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Generation and properties of the 1,3-dimethyl-2,4-dioxo-1*H*,2*H*,3*H*,4*H*-pyrano[4,3-*d*]pyrimidinium cation in a chloroform–trifluoroacetic acid solution

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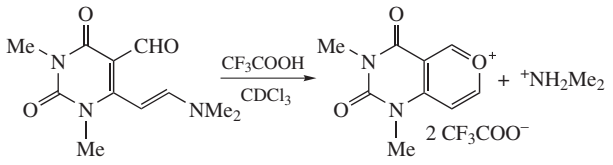
The 1,3-dimethyl-2,4-dioxo-1*H*,2*H*,3*H*,4*H*-pyrano[4,3-*d*]pyrimidinium cation has been prepared by means of acid-catalyzed cyclization of 1,3-dimethyl-6-(2-dimethylaminoethenyl)pyrimidine-2,4(1*H*,3*H*)-dione in a chloroform–trifluoroacetic acid solution, and its reactivity towards N-nucleophiles has been determined.

Pyrylium salts are widely used in organic chemistry due to their capability of nucleophilic substitution for oxygen atom.[1,2] Current studies in the field of pyrylium cations deal with their heteroannelated systems,[3–5] as they develop possibilities to synthesize new heterocycles, which hardly could be obtained *via* other methods. At the same time, compounds containing the uracil ring are widespread in nature and have versatile biological activity; therefore, they are very interesting to be studied.

Recently, we reported the convenient synthesis of 5-aryl and 5,7-diaryl-1,3-dimethyl-2,4-dioxo-1*H*,2*H*,3*H*,4*H*-pyrano[4,3-*d*]-pyrimidinium salts and investigated their reactivity in respect to nitrogen-based nucleophiles.[6]

Here, we report on the generation of 1,3 dimethyl-2,4-dioxo-1*H*,2*H*,3*H*,4*H*-pyrano[4,3-*d*]pyrimidinium cation containing no substituents in the pyrylium ring and its behaviour under the action of N-nucleophiles.

Enamine **1** was used as a starting material for the synthesis of target cation **2**. We were not able to isolate compound **2** in a crystalline state *via* acid-catalyzed cyclization. To find out that the conversion took place, the NMR spectroscopy of reaction solution[7,8] was employed. In a chloroform–trifluoroacetic acid (4:3) solution, the cyclization finished at room temperature in 2 h (Scheme 1).† The ^{1}H and ^{1}H decoupled ^{13}C NMR spectra



1 **2**

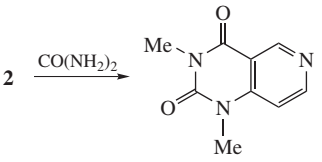
Scheme 1

† The IR spectra of compounds were recorded on a Specord IR-71 spectrometer in Nujol. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX-250 spectrometer; HMDS was used as the internal standard. Enamine **1** was obtained according to a published procedure.[12]

*Generation of 1,3-dimethyl-2,4-dioxo-1*H,2H,*3*H,*4*H-*pyrano[4,3-*d*]*pyrimidinium cation* **2** *in chloroform–trifluoroacetic acid solution*. Trifluoroacetic acid (0.3 ml) was added to a solution of enamine **1** (47.4 mg, 0.2 mmol) in 0.4 ml of $CDCl_3$. The solution was kept for 2 h at room temperature. ^{1}H NMR, δ: 2.86 (t, 6H, NMe_2, J 5.8 Hz), 3.51 (s, 3H, N^{3}Me), 3.78 (s, 3H, N^{1}Me), 7.00 (s, 2H, NH_2), 7.85 (d, 1H, C^{8}H, J 5.6 Hz), 9.03 (d, 1H, C^{7}H, J 5.6 Hz), 9.63 (s, 1H, C^{5}H). ^{13}C NMR, δ: 29.5 (N^{3}Me), 33.0 (N^{1}Me), 36.1 (NMe_2), 109.7 (C^8), 113.0 (C^{4A}), 148.6(C^{8A}), 157.2, 157.6 (C^{2}O, C^{4}O), 165.0 (C^7), 166.8 (C^5).

do not contain the signals of starting compound **1**. At the same time, one can see the signals of target cation **2** and also dimethylammonium cation formed simultaneously during the reaction. The signals of carbon atoms in ^{13}C NMR spectrum were assigned due to ^{1}H–^{13}C HETCOR experiment.

We found that cation **2** did not react with ammonium acetate and aliphatic amines. However, using urea as a nucleophile, we isolated pyrido[4,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione **3** described previously[9] (Scheme 2) (*cf.* similar interaction of monocyclic pyrylium salts with urea).[10]



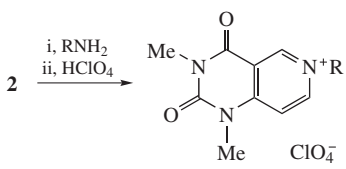
3

Scheme 2

It was also shown that cation **2** reacts with aromatic amines, hydrazine and phenylhydrazine under similar conditions, transforming into corresponding 6-R-pyrido[4,3-*d*]pyrimidinium salts **4a–e** (Scheme 3).‡

The structures of compounds **4a–e** were confirmed by ^{1}H, ^{13}C NMR and IR spectroscopy.

Thus, the possibility of nucleophilic substitution is determined by the nature of nucleophile. Ammonium acetate and aliphatic amines are more basic (p$K_b \leq 4.73$)[11] than urea, aromatic amines and phenylhydrazine (p$K_b \geq 8.71$). Evidently, in the test solution ammonium acetate and aliphatic amines exist completely in protonated forms and do not react with cation **2**. The basicity of hydrazine is comparable with ammonium acetate and aliphatic amines (p$K_{b1} = 5.89$). However, it easily enters into the interaction due to the presence of the second nucleophilic centre, which is not protonated under experimental conditions (p$K_{b2} = 14.88$).



4a–e

a R = Ph
b R = 4-BrC_6H_4
c R = 4-MeOC_6H_4
d R = NH_2
e R = PhNH

Scheme 3

In summary, the generation of 1,3-dimethyl-2,4-dioxo-1*H*,2*H*,3*H*,4*H*-pyrano[4,3-*d*]pyrimidinium cation has been elaborated and its reactivity to urea, primary arylamines, hydrazine and phenylhydrazine has been investigated. On this basis new fused uracil derivatives have been synthesised.

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‡ *General procedure for the synthesis of compounds* **4**. Trifluoroacetic acid (0.75 ml) was added to a solution of enamine **1** (118.5 mg, 0.5 mmol) in 1.0 ml of $CHCl_3$. The solution was kept for 2 h at room temperature. Corresponding nucleophile (0.53 mmol) was added. The reaction mixture was kept for 30 min, evaporated and treated by EtOH (2 ml) and 70% $HClO_4$ (0.088 ml, 1 mmol). After that, in the cases of compounds **4a** and **4b**, the precipitate formed was filtered off. In the cases of compounds **4c–e**, the alcoholic solution was decanted. The residue was crystallized from Et_2O. The NMR spectra of compounds **4a–e** were recorded in [$^2H_6$]DMSO.

*1,3-Dimethyl-2,4-dioxo-6-phenyl-1*H,*2*H,*3*H,*4*H-*pyrido[4,3-*d*]*pyrimidinium perchlorate* **4a**. Yield 54%, mp 181–182 °C. ^{1}H NMR, δ: 3.34 (s, 3H, N^{3}Me), 3.64 (s, 3H, N^{1}Me), 7.63–7.76 (m, 3H, Ph), 7.80–7.91 (m, 2H, Ph), 8.13 (d, 1H, C^{8}H, *J* 7.4 Hz), 9.28 (dd, 1H, C^{7}H, $J_{7,8}$ 7.3 Hz, $J_{7,5}$ 1.8 Hz), 9.51 (d, 1H, C^{5}H, *J* 1.8 Hz). ^{13}C NMR, δ: 29.5 (N^{3}Me), 32.9 (N^{1}Me), 113.6 (C^8), 114.1 (C^{4A}), 125.5 (C$^{3'}$, C$^{5'}$), 131.0 (C$^{2'}$, C$^{6'}$), 131.7 (C$^{4'}$), 142.6 (C$^{1'}$), 145.7 (C^7), 147.7 (C^5), 150.8, 151.9 (C^{2}O, C^{4}O), 159.2 (C^{8A}). IR (ν/cm^{-1}): 1090 (br., Cl–O), 1660, 1720 (C=O).

*6-(4-Bromophenyl)-1,3-dimethyl-2,4-dioxo-1*H,*2*H,*3*H,*4*H-*pyrido[4,3-*d*]*pyrimidinium perchlorate* **4b**. Yield 69%, mp 215–218 °C. ^{1}H NMR, δ: 3.37 (s, 3H, N^{3}Me), 3.67 (s, 3H, N^{1}Me), 7.86 (d, 2H, Ar, *J* 9.0 Hz), 7.95 (d, 2H, Ar, *J* 9.0 Hz), 8.17 (d, 1H, C^{8}H, *J* 7.4 Hz), 9.28 (dd, 1H, C^{7}H, $J_{7,8}$ 7.4 Hz, $J_{7,5}$ 1.8 Hz), 9.57 (d, 1H, C^{5}H, *J* 1.7 Hz). ^{13}C NMR, δ: 29.5 (N^{3}Me), 32.9 (N^{1}Me), 113.6 (C^8), 114.0 (C^{4A}), 125.1 (C$^{4'}$), 127.8 (C$^{3'}$), C$^{5'}$), 133.8 (C$^{2'}$, C$^{6'}$), 141.8 (C$^{1'}$), 145.8 (C^7), 147.6 (C^5), 150.7, 152.0 (C^{2}O, C^{4}O), 159.2 (C^{8A}). IR (ν/cm^{-1}): 1095 (br., Cl–O), 1640, 1690 (C=O).

*1,3-Dimethyl-2,4-dioxo-6-(4-methoxyphenyl)-1*H,*2*H,*3*H,*4*H-*pyrido[4,3-*d*]*pyrimidinium perchlorate* **4c**. Yield 39%, mp 109–112 °C. ^{1}H NMR, δ: 3.35 (s, 3H, N^{3}Me), 3.67 (s, 3H, N^{1}Me), 3.86 (s, 3H, OMe), 7.24 (d, 2H, Ar, *J* 7.5 Hz), 7.84 (d, 2H, Ar, *J* 7.9 Hz), 8.13 (d, 1H, C^{8}H, *J* 6.6 Hz), 9.26 (d, 1H, C^{7}H, *J* 5.5 Hz), 9.48 (s, 1H, C^{5}H). ^{13}C NMR, δ: 29.5 (N^{3}Me), 32.8 (N^{1}Me), 56.8 (OMe), 113.6 (C^8), 114.0 (C^{4A}), 116.0 (C$^{3'}$, C$^{5'}$), 126.8 (C$^{2'}$, C$^{6'}$), 135.7 (C$^{1'}$), 145.5 (C^7), 147.7 (C^5), 150.8, 151.5 (C^{2}O, C^{4}O), 159.2 (C^{8A}), 161.7 (C$^{4'}$). IR (ν/cm^{-1}): 1095 (br., Cl–O), 1635, 1715 (C=O).

*6-Amino-1,3-dimethyl-2,4-dioxo-1*H,*2*H,*3*H,*4*H-*pyrido[4,3-*d*]*pyrimidinium perchlorate* **4d**. Yield 63%, mp 145–147 °C. ^{1}H NMR, δ: 3.32 (s, 3H, N^{3}Me), 3.56 (s, 3H, N^{1}Me), 7.94 (d, 1H, C^{8}H, *J* 7.7 Hz), 8.04 (s, 2H, NH$_2$), 8.84 (dd, 1H, C^{7}H, $J_{7,8}$ 7.3 Hz, $J_{7,5}$ 1.9 Hz), 9.26 (d, 1H, C^{5}H, *J* 1.9 Hz). ^{13}C NMR, δ: 29.4 (N^{3}Me), 32.5 (N^{1}Me), 114.0 (C^8), 114.1 (C^{4A}), 140.7 (C^7), 144.2 (C^5), 148.3, 150.8 (C^{2}O, C^{4}O), 159.2 (C^{8A}). IR (ν/cm^{-1}): 1100 (br., Cl–O), 1680, 1720 (C=O), 3275, 3330 (NH$_2$).

*1,3-Dimethyl-2,4-dioxo-6-phenylamino-1*H,*2*H,*3*H,*4*H-*pyrido[4,3-*d*]*pyrimidinium perchlorate* **4e**. Yield 60%, mp 107–109 °C. ^{1}H NMR, δ: 3.34 (s, 3H, N^{1}Me), 3.66 (s, 3H, N^{3}Me), 6.73 (d, 2H, Ar, *J* 7.7 Hz), 7.09 (t, 1H, Ar, *J* 7.1 Hz), 7.35 (t, 2H, Ar, *J* 7.8 Hz), 8.10 (d, 1H, C^{8}H, *J* 7.7 Hz), 9.20 (d, 1H, C^{7}H, *J* 6.9 Hz), 9.50 (s, 1H, C^{5}H), 10.60 (s, 1H, NH). ^{13}C NMR, δ: 29.5 (N^{3}Me), 32.9 (N^{1}Me), 115.2 (C^8), 115.4 (C$^{3'}$, C$^{5'}$), 115.5 (C^{4A}), 124.1 (C$^{4'}$), 130.5 (C$^{2'}$, C$^{6'}$), 146.8 (C$^{1'}$), 147.7 (C^7), 149.9 (C^5), 150.7, 151.9 (C^{2}O, C^{4}O), 159.0 (C^{8A}). IR (ν/cm^{-1}): 1090 (br., Cl–O), 1630, 1680 (C=O), 3270 (NH).