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

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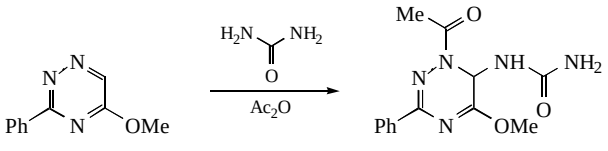
A tandem of S_N^H and S_N^{ipso} reactions leading to imidazo[4,5-*e*]-1,2,4-trazines (6-azapurines) has been observed in the interaction of 5-methoxy-1,2,4-triazines with ureas in the presence of acylating agents.

Synthetic routes to azapurines (imidazo[4,5-*e*]-1,2,4-triazines) described in the literature suggest multistage syntheses from uracil derivatives[1,2] or involve rearrangements of 7-azalumazines.[3,4] Another approach of considerable current use is based on condensation of 5,6-diamino-1,2,4-triazines with C^1-synthons.[5–7] At the same time, the high electrophilicity of a triazine ring and its tendency to *ortho*-cyclization reactions,[8,9] 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[10] and ureas (Scheme 2). These transformations belong to interactions of π-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,[11] which is a common phenomenon in this case, nucleophilic substitution of hydrogen (S_N^H) can be reached under appropriate conditions.[12] 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.

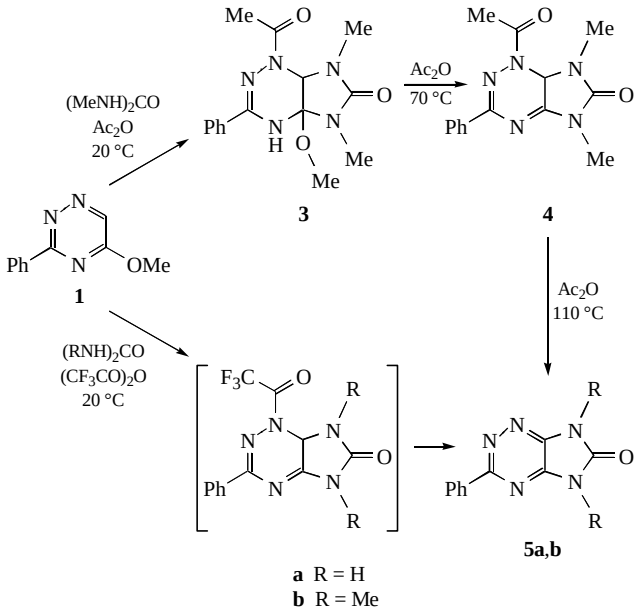
The presence of an acylating agent is a decisive factor. Thus, 5-methoxy-3-phenyl-1,2,4-triazine reacts with ureas in the presence of acetic anhydride to afford imidazo[4,3-*e*]-1,2,4-triazine (6-azapurine) derivatives. This reaction involves a number of successive steps and, depending on the reaction 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).†



1 **2**

Scheme 1

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 compound **3** isolated as crystals.‡ This is a rare case of isolation of a crystalline σ^{ipso}-adduct.



3 **4** **1** **5a**,**b**

a R = H
b R = Me

Scheme 2

Upon refluxing a solution of compound **3** in $CHCl_3$ for a long time, a molecule of methanol was eliminated to afford dihydrotriazine **4** in 85% yield.§ 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.

† ^{1}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. ^{1}H NMR ([$^2H_6$]DMSO) δ: 2.33 (s, 3H, Ac), 3.99 (s, 3H, OMe), 5.60 (br. s, 2H, NH_2), 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 $C_{13}H_{15}N_5O_3$ (%): C, 53.97; H, 5.23; N, 24.21.

‡ *1-Acetyl-5,7-dimethyl-4*a*-methoxy-3-phenyl-4,4*a,*5,6,7,7*a*-hexahydro-1*H*-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.). ^{1}H NMR ([$^2H_6$]DMSO) δ: 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 $C_{15}H_{19}N_5O_3$ (%): C, 56.77; H, 6.03; N, 22.07.

§ *1-Acetyl-5,7-dimethyl-3-phenyl-5,6,7,7*a*-tetrahydro-1*H*-imidazo[4,5-*e*]-1,2,4-triazin-6-one* **4**. Method 1: A solution of **3** (100 mg, 0.31 mmol) in $CHCl_3$ (2 ml) was refluxed for 48 h. After evaporation of the solvent *in vacuo*, the residue was dissolved in CH_2Cl_2 and chromatographed on silica gel. Yield 77 mg (87%); mp 141–143 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 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 $C_{14}H_{15}N_5O_2$ (%): 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**.¶

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¶ *3-Phenyl-6,7-dihydro-5*H-*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) trifluoracetic 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. ^{1}H NMR ([$^2H_6$]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 $C_{10}H_7N_5O$ (%): C, 56.33; H, 3.31; N, 32.85.

*5,7-Dimethyl-3-phenyl-6,7-dihydro-5*H-*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 stirrting. 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. ^{1}H NMR ($CDCl_3$) 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 $C_{12}H_{11}N_5O$ (%): 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_2Cl_2 trifluoracetic 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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