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REACTIONS OF 1,2,4-TRIAZINES WITH NUCLEOPHILES. 6*. USE OF S_N^H METHODOLOGY FOR THE DIRECT INTRODUCTION OF CYCLIC DIKETONE RESIDUE INTO THE 1,2,4-TRIAZINE RING

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3-R-6-Phenyl-1,2,4-triazine 4-oxides react with cyclic β-diketones (dimethylbarbituric acid, dimedone, and indan) in both acidic (substrate activation) and basic conditions (nucleophile activation) with formation of σ^H-adducts, intermediates in the nucleophilic substitution of hydrogen (S_N^H) in 3-R-5-Nu-4-hydroxy-6-phenyl-4,5-dihydro-1,2,4-triazines. Oxidative aromatisation of these intermediates or auto-aromatisation of acylated (benzoyl chloride) at the NOH σ-adducts with elimination of benzoic acid gave the corresponding substituted 1,2,4-triazine 4-oxides or 1,2,4-triazines.

Keywords: 1,2,4-triazines, nucleophilic substitution of hydrogen, cyclic β-diketones.

Azine N-oxides undergo nucleophilic substitution of hydrogen (S_N^H) with CH active compounds in the presence of acylating agents relatively easily to give the corresponding substituted azines with loss of the N-oxide function [2]. Only one example of a successful reaction with CH active compounds is known in the 1,2,4-triazine N-oxide series. Reaction of 3,6-diphenyl-1,2,4-triazine 4-oxide with benzoylacetone in the presence of triethylamine gave 5-benzoylmethyleno-3,6-diphenyl-4H-1,2,4-triazine [3]. Attempts to carry out similar reactions with 6-phenyl-1,2,4-triazine 4-oxide, which has no substituent at position 3 gave products of the heterocycle degradation.

In the present paper the interaction of 3-R-6-phenyl-1,2,4-triazine 4-oxides (**1**) with cyclic β-diketones has been studied. We have shown that oxides **1** do not react with dimedone, indan, or 1,3-dimethylbarbituric acid without the additional activation of the reagent or the substrate. To activate the substrate we chose the well recommended method of protonation [1, 5]. Thus, the oxides **1a-d**, independent of the substituent at position 3, react with cyclic β-diketones at room temperature in the presence of trifluoroacetic acid to form stable σ^H-adducts **2-4**. The addition products with dimedone were isolated as their trifluoroacetic acid salts **2a-d** (Scheme 1).

* For part 5, see [1].

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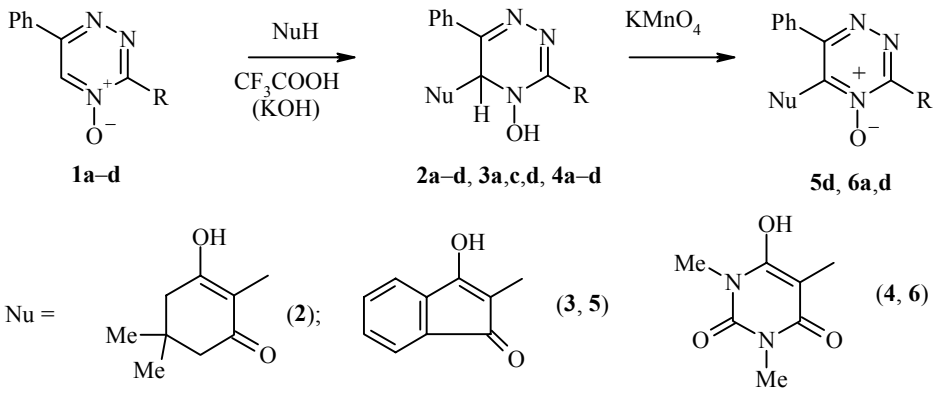
Scheme 1



a R = H, **b** R = Me, **c** R = Et, **d** R = Ph

Reactions with cyclic β-diketones also occurs under basic conditions, i.e., activation of the nucleophile by forming the anion. For example, in the reaction of oxides **1** with indanedione-1,3 in DMSO in the presence of triethylamine or with 1,3-dimethylbarbituric acid in ethanol in the presence of KOH the corresponding 4-hydroxytriazines **3d** and **4d** (Scheme 1) were isolated in 75-90% yields.

The ^{1}H NMR spectra of compounds **2-4** contain a one proton singlet in the 6.2-6.4 ppm region, corresponding to a proton on the sp^3-carbon atom in position 5 (Table 1) which is characteristic for adducts of this type [1, 4].

TABLE 1. ^{1}H NMR Spectra of Compounds **2-7**

Compound	Chemical shifts δ, ppm (DMSO-d_6)	
	H(5), s	other signals
2a	6.28	0.76 (6H, s, $2CH_3$); 2.22 (4H, s, $2CH_2$); 7.36-7.75 (5H, m, Ph); 9.01 (1H, s, H(3))
2b	6.27	0.82 (6H, s, $2CH_3$); 2.34 (3H, s, CH_3); 2.23 (4H, s, $2CH_2$); 7.31-7.85 (5H, m, Ph); 12.6 (1H, br. s, OH)
2c	6.35	0.83 (6H, s, $2CH_3$); 1.3 (3H, t, $C\underline{H}_3CH_2$); 2.3 (4H, s, $2CH_2$); 2.74 (2H, q, $CH_3C\underline{H}_2$); 7.3-7.9 (5H, m, Ph)
2d	6.40	0.8 (6H, s, $2CH_3$); 2.27 (4H, s, $2CH_2$); 7.40-7.83 (10H, m, 2Ph); 10.28 (1H, br. s, OH); 12.9 (1H, br. s, OH)
3a	5.74	7.08-7.97 (9H, m); 9.05 (1H, s, H(3)); 12.67 (1H, s, OH)
3c	5.75	1.3 (3H, t, $C\underline{H}_3CH_2$); 2.6 (2H, q, $CH_3C\underline{H}_2$); 7.0-8.1 (9H, m)
3d	5.86	7.15-8.08 (14H, m); 13.0 (1H, s, OH)
4a	6.20	3.07 (6H, s, $2NCH_3$); 7.3-8.0 (5H, m, Ph); 8.96 (1H, d, H(3)); 11.78 (1H, br. s, OH); 12.50 (1H, br. d, NOH)
4b	6.19	2.26 (3H, s, CH_3); 3.03 (6H, s, $2NCH_3$); 7.25-7.99 (5H, m, Ph); 12.36 (1H, br. s, OH)
4c	6.19	1.21 (3H, t, $C\underline{H}_3CH_2$); 2.59 (2H, q, $CH_3C\underline{H}_2$); 3.03 (6H, s, $2NCH_3$); 7.25-8.10 (5H, m, Ph); 12.33 (1H, s, OH)
4d	6.34	3.07 (6H, s, $2NCH_3$); 7.32-8.06 (10H, m, 2Ph); 11.62 (1H, br. s, OH); 12.78 (1H, br. s, OH)
5Ad*	—	5.36 (1H, s, H-(dioxoindanyl)); 7.40-8.18 (14H, m)
5Bd*	—	7.40-8.18 (14H, m), 12.2 (1H, br. s, OH)
6a	—	2.97 (6H, s, N-CH_3); 7.38-7.63 (5H, m, Ph); 9.40 (1H, s, H(3))
6d	—	2.98 (1H, s, 2N-CH_3); 7.36-8.18 (10H, m, 2Ph)
7d	—	3.07 (6H, s, 2N-CH_3); 7.3-8.5 (10H, m, 2Ph)

* Compound **5d** exists in DMSO-d_6 as a 3:7 equilibrium mixture of the enol **5B** and diketone **5A** forms.

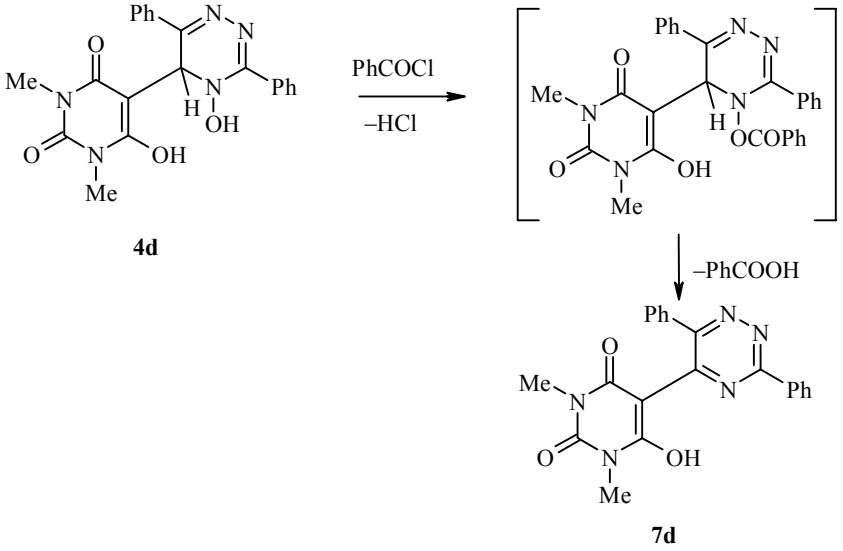
It should be noted that in distinction from literature examples for reactions of unsubstituted at the atom $C_{(3)}$ oxide **1a** [4] with CH active compounds, in the given reaction conditions the formation of open chain products obtained by nucleophilic addition to this position was not determined.

The isolated σ^H-adducts **2-4** are intermediates in the S_N^H reaction, the spontaneous *auto*-aromatisation by elimination of water molecules characteristic for similar reactions with azine N-oxides was not observed. However we succeeded in carrying out oxidative aromatisation of these compounds. For example, treatment of compounds **3d** and **4c,d** with potassium permanganate in acetone gave the corresponding 5-substituted oxides **5d** and **6c,d**.

In contrast to those of the initial adducts the ^{1}H NMR spectra of the oxides **5c** and **6c,d** did not contain signals for a proton at $C_{(5)}$ in the 6.2-6.4 ppm region nor for the N–OH proton at 12.5 ppm, while signals of the protons of the substituent R underwent a low field shift (Table 1).

Aromatisation of adduct **4d** with loss of the N-oxide unit was readily achieved with acylating agents, e.g., benzoyl chloride. In all probability aromatisation with loss of a benzoic acid moiety occurs after benzoylation of the N–OH σ^H-adduct **4d**. Triazine **7d** (Scheme 2) was obtained in 67% yield on treatment of the triazine **4d** with benzoyl chloride in dioxane. Elemental analysis results and ^{1}H NMR spectroscopy confirm the structure of **7d**.

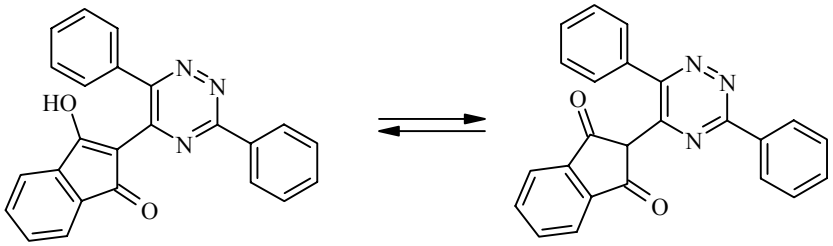
Scheme 2



According to ^{1}H NMR spectroscopy, the β-diketone fragment in adducts **2-4** exists in the enol form. This is indicated by the absence o coupling between the proton at position 5 of the 1,2,4-triazine system and the proton of the nucleophilic unit and also the absence of a methyne proton and the presence of an OH proton signal in the 11.5-11.7 ppm region. The same picture is observed for the triazine **7d** and the oxides **6a,d** which contain the dimethylbarbituric acid unit. The oxide **5d** exists in DMSO-d_6 as mixture of two tautomers in which the dioxoindanyl fragment is found as the diketone **5A,d** and enol **5B,d** forms. Thus in the ^{1}H NMR spectrum of this compound, apart from the aromatic protons of two phenyl groups there are a one proton singlet of the methyne proton of the diketo form **5Ad** at 5.36 ppm and a broad one proton singlet of the hydroxyl of the enol form **5Bd** at 12.2 ppm (Table 1). Comparison of the integrated intensities of these signals shows that the ratio of the tautomers **5Ad** and **5Bd** is 7:3.

TABLE 2. Characteristics of the Compounds Synthesized, **2-7**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
2a	$C_{17}H_{19}N_3O_3 \cdot CF_3CO_2H$	53.19 / 53.40	4.71 / 4.72	9.70 / 9.83	156-160	71
2b	$C_{18}H_{21}N_3O_3 \cdot CF_3CO_2H$	54.21 / 54.42	5.20 / 5.02	9.39 / 9.52	183-187	67
2c	$C_{19}H_{23}N_3O_3 \cdot CF_3CO_2H$	55.21 / 55.38	5.48 / 5.31	9.07 / 9.23	215-219	70
2d	$C_{23}H_{23}N_3O_3 \cdot CF_3CO_2H$	59.50 / 59.64	4.99 / 4.80	8.23 / 8.35	>250	74
3a	$C_{18}H_{13}N_3O_3$	67.49 / 67.71	4.25 / 4.10	13.09 / 13.16	156-159	61
3c	$C_{20}H_{17}N_3O_3$	69.00 / 69.15	4.99 / 4.93	12.01 / 12.10	173-176	58
3d	$C_{24}H_{17}N_3O_3$	72.75 / 72.90	4.36 / 4.33	10.65 / 10.63	181-185	65
4a	$C_{15}H_{15}N_5O_4$	54.83 / 54.71	4.41 / 4.59	21.12 / 21.27	>250	79
4b	$C_{16}H_{17}N_5O_4$	55.81 / 55.97	5.12 / 4.99	20.29 / 20.40	>250	75
4c	$C_{17}H_{19}N_5O_4$	57.27 / 57.14	5.28 / 5.36	19.48 / 19.60	>250	71
4d	$C_{21}H_{19}N_5O_4$	62.10 / 62.22	4.85 / 4.72	17.21 / 17.27	>250	87
5d	$C_{24}H_{15}N_3O_3$	73.32 / 73.27	3.79 / 3.84	10.57 / 10.68	>250	53
6a	$C_{15}H_{13}N_5O_4$	55.19 / 55.05	4.15 / 4.00	21.26 / 21.40	>250	60
6d	$C_{21}H_{17}N_5O_4$	62.37 / 62.53	4.33 / 4.25	17.21 / 17.36	>250	68
7d	$C_{21}H_{17}N_5O_3$	65.24 / 65.11	4.56 / 4.42	18.00 / 18.08	228-229	78



5Bd **5Ad**

Thus we have developed a suitable method for the introduction of cyclic β-diketone residue in position 5 of the 1,2,4-triazine ring. The proposed method for aromatisation of the σ^H-adducts affords the preparation of both the functionalised 1,2,4-triazines and their N-oxides.

EXPERIMENTAL

^{1}H NMR spectra were recorded with a Bruker WM-250 spectrometer (250.135 MHz, internal standard TMS). The course of reactions and the purity of products were monitored by TLC (Silufol UV-254, ethyl acetate, revelation by UV light).

General Method for Preparation of 3-R-5-(3-Hydroxy-5,5-dimethyl-1-oxocyclohex-2-en-2-yl)-4-hydroxy-6-phenyl-4,5-dihydro-1,2,4-triazine Trifluoroacetates (2a-d). Dimedone (560 mg, 4 mmol) was added to a solution of an oxide **1a-d** (4 mmol) in a mixture of methylene chloride (10 ml) and trifluoroacetic acid (0.5 ml). After 72 h at room temperature the precipitate was filtered off and washed with methylene chloride.

General Method for the Preparation of 3-R-5-(3-Hydroxy-1H-1-oxoinden-2-yl)-4-hydroxy-6-phenyl-4,5-dihydro-1,2,4-triazines (3a,c,d). A. Indandione (584 mg, 4 mmol) was added to a solution of an oxide **1a,c,d** (4 mmol) in trifluoroacetic acid (2 ml). After standing for 72 h at room temperature the reaction mixture was diluted with ethanol (8 ml). The precipitate which separated after refrigeration was filtered off and washed with ethanol.

B. A mixture of an oxide **1a,c,d** (4 mmol) and indandione (584 mg, 4 mmol) was dissolved in DMSO (2 ml) and triethylamine (0.5 ml). After standing for 48 h at room temperature the reaction mixture was diluted with water and acidified with acetic acid (1 ml). The precipitate was filtered and washed with a great deal of ethanol.

General Method for the Preparation of 3-R-5-(6-Hydroxy-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-4-hydroxy-6-phenyl-4,5-dihydro-1,2,4-triazines (4a-d). A. N,N'-Dimethyl-barbituric acid (624 mg, 4 mmol) was added to a solution of an oxide **1a-d** (4 mmol) in trifluoroacetic acid (2 ml). After standing for 48 h at room temperature the reaction mixture was diluted with water, the precipitate was filtered off and washed with ethanol.

B. A solution of an oxide **1a-d** (4 mmol), N,N'-dimethylbarbituric acid (624 mg, 4 mmol), and KOH (230 mg) in ethanol (50 ml) was kept at room temperature for 24 h. The precipitate obtained after acidification with acetic acid was filtered off and washed with ethanol.

5-(3-Hydroxy-1H-1-oxoinden-2-yl)-3,6-diphenyl-1,2,4-triazine 4-Oxide (5d). Adduct **3d** (1.185 g, 3 mmol) was added to a solution of potassium permanganate (330 mg, 2.1 mmol) in acetone (50 ml). The suspension was stirred for 2 h at room temperature. Manganese dioxide was filtered off, the filtrate was acidified with acetic acid and heated to eliminate the residual manganese dioxide. The solution was diluted with water, the precipitate was filtered off and recrystallized from isopropanol.

General Method for the Preparation of 3-R-5-(6-Hydroxyl-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-6-phenyl-1,2,4-triazine 4-Oxides (6a,d). An adduct **4a,d** (3 mmol) was added to a solution of potassium permanganate (330 mg, 2.1 mmol) in acetone (5 ml). The suspension was stirred for 3 h at room temperature. Manganese dioxide was filtered off, the filtrate was evaporated to dryness in vacuum and the residue was recrystallized from *n*-butanol.

5-(6-Hydroxy-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-3,6-diphenyl-1,2,4-triazine (7d). Benzoyl chloride (0.12 ml, 1 mmol) was added to a solution of adduct **4d** (387 mg, 1 mmol) in dioxane (5 ml). The mixture was kept for 2 h, filtered, and diluted with ether. The yellowish precipitate was filtered off and reprecipitated from dioxane with ether.

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