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Nucleophilic substitution of hydrogen in 3,6-diphenyl-1,2,4-triazine 4-oxide

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Reactions of 3,6-diphenyl-1,2,4-triazine 4-oxide 1 with indoles 2a,b in the presence of acid give the products of substitution of the H(5) atom, 5-(indolyl-3)-1,2,4-triazines 3a,b; the reaction of 1 with CH-acids in the presence of triethylamine also yields substitution products 5, and the derivative of ditriazinylmethane 6 was isolated along with product 5 in the reaction of 1 with acetyl- and benzoylacetone.

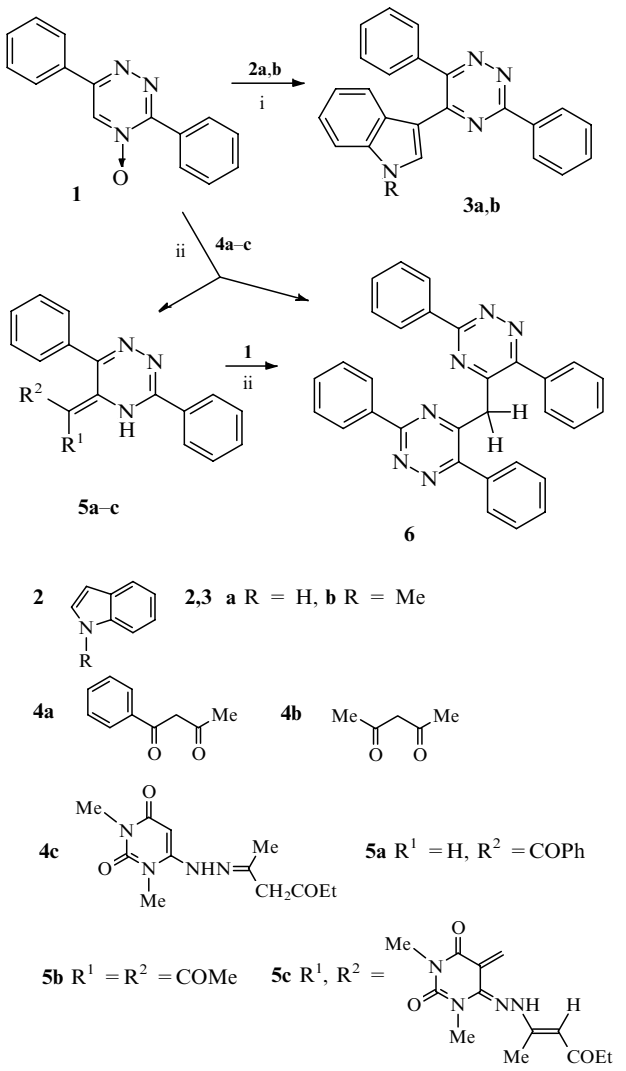
It is known that derivatives of 1,2,4-triazine 4-oxides with hydrogen substituents at C(3) and C(5) react with water in the presence of acid or base to open the triazine ring at the C(3)–C(4) bond. In the presence of benzoyl chloride, these compounds react with water to give 1,2,4-triazin-5-ones.[1] 6-Phenyl-1,2,4-triazine 4-oxide in reactions with some C-nucleophiles behaves differently, playing the role of a one-carbon cyclizing or linking agent.[2]

In this work, we found that 3,6-diphenyl-1,2,4-triazine 4-oxide **1** (Scheme 1) readily reacts with indoles **2a**,**b** on heating in butanol in the presence of trifluoroacetic acid to form products of substitution of the hydrogen atom at the C(5) atom **3a**,**b**.† The mass of **3a**,**b** as determined by mass spectrometry, corresponds to their calculated value. The most intense peaks in the mass-spectra of compounds **3a**,**c** correspond to cleavage of the triazine ring and detachment of the $PhCNN_2$ fragment with a mass of 131. We found unusual transformations in the reaction of compound **1** with benzoylacetone **4a**.‡ For example, the reaction of the *N*-oxide of **1** with benzoylacetone in dimethyl sulfoxide in the presence of triethylamine results in the formation of the product of substitution of hydrogen at the C(5) atom **5a**. It is of interest that no acetyl group is observed in the residue of benzoylacetone incorporated into the product. The derivative of ditriazinylmethane **6** was isolated from the reaction mass along with product **5a**. Compound **6** was also obtained by the reaction of equimolar amounts of compounds **1** and **5a** in dimethyl sulfoxide in the presence of triethylamine. Similar

† *Synthesis of the* 5-*indolyl*-3,6-*diphenyl*-1,2,4-*triazines* **3a,b**: 3,6-diphenyl-1,2,4-triazine 4-oxide **1** (0.5 mmol) and the indole **2a** or **2b** (0.5 mmol) butanol (3 ml) in trifluoroacetic acid (0.5 ml) were refluxed for 3 h. The mixture was cooled, the precipitate filtered off and recrystallized from ethanol.

3a: 56 mg (30%) yield; mp 291–292 °C; *m*/*z* 348 (M^+), 217 ($M^+ - PhCNN_2$).

3b: 95 mg (55%) yield; mp 206–207 °C; *m*/*z* 362 (M^+), 231 ($M^+ - PhCNN_2$).



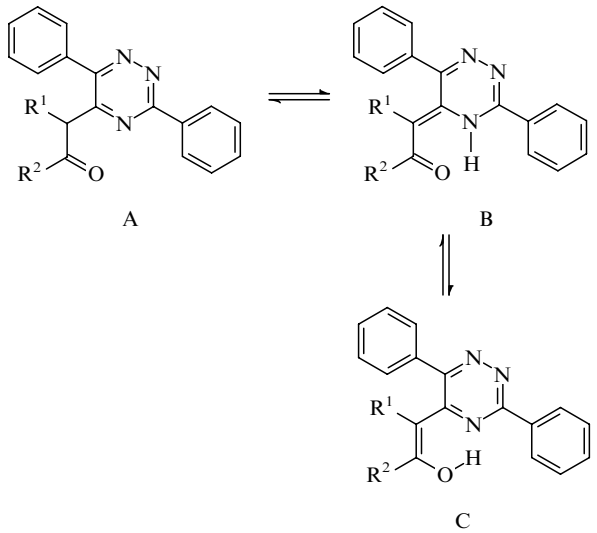
Scheme 1 *Reagents and conditions*: i, butanol, CF_3CO_2H, 117 °C; ii, DMSO, Et_3N, 20 °C.

transformations also occur in the reaction of the *N*-oxide of **1** with acetylacetone **4c**. This reaction also results in the formation of compound **6** and the substitution product **5c**.

The product of hydrogen substitution at C(5) in **1** is obtained under similar conditions by the reaction of **1** with the multicentred nucleophile 1,3-dimethyluracil-6-hydrazone **4c**. In this case, the nucleophile **4c** reacts with its CH-active centre (C5) of the uracil fragment, in a similar fashion to the reactions described in refs. 2 and 3.

It should be noted that the residue of the acetoacetic fragment of the molecule of compound **5c** formed has the enhydrazine structure in dimethyl sulfoxide solution. In fact, the signal of the C atom of the CH group of enhydrazine **5c** (δ = 111.42 ppm) in the ^{13}C NMR spectrum appears as the doublet of the quartet (^1J = 164 Hz, ^3J = 4.4 Hz).

Compounds **5** can exist as three tautomeric structures A–C, in which B and C are stabilized by intramolecular hydrogen bonds (Scheme 2).



Scheme 2

The absence of a signal due to a methylene group in the ^1H NMR spectrum of a chloroform solution of compound **5a** and the signal of the proton of the methine group at 6.4 ppm[§] allows one to exclude structure A from consideration. At the same time, the high value of the chemical shift of the carbonyl carbon (δ = 180.73 ppm) testifies in favour of the tautomeric keto-form B.

The small value of the chemical shift of the signal of one of the methyl groups (δ = 1.5 ppm) of compound **5b** is of interest. This is likely to be related to anisotropic screening of these protons by the C(6)-phenyl substituent.

For the methylene protons in compound **6** two doublets at 3.10 and 5.40 ppm (J = 12.2 Hz) were observed. This substantial difference in chemical shifts is caused by an anisotropic effect due to the phenyl groups and heterocyclic rings.

The formation of substitution products **3** and **5** agrees with the concept of the mechanism of substitution of a hydrogen atom in the heterocyclic *N*-oxides.[4]

[‡] *Synthesis of* **5a–c** *and* **6**: (*a*) 3,6-diphenyl-1,2,4-triazine 4-oxide **1** (0.5 mmol), benzoylacetone **4a** (0.5 mmol) and triethylamine (0.06 ml) in dimethyl sulfoxide (1 ml) was stirred for 24 h at 20 °C. The reaction mixture was diluted with water (2 ml) and acidified to pH 5–6 with HCl (10%). The precipitate was filtered off, treated with hot ethanol (5.0 ml) and **6** separated by filtration of the hot solution. The filtrate was diluted with water (5 ml) and acidified with HCl (0.05 ml, 10%). **5a** was separated by filtration and recrystallised from acetic acid.

5a: 30 mg (9%); mp 198–199 °C; *m*/*z* 351 (M^+).

6: 40 mg (10%); mp 220–221 °C; *m*/*z* 478 (M^+).

3,6-Diphenyl-1,2,4-triazine 4-oxide **1** (0.05 mmol), 4,5-dihydro-5-(benzoylmethylenyl)-3,6-diphenyl-1,2,4-triazine **5a** (0.05 mmol), and triethylamine (0.01 ml) was stirred for 24 h at 20 °C. The precipitate was filtered off, and recrystallised from acetic acid. Yield of **6**: 14 mg, 60%.

(*b*) **1** (0.5 mmol), acetylacetone **4b** (1.0 mmol) and triethylamine (0.05 ml) in dimethyl sulfoxide (1 ml) was stirred for 48 h at 20 °C. Work-up as (*a*).

5b: 30 mg (10%); mp 109–110 °C (ethanol); *m*/*z* 331 (M^+), 316 ($M^+ - Me$).

6: 20 mg (4%).

(*c*) **1** (0.3 mmol), the hydrazone **4c** (0.3 mmol) and triethylamine (0.04 ml) in dimethylformamide (1 ml) was stirred for 24 h at 20 °C. The reaction mixture was diluted with water (1 ml) and acidified with HCl (10%) to pH 4–5. The precipitate was filtered off and recrystallized from ethanol.

5c: 60 mg (35%); mp 256–257 °C; *m*/*z* 513 (M^+).

[§] *Spectral data*. ^1H NMR **5a**: ($CDCl_3$), 6.40 (1H, s, CH), 7.30–8.40 (15H, m, CH_{Ar}), 15.80 (1H, s, NH).

5b: ([$^2H_6$]DMSO): 1.50 (3H, s, CH_3), 2.60 (2H, s, CH_2), 7.10–8.10 (10H, m, CH_{Ar}).

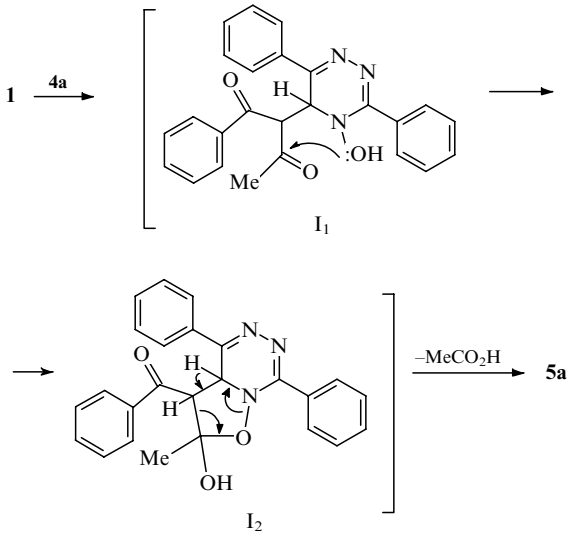
5c: ([$^2H_6$]DMSO): 1.10 (3H, t, J = 7.0 Hz, CH_3), 2.50 (3H, br.s, CH_3), 3.10 (3H, s, CH_3), 4.00 (2H, q, J = 7.0 Hz, CH_2), 6.10 (1H, q, J = 0.9 Hz, CH), 7.30–7.80 (10H, m, CH_{Ar}).

6: ([$^2H_6$]DMSO): 3.10 (1H, d, J = 12.2 Hz, CH), 5.40 (1H, d, J = 12.2 Hz, CH), 7.10–8.10 (20H, m, CH_{Ar}).

^{13}C NMR ($CDCl_3$) for **5a**: 90.01 (CH), 126.83, 127.65, 128.79, 128.96, 129.12, 129.29, 130.20, 131.86, 132.50, 134.49, 136.23 (Car), 149.36, 154.32, 155.63 (C3, C5, C6); 180.73 (CO).

To date, no examples of hydrogen atom substitution by C-nucleophiles have been described for *N*-4-oxides of 1,2,4-triazine, an occurrence which is most likely related to the easy ring-opening of these compounds at the C(3)–N(4) bond. However, the same time, the addition of C-nucleophiles to the C(5) atom followed by oxidation of the adducts formed to give the products of the H(5) atom substitution is described for 3-phenyl-6-methyl-1,2,4-triazine.[5]

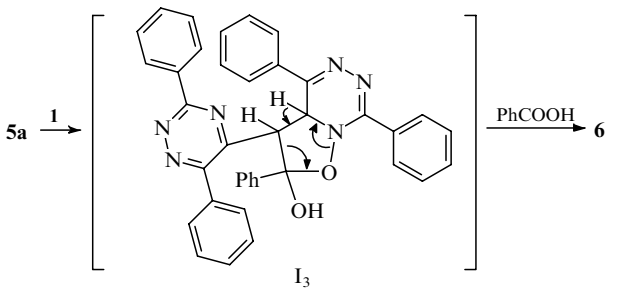
The formation of **5a** and **6** in the reaction of **1** with benzoylacetone can be explained by the following mechanism: addition of benzoylacetone to C(5) of **1** gives the intermediate I_1 . The orientation of the N–OH and acetyl groups can easily lead to the elimination of acetic acid either by direct transfer of the hydroxyl group or *via* intermediate I_2 (Scheme 3).



Scheme 3

The product **5a** formed can react as a nucleophile with the initial compound **1** to give intermediate I_3, from which benzoic acid is eliminated to yield compound **6** (Scheme 4).

The formation of **5b** and **6** in the reaction of **1** with acetylacetone **4b** shows that intermediate I_4 can react in two ways: first, by the elimination of water and the formation of **5b** (route A) and, second, by the elimination of acetic acid and the reaction of intermediate I_5, which cannot be isolated, with a second molecule of **1** (route B) (Scheme 5).



Scheme 4

It is evident that the formation of **5a** and **6** is possible only when the reaction rates of **1** + **4a** → **5a** and **5a** + **1** → **6** are comparable.

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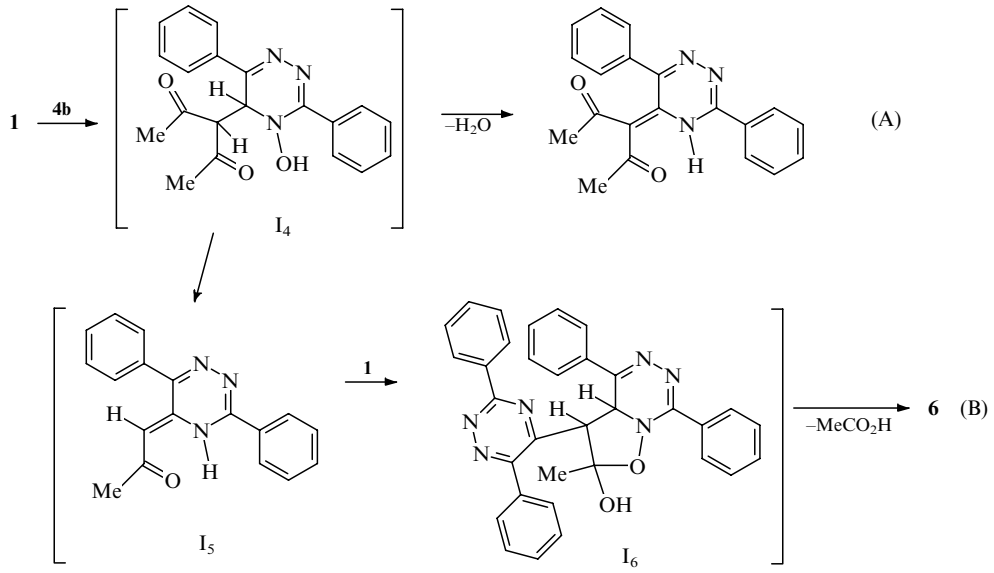

Scheme 5