

## Interaction of 5-methoxy-1,2,4-triazines with ureas as a new route to 6-azapurines

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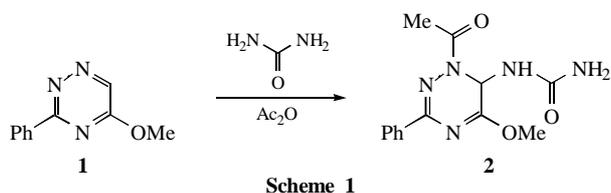
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A tandem of  $S_N^H$  and  $S_N^{ipso}$  reactions leading to imidazo[4,5-*e*]-1,2,4-triazines (6-azapurines) has been observed in the interaction of 5-methoxy-1,2,4-triazines with ureas in the presence of acylating agents.

Synthetic routes to azapurines (imidazo[4,5-*e*]-1,2,4-triazines) described in the literature suggest multistage syntheses from uracil derivatives<sup>1,2</sup> or involve rearrangements of 7-azalumazines.<sup>3,4</sup> Another approach of considerable current use is based on condensation of 5,6-diamino-1,2,4-triazines with C<sup>1</sup>-synthons.<sup>5–7</sup> At the same time, the high electrophilicity of a triazine ring and its tendency to *ortho*-cyclization reactions,<sup>8,9</sup> suggest the possibility for direct annelation of the imidazole ring by interactions of triazines with 1,3-N,N'-binucleophiles due to a nucleophilic attack on unsubstituted carbon atoms of the triazine ring.

We have developed a very simple one-step procedure for the synthesis of azapurines from easily accessible 5-methoxy-3-phenyl-1,2,4-triazine<sup>10</sup> and ureas (Scheme 2). These transformations belong to interactions of  $\pi$ -deficient heteroaromatic compounds bearing good leaving groups X (in this case, it is the methoxy group) with nucleophiles. In addition to the replacement of the group X,<sup>11</sup> which is a common phenomenon in this case, nucleophilic substitution of hydrogen ( $S_N^H$ ) can be reached under appropriate conditions.<sup>12</sup> We found a tandem of  $S_N^H$  and  $S_N^{ipso}$  reactions leading to azapurines by studying the interaction of 5-methoxy-1,2,4-triazines with ureas in the presence of acylating agents.

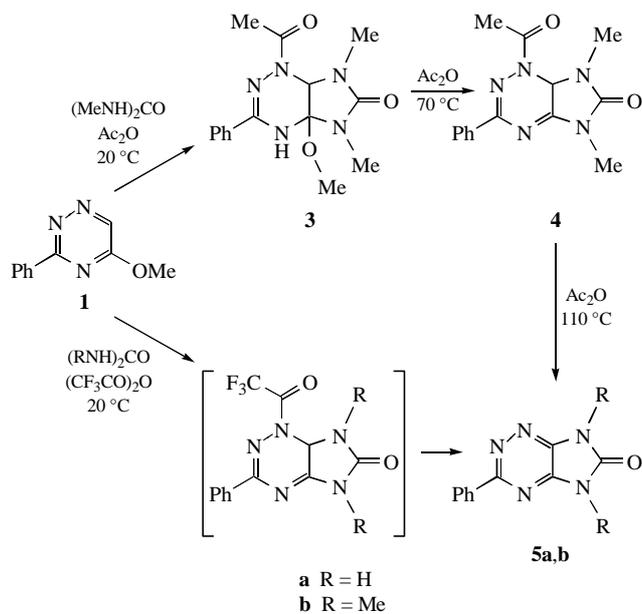
The presence of an acylating agent is a decisive factor. Thus, 5-methoxy-3-phenyl-1,2,4-triazine reacts with ureas in the presence of acetic anhydride to afford imidazo[4,3-*e*]-1,2,4-triazine (6-azapurine) derivatives. This reaction involves a number of successive steps and, depending on the reaction conditions and the nature of reagents and acylating agents, it affords either open-chain adducts or cyclization products. Note that the nucleophilic attack takes place first at the unsubstituted 6-position, although the replacement of a methoxy group in the 5-position can be expected in accordance with the classic theory of  $S_N^{ipso}$  reactions and quantum-chemical calculations. Thus, the reaction of urea with 5-methoxy-3-phenyl-1,2,4-triazine in acetic anhydride under mild conditions (20 °C) affords compound **2** (Scheme 1).<sup>†</sup>



Unlike the reaction with urea, the interaction of *N,N*-dimethylurea with triazine **1** at 20 °C did not stop at the stage of mono-adduct formation, and the only product is cyclic com-

<sup>†</sup> <sup>1</sup>H NMR spectra were measured on Bruker WM-300 and ARX-300 spectrometers, TMS was used as a standard.

**1-Acetyl-5-methoxy-3-phenyl-6-(ureido)-1,6-dihydro-1,2,4-triazine 2.** A mixture of 5-methoxy-3-phenyl-1,2,4-triazine (50 mg, 0.27 mmol) and urea (16 mg, 0.27 mmol) in acetic anhydride (0.7 ml) was stirred for 48 h at 20 °C. The precipitate formed was filtered off and washed with hot methanol to yield 51 mg (65%) of **2**; mp 210–212 °C. <sup>1</sup>H NMR ([<sup>2</sup>H<sub>6</sub>]DMSO)  $\delta$ : 2.33 (s, 3H, Ac), 3.99 (s, 3H, OMe), 5.60 (br. s, 2H, NH<sub>2</sub>), 6.39 (d, 1H, CH, *J* 8.5 Hz), 7.22 (d, 1H, NH, *J* 8.5 Hz), 7.45–7.48 (m, 3H, Ph), 8.09–8.12 (m, 2H, Ph). Found (%): C, 53.58; H, 5.27; N, 24.25. Calc. for C<sub>13</sub>H<sub>15</sub>N<sub>5</sub>O<sub>3</sub> (%): C, 53.97; H, 5.23; N, 24.21.



ound **3** isolated as crystals.<sup>‡</sup> This is a rare case of isolation of a crystalline *ipso*-adduct.

Upon refluxing a solution of compound **3** in CHCl<sub>3</sub> for a long time, a molecule of methanol was eliminated to afford dihydrotriazine **4** in 85% yield.<sup>§</sup> The reaction time can be shortened using acetic anhydride at a higher temperature. Thus, heating a mixture of equimolar amounts of 1,2,4-triazine **1** and dimethylurea in acetic anhydride at 70 °C gives dihydrotriazine **4** in 45% yield without isolation of any intermediates.

<sup>‡</sup> **1-Acetyl-5,7-dimethyl-4a-methoxy-3-phenyl-4,4a,5,6,7,7a-hexahydro-1H-imidazo[4,5-*e*]-1,2,4-triazin-6-one 3.** A solution of 5-methoxy-3-phenyl-1,2,4-triazine (50 mg, 0.27 mmol) and *N,N'*-dimethylurea (24 mg, 0.27 mmol) in acetic anhydride (1 ml) was stirred for 48 h at 20 °C. After evaporation of the solvent *in vacuo*, the oil residue was dissolved in diethyl ether (1 ml). The precipitated colourless crystals were filtered off to yield 55 mg (64%) of compound **3**; mp 110–112 °C (decomp.). <sup>1</sup>H NMR ([<sup>2</sup>H<sub>6</sub>]DMSO)  $\delta$ : 2.34 (s, 3H, Ac), 2.59 (s, 3H, N-Me), 2.78 (s, 3H, N-Me), 3.27 (s, 3H, OMe), 6.12 (s, 1H, CH), 7.45–7.55 (m, 3H, Ph), 7.80–7.83 (m, 2H, Ph). Found (%): C, 56.62; H, 5.99; N, 22.13. Calc. for C<sub>15</sub>H<sub>19</sub>N<sub>5</sub>O<sub>3</sub> (%): C, 56.77; H, 6.03; N, 22.07.

<sup>§</sup> **1-Acetyl-5,7-dimethyl-3-phenyl-5,6,7,7a-tetrahydro-1H-imidazo[4,5-*e*]-1,2,4-triazin-6-one 4.** Method 1: A solution of **3** (100 mg, 0.31 mmol) in CHCl<sub>3</sub> (2 ml) was refluxed for 48 h. After evaporation of the solvent *in vacuo*, the residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> and chromatographed on silica gel. Yield 77 mg (87%); mp 141–143 °C. <sup>1</sup>H NMR ([<sup>2</sup>H<sub>6</sub>]DMSO)  $\delta$ : 2.43 (s, 3H, Ac), 3.26 (s, 3H, N-Me), 3.32 (s, 3H, N-Me), 4.72 (s, 1H, CH), 7.40–7.44 (m, 3H, Ph), 8.07–8.11 (m, 2H, Ph). Found (%): C, 59.05; H, 5.26; N, 24.41. Calc. for C<sub>14</sub>H<sub>15</sub>N<sub>5</sub>O<sub>2</sub> (%): C, 58.94; H, 5.30; N, 24.55.

Method 2: A mixture of 5-methoxy-3-phenyl-1,2,4-triazine (200 mg, 1.08 mmol), *N,N'*-dimethylurea (95 mg, 1.08 mmol) and acetic anhydride (3 ml) was stirred for 1.5 h at 85–90 °C. The solvent was removed *in vacuo*. The colourless crystals were washed with diethyl ether to yield 140 mg (45%) of compound **4**; mp 144–146 °C.

Increasing the temperature to 110 °C facilitates the aromatization of dihydrotriazine to imidazo[4,3-*e*]-1,2,4-triazine **5**.

Trifluoroacetic anhydride is a stronger activator for the reaction of 1,2,4-triazine with ureas. Moreover, the aromatization of acylated compounds proceeds more easily with trifluoroacetic anhydride. The reaction of 5-methoxy-1,2,4-triazine **1** with ureas under mild conditions afforded aromatic azapurines **5a,b**.<sup>†</sup>

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<sup>†</sup> 3-Phenyl-6,7-dihydro-5H-imidazo[4,5-*e*]-1,2,4-triazin-6-one **5a**. To a solution of 5-methoxy-3-phenyl-1,2,4-triazine (80 mg, 0.43 mmol) in dry dichloromethane (1 ml) trifluoroacetic anhydride was added. The mixture was stirred for 15 min at 20 °C. Next, urea (26 mg) was added, and the mixture was stirred for 48 h. The reaction mixture was concentrated at a reduced pressure. The oil residue was washed with diethyl ether. Next, the precipitate was filtered off and washed with diethyl ether to yield 73 mg (80%) of compound **5a**; mp 232–233 °C. <sup>1</sup>H NMR ([<sup>2</sup>H<sub>6</sub>]DMSO) δ: 7.33 (br. s, NH), 7.56–7.65 (m, 3H, Ph), 8.00–8.12 (m, 2H, Ph). Found (%): C, 56.09; H, 3.34; N, 32.71. Calc. for C<sub>10</sub>H<sub>7</sub>N<sub>5</sub>O (%): C, 56.33; H, 3.31; N, 32.85.

5,7-Dimethyl-3-phenyl-6,7-dihydro-5H-imidazo[4,5-*e*]-1,2,4-triazin-6-one **5b**. Method 1: A solution of 5-methoxy-3-phenyl-1,2,4-triazine (50 mg, 0.27 mmol) and *N,N'*-dimethylurea (24 mg, 0.27 mmol) in acetic anhydride (1.5 ml) was heated at 110 °C for 6 h with stirring. The solvent was evaporated *in vacuo*, and the colourless precipitate was filtered off and washed with diethyl ether to give 31 mg (48%) of compound **5b**; mp 198–200 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 3.47 (s, 3H, NMe), 3.53 (s, 3H, NMe), 7.40–7.46 (m, 3H, Ph), 8.34–8.40 (m, 2H, Ph). Found (%): C, 59.50; H, 4.42; N, 28.88. Calc. for C<sub>12</sub>H<sub>11</sub>N<sub>5</sub>O (%): C, 59.74; H, 4.60; N, 28.88.

Method 2: To a solution of 5-methoxy-3-phenyl-1,2,4-triazine (50 mg, 0.27 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub>, trifluoroacetic anhydride (0.2 ml) was added, and the mixture was stirred for 15 min at 20 °C. *N,N'*-Dimethylurea (24 mg, 0.27 mmol) was added, and the solution was stirred for 48 h. The reaction mixture was concentrated under a reduced pressure, and the oil residue was filtered off and washed with diethyl ether. Next, the precipitate was filtered off and recrystallised from methanol to give 30 mg (46%) of compound **5b**.

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