Auto-aromatization of the σ^H-adducts of 1,2,4-triazine 4-oxides with carbanions in reactions of nucleophilic substitution of hydrogen

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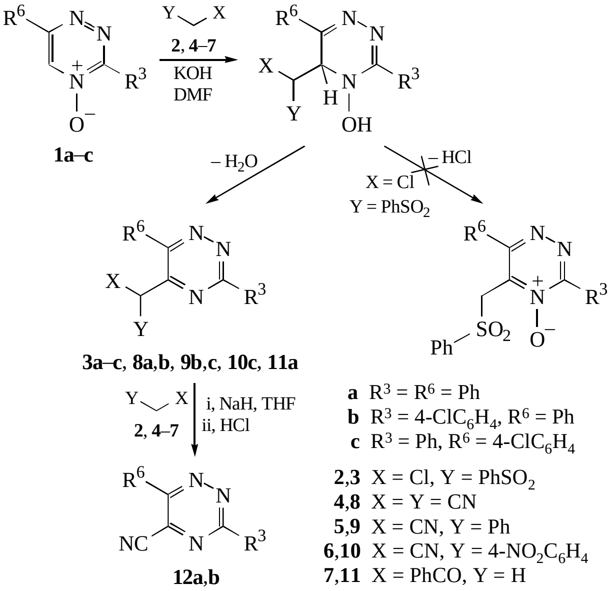
1,2,4-Triazine 4-oxides react with stable carbanions to form 5-substituted 1,2,4-triazines as the products of deoxygenation nucleophilic substitution of hydrogen.

The general feature of the reactions of nucleophilic substitution of hydrogen (S_N^H) and good leaving groups (S_N^{ipso}) is a two-step mechanism involving the formation and aromatization of σ-adducts.[1,2] Because the elimination of a hydride anion is unlikely (in contrast to the *ipso*-substitution of good leaving groups) as a result of the instability of the hydride anion, the oxidative aromatization and auto-aromatization of σ^H-adducts take place in S_N^H reactions. The latter proceeds *via* rearrangements of the σ^H-adduct molecule without the action of external oxidants and involves the elimination of hydrogen together with an auxiliary group that forms a stable anion. Three general types of auto-aromatization can be mentioned. In one of them, so-called vicarious nucleophilic substitution of hydrogen (VNS^H), an auxiliary group is introduced into the σ^H-adduct as a part of the nucleophile.[3,4] The second type, *cine*- and *tele*-substitution reactions, deals with the elimination of hydrogen together with an auxiliary group initially occurring in a substrate molecule. Finally, an auxiliary group can be formed after the addition of a nucleophile. Thus, the elimination of hydrogen together with *N*-hydroxyl is the most common way for the aromatization of σ^H-adducts in reactions of heterocyclic *N*-oxides[5] and in S_N^H reactions of nitroarenes to form nitrosoarenes.[6] Usually, only one of several auto-aromatization pathways in a particular reaction system is preferable. Thus, the reactions of quinoline *N*-oxides with the 'vicarious' nucleophile chloromethyl phenyl sulfone proceed with the retention of the *N*-oxide group by the VNS^H pathway resulting in 2-phenylsulfonylmethylquinoline *N*-oxides.[7] In the same manner, the reaction of 3-methoxy-1,2,4-triazine 1-oxide with chloromethyl phenyl sulfone gave 3-methoxy-5-phenylsulfonylmethyl-1,2,4-triazine 1-oxide.[8]

Here we report the reactions of 3-R^3-6-R^6-1,2,4-triazine 4-oxides **1a**–**c** with stable carbanions, including carbanions containing good leaving groups at the reaction centres (reagents for VNS^H reactions).[†] We found that the reactions of 1,2,4-triazine 4-oxides **1a**–**c** with chloromethyl phenyl sulfone **2** in DMF in the presence of an excess of powdered KOH lead to corresponding 3-R^3-6-R^6-5-(α-chloro-α-phenylsulfonylmethyl)-1,2,4-triazines **3a**,**b** in 70–90% yields. In this case of S_N^H reactions, the deoxygenation (an auxiliary group is in the substrate) rather than the vicarious (an auxiliary group is in the nucleophile) pathway takes place.

In the same manner, 1,2,4-triazine 4-oxides **1a**–**c** react with carbanions generated from malononitrile **4**, phenylacetonitrile **5** and 4-nitrophenylacetonitrile **6** under above conditions to form 3-R^3-6-R^6-5-(α-X-α-cyanomethyleno)-1,2,4-triazines **8a**,**b**, **9a**–**c**, **10c**. The reactions of 1,2,4-triazine 4-oxide **1a** with acetophenone under the same conditions gives 3,6-diphenyl-5-phenacyl-1,2,4-triazine **11a**.

The structures of the compounds obtained are consistent with the data of NMR and mass spectrometry.[‡] The structures of compounds **8a**,**b**, **9b** and **11a** were confirmed by an independent synthesis[9] *via* substitution of the cyano group in 5-cyano-1,2,4-triazines **12a**,**b** for the residue of malononitrile **4**, phenylacetonitrile **5** or acetophenone **7**.[§]



Scheme 1

The reactivity of 1,2,4-triazine 4-oxides seems unique for azine *N*-oxides. It is well known that deoxygenation aromatization of the σ^H-adducts does not takes place in the reactions of nucleophilic substitution of hydrogen in uncharged azine *N*-oxides. Thus, quinoline *N*-oxides react with carbanions *via* oxidative or vicarious nucleophilic substitution of hydrogen depending on the structure of the nucleophile (cyanide anions, acetone, acetophenone or 'vicarious' nucleophiles in the presence of a base) with the retention of the *N*-oxide group.[1]

[†] *A typical reaction procedure is as follows*: a corresponding precursor of carbanions (1.1 mmol) and 1,2,4-triazine 4-oxide **1a**–**c** (1 mmol) were added to a suspension of powdered KOH (500 mg) in 3 ml of DMF. The reaction mixture was stirred at room temperature for 1 h, kept overnight. Then, it was poured into water and acidified with dilute HCl. Crystals were filtered off and recrystallised from ethanol or AcOH.

[‡] All of the compounds exhibited satisfactory analytical data (maximum differences between the calculated and found data were no higher than 0.10% for C and H and 0.25% for N). The ^{1}H NMR spectra were recorded on a Bruker WM-250 spectrometer at a frequency of 250.137 MHz; [^{2}H$_6$]DMSO was a solvent. The mass spectra (electron ionisation) were measured on a Varian MAT-311 spectrometer. The occurrence of the M, M + 2 and M + 4 characteristic peaks in the mass spectra confirms that the compounds have one or two chlorine atoms, respectively.

For **3a**: yield 78%, mp 138 °C. ^{1}H NMR, δ: 6.26 (s, 1H), 7.5–7.7 (m, 8H), 7.7–7.9 (m, 5H), 8.2 (m, 2H).

For **9b**: yield 89%, mp > 270 °C. ^{1}H NMR, δ: 6.9–8.3 (m, 14H), 13.6 (br. s, 1H, NH).

For **10c**: yield 92%, mp > 270 °C. ^{1}H NMR, δ: 7.4–7.8 (m, 8H), 8.0–8.4 (m, 5H), 14.0 (br. s, 1H, NH).

[§] *A typical procedure for the reactions of 5-cyano-1,2,4-triazines* **12a**,**b** *with malononitrile* **4**, *phenylacetonitrile* **5** *and acetophenone* **7**. A solution of compound **4**, **5** or **7** (1.05 mmol) in 2 ml of DMF was added dropwise to a suspension of NaH (1.1 mmol) in 4 ml of THF. Next, corresponding 5-cyano-1,2,4-triazine **12a**,**b** was added as crystals to the reaction mixture, which was stirred for 2 h at room temperature. After the removal of the solvent, the residue was dissolved in water and acidified with dilute HCl. Crystals were filtered off and recrystallised from ethanol.

The difference between monoazine *N*-oxides and 1,2,4-triazine 4-oxides in reactivity suggests that the heterocyclic ring structure strongly affects the direction of the reaction. We believe that the presence of three electron-withdrawing nitrogen atoms in the 1,2,4-triazine ring increases the lability of protons at the sp^3-hybridised carbon in intermediate σ^H-adducts, and this facilitates the aromatization by dehydration according to the E1cb mechanism.

Obviously, other reactions of 1,2,4-triazine 4-oxides with anionic nucleophiles such as cyanide anions[10] or cyanamide[11] anions, which lead to 5-cyano- or 5-cyanamino-1,2,4-triazines, proceed according to the proposed mechanism.

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