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Unusual reactions of 4,6-dichloro-5-nitropyrimidine with C-nucleophiles

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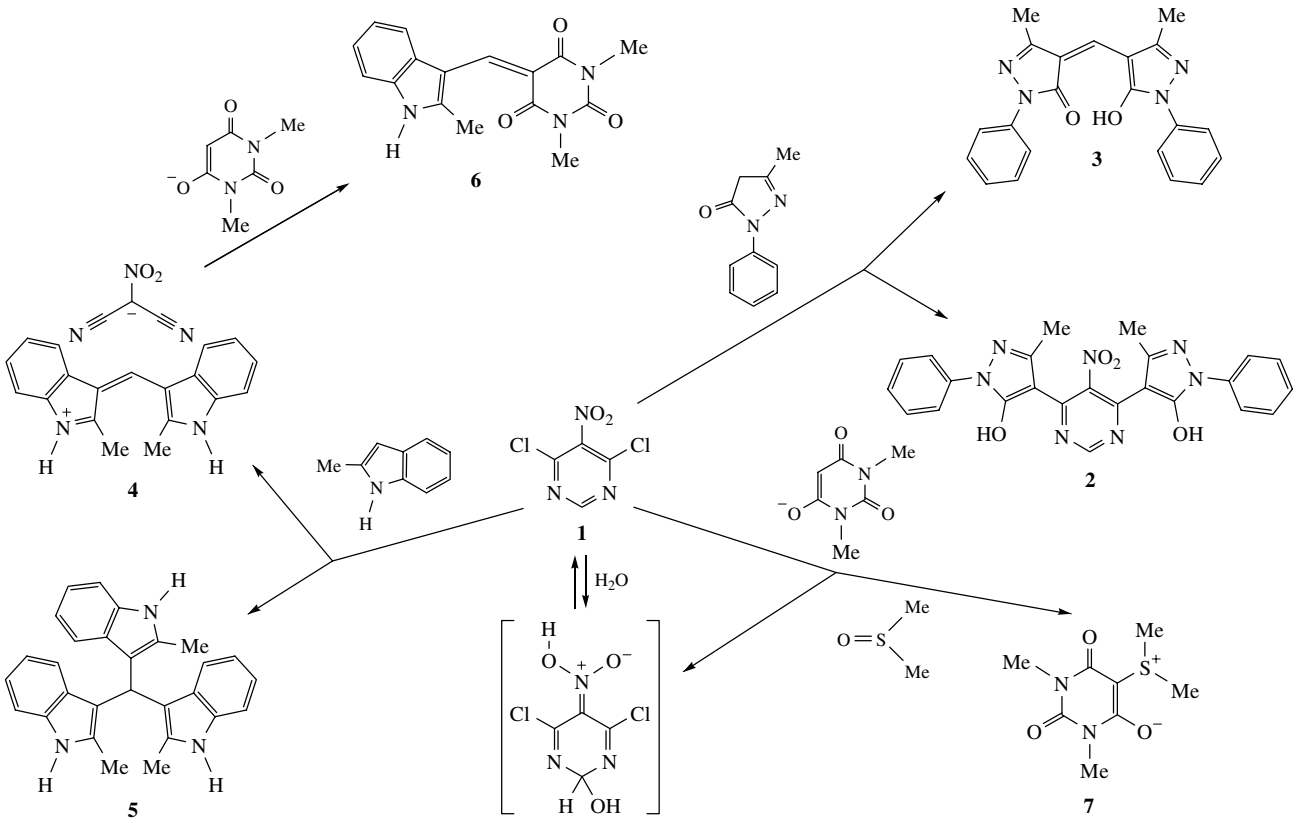
The interaction of 4,6-dichloro-5-nitropyrimidine 1 with 1-phenyl-3-methylpyrazol-5-one led to the 4,6-dipyrazolyl derivatives of 5-nitropyrimidine 2 and dipyrazolylmethane 3; 2-methylindole reacts with 1 to form diindolylmethane 4 and trisindolylmethane 5; 1,3-dimethylbarbituric acid displaces an indolyl residue in diindolylmethane 4 to form diheterylmethane 6.

4,6-Bis(benzylthiopyrimidines) show an antitumor activity.[1] The anticarcinogenic action of condensed pyrimidines (purinethiols) is related to their ability to be included in the nucleic acids of tumoral cells.[2]

o-Nitroamino-substituted pyrimidines are suitable starting materials for the synthesis of condensed pyrimidines, such as purines and pteridines. The latter are constituents of natural heterocyclic systems.[3–5]

Various 4,6-substituted 5-nitropyrimidines can be synthesised starting from 4,6-dichloro-5-nitropyrimidine **1**. Depending on the nature of the nucleophile (O-, N- or S-nucleophile) and reaction conditions, replacement products of one or two halogen



Scheme 1

atoms can be produced.[6] In case of the reaction of 4,6-dichloro-5-nitropyrimidine **1** with C-nucleophiles, there is a substitution of the hydrogen atom at C(2) of the pyrimidine cycle and reduction of the nitro group at C(5), leading to the formation of 2-substituted 5-aminopyrimidines.[7]

We found new unusual transformations of 4,6-dichloro-5-nitropyrimidine **1** with C-nucleophiles. By the interaction of compound **1** (Scheme 1)† with 1-phenyl-3-methylpyrazol-5-one in the presence of triethylamine in dimethyl sulfoxide at room temperature, 4,6-dipyrazolyl derivatives of 5-nitropyrimidine **2** and dipyrazolylmethane **3** were obtained. Note that the interaction of **1** with pyrazolone proceeds with appreciable heating of the reaction mixture and formation of compound **3** as the major product (40%). Compound **3** is identical by ^{1}H NMR, mass spectrum‡ and melting point with dipyrazolylmethane described.[8] The molecular mass of compound **2**, as determined by mass spectrometry, corresponds to a disubstitution product. In the ^{1}H NMR spectrum, the signals of the methyl group (2.26 ppm) and the phenyl protons (7.30–7.60 ppm) of 1-phenyl-3-methylpyrazol-5-one are observed. The H-2 signal of the pyrimidine nucleus is observed at 8.66 ppm.

As a result of short heating of compound **1** with a 2.5 mol surplus of 2-methylindole in ethanol, the salt of (2-methylindol-3-yl)methane with nitromalonodinitrile **4** and tris(2-methylindol-3-yl)methane **5** were obtained.

† *Reaction of 4,6-dichloro-5-nitropyrimidine* **1** *with 1-phenyl-3-methylpyrazol-5-one*. 0.077 g (0.4 mmol) of compound **1**, 0.1 ml of triethylamine and 0.140 g (0.8 mmol) of 1-phenyl-3-methylpyrazol-5-one were kept in 1 ml of DMSO for 48 h at 20–25 °C. Solid dipyrazolylmethane **3** was filtered off and recrystallised from ethanol. The mother liquor was diluted (1:1) with water and acidified to pH 3–4. A precipitate filtered and divided by preparative TLC on plates with kiselgel 60pf254. Eluent: CH_2Cl_2. The disubstitution product **2** was taken from a zone with R_f 0.35.

Reaction of 4,6-dichloro-5-nitropyrimidine **1** *with 2-methylindole*. 0.102 g (0.53 mmol) of compound **1** was boiled with 0.170 g (1.30 mmol) of 2-methylindole in 4 ml of ethanol for 35–40 min. The reaction mixture was cooled in an ice bath; solid salt **4** was filtered off and recrystallised from ethanol. The mother liquor was evaporated in a vacuum. The solid was precipitated from a solution of DMSO–EtOH (1:1, 2 ml) with water (1 ml). Product **5** was filtered off and washed with water.

Reaction of salt **4** *with 1,3-dimethylbarbituric acid*. 0.032 g (0.2 mmol) of 1.3-dimethylbarbituric acid and 0.02 ml of triethylamine were added to 0.038 g (0.1 mmol) of compound **4** in 0.5 ml of DMSO. The reaction mixture was kept at 20–25 °C for 24 h, and then diluted with water (1:6). The precipitate of **6** formed was filtered off. Product **7** was precipitated from DMF with water.

(*1,3-Dimethyl-2,4,6-trioxohexahydropyrimidin-5-yl)dimethylsulfonium betaine* **7**. To 0.058 g (0.3 mmol) of compound **1** in 0.5 ml of DMSO 0.094 g (0.6 mmol) of 1.3-dimethylbarbituric acid was added. The reaction mixture was kept at 20–25 °C for 24 h. Solid **7** was filtered off and washed with ethanol.

‡ ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 200 spectrometer ([$^2H_6$]DMSO, 200 MHz for ^{1}H) using DMSO as an internal standard.

EI mass spectra were measured on a Finnigan MAT 95 double-focusing mass spectrometer. EI conditions: 70 eV electron energy and 200 °C ion source temperature. ESI mass spectra were acquired on a Bruker Esquire-LC ion trap mass spectrometer. Samples were dissolved in acetonitrile at concentrations of *ca.* 10^{-5} to 10^{-6} mol dm^{-3} and injected into the mass spectrometer *via* a syringe pump at a flow rate of 2 μl min^{-1}. Spectra were recorded in positive and negative ion modes for 1 min and averaged to correct for signal fluctuations. Conditions were chosen such as to minimise the degree of collision-induced fragmentation.

Compounds **2**–**7** gave satisfactory elemental analyses.

For **2**: yield 5–10%, mp 118–120 °C. ^{1}H NMR, δ: 2.26 (s, 3H 2Me), 6.32 (s, 2H, 2OH), 7.30–7.60 (m, 10H, CH_{arom}), 8.66 (s, 1H, H-2). MS, *m*/*z* (%): 469 (28).

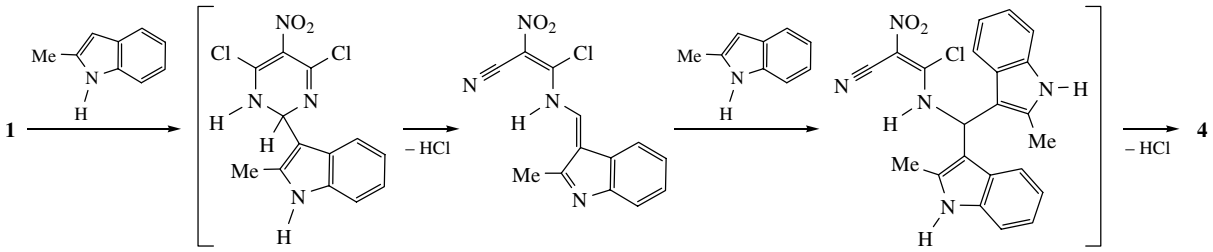
For **3**: yield 35–40%. Compound **3** is identical to dipyrazolylmetane.[8,10]

For **4**: yield 40–45%, mp 193–195 °C. ^{1}H NMR, δ: 2.91 (s, 6H, 2Me), 6.94 (m, 2H, $2CH_{arom}$), 7.29 (m, 2H, $2CH_{arom}$), 7.43 (m, 2H, $2CH_{arom}$), 7.64 (m, 2H, $2CH_{arom}$), 8.98 (s, 1H, –CH=), 13.81 (s, 2H, 2NH). ^{13}C NMR, δ: 14.20, 114.43, 118.48, 124.51, 124.85, 125.58, 126.42, 139.31, 148.60, 161.60.

For **5**: yield 10–15%, mp >300 °C. ^{1}H NMR, δ: 1.93 (s, 9H, 3Me), 6.10 (s, 1H, CH), 6.50–7.40 (m, 12H, CH_{indole}), 1062 (s, 3H, $3NH_{indole}$). MS, *m*/*z* (%): 403 (85).

For **6**: yield 30–35%, mp >250 °C. ^{1}H NMR, δ: 2.55 (s, 3H, Me), 3.22 (s, 3H, Me), 3.25 (s, 3H, Me), 6.50–7.50 (m, 4H, CH_{indole}), 8.57 (s, 1H, $C_{sp^3}H$), 12.60 (s, 1H, NH_{indole}). MS, *m*/*z* (%): 297 (100).

For **7**: yield 65–70%. Compound **7** is identical to compound described earlier.[11]



Scheme 2

The signals of 2-Me protons (2.91 ppm) and NH groups (13.81 ppm) in the ^{1}H NMR spectrum of salt **4** are in the weak-field region, which confirms the protonation of the diindolylmethane molecule. The signal of the =CH groups is observed at 8.98 ppm. In the ^{13}C NMR spectrum, ten signals of the carbon atoms of the diindolylmethane cation are observed ([$^2H_6$]DMSO, δ: 14.20, 114.43, 118.48, 124.51, 124.85, 125.58, 126.42, 139.31, 148.60 and 161.60) owing to the paired equivalence of the indolyl fragments and the symmetry of the molecule.

The positive-ion electrospray ionisation (ESI) mass spectrum of compound **4** showed only one peak at *m*/*z* 273, with the intensity of the ^{13}C isotopic peak indicating a number of 19 atoms.

The only major ion in the negative ion ESI mass spectrum was *m*/*z* 110, which was attributed to $[NO_2–C(CN)_2]^–$.

In the IR spectrum, the low frequency of the nitrile group stretching vibration (KBr, 2215 and 2200 cm^{-1}) indicates the presence of the electron-accepting NO_2 group at the α-carbon atom of the malononitrile anion of salt **4**. The absorption of the NO_2 group is observed at 1565, 1520, 1338 and 1320 cm^{-1}.

The electron impact (EI) spectrum of compound **5** showed an intense peak at *m*/*z* 403 (85%). Product **5** was identified[9] as tris(2-methylindol-3-yl)methane by ^{1}H NMR spectroscopy and melting point. Thus, the ^{1}H NMR spectrum contains proton signals of the indolyl moiety (6.50–7.40 ppm). The proton signal at the *sp*^{3}-hybridised C(2) atom is also observed at 6.10 ppm, and it can serve as a diagnostic attribute for triheterylmethane derivatives.

The mechanism of formation of salt **4** can be explained by Scheme 2. The unusually easy reaction of **1** with indole can be explained by evolving HCl, which catalyses indole addition and disintegration of the intermediate.

It is obvious that tris(2-indol-3-yl)methane **5** results from the addition of the third molecule of methylindole to diindolylmethane **4**. Similar addition reactions of 1-phenyl-3-methylpyrazol-5-one to diheterylmethanes were described earlier.[10]

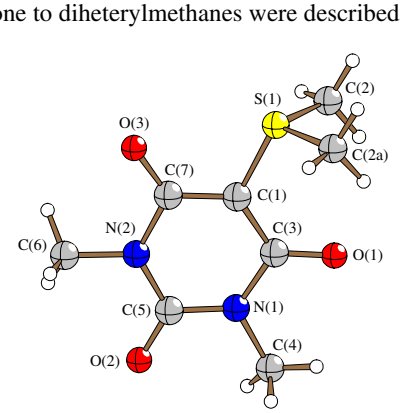


Figure 1 Molecular structure of compound **7**. Selected bond lengths (Å): C(1)–C(7) 1.400(6), C(1)–C(3) 1.430(5), C(1)–S(1) 1.724(4), S(1)–C(2) 1.781(3), S(1)–C(2a) 1.781(3), C(3)–O(1) 1.222(5), C(3)–N(1) 1.409(5), N(1)–C(5) 1.363(5), N(1)–C(4) 1.472(5), C(5)–O(2) 1.218(5), C(5)–N(2) 1.395(5), N(2)–C(7) 1.416(5), N(2)–C(6) 1.456(5), C(7)–O(3) 1.238(5); selected bond angles (°): C(7)–C(1)–C(3) 124.3(4), C(7)–C(1)–S(1) 114.8(3), C(3)–C(1)–S(1) 120.9(3), C(1)–S(1)–C(2) 106.26(13), C(1)–S(1)–C(2a) 106.26(13), C(2)–S(1)–C(2a) 102.6(2), O(1)–C(3)–N(1) 120.0(3), O(1)–C(3)–C(1) 125.5(4), N(1)–C(3)–C(1) 114.5(4), C(5)–N(1)–C(3) 125.1(3), C(5)–N(1)–C(4) 116.5(4), C(3)–N(1)–C(4) 118.4(3), O(2)–C(5)–N(1) 121.7(4), O(2)–C(5)–N(2) 121.2(4), N(1)–C(5)–N(2) 117.1(4), C(5)–N(2)–C(7) 123.8(4), C(5)–N(2)–C(6) 118.3(4), C(7)–N(2)–C(6) 117.9(3), O(3)–C(7)–C(1) 126.6(4), O(3)–C(7)–N(2) 118.2(4), C(1)–C(7)–N(2) 115.2(3).

Interestingly, by reaction of salt **4** with 1,3-dimethylbarbituric acid in DMSO in the presence of triethylamine, the replacement of one indolyl moiety occurs to give product **6**.

In the EI spectrum of compound **6**, an intense peak due to the molecular ion at *m*/*z* 297 (100%) was observed.

In the ^{1}H NMR spectrum, the signals of Me protons (2.55 ppm), CH_{arom} (6.60–7.50 ppm) and indolyl NH groups (12.60 ppm) are observed. Proton signals of the barbituric acid Me groups are detected at 3.22 and 3.24 ppm. The pyrimidine ring H-2 proton signal is at 8.57 ppm. Note that a compound analogous to **6**, *i.e.*, 1,3-dimethyl-5[(1*H*-indol-3-yl)methylidene]-2,4,6-(1*H*,3*H*,5*H*)-pyrimidinetrione, was synthesised by heating indole with 1,3-dimethyl-5-dimethylaminomethylidene-2,4,6-(1*H*,3*H*,5*H*)-pyrimidinetrione in glacial acetic acid for 5 h.[9]

We found unexpected transformations by studying the reaction of compound **1** with 1,3-dimethylbarbituric acid in DMSO at room temperature. As a result of this reaction, product **7** with a molecular mass of 216.05686 and the empirical formula $C_8H_{12}N_2O_3S$ is formed. This empirical formula corresponds to (1,3-dimethyl-2,4,6,-trioxohexahydropyrimidin-5-yl)dimethylsulfonium betaine **7**. The structure of betaine **7** crystals was investigated by X-ray diffraction analysis (Figure 1).§

Thus, dimethylbarbituric acid reacts with DMSO, and compound **1** acts as a dehydrating reagent.

It is interesting that the signal intensity of the proton at the C(2) atom at 9.17 ppm in the ^{1}H NMR spectrum of compound **1** in DMSO decreases upon addition of water, and the intensity of a weak signal at 8.45 ppm eventually increases. Similar changes in the ^{1}H NMR spectrum may be explained by the existence of an equilibrium mixture of a covalent hydrate and unhydrated form **1** in a DMSO solution.

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§ *Crystal data for* **7**. At 173(2) K, a crystal of $C_8H_{12}N_2O_3S$ (0.50× ×0.10×0.10 mm) is monoclinic, a = 857.36(17), b = 692.60(14) and c = = 885.30(18) pm, β = 118.29(3)°, V = 0.46290(16) nm^3, space group $P2_1/m$, Z = 2, d_{calc} = 1.552 g cm^{-3}, μ = 0.332 mm^{-1}, λ = 71.073 pm, $F(000)$ = 228, diffractometer Siemens P4, θ range for data collection 2.61–25.98°, index ranges $-10 \le h \le 10$, $-8 \le k \le 8$, $-10 \le l \le 10$, reflections collected 3592, independent reflections 976 (R_{int} = 0.1820), completeness to θ = 25.98° 99.1%, refinement method full-matrix least-squares on F^2, data/restraints/parameters 976/0/86, Goodness-of-fit on F^2 0.997, final R indices [$I > 2\sigma(I)$] R_1 = 0.0651, wR_2 = 0.1390, R indices (all data) R_1 = 0.0854, wR_2 = 0.1495, largest diff. peak and hole 0.526 and –0.522 eÅ^{-3}. The structure was solved by direct methods, subsequent least-squares refinement located the positions of the remaining atoms in the electron density maps. All non-hydrogen atoms were refined with individual anisotropic deflection parameters. H-atoms were calculated with common isotropic.

Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). These data can be obtained free of charge *via* www.ccdc.cam.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk). Any request to the CCDC for data should quote the full literature citation and CCDC reference number 283414. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2005.

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