Stable σ-adducts of 6-phenyl-1,2,4-triazine 4-oxides with phenols

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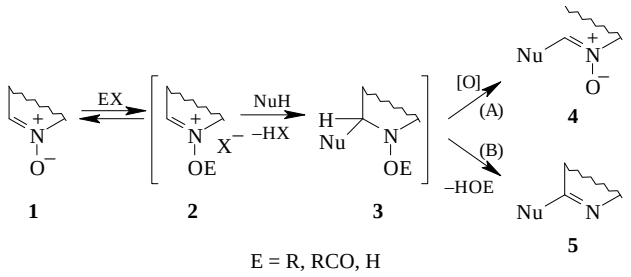
The formation of some very stable adducts of phenols with 1,2,4-triazine 4-oxides, and their oxidation, has been studied.

The formation of adduct **3** (Scheme 1) is usually postulated for nucleophilic substitution reactions of hydrogen in aromatic *N*-oxides **1** and *N*-alkoxy and *N*-acyloxyazinium salts **2**. Aromatization of the adducts **3** proceeds usually *via* two general pathways.[1] The first (A) results in substituted *N*-oxides and is achieved in the presence of oxidizing agents. The reactions of quinoline and phthalazine *N*-oxides with cyanide ion[2] or CH-active compounds,[3] as well as amination of pyridazine[4] or 1,2,4-triazine[5] in liquid ammonia, are examples of this type of reaction. The second path (B) involves auto-aromatization by elimination of an HOE fragment from the adduct **3** resulting in the formation of substituted azines **5**. According to this pathway the following reactions are known to proceed: interaction of quinoline *N*-oxides with organomagnesium compounds,[6] cyanation of 1-methoxypyridinium salts,[7] as well as the reaction of quinolinium or pyridazinium *O*-acylated salts generated *in situ* with alkoxides, thiolates, amines, CH-active compounds, indoles or dimethylaniline.[8]



Scheme 1

We have succeeded for the first time in recording and isolating the adducts of type **3** (Nu = 2,4-dihydroxyphenyl, 2,4,6-trihydroxyphenyl, 2-hydroxyphenyl, 3,5-dimethyl-4-hydroxyphenyl, 2-ethoxyphenyl or 4-ethoxyphenyl, E = H). Resorcinol was found to react readily with 6-aryl-1,2,4-triazine-4-oxides **6a**–**c** in the presence of trifluoroacetic acid yielding 6-aryl-5-(2,4-dihydroxyphenyl)-4,5-dihydro-4-hydroxy-1,2,4-triazines **7a**–**c** (Scheme 2). The reaction of resorcinol with a two-fold excess of triazine *N*-oxide **6a** leads to the addition of two triazine molecules, yielding 2,4-bis-(6′-phenyl-4′,5′-dihydro-4′-hydroxy-1′,2′,4′-triazin-5′-yl)-5-hydroxyphenol **8a**.

Interaction of 6-aryl-1,2,4-triazine 4-oxides **6a**,**b** with phenol affords only *ortho*-products **9a**,**b**. At the same time, a similar reaction with phenetole leads to a mixture of *ortho*- and *para*-substituted phenetoles **10a**, **11a** in the ratio 1:1. The unusual[1] regioselectivity for the reaction of *N*-oxides **1** with phenol can obviously be explained by the formation of hydrogen bonds with the *N*-oxide fragment; these H-bonds determine the orientation of the reagents. Use of 2,6-dimethylphenol in the same reaction gave 6-aryl-5-(3′,5′-dimethyl-4′-hydroxyphenyl)-4,5-dihydro-4-hydroxy-1,2,4-triazines **12a**,**b** (Scheme 2).†

The adducts yielded are fairly stable, this stability being possibly determined by hydrogen bonds between the phenols and the *N*-oxide hydroxy groups. Thermal dehydration (pathway B, Scheme 1) by refluxing in butanol, DMF or trifluoroacetic acid, does not take place. At the same time, oxidation of the adducts (pathway A, Scheme 1) proceeds very readily, yielding oxidized products in practically theoretical amounts. Treatment of compounds **7a**,**b**, **12a**,**b** with potassium permanganate leads to the 6-aryl-5-R-1,2,4-triazine 4-oxides **13a**,**b**, **14a**,**b** (Scheme 2), thus confirming that this simple method can be used for modification of 1,2,4-triazines with retention of the *N*-oxide group.

† *General procedure for* **7a**,**b**, **9a**,**b**, **10a**, **11a**, **12a**,**b**. Equimolar amounts of the triazine 4-oxide **6a**,**b** and corresponding phenol were dissolved in a mixture of CH_2Cl_2–trifluoroacetic acid 3:1 and left at room temperature for 0.5–5 h. Triethylamine was added and the resulting precipitate was filtered off and recrystallized from ethanol.

General procedure for **13a**,**b**, **14a**,**b**. The adduct **7a**,**b** or **12a**,**b** (3 mmol) and potassium permanganate (2 mmol) were mixed at room temperature in 100 ml of acetone for 1–2 h. After removal of magnesium oxide the solution was evaporated and the residue recrystallized from ethanol.

Spectral data for the compounds obtained. For all compounds satisfactory analytical data were obtained.

For **7a**: mp > 300 °C, ^{1}H NMR ([$^2H_6$]DMSO) δ/ppm: 6.05 (s, 1H, H^5), 6.32 (dd ,1H), 6.42 (d, 1H), 7.15 (d ,1H), 7.3–7.9 (m, 5H, Ph), 9.4 (br. s, 1H, OH), 12.3 (br. s, 2H, 2OH); MS, *m*/*z*: 283 (22.3, M^+), 265 (38.2), 236 (12), 224 (22.7), 210 (100), 181 (20), 165 (10), 152 (33), 136 (40).

For **7b**: mp > 250 °C; ^{1}H NMR ([$^2H_6$]DMSO) δ/ppm: 6.00 (s, 1H, H^5), 6.10–6.47 (m, 3H), 7.38–7.72 (m, 4H, *p*-Cl-Ph), 8.40 (s, 1H, H^3), 9.4 (br. s, 1H, OH), 11.5–13.0 (br. s, 2H, 2OH).

For **7c**: mp > 250 °C; ^{1}H NMR ([$^2H_6$]DMSO) δ/ppm: 2.37 (s, 3H, C^3-Me), 6.22 (dd, 1H), 6.25 (s, 1H, H^5), 6.28 (d, 1H), 7.21 (d, 1H), 7.35–7.83 (m, 5H, Ph), 9.6 (br. s, 1H, OH), 11.8 (br. s, 2H, 2OH).

For **8a**: mp > 250 °C; ^{1}H NMR ([$^2H_6$]DMSO) δ/ppm: 6.31 (br. s, 2H), 6.40 (s, 1H), 7.23–7.76 (m, 11H), 9.17 (s, 2H), 7.0–11.0 (br. s, 4H, 4OH).

For **9a**: mp 184 °C; ^{1}H NMR ([$^2H_6$]DMSO) δ/ppm: 6.45 (s, 1H, H^5), 6.6–8.0 (m, 9H), 9.21 (s, 1H, H^3).

For **9b**: mp > 250 °C; ^{1}H NMR ([$^2H_6$]DMSO) δ/ppm: 5.71 (s, 1H, H^5), 6.4–7.3 (m, 4H), 7.41–7.49 (dd, 2H), 7.63–7.77 (dd, 2H), 7.95 (s, 1H, H^3).

For **10a**: mp 101 °C; ^{1}H NMR ([$^2H_6$]DMSO) δ/ppm: 1.3–1.5 (t, 3H, Me), 3.9–4.2 (q, 2H, CH_2), 6.46 (s, 1H, H^5), 6.9–7.9 (m, 9H), 9.22 (s, 1H, H^3).

For **11a**: mp 105 °C; ^{1}H NMR ([$^2H_6$]DMSO) δ/ppm: 1.2–1.4 (t, 3H, Me), 3.9–4.2 (q, 2H, CH_2), 6.30 (s, 1H, H^5), 6.9–7.9 (m, 9H), 9.17 (s, 1H, H^3).

For **12a**: mp 243 °C; ^{1}H NMR ([$^2H_6$]DMSO) δ/ppm: 2.13 (s, 6H, 2Me), 6.16 (s, 1H, H^5), 7.00 (s, 2H), 7.4–8.0 (m, 5H, Ph), 9.14 (s, 1H, H^3), 8.0–10.0 (br. s, 3H, 3OH).

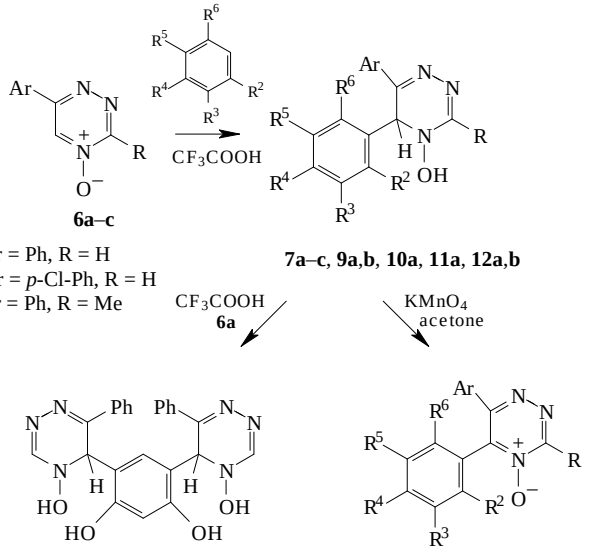
For **12b**: mp 211–213 °C; ^{1}H NMR ([$^2H_6$]DMSO) δ/ppm: 2.12 (s, 6H, 2Me), 5.62 (s, 1H, H^3), 6.95 (s, 2H), 7.3–8.8 (m, 4H, *p*-Cl-Ph), 7.92 (s, 1H, H^3), 8.45 (br. s, 1H, OH), 10.5–11.5 (br. s, 1H, OH).

For **13a**: mp > 250 °C; ^{1}H NMR ([$^2H_6$]DMSO) δ/ppm: 6.24 (dd, 1H), 6.28 (d, 1H), 6.95 (d, 1H), 7.41 (s, 4H, Ph), 9.60 (br. s, 3H, 2OH, H^3).

For **13b**: mp > 250 °C; ^{1}H NMR ([$^2H_6$]DMSO) δ/ppm: 6.24–7.00 (m, 3H), 7.41 (s, 4H, *p*-Cl-Ph), 9.60 (br. s, 3H, H^3 and 2OH), MS, *m*/*z*: 317 (24), 315 (54), 316 (24), 299 (19), 272 (29), 270 (91), 244 (48), 235 (100), 178 (17), 152 (80), 139 (18).

For **14a**: mp 202–204 °C; ^{1}H NMR ([$^2H_6$]DMSO) δ/ppm: 2.08 (s, 6H, 2Me), 6.98 (s, 2H), 7.39 (s, 5H, Ph), 9.63 (s, 1H, H^3).

For **14b**: mp 233–235 °C; ^{1}H NMR ([$^2H_6$]DMSO) δ/ppm: 2.12 (s, 6H, 2Me), 6.95 (s, 2H), 7.4 (s, 4H, *p*-Cl-Ph), 9.63 (s, 1H, H^3).



	Ar	R	R^2	R^3	R^4	R^5	R^6
7a, **13a**	Ph	H	OH	H	OH	H	H
7b, **13b**	*p*-Cl-Ph	H	OH	H	OH	H	H
7c	Ph	Me	OH	H	OH	H	H
9a	Ph	H	OH	H	H	H	H
9b	*p*-Cl-Ph	H	OH	H	H	H	H
10a	Ph	H	OEt	H	H	H	H
11a	Ph	H	H	H	OEt	H	H
12a, **14a**	Ph	H	OH	Me	H	H	Me
12b, **14b**	*p*-Cl-Ph	H	OH	Me	H	H	Me

Scheme 2

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