Transformations of 6-Phenyl-1,2,4-triazine 4-Oxides in Reactions with Nucleophiles

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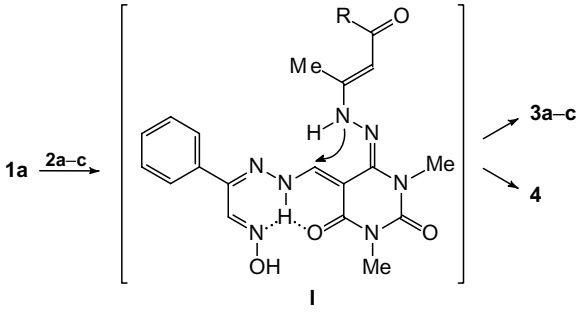
Reaction of 6-phenyl-1,2,4-triazine 4-oxide **1a** with 1,3-dimethyluracil-6-hydrazones **2a**–**c** in dimethylformamide in the presence of triethylamine affords the pyrazolo[3,4-*d*]pyrimidines **3a**–**c**; under similar conditions 1,2,4-triazine 4-oxide **1b** reacts with 1-phenyl-3-methylpyrazolone **7** to give the hydrazone derivative **8** and the dipyrazolylmethane derivative **9**.

It is known that 1,2,4-triazine 4-oxides react with water as well in acidic as in basic media by opening of the 1,2,4-triazine ring at the C(3)–N(4) bond. On the other hand, 1,2,4-triazine 4-oxides form 1,2,4-triazin-5-ones when treated with water in the presence of benzoyl chloride.[1] In this work we report that 6-phenyl-1,2,4-triazine 4-oxide **1a** reacts with the hydrazones **2a**–**c** in dry dimethylformamide (DMF) in the presence of triethylamine to give the pyrazolo[3,4-*d*]pyrimidines **3a**–**c** in 60–80% yield. Addition of 2-nitrobenzaldehyde at room temperature to the mother liquor obtained after separation of **3** affords the hydrazone **6a**, which confirms the existence of the hydrazine derivative **4** in the reaction mixture (Scheme 1).†

The formation of **3a**–**c** as well as **4** can be explained by formation of the intermediates **I**, cyclization of which affords **3a**–**c** and **4**.

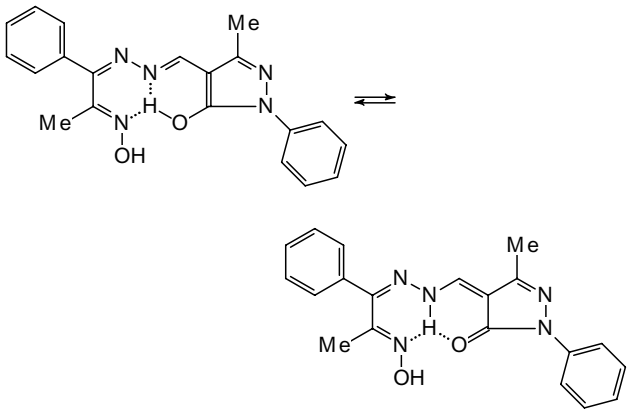


I

The pyrazolo[3,4-*d*]pyrimidine **3a** has already been isolated from the reaction of hydrazone **2a** with 6,8-dimethylpyrimido[5,4-*e*]-1,2,4-triazine-5,7-dione 4-oxide (fervenulin 4-oxide) under similar conditions in 42% yield.[2] The lower yield of **3a** in the reaction of **2a** with fervenulin 4-oxide can be explained by the more complex reaction pattern. In fact, the 5-nitroso-6-hydrazinouracil, formed in the reaction of **2a** with fervenulin 4-oxide, can react with **2a**, whereas in the reaction of **1** and **2a** the hydrazine derivate **4** is formed, which does not react with the hydrazone **2a**. From these results it follows that 6-phenyl-1,2,4-triazine 4-oxide **1a** is the more accessible and more effective (compared to fervenulin 4-oxide) one-carbon ring-forming agent in the synthesis of pyrazolo[3,4-*d*]pyrimidines from (1,3-dimethyl-2,4-dioxopyrimidin-6-yl)hydrazones of esters or amides of acetoacetic acid.

Reaction of 5-methyl-6-phenyl-1,2,4-triazine 4-oxide **1b** with 3-methyl-1-phenyl-5-pyrazolone **7** in dimethyl sulfoxide (DMSO) in the presence of triethylamine led to the isolation of the hydrazono oxime **8a** and the dipyrazolylmethane derivative **9**.‡ Compound **9** was also obtained by treatment of the hydrazono oxime **8a** with the pyrazolone **7** in DMSO in the presence of triethylamine. The normal hydroxy-pyrazole–pyrazolone tautomerism can be discussed for compound **8a**.§ In this case both tautomers have the same geometric structure, stabilized by hydrogen bonds.

The high electrophilicity and reactivity of C(6) in **8a**

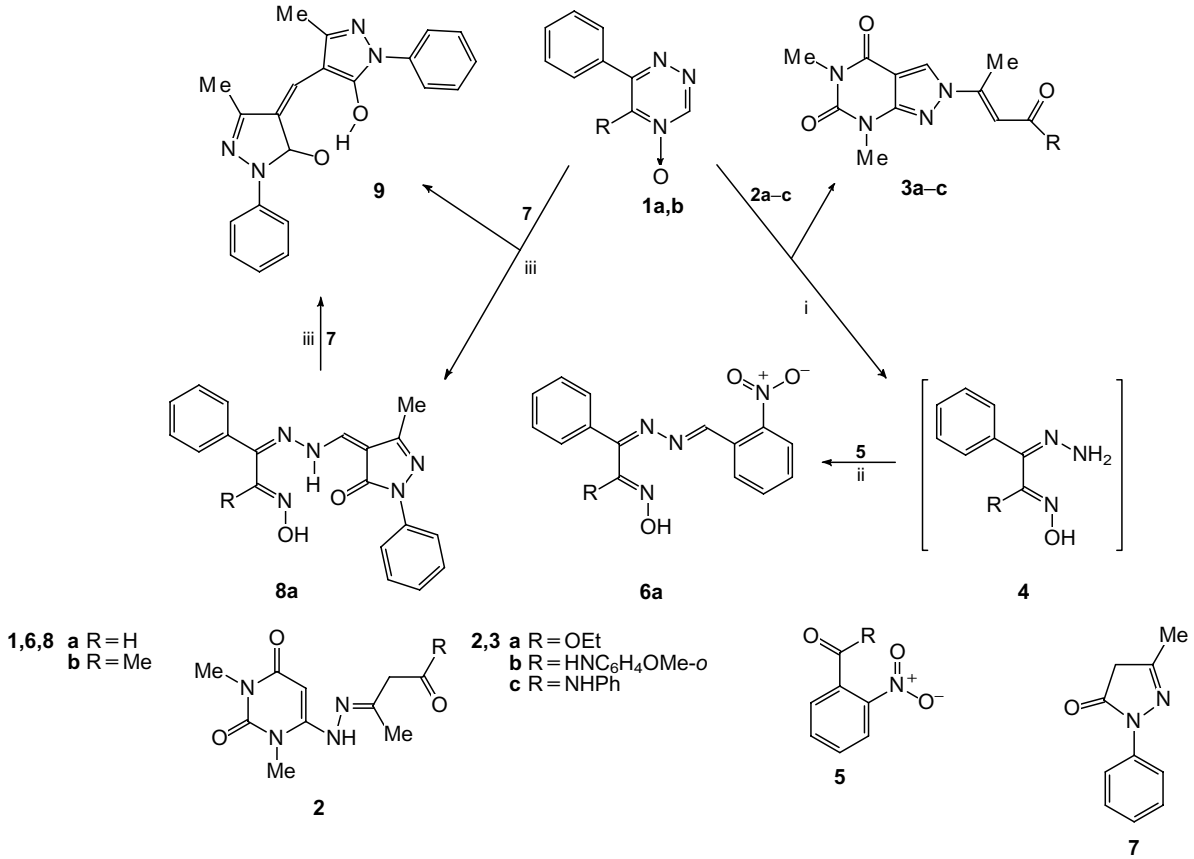


probably results from the electron-accepting aza or carbonyl groups and considerable conjugation in the six-membered pseudo-ring. A significant downfield shift of the signal for hydrogen (8.54 ppm) and carbon (148.57 ppm) atoms of the methine group (Figure 1) also supports this assumption. Only nine signals for carbon atoms are observed in the ^{13}C NMR spectrum of compound **9**. The reason for this is that the atoms of both phenylpyrazole fragments are equivalent due to the symmetry of the molecule. There is an axis of symmetry passing through the methine carbon and the hydrogen of the central eight-membered ring. According to X-ray diffraction

† General procedure for the synthesis of pyrazolo[3,4-*d*]pyrimidines **3a**–**c** and the hydrazone **6a**: the hydrazones **2a**–**c** (0.5 mmol) and triethylamine (0.5 mmol) were added to a solution of 6-phenyl-1,2,4-triazine 4-oxide **1a** (0.5 mmol) in DMF. The reaction mixture was kept at 20–25 °C for 48 h. The precipitate of **3a**–**c** formed was filtered and recrystallized from DMF. 2-Nitrobenzaldehyde (0.5 mmol), ethanol (3 ml) and 1 drop of conc. HCl were added to the mother liquor and the mixture was stirred for 5–10 min. The precipitate of **6a** was filtered and recrystallized from aqueous DMF. Compound **6a** was identical with the known compound formed from 4- and 2-nitrobenzaldehyde. Number of compound, m.p., yield: **3a**, 203–204 °C, 65% (**6a**, 205–206 °C, 30%); **3b**, 235–236 °C, 80% (**6a**, 40%); **3c**, 285–286 °C, 60% (**6a**, 50%).

‡ Preparation of **8a** and **9**:
(*a*) A mixture of 5-methyl-6-phenyl-1,2,4-triazine 4-oxide **1b** (0.5 mmol), 3-methyl-1-phenyl-5-pyrazolone **7** (0.5 mmol) and triethylamine (0.5 mmol) in DMSO (1 ml) was kept at 20–25 °C for 40 h. The reaction mixture was diluted with water (1:1) and acidified with 10% HCl until weakly acidic. The precipitate formed was filtered off and recrystallized from ethanol to give **9** in 20% yield, m.p. 181–182 °C. Evaporation of the ethanolic solution to 2/3 of its starting volume followed by filtration gave **8a** in 25% yield, m.p. 244–245 °C. (*b*) A mixture of compound **8a** (0.1 mmol) and **7** (0.1 mmol) in DMSO (1 ml) was kept at 20–25 °C for 24 h. The reaction mixture was diluted with water (1:1). Filtration of the precipitate and recrystallization from aqueous ethanol afforded **9** in 60% yield.

§ *Spectral data*. ^1H NMR ($[^2H_6]$DMSO) for **8a**: 2.03 (3H, s, Me), 2.18 (3H, s, Me), 7.10–7.97 (10H, m, CH_{arom}), 8.54 (1H, s, CH), 12.36 (1H, s, OH). ^{13}C NMR ($[^2H_6]$DMSO) for **8a**: 12.49 (Me), 14.13 (Me), 101.02 (C4), 117.61 (C18, C22), 123.82 (C20), 127.42 (C12, C16), 128.70 (C19, C21), 128.76 (C13, C15), 130.42 (C14), 134.27 (C11), 138.76 (C17), 148.57 (C6), 148.77 (C3), 148.95 (C9), 151.95 (C10), 164.42 (C5). ^1H NMR ($CDCl_3$) for **9**: (6H, s, Me), 7.22 (1H, s, CH), 7.24–7.92 (10H, m, CH_{arom}), 14.37 (^1H, s, OH). ^{13}C NMR ($CDCl_3$) for **9**: 13.02 (2Me), 109.60 (C2, C13), 121.17 (C8, C12, C19, C23), 126.64 (C10, C21), 129.01 (C9, C11, C20, C22), 137.75 (C7, C18), 138.38 (C1), 152.82 (C6, C17), 161.36 (C3, C14).



Scheme 1 *Reagents and conditions*: i, DMF, NEt_3, 20 °C; ii, DMF–EtOH, HCl, 20 °C; iii, DMSO, NEt_3, 20 °C.

data[¶] (Figure 2, Table 1), molecule **9** is composed of two pyrazole fragments, connected by a CH bridge and an intramolecular hydrogen bond. The phenylpyrazole fragments are almost planar. The dihedral angles between the plane of the phenyl and pyrazole rings are 8.53° and 12.81°. The central H-bonded eight-membered ring has a coplanar arrangement of the non-hydrogen atoms. The bond distances in **9** are close to the corresponding values in nitrogen-containing compounds with conjugated bonds.[3] The C(6)–N(5) (1.304 A) and C(17)–N(16) (1.297 A) bonds are double bonds. The observed bond lengths in the central ring indicate equal contributions of the two tautomeric forms to the structure. The hydrogen atom is located in the middle between O(24) and O(25). The O–H···O angle is 174.10° and the distance between O(24) and O(25) is 2.408 A. It is evident that the formation of the dipyrazolylmethane **9** results from nucleophilic attack of the pyrazolone **7** at **8a**. The intermediate formed is cleaved with formation of **9**. The reaction of **7** with **8a** is possible if the rate of this reaction is comparable with the rate of the reaction of **1b** with **7**. The observed transformations of 1,2,4-triazine 4-oxides in the

Table 1 Selected bond lengths and bond angles for compound **7**.

Bond length/Å		Bond angle/°	
C(1)–C(2)	1.387(3)	HO(24)C(3)	116.6(10)
C(2)–C(6)	1.433(2)	O(24)C(3)C(2)	131.2(2)
C(6)–C(26)	1.487(3)	C(3)C(2)C(1)	132.2(2)
C(6)–N(5)	1.304(2)	C(2)C(1)C(13)	136.8(2)
N(5)–N(4)	1.404(2)	C(1)C(13)C(14)	132.9(2)
C(3)–O(24)	1.274	C(13)C(14)O(25)	131.3(2)
O(24)–H	1.22(3)	C(14)O(25)H	115.4(11)
O(25)–H	1.19(3)	O(24)C(3)N(4)	122.3(2)
O(25)–C(14)	1.284(2)	C(2)C(3)N(4)	106.5(2)
C(14)–C(13)	1.420(3)	C(3)C(2)C(6)	104.1(2)
C(13)–C(17)	1.436(3)	C(2)C(6)N(5)	112.1(2)
C(17)–C(27)	1.487(3)	C(6)N(5)N(4)	105.8(2)
C(17)–N(16)	1.297(2)	N(5)N(4)C(3)	111.5(2)
N(16)–N(15)	1.402(2)	N(5)N(4)C(7)	118.1(2)
N(15)–C(14)	1.345(2)	C(12)C(7)C(8)	119.3(2)
N(15)–C(18)	1.427(2)	C(7)C(8)C(9)	119.8(2)
C(18)–C(19)	1.376(3)	C(8)C(9)C(10)	120.9(2)
C(19)–C(20)	1.369(3)	C(9)C(10)C(11)	119.3(2)
C(20)–C(21)	1.364(3)	C(10)C(11)C(12)	120.6(2)
C(21)–C(22)	1.362(3)	C(11)C(12)C(7)	120.1(2)
C(22)–C(23)	1.377(3)	C(14)C(13)C(17)	103.5(2)
C(23)–C(18)	1.370(3)	C(13)C(17)C(27)	127.5(2)
N(4)–C(7)	1.421(2)	C(27)C(17)N(16)	119.9(2)
C(7)–C(8)	1.376(3)	C(17)N(16)N(15)	105.5(2)
C(8)–C(9)	1.376(3)	N(16)N(15)C(14)	111.5(2)
C(9)–C(10)	1.365(1)	C(14)N(15)C(18)	130.6(2)
C(10)–C(11)	1.369(3)	N(15)C(18)C(23)	118.9(2)
C(11)–C(12)	1.373(3)	N(15)C(18)C(19)	121.3(2)
C(12)–C(7)	1.381(3)	C(19)C(18)C(23)	110.8(2)
		C(18)C(23)C(22)	119.6(2)
		C(23)C(22)C(21)	120.8(2)
		C(22)C(21)C(20)	119.2(2)
		C(21)C(20)C(19)	121.1(2)
		C(20)C(19)C(18)	119.5(2)

[¶] Crystal data and structure refinement for **9**. $C_{21}H_{18}N_4O_2$; M = 358.59; T 295 K. λ 0.71069 Å, monoclinic; space group $P21/c$; a = 12.818(2) Å, α = 90°, b = 19.300(5) Å, β = 94.54(2)°, c = 7.290(2) Å, γ = 90°. V = 1797.8(7) Å^3, Z = 4; D_c = 1.324 mg m^{-3}; absorption coefficient 0.088 mm^{-1}; F(000) 752; crystal size 1.75× 0.125 × 0.0375 mm; Q range for data collection 1.59 to 22.98°; index ranges $-14 < h < 14$, $0 < k < 21$, $-8 < l < 5$; 4620 reflections collected; 2487 independent reflections [R(int) = 0.0313]; absorption correction Psi-scan; max. and min. transmission 0.999 and 0.965; refinement method – full-matrix least-squares on F^2; data/restraints/parameters 2487/0/249; goodness-of-fit on F^2 1.017; final R indices [$I > 2\sigma(I)$] $R1$ = 0.0358, $wR2$ = 0.0887; R indices (all data) $R1$ = 0.0661, $wR2$ = 0.1036; extinction coefficient 0.023(2), largest diff. peak and hole 0.137 and −0.149 e Å^{-3}. Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC), see Notice to Authors, *Mendeleev Commun.*, 1995, issue 1.

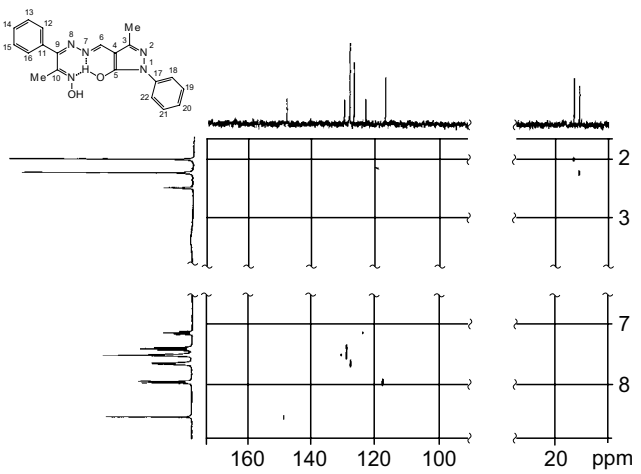


Figure 1 CH correlation for compound **8a**.

reaction with C-nucleophiles involve the following general steps: (1) addition of the nucleophile at C(3) of the 1,2,4-triazine ring; (2) opening of the 1,2,4-triazine ring at the C(3)–N(4) bond with formation of the corresponding hydrazine derivatives, which have an active electrophilic centre, the hydrazone carbon atom [the former C(3) of compounds **1**]. The direction of further transformations of the hydrazine intermediate formed depends on the competitive reactivity of nucleophiles present in the reaction mixture. This can be either a nucleophilic centre in the hydrazine intermediate (reaction of **1** and **2**) or unreacted starting material (reaction of **1** and **7**). It should be noted that although some regularities in the rehydrazination reactions are already known,[4] the addition of CH acids to hydrazones has been studied insufficiently.[5] The mechanism for the splitting of the hydrazine derivative **8** under the action of a C-nucleophile, observed in this work, has to be studied in detail. The peculiarity and the practical importance of the transformations found lie in the fact that 6-phenyl-1,2,4-triazine 4-oxides play an unusual role of donor of a one-carbon fragment and can be used as a ring-forming agent (when several active nucleophilic centres exist in the molecule) or as a reagent linking two nucleophilic molecules.

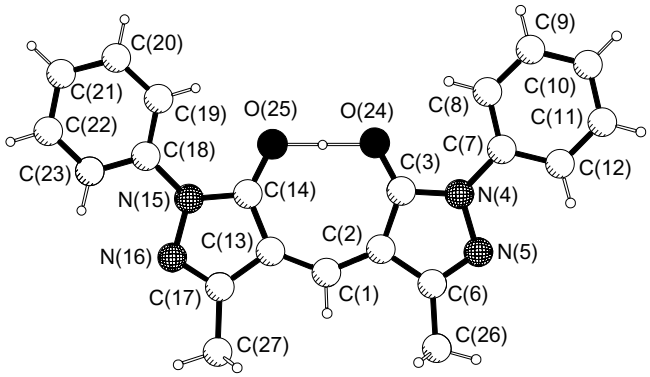


Figure 2 Molecular structure of **7**.

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References

1 H. Neunhoeffer and V. Böhnisch, *Liebigs Ann. Chem.*, 1976, 153.
2 Yu. A. Azev, I. I. Mudretsova, E. L. Pidemskii, A. F. Goleneva, G. A. Aleksandrova and N. A. Klyuev, *Khim.-Farm. Zh.*, 1985, **10**, 1202 (in Russian).
3 F. H. Allen, O. Kennard, D. G. Watson, L. Brammer, A. G. Orpen and R. Taylor, *J. Chem. Soc., Perkin Trans. 2*, 1987, 1.
4 B. V. Ioffe, M. F. Kuznetsov and A. A. Potekhin, *Khimiya organicheskikh proizvodnykh gidrazina (Chemistry of Organic Derivatives of Hydrazine)*, Khimiya, Leningrad, 1979, p. 75 (in Russian).
5 Yu. P. Kitaev and B. I. Buzykin, in *Gidrazony (Hydrazones)*, Nauka, Moscow, 1974, p. 205 (in Russian).

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