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Reactions of 3-phenyl-1,2,4-triazine with some C-nucleophiles

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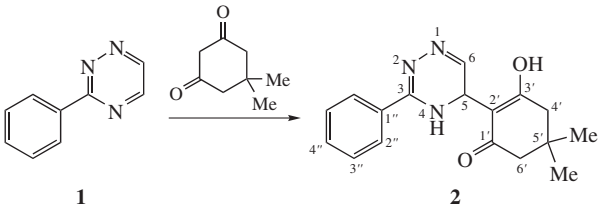
Dimedone is added at C(5) of 3-phenyl-1,2,4-triazine to give stable dihydro derivative. Its reaction with 1-aryl-3-methylpyrazol-5-ones proceeds with fragmentation affording 1,1,2,2-tetrakispyrazolylethane and amidrazone derivatives.

The triazine ring is present in a number of natural and synthetic physiologically active compounds,[1] therefore studies of their chemical modification are promising. CH-acids such as acetylacetone, phenylacetone and acetophenone are added to 6-methyl-3-phenyl-1,2,4-triazine in the presence of sodium hydride to give adducts that are readily oxidized with oxygen to produce stable 5-substituted 6-methyl-3-phenyl-1,2,4-triazines.[2] An addition of two indole molecules to 1-alkyl-1,2,4-triazinium salts results in 5,6-diindolyl σ-adducts.[3] Acetoacetic amides react with quaternary and protic salts of 1,2,4-triazine to form bisadducts with annelation of the pyrrole ring at the C^5–C^6 bond of the triazine ring.[4] In some cases, hydrogen replacement in 1,2,4-triazines allows one to perform their smooth functionalization. However, even now there are no unambiguous criteria for determining the direction of nucleophilic attack and the depth of conversion of these compounds if various methods of reagent activation and various nucleophile types are used. Moreover, reactions of *as*-triazines with pyrazol-5-ones as C-nucleophiles have not been studied.

Herein, we have discovered that 3-phenyl-1,2,4-triazine **1** smoothly reacts with dimedone in DMSO in the presence of an acid (or a base) at room temperature to give stable 5-σ-adduct **2** (Scheme 1).†



1 **2**

Scheme 1

† *5,5-Dimethyl-2-(3-phenyl-1,4-dihydro-1,2,4-triazin-5-yl)cyclohexane-1,3-dione* **2**. A mixture of 3-phenyl-1,2,4-triazine **1** (0.075 g, 0.48 mmol) and dimedone (0.070 g, 0.50 mmol) was kept in DMSO (1 ml) in the presence of concentrated HCl (0.1 ml) at room temperature for 48–50 h. The reaction mixture was diluted with water (1:1) and adjusted to pH 6–7 with 15% aqueous ammonia. The precipitate formed was filtered off and recrystallized from aqueous ethanol to give 0.090 g (63%) of product **2**, mp 168–169 °C. ^{1}H NMR (500.1 MHz, DMSO-d_6) δ: 1.00 (s, 6H, 2Me), 2.12–2.05 (AB system, 4H, $H^{4'}$, $H^{6'}$), 4.96 (d, 1H, H^5, *J* 2.4 Hz), 6.75 (d, 1H, H^6, *J* 2.4 Hz), 7.56 (dd, 2H, $H^{3''}$, *J* 8.4 and 7.5 Hz), 7.65 (tt, 1H, $H^{4''}$, *J* 7.5 and 1.4 Hz), 7.71 (dd, 2H, $H^{2''}$, *J* 8.4 and 1.4 Hz), 12.5–11.0 (br. s, 2H, NH, OH). ^{13}C NMR (125.7 MHz, DMSO-d_6) δ: 28.45 (2Me), 31.33 ($C^{5'}$), 46.84 (C^5), 49.10 ($C^{4'}$, $C^{6'}$), 107.46 ($C^{2'}$), 127.64 ($C^{2''}$), 127.91 ($C^{1''}$), 128.87 ($C^{3''}$), 132.69 ($C^{4''}$), 143.37 (br. s, C^6), 153.55 (C^3), 187.59 ($C^{1'}$, $C^{3'}$). HRMS (ESI), *m/z*: 296.1406 $[M - H]^-$ (calc. for $C_{17}H_{18}N_3O_2$, *m/z*: 296.1405).

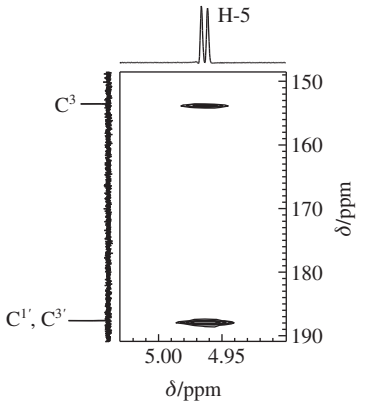


Figure 1 Fragment of a 2D ^{1}H-^{13}C HMBC spectrum (500 MHz, DMSO-d_6) of compound **2**.

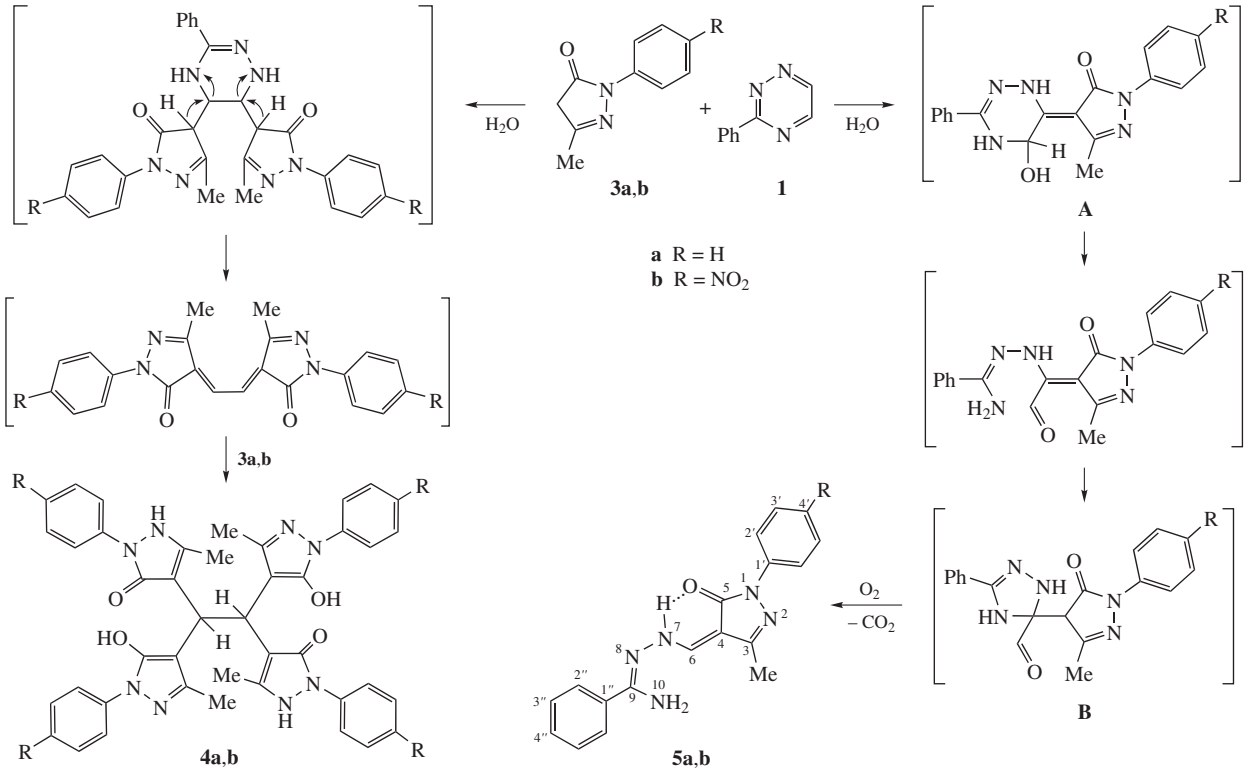
The structure of product **2** was confirmed by ^{1}H and ^{13}C NMR spectra and 2D ^{1}H-^{13}C HSQC, HMBC experiments. Its ^{1}H-^{13}C HMBC spectrum (Figure 1) displays cross-peaks between the doublet of the H^5 proton (δ 4.96, *J* 2.4 Hz) and the $C^{1'}$, $C^{3'}$ (δ 187.59 ppm) and C^3 carbon atoms (δ 153.55 ppm). In turn, assignment of the latter is confirmed by correlations with the *ortho*-protons of the phenyl substituent.

The ^{1}H and ^{13}C spectra of adduct **2** in DMSO-d_6 matches a structure with fast tautomeric transition between two enol forms of dimedone resulting in averaged shifts of protons and carbons in the dimedone moiety. The resonances of protons H^5 (δ 4.96 ppm) and H^6 (δ 6.75 ppm) coupled by spin–spin interaction are characteristic.

Unusual transformations occurred during the reaction of 3-phenyl-1,2,4-triazine **1** with 1-aryl-3-methylpyrazol-5-ones **3a**,**b** (Scheme 2): 1,1,2,2-tetrakis(5-methyl-2-oxo-2-phenyl-1,2-dihydro-3*H*-pyrazol-4-yl)ethanes **4a**,**b** were obtained at room temperature in DMSO in the presence of base.‡

‡ *Reaction of 3-phenyl-1,2,4-triazine* **1** *with 3-methyl-1-phenylpyrazol-5-ones* **3a**,**b**. A mixture of compound **1** (0.40 mmol), the corresponding 1-aryl-3-methyl-pyrazol-5-one **3** (1.60 mmol) and triethylamine (0.1 ml) in DMSO (1 ml) was kept at room temperature for 48 h. The reaction mixture was diluted with water (1 : 1) and acidified to pH 5–6 with 15% aqueous HCl. The resulting precipitate was filtered off and washed with ethanol (5 ml) at 55–60 °C. The residue on the filter was compound **4a**,**b**. The ethanolic washings were evaporated to dryness *in vacuo*. The solid was treated with chloroform (5 ml) and insoluble admixtures were filtered off. The mother liquor was evaporated *in vacuo* to give amidrazones **5**.

Compound **4a**, yield 50–55%. Its melting point and ^{1}H NMR spectra are identical to those of tetrapyrazolylethane derivative reported earlier.[5]



Scheme 2

Product **4a** is identical in the melting point and spectral characteristics to that reported previously.[5] The high-resolution mass spectrum (ESI) of compound **4b** reveals a molecular ion peak: 899.2468 $[M+H]^+$ (calc. for $C_{42}H_{35}N_{12}O_{12}$: 899.2492). Its ^{1}H NMR spectrum contains a characteristic two-proton singlet of ethane bridge at δ 4.73 ppm, as well as all appropriate signals of protons of the pyrazolone moieties.

In addition to products **4**, amidrazones **5a**,**b** were also obtained. In their HRMS (ESI) spectra molecular ion peaks with the proper molecular masses are observed.

It is interesting that the two singlets in the ^{1}H NMR spectrum of compound **5a** at δ_H 9.02 and 8.58 ppm correspond to non-equivalent protons at one nitrogen atom, N^{10} (δ_N 99.0 ppm). This is confirmed by direct connectivities in the ^{1}H-^{15}N HMQC spectrum. A signal of another NH proton is observed in very low field at δ_H 17.46 ppm indicative of a strong intramolecular hydrogen bond. It has also been justified by a ^{1}H-^{15}N HMQC experiment that this proton is bound to the N^7 atom (δ_N 186.9 ppm). ^{1}H-^{13}C HMBC 2D experiment (Figure 2), shows that H^7 proton has coupling constants through two or three bonds with the C^9 (δ_C 156.35 ppm) and C^6 (δ_C 145.30 ppm) carbon atoms, while the H^{10a} and H^{10b} protons have coupling constants with the C^9 and $C^{1''}$ carbon atoms (δ_C 127.82 ppm). The H^6 proton manifests long-range correlations with the C^3 (δ_C 148.50 ppm), C^4 (δ_C 98.29 ppm) and C^5 carbon atoms (δ_C 161.56 ppm) in the ^{1}H-^{13}C HMBC spectrum, as well as with the N^7 (δ_N 186.9 ppm) and N^8 nitrogen atoms (δ_N 274.6 ppm) in the ^{1}H-^{15}N HMBC spectrum.

*1,2-Bis[5-hydroxy-3-methyl-1-(4-nitrophenyl)-1*H*-pyrazol-4-yl]-1,2-bis-[5-methyl-2-(4-nitrophenyl)-3-oxo-1,2-dihydropyrazol-4-yl]ethane* **4b**: yield 55–60%, mp > 250 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.22 (s, 12 H, 4 Me), 4.73 (s, 2 H, CH_{aliph}), 8.04 (d, 8 H, *J* 8.8 Hz, CH_{arom}), 8.22 (d, 8 H, CH_{arom}, *J* 8.8 Hz), 14.20 [br.s, 2 H, OH (NH)]. HRMS (ESI), *m/z*: 899.2468 $[M+H]^+$ (calc. for $C_{42}H_{35}N_{12}O_{12}$, *m/z*: 899.2492).

N′*-[(Z)-(3-Methyl-5-oxo-1-phenyl-1,5-dihydro-4*H*-pyrazol-4-ylidene)-methyl]benzenecarbohydrazonamide* **5a**. Yield 20–25%, mp 108–110 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.17 (s, 3 H, Me), 7.07 (tt, 1H, $H^{4'}$, *J* 7.4 and 1.1 Hz), 7.25 (s, 1H, H^6), 7.33 (dd, 2 H, $H^{3'}$, *J* 8.5 and 7.4 Hz), 7.64 (t, 2 H, $H^{3''}$, *J* 7.7 Hz), 7.71 (tt, 1H, $H^{4''}$, *J* 7.4 and 1.2 Hz), 7.92 (m, 4 H, $H^{2'}$, $H^{2''}$), 8.58 (s, 1H, H^{10b}), 9.02 (s, 1H, H^{10a}), 17.46 (s, 1H, H^7). ^{13}C NMR (126 MHz, DMSO-d_6) δ: 12.83 (Me), 98.29 (C^4), 118.68 ($C^{2'}$), 123.42 ($C^{4'}$), 127.54 ($C^{2''}$), 127.82 ($C^{1''}$), 128.42 ($C^{3'}$), 129.12 ($C^{3''}$), 132.94 ($C^{4''}$), 139.98 ($C^{1'}$), 145.30 (C^6), 148.50 (C^3), 156.35 (C^9), 161.56 (C^5). ^{15}N NMR (50.7 MHz, DMSO-d_6) δ: 99.0 (N^{10}), 186.9 (N^7), 190.6 (N^1), 272.2 (N^2), 274.6 (N^8). HRMS (ESI), *m/z*: 318.1357 $[M-H]^-$ (calc. for $C_{18}H_{16}N_5O$, *m/z*: 318.1360).

N′*-[(Z)-[3-Methyl-1-(4-nitrophenyl)-5-oxo-1*H*-pyrazol-4(5*H*)-ylidene]-methyl}benzohydrazonamide* **5b**. Yield 35–40%, mp 138–139 °C (decomp.). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.20 (s, 3 H, Me), 7.23 (s, 1H, CH), 7.60–7.70 (m, 2 H, CH_{arom}), 7.70–7.80 (m, 1H, CH_{arom}), 7.90–7.97 (m, 2 H, CH_{arom}), 8.21 (d, 2 H, CH_{arom}, *J* 8.0 Hz), 8.26 (d, 2 H, CH_{arom}, *J* 8.0 Hz), 8.65 (s, 1H, NH), 9.16 (s, 1H, NH). HRMS (ESI), *m/z*: 365.1326 $[M+H]^+$ (calc. for $C_{18}H_{17}N_6O_3$, *m/z*: 365.1357).

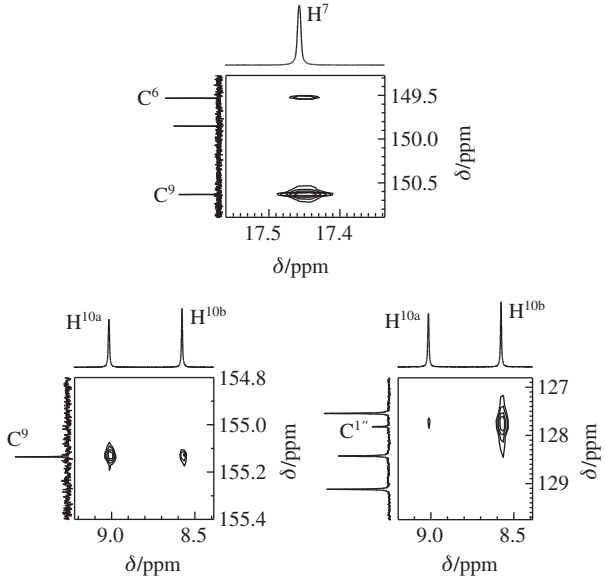


Figure 2 Fragment of a 2D ^{1}H-^{13}C HMBC spectrum (500 MHz, DMSO-d_6) of compound **5a**.

The signals of two nonequivalent protons at N^{10} typical of amidrazones **5** are also observed in the ^{1}H NMR spectrum of compound **5b** at δ 8.65 and 9.16 ppm.

The mechanism of formation of tetrapyrazolyl ethane derivatives **4** from triazino derivative **1** is likely to be similar to that of the previously reported[5] reactions of quinoxaline with 3-methyl-1-phenylpyrazol-5-one (see Scheme 2). The formation of amidrazones 5 presumably occurs as initial attack of the pyrazolone to C^6 and hydroxyl addition to C^5, which is followed by cleavage of the N^1–C^6 bond in intermediates **A**, oxidation of the aldehyde group in intermediates **B** and decarboxylation of the resulting acid.

The formation of amidrazones **5** can also be assumed to proceed through an alternative pathway which involves a nucleophilic attack of the pyrazolone to the C^5 atom and the hydroxyl to the C^6 atom. Accordingly, it is assumed in this case that elimination of the C^6 atom of the triazine ring occurs.

To conclude, depending on the nature of the attacking nucleophile, 3-phenyl-1,2,4-triazine **1** either gives stable 5-σ-adducts (the reaction with dimedone) or formally acts as a two-carbon synthon which 'cross-links' four molecules of 3-methyl-1-phenylpyrazol-5-ones. Furthermore, it is likely that competitive reactions of triazine **1** with pyrazolone and water result in simultaneous cleavage of the triazine ring with elimination of one carbon atom and formation of stable acyclic amidrazones.

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