Liquid Ammonia/Potassium Permanganate, A Useful Reagent in the Chichibabin Amination of 1,2,4-Triazines[1]

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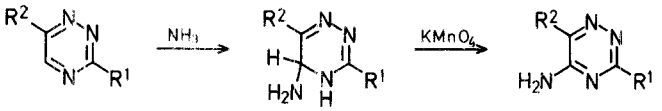
Amino-1,2,4-triazines have attracted interest as synthons for the preparation of fused heterocycles[2]. Although methods are known for preparing 5-amino-1,2,4-triazine and some functionalized derivatives[2,3] a convenient method for a good-yield preparation of 5-amino-1,2,4-triazine and its alkyl and aryl derivatives is not available. We present here a new entry to the preparation of 5-amino-1,2,4-triazines. The method is based on the use of potassium permanganate as reagent for oxidizing σ-adducts, formed between highly electron-deficient azines and liquid ammonia. The liquid ammonia/potassium permanganate system has already been succesfully applied to the introduction of an amino group into tetrazines[4], pteridines[5], 3-nitro-1,x-naphthyridines[6,7,8], and 5-nitropyrimidine[9].

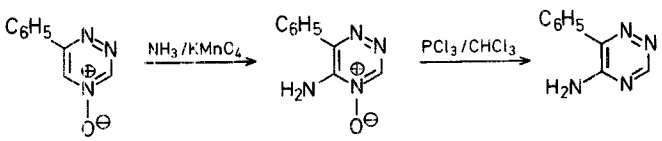
It has already been found that 1,2,4-triazine and some of its derivatives having an unoccupied C-5 position react with liquid ammonia to give the σ-adducts 5-amino-4,5-dihydro-1,2,4-triazines **(2)**[10]. We have now tried to oxidize these σ-adducts to the corresponding 5-amino-1,2,4-triazines **(3)** with potassium permanganate. We indeed observed that addition of potassium permanganate to a solution of 1,2,4-triazine **(1a)** in liquid ammonia at −35 °C (Method A) gave 5-amino-1,2,4-triazine **(3a)** in >95% yield. This product was identified by microanalysis, mass- and ^{1}H-N.M.R. spectrometry, and by comparison with an authentic specimen[3]. This method was also succesfully applied to the amination of 3-methyl- **(1b)**, 3-phenyl- **(1c)**, 6-phenyl- **(1d)**, 3-methoxy- **(1e)**, 3-amino- **(1f)**, and 3-amino-6-bromo-1,2,4-triazine **(1g)** to the 5-amino compounds **(3b–g)**. It is evident that the σ-adducts **2b–g** are intermediates in these Chichibabin amination reactions. Evidence for the intermediacy of **2b–e** was obtained by ^{1}H-N.M.R. spectrometry; however the existence of **2f,g** could not be proven, indicating that the rate of formation of these adducts is lower than their conversion into **3f,g**.



1 a-j **2 a-j** **3 a-j**

Also 1,2,4-triazines containing a nucleofugal substituent at C-3 were found to undergo the Chichibabin amination at C-5 without replacement of the substituent at C-3 by an amino group. However, in these cases the amination procedure has to be modified slightly. Instead of adding potassium permanganate to a solution of substrate in liquid ammonia (Method A), the substrate was added to a solution of potassium permanganate in liquid ammonia (Method B). By using Method B one can avoid that replacement of the substituent at C-3 takes place before oxidation of adduct **2** to **3**. Thus, by Method B 3-methylthio-1,2,4-triazine **(1h)** and 3-chloro-6-phenyl-1,2,4-triazine **(1i)** could be succesfully aminated to the corresponding 5-amino compounds **(3h,i)**.

Up to now, the successful amination of heteroarene *N*-oxides by use of liquid ammonia/potassium permanganate has not been described. We now report that 6-phenyl-1,2,4-triazine *N*-oxide **(4)** can be aminated by Method B to give 5-amino-6-



4 **5** **3d**

Table. Aminated 1,2,4-Triazines (**3, 5**)

Product	R^1	R^2	Method	Yield[a] [%]	m.p. [°C][b] (solvent)	Molecular Formula[c] or m.p. [°C] reported	M.S. (70 eV) *m/e* (M^+)	^{1}H-N.M.R. (DMSO-d_6/TMS_{int})[d] δ [ppm]
3a	H	H	A	95	230–231° (ethanol)	231–232°[3]	96	8.72 (d, 1H, J = 2.5 Hz); 8.83 (d, 1H, J = 2.5 Hz)
3b	CH_3	H	A	63	260–261° (ethanol/chloroform)	$C_4H_6N_4$ (110.1)	110	8.5 (s, 1H); 2.4 (s, 3H)
3c	C_6H_5	H	A	89	252–253° (ethanol)	249–250°[12]	172	8.65 (s, 1H); 7.5–7.9 (m, 3H); 8.4–8.6 (m, 2H)
3d	H	C_6H_5	A	85	124° (ethanol/chloroform)	123–124°[13]	172	8.8 (s, 1H); 7.6–7.9 (m, 5H)
3e	OCH_3	H	A	80	177–178° (ethanol/chloroform)	176–178°[3]	124	8.35 (s, 1H); 3.95 (s, 3H)
3f	NH_2	H	A	30	244–245° (benzene/methanol)	$C_3H_5N_5$ (111.1)	111	7.71 (s, 1H)
3g[d]	NH_2	Br	A	56	320° (dec)	$C_3H_4BrN_5$ (190.0)	189/191	
3h	SCH_3	H	B	87	222–223 (ethanol/chloroform)	$C_4H_6N_4S$ (142.1)	142	
3i	Cl	C_6H_5	B	43	198–199° (chloroform)	$C_9H_7ClN_4$ (206.6)	206/208	
5	–	–	B	28	231–232° (chloroform)	$C_9H_8N_4O$ (188.2)	188	9.32 (s, 1H); 7.6–7.8 (m, 5H)

[a] Yield of isolated pure product.
[b] Melting points are uncorrected.
[c] The microanalyses were in good agreement with the calculated values: C ±0.33, H ±0.17, N ±0.23.
[d] Recorded on a Varian EM 390 instrument at 90 MHz.
[e] Compound **3g** was isolated together with starting material **1g**. Compounds **3g** and **1g** were separated by preparative T.L.C. on silica gel (methanol/butyl methyl ether 1/1 as eluent).

phenyl-1,2,4-triazine 4-oxide (**5**). The structure of **5** was proven by deoxygenation of **5** to 5-amino-6-phenyl-1,2,4-triazine (**3d**) using phosphorus(III) chloride in chloroform.

Amination experiments with 5-phenyl- and 3,5-diphenyl-1,2,4-triazine showed that both compounds are nearly unreactive. With 5-phenyl-1,2,4-triazine, only a few percent of 3-amino-5-phenyl-1,2,4-triazine was obtained.

In conclusion, the liquid ammonia/permanganate method is a simple and convenient method for the selective amination of 1,2,4-triazines at C-5. This orientation is in agreement with previous observations[10] and theoretical considerations[11].

5-Amino-1,2,4-triazine (3a); Typical Procedure (Method A):
To a solution of 1,2,4-triazine (**1a**; 0.08 g, 1 mmol) in dry liquid ammonia (20 ml), an excess of potassium permanganate (0.2 g) is added in one portion and the mixture is stirred for an additional 30 min. Ammonia is evaporated and the residue is extracted with hot isopropanol. The crude product remaining after evaporation of the solvent is crystallized from ethanol to give the pure product **3a**; yield: 91 mg (95%), m.p. 230–231 °C.

5-Amino-3-methylthio-1,2,4-triazine (3h); Typical Procedure (Method B):
3-Methylthio-1,2,4-triazine (**1h**; 1.306 g, 10 mmol) is added in small portions to a solution of potassium permanganate (2.0 g) in dry liquid ammonia (100 ml) at −33 °C with stirring. The mixture is kept at −33 °C for 15 min. Ammonia is then evaporated and the residue is extracted with hot isopropanol (50 ml). Removal of the solvent and recrystallization from ethanol gives the pure product **3h**; yield: 1.23 g (87%); m.p. 222–223 °C.

Deoxygenation of 5-Amino-6-phenyl-1,2,4-triazine 4-Oxide (5):
To a well stirred suspension of compound **5** (0.37 g, 2 mmol) in chloroform (20 ml), phosphorus(III) chloride (0.42 g, 2.1 mmol) is added dropwise. The mixture is heated to reflux on a water bath for 1 h, then poured onto ice (20 g), basified with sodium carbonate, and continuously extracted with chloroform. The organic extract is dried with potassium carbonate. The solvent is distilled off and the residue is crystallized from ethanol to give *5-amino-6-phenyl-1,2,4-triazine* (**3d**); yield: 0.11 g (32%); m.p. 123–124 °C (Ref.[13], m.p. 124 °C).

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