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New cascade transformations of 3-(2-aminophenylamino)-5,5-dimethyl-2-cyclohexen-1-one

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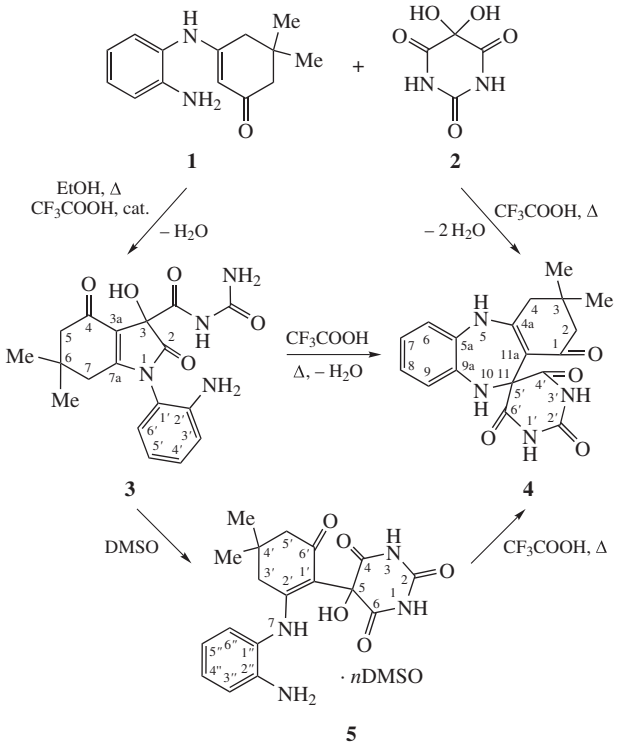
The reaction of 3-(2-aminophenylamino)-5,5-dimethyl-2-cyclohexen-1-one with alloxan results in 3,3-dimethyl-1,2,3,4,10,11-hexahydrospiro(1*H*-dibenzo[*b*,*e*][1,4]diazepine)-11,5′-pyrimidine-1,2′,4′,6′-tetraone or *N*-aminocarbonyl-1-(2-aminophenyl)-3-hydroxy-6,6-dimethyl-2,4-dioxo-2,3,4,5,6,7-hexahydro-1*H*-indole-3-carboxamide. The latter undergoes isomerization on dissolution in DMSO or DMF to give 5-[2-(2-aminophenylamino)-4,4-dimethyl-6-oxocyclohexenyl]-5-hydroxypyrimidine-2,4,6(1*H*,3*H*,6*H*)-trione, thus demonstrating a new example of ring–ring tautomerism.

3-(2-Aminophenylamino)-5,5-dimethyl-2-cyclohexen-1-one **1** is a valuable compound in synthetic and medicinal chemistry.[1–3] Its reactions with isatins give spiro derivatives incorporating dibenzodiazepinone and oxindole moieties.[4] The reaction of compound **1** with 2,6-di-*tert*-butyl-1,4-benzoquinone affords phenazine derivative with a 4,6-di-*tert*-butylphenol substituent,[5,6] while those with 3,5-di-*tert*-butyl-1,2-benzoquinone or 1,2-naphthoquinone lead to nine-membered macrolactones.[7,8] A common feature of all these processes is that cyclization involves the free amino group of compound **1**.

In the present study, we found that short refluxing of equimolar amounts of **1** and alloxan **2** in EtOH containing a catalytic amount of CF_3COOH gave hitherto unknown *N*-aminocarbonyl-1-(2-aminophenyl)-3-hydroxy-6,6-dimethyl-2,4-dioxo-2,3,4,5,6,7-hexahydro-1*H*-indole-3-carboxamide **3** (Scheme 1).[†] In other



Scheme 1

[†] Spectral studies were carried out using the equipment of the User Facilities Center 'Molecular Spectroscopy' at the Southern Federal University.

*N-Aminocarbonyl-1-(2-aminophenyl)-3-hydroxy-6,6-dimethyl-2,4-dioxo-2,3,4,5,6,7-hexahydro-1*H*-indole-3-carboxamide* **3**. A mixture of compound **1** (0.46 g, 2 mmol), compound **2** (0.38 g, 2 mmol), EtOH (10 ml) and 2 drops of CF_3COOH was refluxed until dissolution (1–2 min), cooled with rubbing by a glass rod, and kept for 1 h in ice. The precipitate was filtered off, then washed with EtOH and light petroleum. The yield of the crude product was 0.5 g (67%). A colourless compound, mp 175–182 °C (decomp.) (Pr^iOH). IR (ν/cm^{-1}): 3463, 3380, 3350, 3300, 3200, 3098 (OH, NH), 1761, 1726, 1686, 1690 (CO), 1531, 1502 (arom.). MS, *m*/*z*: 372 $[M]^+$. The NMR spectra of compound **3** in DMSO-d_6 or DMF-d_7 match those of isomeric compound **5**.

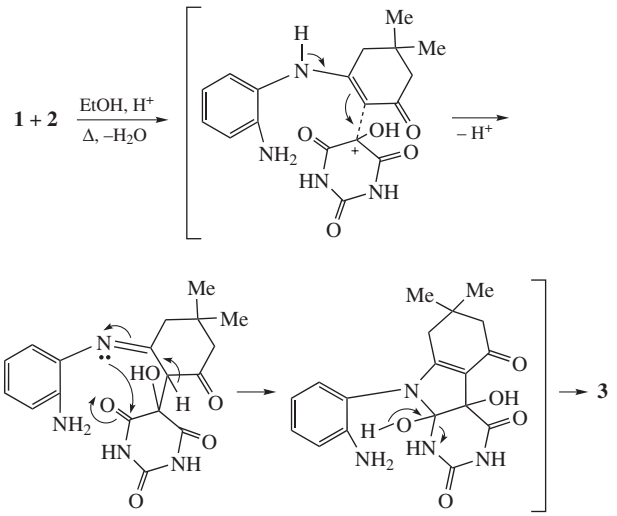
*3,3-Dimethyl-2,3,4,5,10,11-hexahydrospiro(1*H*-dibenzo[*b*,e*][1,4]-diazepine)-11,5′-pyrimidine-1,2′,4′,6′-tetraone* **4**.

(A) A mixture of compound **1** (0.23 g, 1 mmol) and compound **2** (0.19 g, 1 mmol) was refluxed for 1–2 min with CF_3COOH (2.5 ml). After cooling, diethyl ether (7 ml) was added to the orange solution and the mixture was cooled on ice. The precipitate was filtered off and washed with diethyl ether. The yield of the crude product was 0.25 g (70%). To obtain the pure compound, the reaction product was recrystallized from methanol. Colourless crystals were formed that gradually darken above 310 °C and decompose with intense gas evolution at 322 °C.

(B) A mixture of compound **3** (0.1 g, 0.27 mmol) and CF_3COOH (0.3 ml) was heated to boiling. The yellowish-red mixture was cooled, then diethyl ether (5 ml) was added. The precipitate was filtered off and washed with Et_2O. The yield of the crude product was 0.082 g (86%). A colourless compound, mp 322 °C (decomp.) (methanol). IR (ν/cm^{-1}): 3325, 3256, 3193, 3149, 3074 (NH), 1736, 1719, 1698 (CO), 1635, 1599, 1578, 1536 (arom.). ^{1}H NMR (DMSO-d_6) δ: 1.06 (s, 6H, Me), 1.99 [s, 2H, C(2)H$_2$], 2.57 [s, 2H, C(4)H$_2$], 6.28 [s, 1H, N(10)H], 6.83 [m, 2H, C(7)H, C(8)H], 6.92 [m, 1H, C(9)H], 7.04 [m, 1H, C(6)H], 9.04 [s, 1H, N(5)H], 10.99 [s, 2H, N(1′)H, N(3′)H]. ^{13}C NMR (DMSO-d_6) δ: 27.45 [C(12), C(12a)], 31.34 [C(3)], 44.46 [C(4)], 48.76 [C(2)], 65.72 [C(11)], 106.44 [C(11a)], 120.16 [C(6)], 121.44 [C(7)], 121.48 [C(9)], 123.41 [C(8)], 132.93 [C(5a)], 135.57 [C(9a)], 150.44 [C(2′)], 155.16 [C(4a)], 169.43 [C(4′)], 169.43 [C(6′)], 194.67 [C(1)]. ^{15}N NMR (DMSO-d_6) δ: 72.50 [N(10)], 120.00 [N(5)], 147.90 [N(1′)], 147.90 [N(3′)]. MS, *m*/*z*: 354 $[M]^+$ (100%). Found (%): C, 61.08; H, 5.32. Calc. for $C_{18}H_{18}N_4O_4$ (%): C, 61.01; H, 5.12.

words, [3+2]-cycloaddition recently reported for **1** analogues[8] involving no amino group occurs in this case. The similar processing in CF_3COOH resulted in 3,3-dimethyl-1,2,3,4,10,11-hexahydrospiro(1*H*-dibenzo[*b*,*e*][1,4]diazepine)-11,5′-pyrimidine-1,2′,4′,6′-tetraone **4**. Here, like in the reactions of **1** with isatins,[4] the amino group is incorporated in the diazepine ring. Finally, we found that compound **3** underwent conversion to compound **4** upon dissolution in CF_3COOH under reflux conditions. On dissolution in DMSO or DMF, compound **3** isomerized to pyrimidine-2,4,6(1*H*,3*H*,6*H*)-trione derivative **5**, which on heating in CF_3COOH yielded the same spiro product **4**.

The possible formation mechanism of compound **3** is presented in Scheme 2. Under conditions of acid catalysis, the reaction starts with elimination of one hydroxy group from alloxan. The resulting carbocation attacks the enamine moiety of molecule **1**. This is followed by cyclization with opening of the alloxan ring and retention of the second hydroxy group and amino group.



Scheme 2

The structure of compound **3** was proved by X-ray diffraction analysis (Figure 1).‡ The stoichiometry was confirmed by the mass spectrum and elemental analysis. However, the number of signals in the ^{13}C and ^{15}N NMR spectra recorded in DMSO-d_6 did not match the expected values. The N(1) nitrogen manifested itself as NH and correlated with C(7)H_2 and C(6′)H protons.

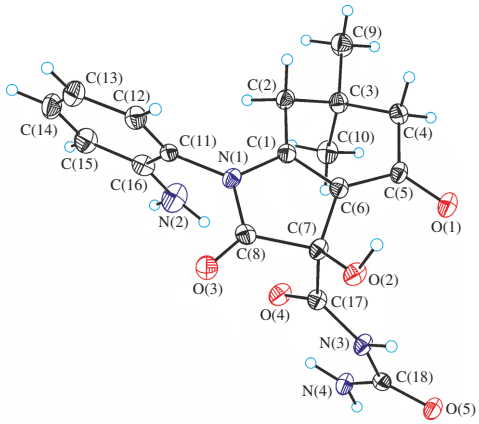
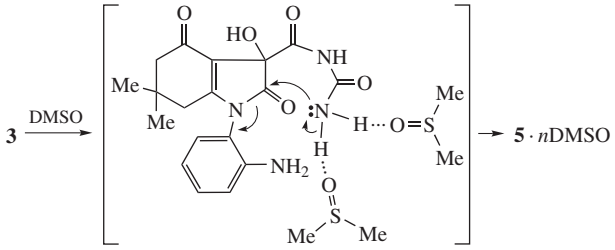


Figure 1 General view of molecule **3** with the atoms presented as atom vibration ellipsoids at 50% probability.

Total assignment of signals in ^1H NMR spectra was performed using the COSY pulse correlation sequence for ^{13}C NMR HMBC and HSQC spectra, and HMBC for ^{15}N NMR spectra (see Online Supplementary Materials). The combination of these data indicates that compound **3** undergoes isomerization to pyrimidine-2,4,6(1*H*,3*H*,6*H*)-trione **5** on dissolution in DMSO (Scheme 3).



Scheme 3

Compound **5** was isolated as a crystal solvate with DMSO. The ^1H NMR spectrum of solvate **5** recorded in DMF-d_7 gives the 'compound : DMSO' ratio of 1 : 1.62, whereas elemental analysis provides 1 : 1.8. A very intense band of stretching vibrations ν_{SO} 1009 cm^{-1} is observed in the IR spectrum of the solvate. Compound **3** undergoes a similar rearrangement in DMF, but we failed to isolate the corresponding solvate. The behaviour of compound **3** in aprotic bipolar solvents is a new example of ring–ring tautomerism.[9]

We assume that the driving force of the isomerization **3** → **5** is provided by specific solvation of the carbamoyl amino group in compound **3** by DMSO (ε = 49)[10] or DMF (ε = 36.7)[10] that facilitates a nucleophilic attack on the C(2) carbon (see Scheme 3). The presence of DMSO or DMF is apparently a prerequisite

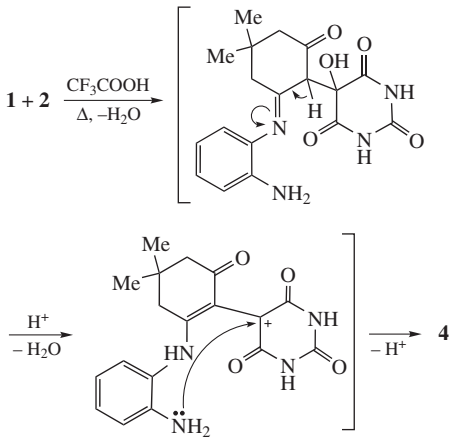
*5-[2-(2-Aminophenylamino)-4,4-dimethyl-6-oxocyclohexenyl]-5-hydroxypyrimidine-2,4,6(1*H*,3*H*,6*H*)-trione·n(Me)$_2$SO* **5**. A mixture of compound **3** (0.1 g, 0.27 mmol) and DMSO (0.25 ml) was slightly heated over a heating stage. Crystallization started right after dissolution. The mixture was cooled, then Pr^iOH (1 ml) and diethyl ether (2 ml) were added. The mixture was cooled with ice while rubbing with a glass rod. The precipitate was filtered off, washed with Et_2O and light petroleum and dried. The yield of a colourless compound was 0.12 g, mp 140–150 °C (decomp.). IR (ν/cm^{-1}): 3441, 3326, 3287, 3212, 3005 (OH, NH), 1740, 1715, 1697 (CO), 1636, 1597, 1542, 1501 (arom.), 1009 (S=O). ^1H NMR (DMSO-d_6) δ: 1.98 [s, 2H, C(5′)H_2], 2.16 [s, 2H, C(3′)H_2], 5.13 (s, 2H, NH_2), 6.57 [t, 1H, C(4″)H, *J* 7.8 Hz], 6.75 [d, 1H, C(3″)H, *J* 7.2 Hz], 7.02 [d, 1H, C(6″)H, *J* 7.5 Hz], 7.04 [t, 1H, C(5″)H, *J* 7.8 Hz], 7.94 (s, 1H, OH), 9.19 [s, 1H, N(7)H], 11.10 [s, 2H, N(1)H, N(3)H]. In the ^1H NMR spectrum of solvate **5** recorded in DMF-d_7, the 'compound : DMSO' ratio is 1 : 1.62, while according to elemental analysis this ratio is 1 : 1.8. The analysis results match the $C_{21.6}H_{30.8}N_4S_{1.8}O_6$ stoichiometry. ^{13}C NMR (DMSO-d_6) δ: 31.97 [C(4′)], 39.96 [C(3′)], 48.91 [C(5′)], 65.72 [C(5)], 106.02 [C(1′)], 114.89 [C(3″)], 116.02 [C(4″)], 128.09 [C(5″)], 128.28 [C(6″)], 150.44 [C(2)], 171.09 [C(4)], 171.09 [C(6)], 192.82 [C(6′)]. ^{15}N NMR (DMSO-d_6) δ: 55.80 (NH_2), 106.70 [N(7)], 147.30 [N(1)], 147.30 [N(3)]. Found (%): C, 50.55; H, 5.88; S, 11.11. Calc. for $C_{21.6}H_{30.8}N_4S_{1.8}O_6$ (%): C, 50.57; H, 6.05; S, 11.25.

‡ *Crystal data for* **3**. $C_{18}H_{20}N_4O_5 \cdot 0.375\,C_2H_6O \cdot 0.25\,H_2O$, triclinic, space group $P\bar{1}$, a = 9.4539(8), b = 10.1566(9) and c = 23.038(2) Å, α = = 79.712(2)°, β = 85.517(2)°, γ = 65.596(2)°, V = 1982.0(3) Å^3, Z = 4, M = 394.16, d_{calc} = 1.321 g cm^{-3}, wR_2 = 0.1530 calculated on F^2_{hkl} for 8611 independent reflections with $2\theta < 54°$ [GOF = 1.045, R = 0.0618 calculated on F_{hkl} for 4676 reflections with $I > 2\sigma(I)$].

Crystal data for **4**. $C_{18}H_{18}N_4O_4 \cdot 2\,MeOH$, 120 K, monoclinic, space group $P2_1/c$, a = 10.047(6), b = 20.773(12) and c = 10.292(6) Å, β = = 99.116(7)°, V = 2121(2) Å^3, Z = 4, M = 418.45, d_{calc} = 1.311 g cm^{-3}, wR_2 = 0.2196 calculated on F^2_{hkl} for 8163 independent reflections with $2\theta < 52°$ [GOF = 0.971, R = 0.0753 calculated on F_{hkl} for 1361 reflections with $I > 2\sigma(I)$].

CCDC 978821 and 992437 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

For details, see Online Supplementary Materials.



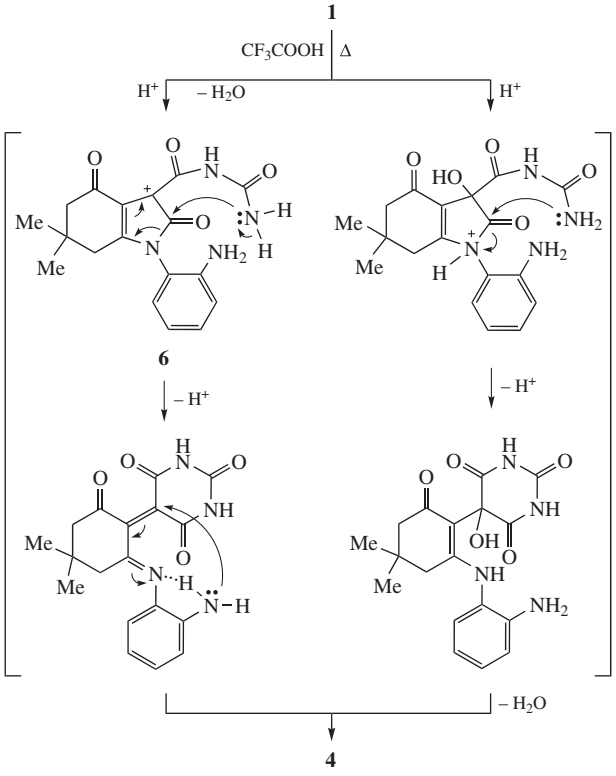
Scheme 4

of the occurrence of structure **5**. On recrystallization of solvate **5** from MeCN, it isomerizes back into compound **3**. We included an intermediate similar to **5** in the assumed scheme of the formation of compound **3** (Scheme 2).

A review[8] of ^{13}C NMR spectra (DMSO-d_6) of analogues of compound **3** leads us to the conclusion that they also undergo isomerization to analogues of compound **5**.

A possible mechanism of the reaction between compounds **1** and **2** in CF_3COOH under reflux conditions involves consecutive elimination of both hydroxy groups and incorporation of the amino group in the diazepine ring (Scheme 4), as it occurs in reactions of **1** with isatins.[4]

The first step of the **3** → **4** conversion in CF_3COOH may also involve elimination of a hydroxy group to afford carbocation **6**, which is then rearranged to compound **4**. However, an alternative route is also possible, namely, protonation of indole nitrogen, indole ring cleavage and alloxan ring closure, followed by hydration to give compound **4** (Scheme 5).



Scheme 5

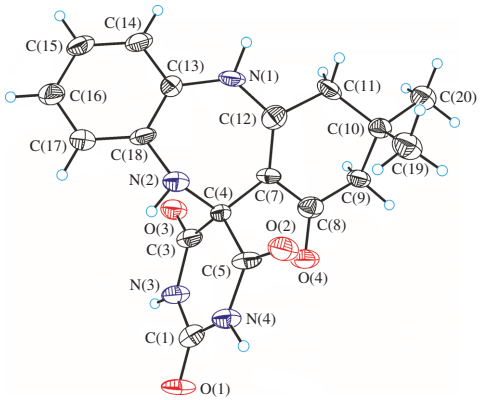


Figure 2 General view of molecule **4** with the atoms presented as atom vibration ellipsoids at 50% probability.

Compound **4** has high thermal stability; it does not change on heating to 310 °C. Molecule **4** demonstrates high resistance to electron impact. The relative intensity of the molecular ion signal in the mass spectrum recorded at an ionization energy of 70 eV is 100%. The structure of compound **4** was confirmed by X-ray diffraction analysis (Figure 2).‡

This study was carried out in accordance with task no. 4.196.2014/K in the framework of the project part of the state task on scientific activity of Southern Federal University.

We dedicate this study to the memory of **Zhanna I. Orlova**, who was our colleague and co-author for many years.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2015.03.020.

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