Conversion of Hexahydrotriazines to Imidazolines

J. Thomas Ippoliti* and Jeffrey Evanson

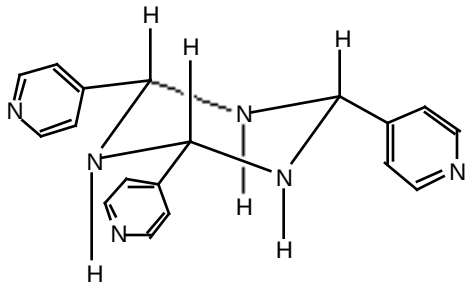
Department of Chemistry, University of St. Thomas, St. Paul, MN 55105

Silas C. Blackstock

Department of Chemistry, Vanderbilt University, Nashville, TN 37235

Abstract: The isolation and characterization of an imidazoline obtained from the reaction of ammonia and an aldehyde is reported. The stereochemistry of the imidazoline is confirmed using x-ray diffraction and is used in support of a mechanism involving the conversion of an intermediate hexahydrotriazine to an imidazoline. The mechanism is also supported by the direct conversion of a hexahydrotriazine to an imidazoline.

The chemistry of hexahydrotriazines has appeared in the literature since the 1800's when it was recognized that ammonia formed trimeric compounds with aldehydes.[1] Most synthetic routes to hexahydrotriazines in the literature employ aqueous solvent systems. Under these conditions hydrates of hexahydrotriazines are normally isolated.[2] Recently we achieved the synthesis of hexahydrotriazines under anhydrous conditions employing acetonitrile as the solvent. These reaction conditions yield crystals of hexahydrotriazines without water present in the lattice. This led to the observation of unique ^{1}H nmr characteristics exhibited by these compounds.[3] When the synthesis of hexahydrotriazine **1** was carried out by this anhydrous route a very small amount of the isomeric hexahydrotriazine **2** was detected by ^{1}H nmr.[4]



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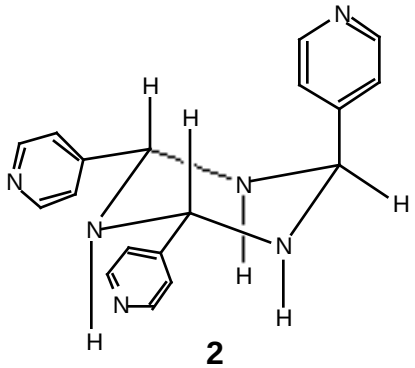
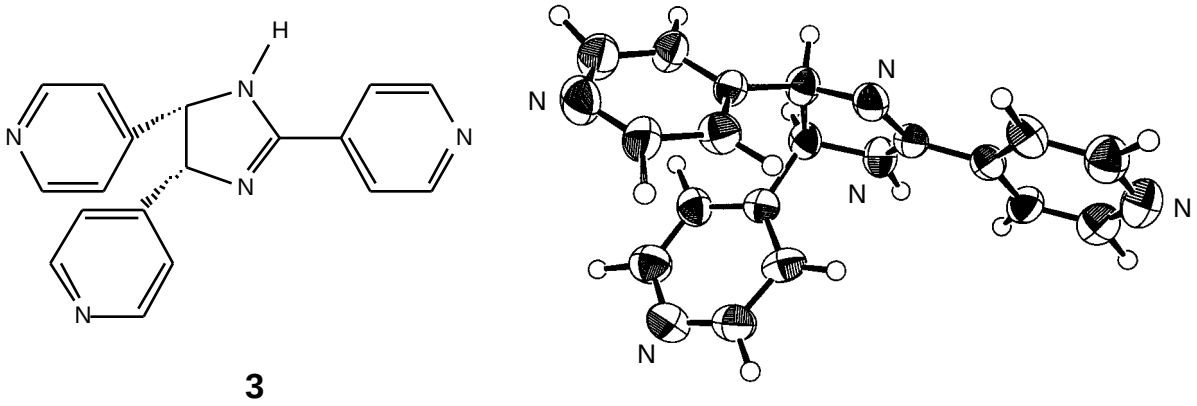


2

In an attempt to isolate **2** the reaction was scaled up and the product crystallized at room temperature instead of at -30°C as done previously. This procedure indeed gave two distinct types of crystals which could be physically separated. The majority of the crystals were in the form of needle-like prisms while the remainder were plate-like crystals. The needle-like crystals were identified as **1** by ^{1}H nmr.[5] The plate-like crystals yielded a ^{1}H nmr spectrum of a molecule that no longer had C_3 symmetry. However, it was not the anticipated hexahydrotriazine **2**. In fact, the 500 MHz ^{1}H nmr spectrum indicated that there were *three different* pyridine rings present. Two

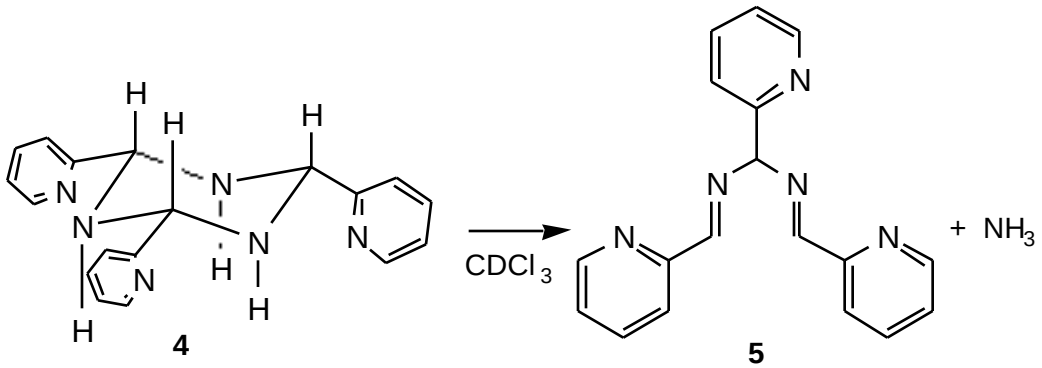
rings were in quite similar environments as deduced from the extremely small chemical shift difference of their protons. Single crystal X-ray analysis of the plate-like crystals proved them to be imidazoline **3**. An ORTEP representation (50% elipsoids) of the determined solid state structure of **3** is shown in Figure 1.[6]



3

Figure 1

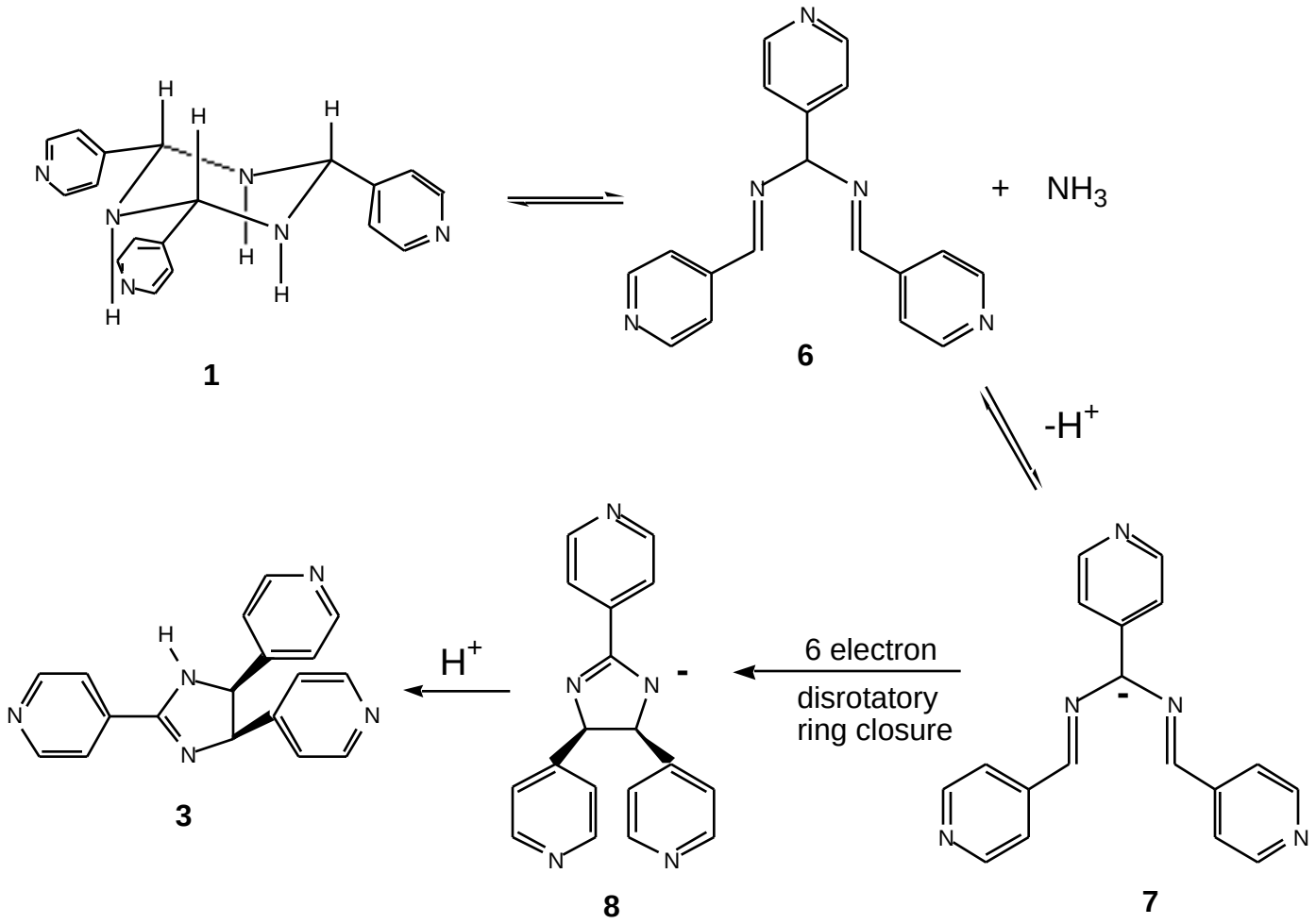
An especially interesting aspect of the structure of this compound was the cis relationship of pyridine rings. The question then became: How did it form? Previous experience with hexahydrotriazines led us to recall that with mild heating and in fact even at room temperature (albeit slowly) hexahydrotriazines decompose to give diimines and ammonia. An example of this process is the decomposition of hexahydrotriazine **4** in $CDCl_3$ which is transformed completely to diimine **5** after sitting at room temperature for 7 days.



4 **5**

Since a hexahydrotriazine was isolated from the reaction along with **3**, we beleive that it is formed first and that formation of **3** is a product of its decomposition, forming a diimine analogous to **5** as an intermediate. The

proposed mechanism is shown in Scheme I.

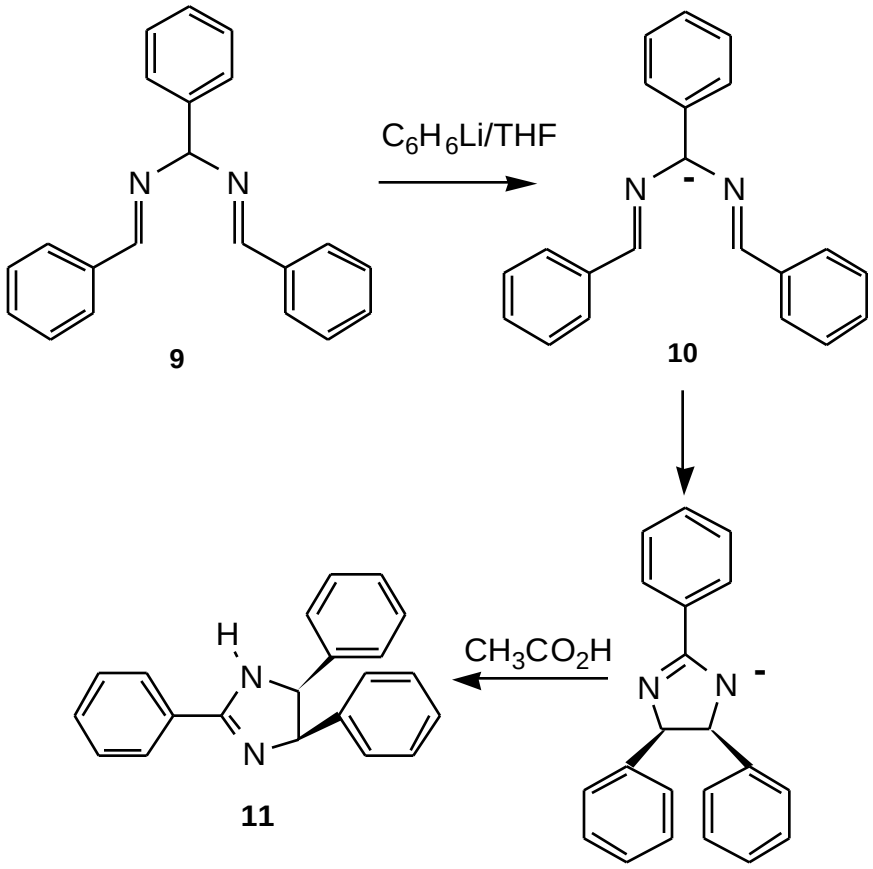


Scheme I

The first step is the formation of hexahydrotriazine **1**, which loses ammonia to give diimine **6**. The trans,trans stereochemistry of **6** is expected from the antiperiplanar Grob-like fragmentation of **1**. Deprotonation by base (probably ammonia since the solution is saturated with it) followed by an allowed disrotatory electrocyclic ring closure gives anion **8**. Anion **8** yields imidazoline **3** upon protonation. This mechanism adequately explains the cis stereochemistry of the pyridine rings in the product. As further proof of this mechanism hexahydrotriazine **1** was dissolved in d_6-DMSO and placed in a sealed tube. The sealed tube was then heated to 110°C for 24 hours. Examination of the solution at that time revealed only imidazoline **3** to be present.

A literature structure search on aryl-substituted imidazolines turned up an example of what appears to be

an analogous anion electrocyclic ring closure for the **9** to **11** conversion shown below.[7] It thus appears that this type of ring closure for aryl substituted β-diimines may be general.



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1. (a) M.A. Laurent, *Ann.* **1837**, *21*, 130. (b) Lenart, G. H. *Liebigs Ann. Chem.* **1915**, *410*, 100. (c) Young, J. A.; Schmidt, J. J.; Krimmel, J. A. *J. Org. Chem.* **1971**, *36*, 347. (d) Nielsen, A.t.; Atkins, R.L.; DiPol, J; Moore, D. W. *J. Org. Chem.* **1974**, *39*, 1349.
2. See for example: Lund, E. W. *Acta. Chem. Scand.* **1958**, *12*, 1768.
3. Most notably the N-H proton resonances were sharp under non-exchanging conditions. A paper describing these unique features is in preparation.
4. Anhydrous ammonia was bubbled through a solution of 4-pyridinecarboxaldehyde (443 mg) in acetonitrile (9 mL). The resulting solution was placed in the freezer for 2-8 hours, after which the crystals formed were isolated by decanting off the solvent and washing with cold acetonitrile.
5. A thorough literature search resulted in a reference in which compound **1** was mentioned: Gu, C.; Gu, W. *New Front. Organomet. Inorg. Chem., Proc. China-Jpn.-U.S.A.* 2nd Trilateral Semin., 1982, 3-15. Edited by: B-K, Teo. Sci. Press: Beijing, Peop. Rep. China 1984. This reference does not include any spectral data or preparation procedures. Therefore, the following spectral data is presented. Compound **1**: 360 MHz ^{1}H NMR ($CDCl_3$) δ 8.65 (6 H, d, J = 5.8 Hz), 7.58 (6 H, d, J = 5.8 Hz), 5.29 (3 H, t, J = 9.8 Hz), 1.62 (3 H, t, J = 9.8 Hz, N-H). 90 MHz ^{13}C NMR ($CDCl_3$) δ 150.19 (CH), 149.12 (tert. C), 121.18 (CH), 71.60 (CH).
6. A colorless rectangular crystal of $C_{18}H_{15}N_5$ having approximate dimensions of 0.48 x 0.30 x 0.25 mm

was mounted on a glass fiber. All measurements were made on a Rigaku AFC6S diffractometer with graphite monochromated Cu Kα radiation. The unit cell constants were a = 10.235 (1)Å, b = 8.846 (2)Å, c = 17.485 (1)Å, α = 90.00, ß = 106.14 (6)°, g = 90.00, V = 1520.7 (6)Å, Z = 4, and the calculated density is 1.316 g/cm (F.W. = 301.35) with a space group (#14) monoclinic P21/c. There were 1626 reflections collected and 269 variables to give R = 0.043, Rw = 0.053, and GOF = 2.111.

7. Hunter, D. H.; Sim, S. K.; *J. Am. Chem.Soc*., **1969**, 91, 6202.

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