Brief Communications

Nucleophilic substitution of hydrogen in the reaction of 1,2,4-triazin-4-oxides with cyanamide

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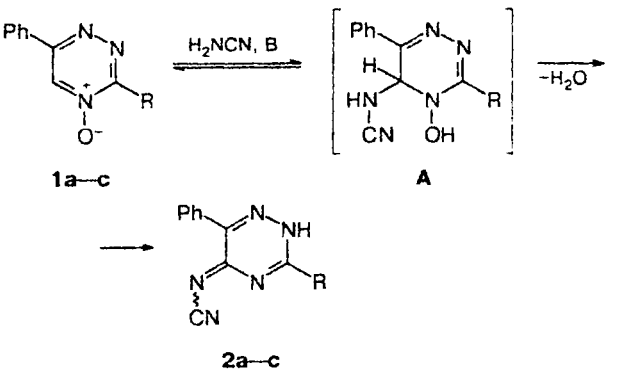
It was shown that cyanamide can successfully be used in reactions of nucleophilic substitution of hydrogen with 1,2,4-triazin-4-oxides in the presence of a base to give 5-cyanoimino-1,2,4-triazines. It was found by ^{13}C NMR spectroscopy that these compounds and their alkylation products at the cyclic nitrogen atom exist in the form of 5-cyanoimino-2,5-dihydro-1,2,4-triazines.

Key words: nucleophilic substitution of hydrogen, cyanamide, 1,2,4-triazin-4-oxides, 5-cyanoimino-1,2,4-triazines, ^1H and ^{13}C NMR spectroscopy.

Nucleophilic substitution of hydrogen (S_N^H) in 1,2,4-triazin-4-oxides makes it possible to perform one-step introduction of indole and phenol residues and the cyano group into the 1,2,4-triazine cycle[1,2]; amination in liquid ammonia affords 5-amino-1,2,4-triazin-4-oxides,[3] and reactions with dialkylamines give the S_N^H products at position 3 of the 1,2,4-triazine cycle.[4] In a continuation of studies in this area, we found the first example[5] of using cyanamide in nucleophilic substitution of hydrogen in azines. The reaction of 6-phenyl-1,2,4-triazin-4-oxides (**1a—c**) with cyanamide in the presence of a base results in the formation of 5-cyanoimino-6-phenyl-1,2,4-triazines (**2a—c**) in moderate yields (Scheme 1). It is most likely that cyanamide enters into the reaction as the anion, and the yields of the products are independent of the strength of the base used (triethylamine, sodium methoxide).

Scheme 1



1a—c **A** **2a—c**

1: **2**: R = H (**a**); Et (**b**); Ph (**c**)
B = NEt_3, MeONa

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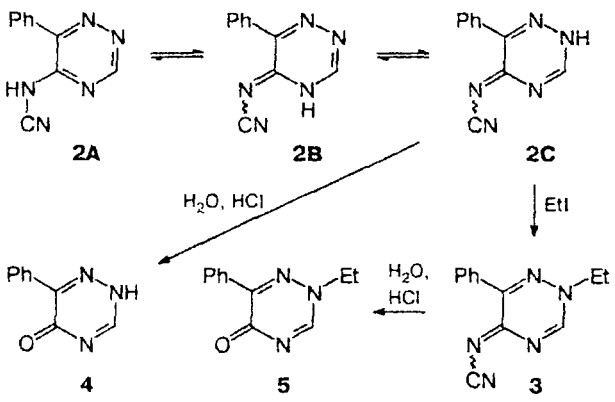
The reaction proceeds with the loss of the *N*-oxide function. Evidently, after the addition of cyanamide to the C(5) atom of the 1,2,4-triazine cycle, the autoaromatization of the σ^H-adducts **A** with the elimination of a water molecule occurs. The elemental analysis data and spectral parameters correspond to structure **2**.

Cyanoiminotriazines **2** can be presented as three tautomeric forms: **2A**, **2B**, and **2C**. In the alkylation of 1,2,4-triazine **2a** with ethyl iodide, position 2 of the heterocycle is the most reactive site, and this reaction affords only 5-cyanoimino-2-ethyl-6-phenyl-2,5-dihydro-1,2,4-triazine (**3**) (Scheme 2). In the ^{13}C NMR spectrum of compound **3**, the signal for the C(3) atom is a doublet of triplets due to spin-spin coupling (SSC) with the adjacent H atom ($^1J_{CH}$ = 211.1 Hz) and protons of the CH_2 group of the ethyl fragment ($^3J_{CNCH}$ = 3.4 Hz), and the signal of the C(5) atom is only a doublet due to SSC with the H(3) atom ($^3J_{CNCH}$ = 8.5 Hz), which corresponds to structure **3** only. Acid hydrolysis of compounds **2a** and **3** results in 6-phenyl-1,2,4-triazin-5(2*H*)-one (**4**) and 2-ethyl-6-phenyl-1,2,4-triazin-5(2*H*)-one (**5**), respectively.

Scheme 2



Comparison of the chemical shifts of the C atoms of the triazine cycle of cyanoiminotriazine **2a**, its alkylation product **3**, and triazinones **4** and **5** suggests that compound **2a** exists in solution in the tautomeric form of 2,5-dihydro-1,2,4-triazine **2C**.

Thus, the S_N^H methodology makes it possible to perform direct functionalization of the 1,2,4-triazine cycle to form new heterocyclic derivatives of cyanamide without preliminary introduction of good leaving groups into the heterocycle.

Experimental

^1H NMR spectra were recorded on a Bruker WM-250 spectrometer (250.1 MHz) using Me_4Si as the internal standard. ^{13}C NMR spectra were recorded on a Bruker DRX-500 spectrometer (125.8 MHz) using DMSO-d_6 as the solvent and Me_4Si as the internal standard. Purity of products was monitored by TLC on Silufol UV-254 plates using ethyl acetate as the eluent; spots were detected in UV light. Melting points were determined on a Boetius stage. Starting 1,2,4-triazin-4-oxides **1a—c** were synthesized as described previously.[6,7]

Synthesis of 5-cyanoimino-3-*R*-6-phenyl-2,5-dihydro-1,2,4-triazines (2) (general procedure). A mixture of cyanamide (0.42 g, 10 mmol) and the corresponding 1,2,4-triazin-4-oxide **1a—c** (5 mmol) was boiled for 30 min in a solution of MeONa prepared from Na (0.23 g, 10 mg-at.) in anhydrous MeOH (5 mL). Then AcOH (1 mL) was added to the reaction mixture, and the resulting solution was diluted with water (5 mL). The precipitate that formed was filtered off and washed with water and ethanol.

5-Cyanoimino-6-phenyl-2,5-dihydro-1,2,4-triazine (2a). Yield 54%, m.p. 253—254 °C (decomp.). ^1H NMR (500 MHz), δ: 7.48 (m, 3 H, Ph); 7.92 (m, 2 H, Ph); 8.85 (s, 1 H, H(3)); 14.7 (br.s, 1 H, NH). ^{13}C NMR (JMOD), δ: 115.91 (CN); 127.84 (Ph); 128.92 (Ph); 130.30 (Ph); 132.11 (Ph); 149.32 (C(6)); 149.42 (C(3)); 161.71 (C(5)). IR, ν/cm^{-1}: 2170 (CN). Found (%): C, 60.91; H, 3.88; N, 35.36. $C_{10}H_7N_5$. Calculation (%): C, 60.91; H, 3.58; N, 35.51.

5-Cyanoimino-3-ethyl-6-phenyl-2,5-dihydro-1,2,4-triazine (2b). Yield 47%, m.p. 274—275 °C (decomp.). ^1H NMR, δ: 1.29 (t, 3 H, Me, ^3J = 7.5 Hz); 2.72 (q, 2 H, CH_2, ^3J = 7.5 Hz); 7.50 (m, 3 H, Ph); 7.95 (m, 2 H, Ph); 14.51 (br.s, 1 H, NH). Found (%): C, 64.07; H, 4.86; N, 30.94. $C_{12}H_{11}N_5$. Calculated (%): C, 63.99; H, 4.92; N, 31.09.

5-Cyanoimino-3,6-diphenyl-2,5-dihydro-1,2,4-triazine (2c). Yield 38%, m.p. 264—266 °C (decomp.). ^1H NMR, δ: 7.48 (m, 3 H, Ph); 7.65 (m, 3 H, Ph); 8.04 (m, 2 H, Ph); 8.25 (m, 2 H, Ph); 14.96 (br.s, 1 H, NH). Found (%): C, 70.34, H, 3.92, N, 25.48. $C_{16}H_{11}N_5$. Calculated (%): C, 70.32; H, 4.06; N, 25.62.

5-Cyanoimino-2-ethyl-6-phenyl-2,5-dihydro-1,2,4-triazine (3). EtI (0.48 mL, 6 mmol) was added to a mixture of triazine **2a** (1 g, 5 mmol), DMF (3 mL), and triethylamine (0.83 mL, 6 mmol), and the mixture was boiled for 30 min. After cooling, the reaction mass was diluted with ethanol (5 mL), and the precipitated crystals were filtered off and washed with ethanol (5 mL). Yield 0.89 g (79%); m.p. 241—242 °C. ^1H NMR, δ: 1.44 (t, 3 H, Me, J = 7 Hz); 4.22 (q, 2 H, CH_2, J = 7 Hz); 7.51 (m, 3 H, Ph); 7.97 (m, 2 H, Ph); 8.89 (s, 1 H, H(3)). ^{13}C NMR (JMOD), δ: 13.67 (Me); 51.54 (CH_2); 115.54 (CN); 127.66 (Ph); 128.77 (Ph); 130.28 (Ph); 131.63 (Ph); 148.61 (C(6)); 149.79 (C(3)); 160.33 (C(5)). Found (%): C, 63.98, H, 4.97, N, 31.13. $C_{12}H_{11}N_5$. Calculated (%): C, 63.99; H, 4.92; N, 31.09.

6-Phenyl-1,2,4-triazin-5(2*H*)-one (4). Triazine **2a** (0.3 g, 1.5 mmol) was dissolved with heating in concentrated HCl (3 mL), and the resulting solution was boiled for 20 min. The precipitate that formed after cooling was filtered off. Yield 0.19 g (72%); m.p. 205—206 °C (*cf.* Ref. 8: 203—205 °C). ^1H NMR, δ: 7.48 (m, 3 H, Ph); 8.8 (m, 2 H, Ph); 8.87 (s, 1 H, H(3)); 14.1 (br.s, 1 H, NH). ^{13}C NMR, δ: 127.60 (Ph); 128.13 (Ph); 129.71 (Ph); 132.73 (Ph); 149.19 (C(6)); 150.97 (C(3)); 159.16 (C(5)). Found (%): C, 62.22; H, 4.02; N, 24.06. $C_9H_7N_3O$. Calculated (%): C, 62.42; H, 4.07; N, 24.26.

2-Ethyl-6-phenyl-1,2,4-triazin-5(2*H*)-one (5). Triazine **3** (0.45 g, 2 mmol) was dissolved with heating in concentrated HCl (3 mL), the resulting solution was boiled for 20 min, and the reaction mixture was cooled and neutralized with a 25% solution of ammonia. The precipitate that formed was filtered off. Yield 0.32 g (80%); m.p. 114—116 °C. ^1H NMR, δ: 1.47

(t, 3 H, Me, J = 7 Hz); 4.14 (q, 2 H, CH_2, J = 7 Hz); 7.4 (m, 3 H, Ph); 8.1 (m, 2 H, Ph); 8.73 (s, 1 H, H(3)). ^{13}C NMR, δ: 14.31 (Me); 50.88 (CH_2); 128.00 (Ph); 128.46 (Ph); 130.22 (Ph); 132.58 (Ph); 148.60 (C(6)); 151.93 (C(3)); 160.85 (C(5)). Found (%): C, 65.52; H, 5.42; N, 20.65. $C_{11}H_{11}N_3O$. Calculated (%): C, 65.66; H, 5.51; N, 20.88.

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