HETEROCYCLES, Vol. 57, No. 1, 2002, pp.45 – 54, Received, 9th October, 2001

LEWIS ACID CATALYZED DIMERIZATION OF 2-AMINO-PYRIMIDINE: SYNTHESIS AND X-RAY STRUCTURES

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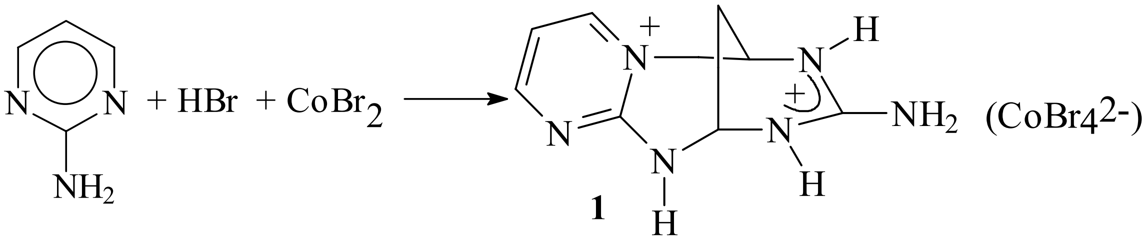
Abstract - Reaction of 2-aminopyrimidine with HBr and CoBr2 in aqueous solution led to dimerization of the pyrimidine and formation of a new heterotricyclic dication. The material has been characterized by IR spectroscopy, combustion analysis and X-Ray diffraction. Subsequent experiments show that the dimerization also occurs in the absense of CoBr2, although more slowly. The same tricyclic product was isolated as the bromide salt and characterized by IR spectroscopy, combustion analysis and X-Ray diffraction.

Introduction

We have been studying the use of substituted heterocycles for the synthesis of compounds with the general formula A_2MX_4, where M is a transition metal ion, X is either chloride or bromide and A is an organic cation, typically a protonated heterocycle. Complexes with a variety of heterocycles have been previously prepared including pyridines, morpholines and pyrimidines.[1-3] We have previously studied a number of compounds in this class where A has been a substituted 2-aminopyridinium ion[4-7] and have begun a program of investigating the associated salts and complexes of 2-aminopyrimidine.[8] We report here the results of an unexpected dimerization of 2-aminopyrimidine.

Results and Discussion

Reaction of 2-aminopyrimidine and $CoBr_2$ in aqueous HBr yielded a green powder over the course of two weeks which IR spectrum did not resemble those typical of simple protonated or coordinated 2-aminopyrimidine.[3]



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Most notably, the absorptions in the 3000 and 1600 cm^{-1} regions of the IR spectrum were significantly different. However, combustion analysis confirmed that the composition of the material was the expected $C_8H_{12}N_6Br_4Co$. The presence of the paramagnetic Co(II) made NMR spectral characterization impossible, but we were successful in growing green crystals suitable for single crystal X-Ray diffraction by slow evaporation of the filtrate. The IR spectra of the crystals and powder were identical.

Compound (**1**) crystallizes in the monoclinic space group $P2_1/n$. The asymmetric unit is shown in Figure 1.

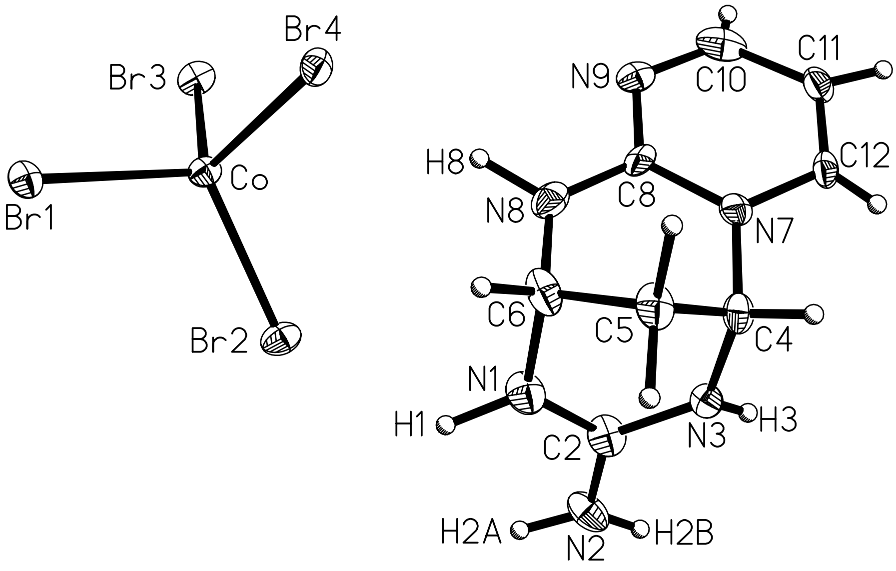

Figure 1 : ORTEP diagram of **1** showing 50% probability ellipsoids. Selected bond lengths (Å) and angles (°): Co-Br1, 2.4139(13); N1-C2, 1.325(10); N1-C6, 1.482(10); C2-N2, 1.338(9);C2-N3, 1.343(9); N3-C4, 1.456(10); C4-N7, 1.510(9); C4-C5, 1.516(11); C5-C6, 1.518(10); C6-N8, 1.472(10); C2-N1-C6, 118.7(6); N1-C2-N2, 119.3(7); N1-C2-N3, 121.0(7); N2-C2-N3, 119.7(7); C2-N3-C4, 123.1(6); N3-C4-N7, 110.9(6); N3-C4-C5, 108.3(6); N7-C4-C5, 108.9(6); N3-C4-H4, 114(5); N7-C4-H4, 99(5); C5-C4-H4, 115(5); C4-C5-C6, 105.0(6); C4-C5-H5A, 112(4); C6-C5-H5A, 107(4); C4-C5-H5B, 112(4); C6-C5-H5B, 109(4); H5A-C5-H5B, 111(5); N8-C6-N1, 111.3(6); N8-C6-C5, 110.5(6); N1-C6-C5, 106.9(6); N8-C6-H6, 116(4); N1-C6-H6, 107(4); C5-C6-H6, 105(4); C8-N8-C6, 124.4(6); C8-N8-H8, 121(4); C6-N8-H8, 113(4).

We were surprised to see that the organic dication was the result of a dimerization of the two 2-aminopyrimidine rings. This dimerization could result from Lewis acid activation (either by proton or by Co^{2+}) of one pyrimidine ring, followed by nucleophilic attack by the second ring and subsequent cyclization.

The structure of the $CoBr_4^{2-}$ ion is unremarkable; bond lengths are typical [average 2.42(2)Å] and the bond angles support a very slightly distorted tetrahedral arrangement [range 106.18(5) to 115.86(5)]. In the organic cation, the bond lengths and angles in the intact pyrimidine ring (N7, C8, N9, C10, C11 and C12) and in the conjugated region of the second ring (N1, C2, N2 and N3) are likewise as expected and do not show significant changes from the starting material except as is usual for protonation of the nitrogens. However, the bond to atoms C4, C5 and C6 have all lengthened significantly, ranging from

1.46(1)Å for C4-N3 to 1.52(1)Å for C5-C6. Similarly, the bond angles around C4, C5 and C6 are also in agreement with their new saturated roles. Finally, N8 retains its putative sp^2 hybridization. The sum of the bond angles about N8 is 358(6)° (the large error results from the uncertainty in the position of H8).

The dimerization was especially surprising in light of the fact that we were unable to locate any previous observation of this phenomena in the literature. A wide variety of 2-aminopyrimidine complexes have be reported previously, isolated from acidic media as well as media containing an assortment of other Lewis acids, including Co^{2+}.[9-14] However, none of these systems report the condensation of the 2-aminopyridinium that we observe. The carbocyclic parent ring (Figure 2a,) with various substituents has been previously observed by several workers.[15-18] Prinzbach and co-workers have prepared a related 3-amino-2,4-diazabicyclo[3.3.1]nonane (Figure 2b) which contains a 4,6-bridged pyrimidine-like ring as in **1**.[19]

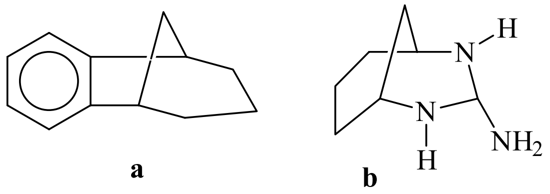

Figure 2: Related ring systems.

Believing the reaction to be promoted by the presence of Lewis acids in the reaction mixture, we attempted the conversion of 2-aminopyrimidine to the dimer in the absence of $CoBr_2$ to see if H$^+$ alone would serve to catalyze the dimerization. 2-Aminopyrimidine was treated with HBr under the similar reaction conditions as previously except for the exclusion of the $CoBr_2$. The reaction was monitored by removing small aliquots of the solution and addition of a 10-fold excess (vol:vol) of acetone to precipitate the organic salts. The IR spectra of the products showed a slow, but steady, conversion of the starting materials to a compound whose IR spectrum strongly resembled that of **1** (see EXPERIMENTAL for data). Quenching of the reaction by addition of acetone and purification from methanol gave colorless crystals of **2** suitable for X-Ray diffraction. The crystal structure of **2** (Figure 3) shows it to contain the same tricyclic dimer, but as the bromide salt with a water of crystallization.

The structure of **2** is commensurate with the structure of **1** with only minor differences in the bond lengths and angels within the cation. A strong hydrogen bond is observed between H3 and the water oxygen [$d_{N3\text{-}H3...O1}$ = 2.879(5)Å; $\angle_{N3\text{-}H3...O1}$ = 173(5)°] with weaker H-bonds seen to the bromide ions from both the water molecule and some of the amino nitrogens. The absence of the paramagnetic cobalt ion also allowed characterization of **2** by ^{1}H- and ^{13}C-NMR spectroscopy. The data and assignments are given in the EXPERIMENTAL. The cationic dimer (**2**) was also isolated by addition of disodium hydrogen phosphate to precipitate the cobalt ion. The spectroscopic properties of **2** were the same from the two preparation methods.

Attempts to induce the dimerization in dilute acid (~1 M) with $CoBr_2$, or using $CoBr_2$ in the absence of HBr led to isolation of the expected salt [(2-aminopyridinium)$_2$CoBr$_4$] and the coordination complex

Co(2-aminopyrimidine)$_2$Br$_2$ respectively. In both these cases, the compounds crystallized within a few days. This leaves the roll of the cobalt uncertain as the cyclization takes place in its absence (the formation of **2**), but is faster in its presence, while there is no evidence for formation of the dimer in the presence of Co^{+2} at moderate pH.

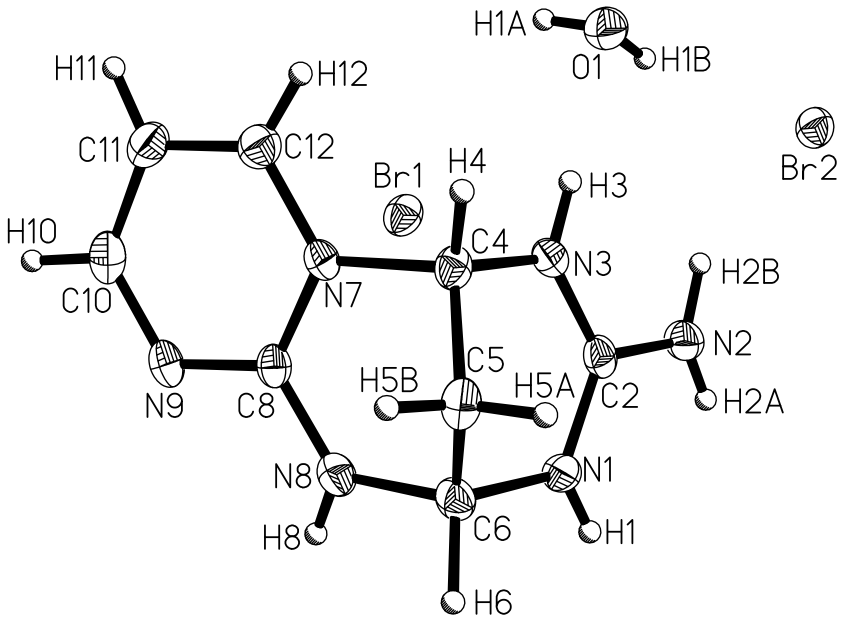

Figure 3: ORTEP plot of **2** showing 50% probability ellipsoids. Selected bond lengths (Å) and angles (°):N(1)-C(2), 1.345(5); N1-C6, 1.449(5); C2-N2, 1.318(5); C2-N3, 1.342(5); N3-C4, 1.434(5); C4-C5, 1.516(5); C4-N7, 1.518(4); C5-C6, 1.524(5); C6-N8, 1.470(5); N7-C12, 1.358(5); N7-C8, 1.363(5); C8-N8, 1.339(5); C8-N9, 1.356(5); N9-C10, 1.333(6); C10-C11, 1.407(6); C11-C12, 1.370(6); C2-N1-C6, 120.5(3); N2-C2-N3, 120.4(4); N2-C2-N1, 119.4(4); N3-C2-N1, 120.1(3); C2-N3-C4, 122.8(3); N3-C4-C5, 110.7(3); N3-C4-N7, 110.2(3); C5-C4-N7, 106.93; N3-C4-H4, 108(3); C5-C4-H4, 113(3); N7-C4-H4, 107(3); C4-C5-C6, 105.8(3); C4-C5-H5A, 111(3); C6-C5-H5A, 110(3); C4-C5-H5B, 103(3); C6-C5-H5B, 1113; H5A-C5-H5B, 115(4); N1-C6-N8, 111.3(3); N1-C6-C5, 108.6(3); N8-C6-C5, 107.5(3); N1-C6-H6, 109(3); N8-C6-H6, 104(3); C5-C6-H6, 116(3); C8-N8-C6, 124.0(3); C8-N8-H8, 121(3); C6-N8-H8, 115(3).

While no mechanism has been established, it is reasonable to believe that the reaction occurs *via* initial attack of a ring nitrogen from one pyrimidine on the 4-carbon of the second ring which has been activated by a Lewis base (E) either H$^+$ or Co^{2+} (See Figure 4). Subsequent protonation of the 5-carbon (now a vinylogous enamine) sets up the ring closing attack by the exocyclic nitrogen of the first ring on the 6-carbon of the second ring (now a vinylogous iminium ion). A proton transfer and metathesis of the E group (if activated by Co^{2+}) completes the formation of the dication to its final state where the formal charges lie one on N7 and the second delocalized between N1, N2 and N3. The bond lengths between C2 and N1, N2, and N3 are the same within experimental error, suggestion a high degree of charge delocalization. Regardless, it is clear that the dimerization of 2-aminopyrimidine occurs in strongly acidic media in the presence, or absence, of Co(II) ion to generate a novel tricylic heterocycle.

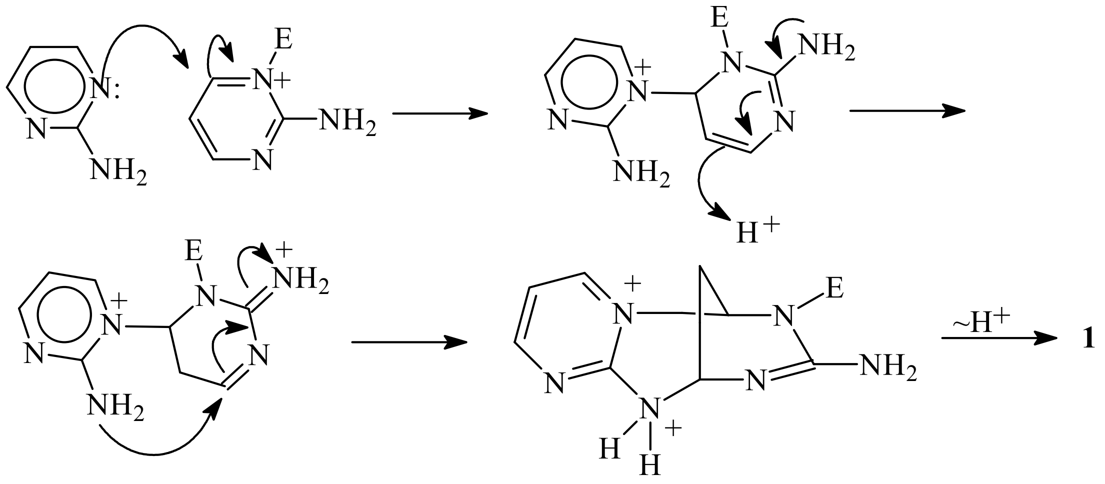

Figure 4: Proposed mechanism for the dimerization of 2-aminopyrimidine.

EXPERIMENTAL

General Remarks: Reactions were carried out using commercial reagent grade chemicals as received. Mp's and NMR spectra were used to confirm purity. NMR spectra were obtained on a Varian Mercury200 spectrometer in DMSO-d_6 and referenced to TMS (^{1}H) or solvent (^{13}C). IR spectra were obtained in KBr matrix on a Perkin-Elmer Paragon 500.

Dimer $CoBr_4$ salt (1): 2-Aminopyrimidine (0.951 g, 10 mmol) was dissolved in 5.4 mL of 48% HBr. An aqueous solution of $CoBr_2$ (1.09g, 5 mmol in 10 mL of H_2O) was added dropwise with stirring. The resulting solution was left to evaporate slowly at rt. Green powder was observed after ~2 weeks. Green single crystals suitable for X-Ray analysis were harvested after 4 weeks. The IR spectrum of the crystals and the powder are identical within instrument resolution. mp 235-236°C Yield: 2.85 g (54%). IR: ν 3345m, 3249m, 3182m, 1667s, 1638s, 1604s, 1157m, 772m cm^{-1}. Anal. Calcd for $C_8H_{12}N_6Br_4Co$: C, 16.83; H, 2.12; N, 14.72. Found: C, 16.71; H, 2.26; N, 14.59.

Dimer bromide salt monohydrate (2): Method 1: 2-Aminopyrimidine (0.475 g, 5 mmol) was dissolved in 2.7 mL of 48% HBr and allowed to stand at rt. Reaction progress was followed by periodically adding a few drops of the solution to a large excess of acetone and the resulting precipitate was examined by IR spectroscopy. After 7 weeks, the reaction was quenched by addition to 25 mL of acetone and the resulting precipitate collected by centrifugation. The residue was then recrystallized from methanol to give colorless crystals. Yield: 1.85 g (48%). Anal. Calcd for $C_8H_{14}N_6OBr_2$: C, 25.97; H, 3.81; N, 22.71. Found: C, 26.08; H, 3.98; N, 22.60. IR: ν 3432w, 3316m, 3162m, 3105m, 1691s, 1635s, 1600m, 1249m, 777m, 748m cm^{-1}. ^{1}H-NMR: δ 11.11 (1H, d, J = 4.6 Hz, N-H), 9.51 (1H, s, N-H), 9.24 (1H, s, N-H), 8.96 (1H, d, J = 4.4 Hz, Ar-H) 8.70 (1H, d, J = 6.6 Hz, Ar-H), 7.90 (2H, s, NH_2), 7.25 (1H, dd, J = 6.6, 4.6 Hz, Ar-H), 6.34 (1H, br s, C-H) 5.43 (1H, br s, C-H), 2.51 (2H, br s, CH_2) ppm. ^{13}C-NMR: δ 167.5, 152.7, 151.4, 148.5, 111.1, 63.4, 51.3, 20.9 ppm.

Method 2: Compound (**1**) (0.080 g, 0.14 mmol) was dissolved in 1 mL of H_2O and a slight excess of Na_2HPO_4 added (0.023 g, 0.16 mmol, dissolved in 0.5 mL of H_2O) to precipitate the cobalt ion. The resulting precipitate was removed by centrifugation and the supernatant solution was evaporated to dryness under vacuum. The residue was recrystallized from MeOH to give compound (**2**). IR, ^{1}H-NMR and ^{13}C-NMR spectra were identical to the product from Method A within experimental error.

X-Ray Crystallographic Study: Data collection, cell refinement and data reduction for compounds (**1**) and (**2**) were done using a Bruker SMART system[20] with Mo-radiation (λ=0.71073 Å) and a graphite monochromator at 168 K via φ and ω scans. The structures were solved via direct methods[21] and refined[22] via full-matrix least-squares. Absorption corrections were made via SADABS.[23] Hydrogen atoms were located in the difference map and their positions refined with a fixed, isotropic U. Neutral scattering factors and anomalous dispersion corrections for non-hydrogen atoms were taken from Ibers and Hamilton.[24] Full crystallographic data may be found in Table 1. Selected bond lengths and angles are given in the figure captions.

Table 1 – Crystallographic data for compounds (**1**) and (**2**).

Compound	**1**	**2**
Molecular Formula	$C_8H_{12}N_6Br_4Co$	$C_8H_{14}N_6O\,Br_2$
Molecular Weight	570.81	370.07
Crystal System	Monoclinic	Triclinic
Space Group	$P2_1/n$	P-1
a	10.258(4)Å	6.691(2)Å
b	12.829(5)Å	9.492(2)Å
c	12.372(5)Å	10.230(3)Å
α	90º	99.274(3)º
β	106.579(5)º	93.525(3)º
γ	90º	96.259(3)º
Z	4	2
Crystal/dimensions	aqua plate, 0.12x0.35x0.35	colorless plate, 0.02x0.55x0.8 (mm)
Rflns measured	15049	8357
Independant rflns	2230	2580
Rflns observed (I>2□)	2031	2442
μ	11.336	6.375
Trans.Coeff.(min/max)	0.5395/1.000	0.51076/1.000

Restraints/parameters/data	0/208/2230	0/196/2580
Final R, Rw (obsvd)	0.0584, 0.1494	0.0481, 0.1377
Final R, Rw (all data)	0.0611, 0.1522	0.0497, 0.1402
Goodness of Fit	1.028	1.082

Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-158644 (compound 1) and CCDC-157685 (compound 2). Copies of the data can be obtained from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code + 44(1223)336-033; E-mail: deposit@ccdc.cam.ac.uk].

ACKNOWLEDGMENTS

Financial support from the NSF (DMR-9803813) and assistance with the X-Ray data collection by Dr. Jan Wikaira (U. of Canterbury) are gratefully acknowledged.

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