemicarbazide according to procedures as outlined before (11,15).

Amination by Potassium Amide/Liquid Ammonia.

Method A.

To a dry liquid ammonia (25 ml) in a three-necked round-bottomed flask (50 ml), equipped with a dry ice/acetone condenser a few crystals of ferric nitrate were added and 160 mg (4.1 mmoles) of potassium. After the mixture was stirred for 30 minutes at -33°, the corresponding 1,2,4-triazine **4a***, **4b***, **4d***, **4f*** or **4h*** was added with the exclusion of moisture. The reaction time and temperature are presented in Table I. The reaction was terminated by the addition of 220 mg (4 mmoles) of ammonium chloride. After the ammonia was evaporated, the residue was thoroughly extracted with warm chloroform and then with absolute ethanol. The combined extracts were concentrated *in vacuo* and the residual mixture was separated by column chromatography or preparative thin-layer chromatography to yield the corresponding 3-amino compounds side-products. The eluent used was chloroform-acetone in the ratio 10:1. The yields of products formed are given in Table I.

Method B.

The amination in ^{15}N-labelled liquid ammonia with ^{15}N-labelled potassium amide of **4c**, **4e** and **4i** was carried out in the same manner. ^{15}N-labelled ammonia was prepared by treatment of ^{15}N-labelled ammonium nitrate containing an ^{15}N excess in the ammonium group with a concentrated solution of hydroxide at 100° for 2 hours. After the experiment, it was reconverted into ^{15}N-labelled ammonium nitrate.

General Procedure for the Amination of 1,2,4-Triazin-3-ones (**4j**, **4k**) With Phenyl Phosphorodiamidate (PPDA).

A mixture of **4j**, **4k** (1 mmole) and PPDA (1 mmole) was immersed into an oil bath, preheated to 150°. The temperature was raised to 235-240° and maintained for 30 minutes. After cooling the fused melt was extracted with boiling *n*-butylamine (15 ml). After filtration the solution was concentrated to a small volume, yield **5a**, 61%; yield **5b** 39%.

Conversion of [x-^{15}N]-3-Amino-1,2,4-triazines (**5***) into the [x-^{15}N]-3-Chloro-1,2,4-triazines (**7***).

The compounds **5a***, **5b*** and **5c*** were converted into the corresponding potassium salt [x-^{15}N]-1,2,4-triazin-3-ones **6a***, **6b*** and **6c*** respectively by the same procedure as described for the unlabelled compounds (14). The conversion of **6a***, **6b*** and **6c*** into [x-^{15}N]-3-chloro-1,2,4-triazines **7a***, **7b*** and **7c*** was performed by the same procedure as described for the unlabelled compounds (2).

Identification of the New Compounds.

5-*t*-Butyl-3-(methylthio)-1,2,4-triazole (**8b**).

This compound had mp 188-190°.

Anal. Calcd. for $C_7H_{13}N_3S$: C, 49.12; H, 7.6; N, 24.56. Found: C, 49.38; H, 7.75; N, 24.52.

3,3'-bis(methylthio)-6,6'-bisphenyl-5,5'-bi-1,2,4-triazine (**10**).

This compound had mp 148-149°.

Anal. Calcd. for $C_{20}H_{16}N_6S_2$: C, 59.46; H, 3.99; N, 20.8. Found: C, 59.38; H, 4.08; N, 20.43.

bis(5-*t*-Butyl-1,2,4-triazin-3-yl)amine (**9**).

This compound had mp 106-108°.

Anal. Calcd. for $C_{14}H_{21}N_7$: C, 58.53; H, 7.31; N, 34.14. Found: C, 58.52; H, 7.38; N, 34.48.

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