Nucleophilic substitution or dipolar 1,3-cycloaddition in reactions of cyanamide with 4-arylpyrimidine 1-oxides

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Pyrimidine 1-oxides with cyanamide afforded 2-ureidopyrimidines as the result of the nucleophilic substitution of hydrogen, whereas the formation of similar 2-trichloroacetylaminopyrimidines occurs as dipolar 1,3-cycloaddition of the same oxides to trichloroacetonitrile under much more drastic conditions and in lower yields.

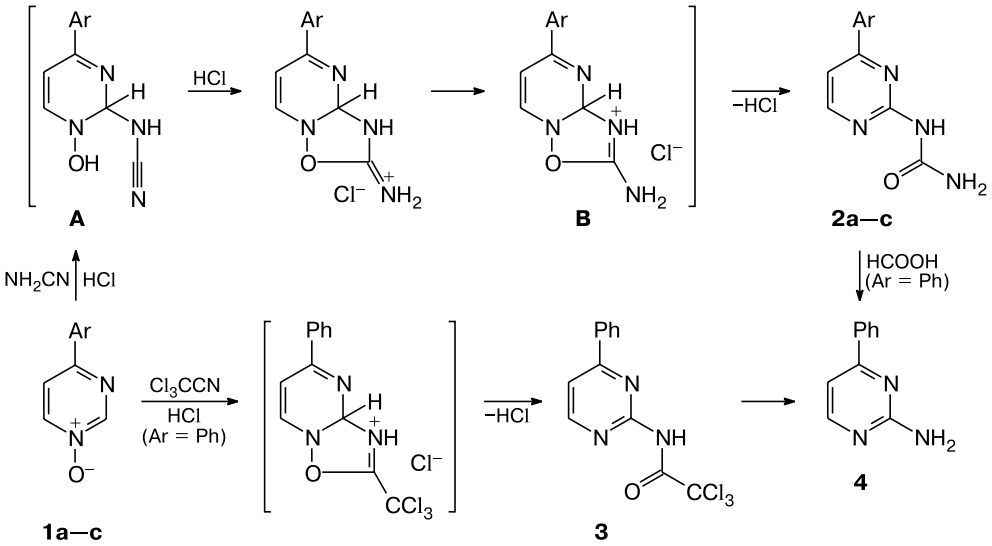
Key words: dipolar 1,3-cycloaddition, nucleophilic substitution of hydrogen, cyanamide, pyrimidine 1-oxides, 2-ureidopyrimidines, 2-aminopyrimidines.

Earlier,[1] we reported that reactions of 1,2,4-triazine 4-oxides with cyanamide in the presence of bases afford 5-cyanamino-1,2,4-triazines; *i.e.*, cyanamide was used for the first time as a nucleophile in reactions of nucleophilic substitution of hydrogen (S_N^H reactions). This study is devoted to reactions of pyrimidine *N*-oxides with cyanamide with the aim of applying the discovered reaction to other heterocyclic systems.

Pyrimidine, which contains only two N atoms, is significantly less electrophilic than 1,2,4-triazine. Obviously, it is for this reason that pyrimidine 1-oxides **1a**—**c** do not react, as distinct from 1,2,4-triazine 4-oxides,[1] with an anion generated from cyanamide in the presence of a base (sodium ethoxide or hydroxide). We found that pyrimidine 1-oxides **1a**—**c** react with cyanamide under acidic conditions (dry HCl) instead of basic ones to give 4-aryl-2-ureidopyrimidines **2a**—**c** in 57—65% yields (Scheme 1).

Structures **2a**—**c** were confirmed by elemental analysis, ^{1}H NMR, and MS data. The location of the urea residue in products **2a**—**c** was unambiguously determined

Scheme 1



Ar = Ph (**a**), 4-ClC$_6$H$_4$ (**b**), 4-MeC$_6$H$_4$ (**c**)

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from the spin-spin coupling between the protons in positions 5 and 6 of the pyrimidine ring in their ^{1}H NMR spectra (J = 4.9—5.3 Hz).

Previous results[1] allowed one to suggest that in this case, nucleophilic substitution of the cyanamide residue for a hydrogen atom in a pyrimidine *N*-oxide is followed by the hydrolysis of the cyano group. However, the same reaction products were obtained in the absence of traces of water. In addition, 2-cyanoaminopyrimidines are known[2] to be resistant to hydrolysis both under acidic and basic conditions. Apparently, the O atom in the urea residue of compounds **2a—c** comes from the *N*-oxide group of the substrate.

On the one hand, this can be due to dipolar cycloaddition with pyrimidine 1-oxides **1a—c** as dipoles and cyanamide as a dipolarophile. This process seemed to be quite possible because cyanamide can react with, *e.g.*, 1,2,4-triazines to give [4+2]-cycloadducts.[3,4] It is also known that dipolar 1,3-cycloaddition of pyrimidine 1-oxides (through the *N*-oxide group) to such dipolarophiles as phenyl isocyanate[5] and dimethyl acetylenedicarboxylate[6] yields 2-aniline- and 2-methoxycarbonylmethylpyridines, respectively.

On the other hand, the *in situ* protonation of pyrimidine 1-oxides **1a—c** makes the substrate significantly more electrophilic, which facilitates, to a large extent, the addition of a nucleophile to give intermediate σ-adducts **A**. A subsequent intramolecular nucleophilic attack of the *N*-hydroxy group on the C atom of the nitrile group affords cyclic intermediate **B** (see Scheme 1). This step can also be facilitated in the presence of HCl by analogy with the well-known formation of imino esters in reactions of nitriles with alcohols. A similar route was proposed for reactions of 1,2,4-triazine 4-oxides with benzoylacetone.[7] It is worth noting that both pathways proposed should proceed *via* formation of the same intermediate cycloadduct **B**, which undergoes the opening of its 1,2,4-oxadiazole ring to give products **2** (see Scheme 1). This process is analogous to aromatization of σ-adducts in reactions of azine *N*-oxides with nucleophiles as a result of elimination of a carboxylic acid molecule following the O-acylation of the *N*-oxide fragment.[8]

For comparison, we studied the reaction of pyrimidine oxide **1a** with trichloroacetonitrile, which exhibit no nucleophilic properties, but is a typical dipolarophile.[9] This reaction yielded 4-phenyl-2-(trichloroacetylamino)pyrimidine **3**, which can be formed only through dipolar cycloaddition, and its hydrolysis product, namely, 2-amino-4-phenylpyrimidine **4**. The same compound **4** was obtained by hydrolysis of ureidopyrimidine **2a** in boiling formic acid.

Hence, the low yield of products and the drastic conditions in the reactions of pyrimidine 1-oxides **1** with trichloroacetonitrile (compared to those with cyanamide) suggest the mechanism of dipolar 1,3-cycloaddition. In the case of cyanamide, the suggested addition of its nucleophilic amino group at position 2 of a pyrimidine 1-oxide is followed by cyclization and subsequent opening of the oxadiazole ring. The aforesaid reactions can be considered to be a convenient approach to the synthesis of aminopyrimidines.

Experimental

^{1}H NMR spectra were recorded on a Bruker WM-250 spectrometer (250.13 MHz) in DMSO-d_6 with Me_4Si as the internal standard. Mass spectra were recorded on a Varian MAT-311A instrument. The starting 4-arylpyrimidine 1-oxides **1** were prepared according to the known procedure.[10]

Synthesis of 2-ureidopyrimidines 2a—c (general procedure). Gaseous dry HCl (0.1 mol) was passed through a mixture of cyanamide (0.19 g, 4.5 mmol) and a corresponding 4-arylpyrimidine 1-oxide **1** (3 mmol) in 40 mL of $CHCl_3$. Then the reaction mixture was refluxed for 15 min. The precipitate that formed was filtered off, washed with $CHCl_3$, and recrystallized from EtOH.

4-Phenyl-2-ureidopyrimidine (2a). Yield 365 mg (57%), m.p. 221—223 °C. Found (%): C, 61.48; H, 4.89; N, 25.95. $C_{11}H_{10}N_4O$. Calculated (%): C, 61.67; H, 4.71; N, 26.15. ^{1}H NMR, δ: 7.06, 8.55 (both br.s, 1 H each, NH_2); 7.51 (m, 4 H, Ph, H(5)); 8.07 (m, 2 H, Ph); 8.59 (d, 1 H, H(6), J = 5.2 Hz); 9.42 (s, 1 H, NH). MS, m/z: 214 $[M]^+$.

4-(4-Chlorophenyl)-2-ureidopyrimidine (2b). Yield 485 mg (65%), m.p. 255—257 °C. Found (%): C, 53.08; H, 3.59; N, 22.49. $C_{11}H_9ClN_4O$. Calculated (%): C, 53.13; H, 3.65; N, 22.53. ^{1}H NMR, δ: 7.18, 8.48 (both br.s, 1 H each, NH_2); 7.65 (m, 3 H, H arom., H(5)); 8.13 (m, 2 H, H arom.); 8.65 (d, 1 H, H(6), J = 5.2 Hz); 9.72 (s, 1 H, NH).

4-Tolyl-2-ureidopyrimidine (2c). Yield 405 mg (59%), m.p. 252—253 °C. Found (%): C, 63.10; H, 5.43, N, 24.41. $C_{12}H_{12}N_4O$. Calculated (%): C, 63.15; H, 5.30; N, 24.55. ^{1}H NMR, δ: 2.39 (s, 3 H, Me); 7.18, 8.47 (both br.s, 1 H each, NH_2); 7.39 (d, 2 H, H arom.); 7.62 (d, 1 H, H(5), J = 5.3 Hz); 8.04 (d, 2 H, H arom.); 8.60 (d, 1 H, H(6), J = 5.3 Hz); 9.75 (s, 1 H, NH).

Reaction of pyrimidine 1-oxide 1a with trichloroacetonitrile. A suspension of pyrimidine 1-oxide **1a** (850 mg, 5 mmol) in 10 mL of trichloroacetonitrile was refluxed for 24 h. Every two hours, the suspension was bubbled with dry HCl through a 1-mm capillary at a rate of 1 bubble per second for 10 min. The solvent was evaporated *in vacuo*, and the residue was chromatographed on Merck 100 silica gel in AcOEt to give products **3** and **4**.

4-Phenyl-2-(trichloroacetylamino)pyrimidine (3). Yield 100 mg (6%), m.p. 125—127 °C (from hexane). Found (%): C, 45.72; H, 2.50; N, 13.07. $C_{12}H_8Cl_3N_3O$. Calculated (%): C, 45.53; H, 2.55; N, 13.27. ^{1}H NMR, δ: 7.70 (m, 3 H, Ph); 7.86 (d, 1 H, H(5), J = 4.9 Hz); 8.23 (m, 2 H, Ph); 8.79 (d, 1 H, H(6), J = 4.9 Hz); 11.38 (br.s, 1 H, NH). MS, m/z: 316, 318, 320 $[M]^+$ (1 : 0.98 : 0.31).

2-Amino-4-phenylpyrimidine (4). Yield 70 mg (6%), m.p. 161 °C (from EtOH) (*cf.* Ref. 11: m.p. 161 °C). Found (%): C, 70.01; H, 5.27; N, 24.68. $C_{10}H_9N_3$. Calculated (%): C, 70.16; H, 5.30; N, 24.54. ^{1}H NMR, δ: 6.42 (br.s, 2 H, NH_2); 7.01 (d, 1 H, H(5), J = 5.2 Hz); 7.46 (m, 3 H, Ph); 8.01 (m, 2 H, Ph); 8.25 (d, 1 H, H(6), J = 5.2 Hz).

Hydrolysis of 4-phenyl-2-ureidopyrimidine (2a) into 2-amino-4-phenylpyrimidine (4). 4-Phenyl-2-ureidopyrimidine (214 mg, 1 mmol) was refluxed in 5 mL of formic acid for two days. The reaction mixture was diluted with water and alkalified with a saturated solution of sodium carbonate to pH 9. The precipitate of 2-amino-4-phenylpyrimidine (**4**) that formed was filtered off and recrystallized from EtOH. The yield of compound **4** was 140 mg (82%), m.p. 160—162 °C.

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