Nucleophilic substitution of hydrogen in the reaction of 1,2,4-triazine-4-oxides with cyanides

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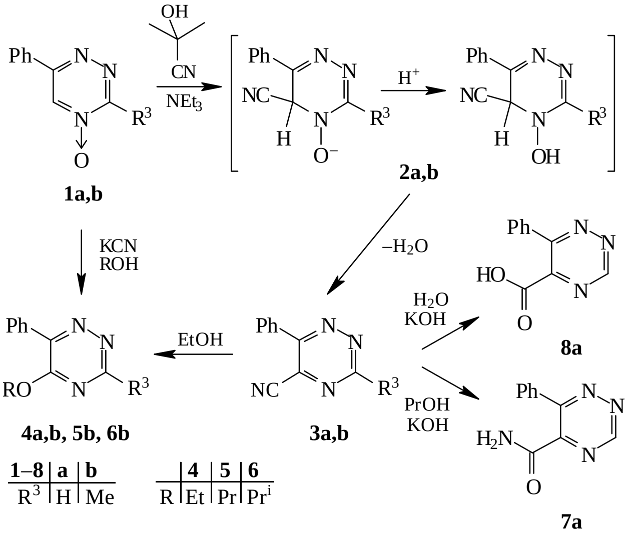
Nucleophilic substitution of hydrogen by cyano and alkoxy groups in 1,2,4-triazine-4-oxides is reported.

In spite of the fact that nucleophilic substitution of hydrogen in 1,2,4-triazines usually proceeds smoothly, the $\mathrm{S_NH}$ reactions with anionic nucleophiles such as alkoxide and cyanides are often impossible due to the dimerization of 1,2,4-triazines.[1,2] There is only one known example of the cyano-dehydrogenation reaction in the series of 1,2,4-triazines, *i.e.* the formation of 3-phenyl-6-methyl-5-cyano-1,2,4-triazine in the reaction of 3-phenyl-6-methyl-1,2,4-triazine with anhydrous HCN.[3,4]

We have found that the cyanation of 1,2,4-triazine-4-oxide using acetone cyanohydrin resulted in an $\mathrm{S_NH}$ process. Thus, treatment of 3-R^3-6-phenyl-1,2,4-triazine-4-oxides **1a,b** with acetone cyanohydrin in the presence of triethylamine affords 3-R^3-6-phenyl-1,2,4-triazine-5-carbonitriles **3a,b** in high yields (Scheme 1).[†,‡] The reaction is accompanied by the loss of the *N*-oxide functionality. It is suggested that after addition of the cyano group and of the proton from the solvent, *auto*-aromatization of the adduct **2** takes place with the elimination of water. Although σ-adducts **2a,b** have not been detected, their formation is likely if similar reactions of 1,2,4-triazine-4-oxides with aromatic carbon-nucleophiles are taken into consideration.[5,6]



Scheme 1

The use of potassium cyanide as a cyanation agent in the reaction of 1,2,4-triazine-4-oxides **1a,b** in alcohols (ethanol, propanol or isopropanol) at room temperature unexpectedly afforded the 3-R^3-5-alkoxy-6-phenyl-1,2,4-triazines **4a,b**, **5b** and **6b** in high yields.[†,‡]

Cyanotriazines **3a,b** were found to react with ethanol at room temperature yielding 3-R^3-6-phenyl-5-ethoxy-1,2,4-triazines **4a,b**. This fact suggests that the first step in the reaction of 1,2,4-triazine-4-oxides **1a,b** with potassium cyanide in alcohols is the formation of the corresponding triazinecarbonitrile **3a,b**, while the second step is the displacement of the cyano group by alcohol. This is in agreement with other reports of related reactions of 1,2,4-triazinecarbonitriles with CH-active and organo magnesium compounds.[7,8]

Basic hydrolysis of compound **3a** leads to 6-phenyl-1,2,4-triazine-5-carboxamide **7a** and 6-phenyl-1,2,4-triazine-5-carboxylic acid **8a**.[†,‡]

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[†] 3-*R*^{3}-6-*Phenyl*-1,2,4-*triazine*-5-*carbonitriles* **3a,b**: Acetone cyanohydrine (0.4 ml) and triethylamine (0.5ml) were added to a solution of 3-R^3-6-phenyl-1,2,4-triazine-4-oxide, **1a,b** (2 mmol). After 0.5 h the solvent was evaporated *in vacuo* and residue recrystallized from isopropanol. 3-*R*^{3}-5-*Alkoxy*-6-*phenyl*-1,2,4-*triazines* **4a,b**, **5b**, **6b**. – Method A: Potassium cyanide (65 mg, 1mmol) was added to a suspension of triazine-4-oxide **1a,b** (4mmol) in alcohol. After 0.5–24 h the reaction mixture was diluted with water and the sediment recrystallized from heptane. Method B: A solution of **3a,b** (2mmol) in ethanol was left to stand for 24h at room temperature. The solvent was evaporated *in vacuo* and the residue recrystallized from heptane. 6-*Phenyl*-1,2,4-*triazine*-5-*carboxamide* **7a**: **3a** (364mg, 2mmol) and KOH (0.2 g) were dissolved in propanol (5 ml) and kept overnight at room temperature. The reaction mixture was diluted with water (10 ml) and the sediment recrystallized from hexane. Yield: 340 mg (85%). 6-*Phenyl*-1,2,4-*triazine*-5-*carboxylic acid* **8a**: **3a** (364mg, 2mmol) was suspended in KOH–water (10 ml, 2 M) and kept for 2h at room temperature. The mixture was then neutralized with acetic acid and the colourless crystals formed filtered and dried. Yield 382 mg (95%).

[‡] Satisfactory analytical data for all compounds **3**–**8** were obtained.

For **3a**: mp 86 °C, ^{1}HNMR ([^{2}H$_6$]DMSO) δ: 7.55–8.18 (m, 3H, 2H), 10.09 (s, 1H, H^3).

For **3b**: mp 88 °C, ^{1}H NMR ([^{2}H$_6$]DMSO) δ: 2.93 (s, 3H, Me), 7.42–8.15 (m, 3H, 2H).

For **4a**: mp 81–82 °C, ^{1}H NMR ([^{2}H$_6$]DMSO) δ: 1.40 (t, 3H), 4.56 (q, 2H), 7.4–8.1 (m, 3H, 2H), 9.18 (s, 1H, H^3).

For **4b**: mp 74 °C, ^{1}H NMR ([^{2}H$_6$]DMSO) δ: 1.40 (t, 3H), 2.66 (s, 3H), 4.51 (q, 2H), 7.4–8.1 (m, 3H, 2H).

For **5b**: mp 41°C, ^{1}HNMR ([^{2}H$_6$]DMSO) δ: 1.00 (t, 3H), 1.81 (m, 1H), 2.66 (s, 3H), 4.42 (t, 2H), 7.4–8.1 (m, 3H, 2H).

For **6b**: mp 64 °C, ^{1}HNMR ([^{2}H$_6$]DMSO) δ: 1.42 (d, 6H), 2.66 (s, 3H), 5.48 (m, 1H), 7.4–8.1 (m, 3H, 2H).

For **7a**: mp 153 °C, ^{1}HNMR ([^{2}H$_6$]DMSO) δ: 6.8 (br.s, 2H, NH$_2$), 7.4–8.2 (m, 3H, 2H), 8.72 (s, 1H, H^3).

For **8a**: mp 180–183°C, ^{1}HNMR ([^{2}H$_6$]DMSO) δ: 7.3–8.3 (m, 3H, 2H), 8.66 (s, 1H, H^3), 13.8 (br.s, 1H, OH).

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