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Heterocyclization of 6-hydroxyimino-6,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidines into 1,2,4-triazolo[1,5-*a*]pyrimido[5,4-*b*]- and -[5,6-*b*]indoles

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6-Hydroxyimino-6,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidines are converted into isomeric 1,2,4-triazolo[1,5-*a*]pyrimido[5,4-*b*]- and -[5,6-*b*]indoles in polyphosphoric acid or under exposure to *para*-nitrobenzoyl chloride in pyridine.

Azaheterocyclic hydroxyimino derivatives undergo O-benzoylation[1] under acylation by *para*-nitrobenzoyl chloride in pyridine and polyphosphoric acid (PPA), as a result of Beckmann rearrangement, form, as a rule, amides.[2–4] The aim of this study is to elucidate the structure of products obtained through the interaction of 5,7-disubstituted 6-hydroxyimino-6,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidines **2a**–**c** with *para*-nitrobenzoyl chloride and PPA.

Oximes **2a**–**c** were obtained by the nitrosation of 4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidines **1a**–**c** with sodium nitrite in glacial acetic acid.[5] The physico-chemical characteristics of compound **2b** were identical to those reported earlier.[5] The structures of substances **2a**,**c** were established by spectroscopic methods and, for oxime **2a**, by X-ray diffraction analysis.[†]

The dihydropyrimidine ring adopts a sofa conformation similar to the 5,7-diphenyl derivative.[6] The deviation of the C(5) atom from the mean plane of remaining atoms coplanar in the limits of 0.01 Å of the ring is 0.22 Å. The methyl and oxyimino groups are turned slightly from each other [the C–C–C–N torsion angle is 8.3(3)°]. The hydroxy group of oxime has an *anti*-configuration with respect to the same bond [the C–C=N–O torsion angle is 179.4(2)°]. The phenyl substituent adopts a pseudoequatorial orientation [the C–N–C–C torsion angle is 106.2(2)°].[7] In the crystal phase, molecules of **2a** form planar networks, which are perpendicular to the crystallographic direction (001), due to intermolecular hydrogen bonds O(1)–H(1O)···N(2)′ $(0.5 - x, -0.5 + y, z)$ (H···N 1.81 Å, O–H···N 171.2°), C(1)–H(1)···N(4)′ $(1.5 - x, 0.5 + y, z)$ (H···N 2.51 Å, C–H···N 148°).

Compounds **3a**–**c**, **4b**,**c** were obtained under the acylation of oximes **2a**–**c** by *para*-nitrobenzoyl chloride in pyridine.[‡] The same products were separated under the heating of initial substances **2a**–**c** in PPA,[§] which allowed us to make a conclusion that the *para*-nitrobenzoyl fragment was absent in their structure.

The presumption on the possible formation of Beckmann rearrangement products was rejected on the basis of the elemental

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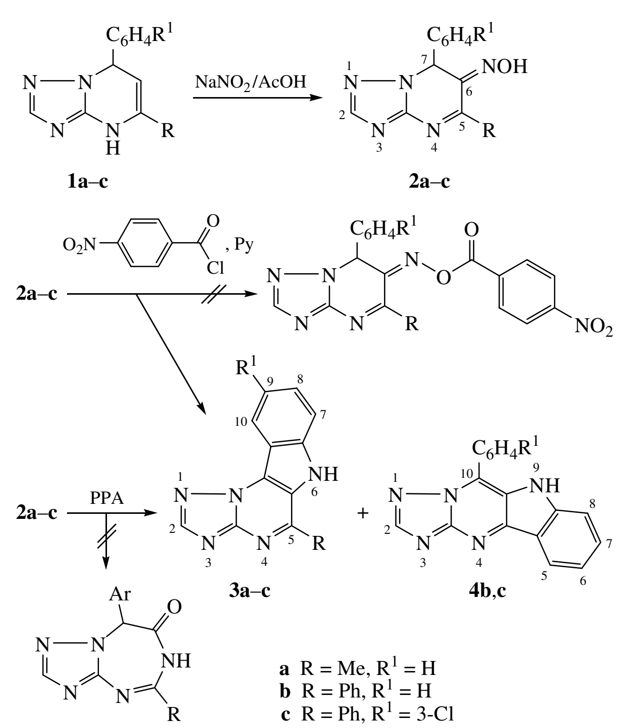
[†] **2a**: yield 72%, mp 244 °C (decomp.). ^{1}H NMR (300 MHz, [^{2}H$_6$]DMSO) δ: 13.16 (s, 1H), 7.90 (s, 1H), 7.28–7.17 (m, 5H), 6.56 (s, 1H), 2.53 (s, 3H). IR (KBr, ν/cm^{-1}): 3168–2640, 1588. Found (%): C, 60.02; H, 4.58; N, 29.08. Calc. for $C_{12}H_{11}N_5O$ (%): C, 59.75; H, 4.56; N, 29.05.

Crystal data for **2a**: $C_{12}H_{11}N_5O$, orthorhombic, space group *Pbca*, $a = 10.399(2)$, $b = 10.345(2)$ and $c = 22.060(4)$ Å, $V = 2373.2(8)$ Å^3, $d_{calc} = 1.350$ g cm^{-3}, $Z = 8$, μ(MoKα) = 0.093 mm^{-1}. Data were measured on an Enraf-Nonius CAD-4 diffractometer ($T = 293$ K, graphite-monochromated MoKα radiation, $\theta/2\theta$ scan, $2\theta_{max} = 60°$). The structure was solved by direct method using the SHELXTL PLUS program package. Refinement against F^2 in an anisotropic approximation (isotropic for the hydrogen atoms) by a full matrix least-squares method for 2698 reflections was carried out to $wR_2 = 0.143$ [207 parameters, $R_1 = 0.054$ for 1563 reflections with $F > 4\sigma(F)$, $S = 1.04$].

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 299598. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2006.

2c: yield 56%, mp 200 °C (decomp.). ^{1}H NMR (300 MHz, [^{2}H$_6$]DMSO) δ: 13.52 (s, 1H), 7.66 (s, 1H), 7.93–7.20 (m, 9H), 6.86 (s, 1H). IR (KBr, ν/cm^{-1}): 3100–2500, 1544. Found (%): C, 60.36; H, 3.53; N, 20.72; Cl, 10.49. Calc. for $C_{17}H_{12}N_5ClO$ (%): C, 60.44; H, 3.56; N, 20.74; Cl, 10.52.



analysis and mass-spectrometric data, which testified that the molecular mass in compounds **3a–c**, **4b**,**c** reduced by 18 units in comparison with initial oximes **2a–c**. Note that the spectra of **3b**, **4b** and **3c**, **4c** are identical. At the first stage of fragmentation, these compounds lose HCN from the indole fragment. The elemental analysis data for products **3b**, **4b** and **3c**, **4c** were also identical, but these substances differed in melting points. All of these results testify to the isomeric structure of compounds **3b**,**c** and **4b**,**c**.

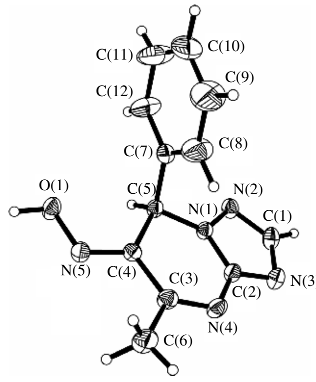
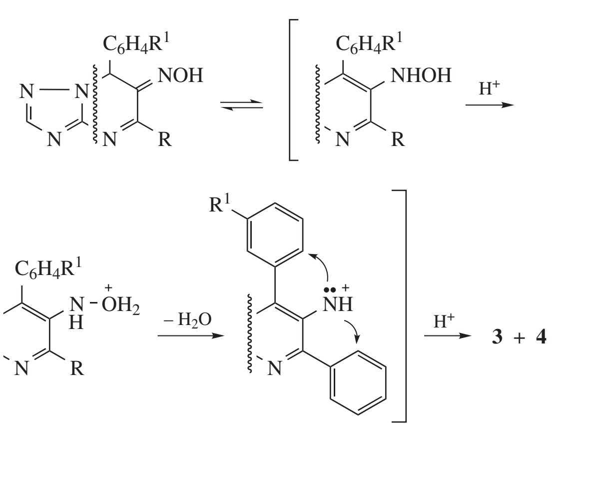


Figure 1 Molecular structure of **2a**. Non-hydrogen atoms are displayed as thermal ellipsoids with 30% probability. Selected bond lengths and angles: C(2)–N(4) 1.377(3) Å, C(3)–C(4) 1.470(3) Å, C(4)–N(5) 1.291(2) Å, N(5)–O(1) 1.371(2) Å, C(4)–N(5)–O(1) 112.5(2)°.

The ^{1}H NMR spectra of compound **3a** contain a methyl group singlet, a broad singlet due to the NH proton at δ 11.99 ppm, which disappears after exchange for deuterium, and a signal of the C(2)H proton (δ 8.61 ppm) is displaced to the weak field in comparison with the last one in the spectra of compound **2a** (δ 7.90 ppm). Additionally, resonance of the CH proton of the pyrimidine ring is absent in the spectra of **3a**, but the most characteristic is the split of aromatic nucleus signals. These protons are exhibited by a doublet and two multiplets with integral intensities for 1, 2 and 1 proton, respectively. On the basis of these data, compound **3a** was characterised as 5-methyl-[1,2,4]triazolo[1,5-*a*]pyrimido[5,6-*b*]indole.

The ^{1}H NMR spectra of **3b**,**c** and **4b**,**c** have differences in the field of aromatic and NH proton resonances. Signals of aryl protons in compounds **3b**,**c** appeared in a broader range of δ than in the spectra of isomers **4b**,**c**, which testifies to a more planar structure of these substances. We connect this with the triazole ring influence on the proton resonance of the $C_6H_4R^1$ fragment. The difference in the anisotropic influence of the $C_6H_4R^1$ substituent appears in the upfield shift of the NH proton in the spectra of isomer **4** in comparison with **3**. This substituent in compounds **4b**,**c** is located outside the heterocyclic scaffold due to the triazole ring influence and has a shielding effect on the NH group. In isomers **3b**,**c**, the phenyl ring is located in the triazolopyrimidine plane and has a disshielding effect on the NH proton.

Aromatic proton signal analysis in the spectra of **3c** allows us to determine the location of the R^1 substituent in the indole fragment. The proton resonance of this unit appears as a singlet, with an integral intensity for 1H, and as a multiplet for 2H, which complies with the *para*-position of the chloride atom toward the NH group. The experimental data allow us to characterise compounds **3** and **4** as 5-phenyl[1,2,4]triazolo[1,5-*a*]pyrimido[5,6-*b*]- and 10-phenyl[1,2,4]triazolo[1,5-*a*]pyrimido[5,4-*b*]indole, respectively.



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‡ A mixture of oxime **2a** (0.002 mol, 0.48 g) and *para*-nitrobenzoyl chloride (0.0025 mol, 0.46 g) in 3 ml of dry pyridine was refluxed for 2 h. After cooling, a solution of HCl (1:1) was added to the reaction mixture, the precipitate was filtered off and crystallised from propan-2-ol. At first, 0.44 g of *para*-nitrobenzoic acid (mp 239–241 °C, lit.,[9] mp 241 °C) was obtained, then 0.12 g of **3a**, 27% yield, was filtered. Compounds **3b**,**c**, **4b**,**c** were synthesised in a similar way with yields of 17, 20, 12 and 14%, respectively.

§ Oxime **2a** (0.002 mol, 0.48 g) in 2 ml of polyphosphoric acid was boiled for 1 h. After cooling, the reaction mixture was neutralised, the precipitate of compound **3a** was filtered off and crystallised from propan-2-ol, yield 39%. Compounds **3b**,**c**, **4b**,**c** were synthesised in a similar manner with yields of 21, 23, 17 and 20%, respectively.

3a: mp 325 °C (decomp.). ^{1}H NMR (300 MHz, [^{2}H$_6$]DMSO) δ: 11.99 (s, 1H), 8.61 (s, 1H), 8.38 (d, 1H), 7.76 (m, 2H), 7.43 (m, 1H), 3.06 (s, 3H). IR (KBr, ν/cm^{-1}): 3068, 1628, 1560, 1492, 1384, 1348. EI MS, *m*/*z* (%): 223 (M$^+$, 100), 196 (10), 181 (25), 169 (20), 155 (30), 143 (15), 129 (45), 103 (40), 77 (35). Found (%): C, 64.59; H, 4.06; N, 31.41. Calc. for $C_{12}H_9N_5$ (%): C, 64.57; H, 4.04; N, 31.39.

3b: mp 330 °C (decomp.). ^{1}H NMR (300 MHz, [^{2}H$_6$]DMSO) δ: 12.29 (s, 1H), 8.79 (s, 1H), 8.46 (d, 1H), 8.19–8.14 (m, 2H), 7.79–7.66 (m, 5H), 7.48–7.41 (m, 1H). IR (KBr, ν/cm^{-1}): 3244, 1628, 1604, 1556, 1480, 1364. EI MS, *m*/*z* (%): 285 (M$^+$, 100), 258 (20), 129 (12), 103 (28), 77 (25). Found (%): C, 71.57; H, 3.87; N, 24.54. Calc. for $C_{17}H_{11}N_5$ (%): C, 71.58; H, 3.86; N, 24.56.

3c: mp > 340 °C (decomp.). ^{1}H NMR (300 MHz, [^{2}H$_6$]DMSO) δ: 12.39 (s, 1H), 8.73 (s, 1H), 8.40 (s, 1H), 8.14 (m, 2H), 7.83–7.50 (m, 5H). IR (KBr, ν/cm^{-1}): 3212, 1636, 1604, 1548, 1484, 1452, 1376. EI MS, *m*/*z* (%): 319 (M$^+$, 100), 292 (14), 215 (10), 164 (17), 137 (21). Found (%): C, 63.83; H, 3.12; N, 21.88; Cl, 11.08. Calc. for $C_{17}H_{10}N_5Cl$ (%): C, 63.85; H, 3.13; N, 21.91; Cl, 11.11.

4b: mp 276 °C (decomp.). ^{1}H NMR (300 MHz, [^{2}H$_6$]DMSO) δ: 11.62 (s, 1H), 8.80 (s, 1H), 8.51 (m, 1H), 8.01 (m, 2H), 7.79–7.62 (m, 6H). IR (KBr, ν/cm^{-1}): 3312, 1632, 1604, 1560, 1476, 1346. EI MS, *m*/*z* (%): 285 (M$^+$, 100), 258 (24), 129 (18), 103 (21), 77 (29). Found (%): C, 71.55; H, 3.88; N, 24.57. Calc. for $C_{17}H_{11}N_5$ (%): C, 71.58; H, 3.86; N, 24.56.

4c: mp 315 °C (decomp.). ^{1}H NMR (300 MHz, [^{2}H$_6$]DMSO) δ: 10.66 (s, 1H), 8.05 (s, 1H), 7.87 (s, 1H), 7.56–7.52 (m, 3H), 7.50–7.35 (m, 5H). IR (KBr, ν/cm^{-1}): 3296, 1630, 1604, 1562, 1478, 1354. EI MS, *m*/*z* (%): 319 (M$^+$, 100), 292 (17), 215 (14), 164 (15), 137 (27). Found (%): C, 63.84; H, 3.11; N, 21.93; Cl, 11.13. Calc. for $C_{17}H_{10}N_5Cl$ (%): C, 63.85; H, 3.13; N, 21.91; Cl, 11.11.

Thus, 6-hydroxyimino-5-methyl-7-phenyl-6,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine undergoes dehydration into 5-methyl-[1,2,4]triazolo[1,5-*a*]pyrimido[5,6-*b*]indole on heating with *para*-nitrobenzoyl chloride in pyridine or PPA. However, 5,7-diaryl-substituted oximes give mixtures of isomeric 5-aryl[1,2,4]triazolo[1,5-*a*]pyrimido[5,6-*b*]- and 10-phenyl[1,2,4]triazolo[1,5-*a*]pyrimido[5,4-*b*]indoles under the same conditions. The identity of the products obtained with the participation of different reagents testifies to the fact that *para*-nitrobenzoyl chloride appears in this case as a source of the acidic medium in which, probably, a nitrenium cation forms.[8] As a result of the successful intramolecular electrophilic attack by this cation of the aryl rings, the isomeric triazolopyrimidoindoles are formed.

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