A general method for the synthesis of 1,2,4-triazine 4-oxides

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A new method for the synthesis of 1,2,4-triazine 4-oxide derivatives has been suggested; this method includes the reaction of isonitrosoketone hydrazones **2** with aldehydes followed by oxidation of 3-R-3,4-dihydro-4-hydroxy-6-phenyl-1,2,4-triazines **3** by lead tetraacetate.

Only one possibility for the synthesis of 1,2,4-triazine 4-oxides **1** (R = Alkyl, Aryl) is known: the reaction of hydrazones of isonitrosoketones **2** with ortho or imino esters.[1] We have found a new pathway from hydrazones **2** to 1,2,4-triazine 4-oxides **1** which allows the use of aldehydes. Thus, interaction of isonitrosoacetophenone hydrazones **2** with any aliphatic, aromatic and heteroaromatic aldehyde and further treatment of the reaction mixture with lead tetraacetate leads to the corresponding 6-phenyl-3-R-1,2,4-triazine 4-oxides **1a**–**d**,**f**–**j**,[†] in good yields (60–70%).

When the hydrazone **2** was treated with acetic, propionic or enanthic aldehyde in benzene, intermediate 3-methyl-, 3-ethyl- or 3-hexyl-3,4-dihydro-4-hydroxy-6-phenyl-1,2,4-triazines **3a**,**b**,**d** were separated from the reaction mixture. The reaction appears to proceed *via* formation of alkylidene hydrazones **4** followed by their transformation into dihydro-1,2,4-triazines **3**, which are oxidized by lead tetraacetate in acetic acid affording 3-methyl-, 3-ethyl- and 3-heptyl-6-phenyl-1,2,4-triazine 4-oxides **1a**,**b**,**d**. Use of glyoxylic acid as aldehyde gave 3-carboxydihydro-1,2,4-triazine **3e**, oxidation of which is accompanied by decarboxylation yielding 6-phenyl-1,2,4-triazine 4-oxide **1j**.

Thus, the reaction of hydrazone **2** with aldehydes is a convenient method of obtaining 1,2,4-triazine 4-oxides with hardly any substituents in the 3-position of the heterocyclic system.

The structure of the compounds obtained was established by ^{1}H NMR[‡] and also confirmed by straightforward syntheses performed for **1a**,**b**,**f**,**g**,**j**.[2,3]

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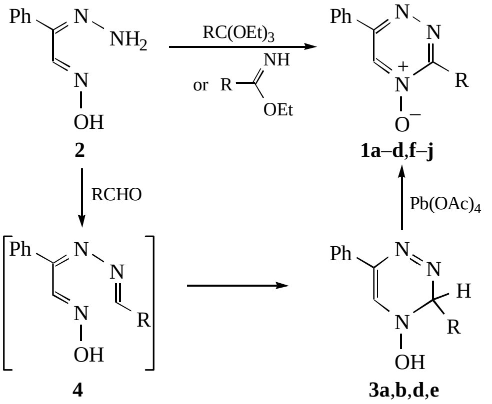

a R = Me
b R = Et
c R = Pr^i
d R = C_7H_{15}
e R = COOH
f R = Ph
g R = p-$NO_2C_6H_4$
h R = p-BrC_6H_4
i R = furan-2-yl
j R = H

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[†] *A typical procedure for the synthesis of* 6-*phenyl*-3-*R*-1,2,4-*triazine* 4-*oxides* **1a**–**d**,**f**–**j**. Method A. The hydrazone of isonitrosoacetophenone **2** (815 mg, 5 mmol) and the corresponding aldehyde (5 mmol) were dissolved in 5 ml of ethanol and kept at room temperature for 1 h. The reaction mixture was evaporated *in vacuo*, added to a freshly prepared solution of lead tetraacetate [obtained by heating Pb_3O_4 (3430 mg) in 15 ml of acetic acid] and stirred at room temperature for 30 min. The reaction mixture was diluted with water (50 ml) and the precipitate obtained was filtered off and recrystallized from ethanol.

Method B. The hydrazone of isonitrosoacetophenone **2** (815 mg, 5 mmol) and aldehyde (5 mmol) were dissolved in 15 ml of benzene and kept at room temperature for 1 h. The sediment of dihydrotriazine **3a**,**b**,**d**,**e** was filtered off and washed with ether. **3a**,**b**,**d**,**e** (3 mmol) was added to a freshly prepared solution of lead tetraacetate [obtained by heating Pb_3O_4 (2050 mg) in 15 ml of acetic acid] and stirred at room temperature for 30 min. The reaction mixture was diluted with water (50 ml) and the precipitate obtained was filtered off and recrystallized from ethanol.

[‡] All new compounds gave satisfactory analytical and spectral data.

For **1a**: mp 182–184 °C (lit.,[2] 184 °C), ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.42 (d, 3H, CH_3), 7.3–7.8 (m, 5H, Ph), 7.90 (s, 1H, H^5).

For **1b**: mp 123–125 °C, ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.38 (t, 3H, CH_2–CH_3), 3.11 (q, 2H, CH_2–CH_3), 7.5–8.3 (m, 5H, Ph), 9.18 (s, 1H, H^5).

For **1c**: mp 111–112 °C, ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.36 [d, 6H, CH–$(CH_3)_2$], 3.6–3.8 [m, 1H, CH–$(CH_3)_2$], 7.5–8.3 (m, 5H, Ph), 9.20 (s, 1H, H^5).

For **1d**: mp 87–88 °C, ^{1}H NMR ([$^2H_6$]DMSO) δ: 0.87 [br. t, 3H, $(CH_2)_6$–CH_3], 1.1–2.0 [m, 10H, CH_2–$(CH_2)_5$–CH_3], 3.07 [t, 2H, CH_2–$(CH_2)_5$–CH_3], 7.5–8.3 (m, 5H, Ph), 9.18 (s, 1H, H^5).

For **1f**: mp 168–171 °C (lit.,[2] 171 °C), ^{1}H NMR ([$^2H_6$]DMSO) δ: 7.3–7.8 (m, 10H, 2Ph), 9.25 (s, 1H, H^5).

For **1g**: mp 280–282 °C (lit.,[3] 282 °C), ^{1}H NMR ([$^2H_6$]DMSO) δ: 7.5–7.7 (m, 3H), 8.2–8.4 (m, 2H), 8.41 (d, 2H), 8.38 (d, 2H), 9.34 (s, 1H, H^5).

For **1h**: mp 248–250 °C, ^{1}H NMR ([$^2H_6$]DMSO) δ: 7.5–8.4 (m, 9H, Ph and p-Br–Ph), 9.33 (s, 1H, H^5).

For **1i**: mp 236–239 °C, ^{1}H NMR ([$^2H_6$]DMSO) δ: 6.84 (dd, 1H), 7.5–7.8 (m, 3H), 8.01 (dd, 1H), 8.1–8.3 (m, 3H), 9.32 (s, 1H, H^5).

For **1j**: mp 139–141 °C (lit.,[2] 141 °C), ^{1}H NMR ([$^2H_6$]DMSO) δ: 7.5–8.3 (m, 5H, Ph), 9.21 (d, 1H, H^5), 9.61(d, 1H, H^3).

For **3a**: mp 180 °C, ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.42 (d, 3H, CH_3), 4.72 (q, 1H, H^3), 7.3–7.8 (m, 5H, Ph), 7.90 (s, 1H, H^5), 8.84 (br. s, 1H, NOH).

For **3b**: mp 159 °C, ^{1}H NMR ([$^2H_6$]DMSO) δ: 0.98 (t, 3H, CH_2CH_3), 1.76 (dq, 2H, CH_2CH_3), 4.66 (t, 1H, H^3), 7.3–7.8 (m, 5H, Ph), 7.88 (s, 1H, H^5), 8.94 (br. s, 1H, NOH).

For **3d**: mp 159 °C, ^{1}H NMR ([$^2H_6$]DMSO) δ: 0.8–2.0 (m, 13H, C_6H_{13}), 4.72 (br. t, 1H, H^3), 7.3–7.8 (m, 5H, Ph), 7.90 (s, 1H, H^5), 8.95 (br. s, 1H, NOH).

For **3e**: mp 187 °C, ^{1}H NMR ([$^2H_6$]DMSO) δ: 5.49 (s, 1H, H^3), 7.3–7.8 (m, 5H, Ph), 8.09 (s, 1H, H^5), 9.60 (br. s, 1H, NOH), 12.3 (br. s, 1H, OH).