Pergamon

Tetrahedron Letters 39 (1998) 4785–4788

TETRAHEDRON
LETTERS

Synthesis of Racemic *cis* and *trans* 2,4,5-Tripyridylimidazolines.

Martin L. Larter,[a] Mimi Phillips,[a] Fernando Ortega,[b] Gerardo Aguirre,[b] Ratnasamy Somanathan,[b] and Patrick J. Walsh[a,b,*]

[a]Department of Chemistry, San Diego State University, San Diego, CA 92182-1030, U.S.A.
[b]Centro de Graduados e Investigación, Instituto Tecnológico de Tijuana, Apartado Postal 1166. 22000 Tijuana, B.C. México

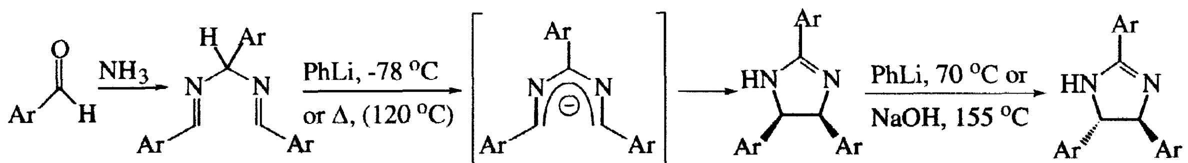
Received 26 February 1998; revised 24 April 1998; accepted 26 April 1998

Abstract: *Reaction of 2-pyridinecarboxaldehyde with ammonium hydroxide gives 1,3,5-triazine **6** which was converted to cis-2,4,5-tripyridylimidazoline, **9**. The intermediate 2,4-diazapentadiene is not observed, but believed to undergo deprotonation and cyclization to afford cis-2,4,5-tripyridylimidazoline. Base catalyzed isomerization (5 mol% KO-t-Bu, 23°C) of cis-2,4,5-tripyridylimidazoline gives trans-imidazoline (**10**). Compounds **6**, **9**, and **10** have been characterized by X-ray crystallography.*

Advances in the field of asymmetric catalysis can be limited by the availability of chiral auxiliaries needed to develop catalysts.[1] The significance of this deficiency is more pronounced on an industrial scale, where many chiral auxiliaries are prohibitively expensive, rendering even efficient processes economically unfavorable. The influence of the limited pool of chiral auxiliaries can be appreciated on examination of successful catalytic asymmetric processes which incorporate chiral diamine based ligands.[2-7] In these systems, the majority of the catalysts employ either *trans*-1,2-diaminocyclohexane[8] or 1,2-diamino-1,2-diphenylethane as the chiral backbone. The motivation for these choices is purely availability; racemic *trans*-1,2-diaminocyclohexane is inexpensive and easily resolved[9,10] and several efficient routes to 1,2-diamino-1,2-diphenyl ethane have been published.[11,12]

In an effort directed toward the synthesis of chiral diamines, we have reexamined the condensation of ammonia hydroxide with aromatic aldehydes. Previous studies indicate that under appropriate conditions (Equation 1), ammonium hydroxide readily reacts with aromatic aldehydes to give 2,4-diazapentadienes (**1**).[13,14] Deprotonation of the 2,4-diazapentadiene with a strong base (PhLi)[14] or under thermal conditions results in formation of the transient 2,4-diazapentadienyl anion (**2**) which cyclizes in a disrotatory fashion to furnish the *cis*-imidazoline **3**.[13] Isomerization of **3** with base[14] and heat provides the *trans*-imidazoline **4**, which can be hydrolyzed to the diamine. In this communication we present our findings employing the heteroaromatic aldehyde 2-pyridinecarboxaldehyde (**5**). The reactivity of this aldehyde, and the subsequent intermediates formed in its reaction with ammonium hydroxide, are significantly different than non-heterocyclic analogs.

Equation 1



1 **2** **3** **4**

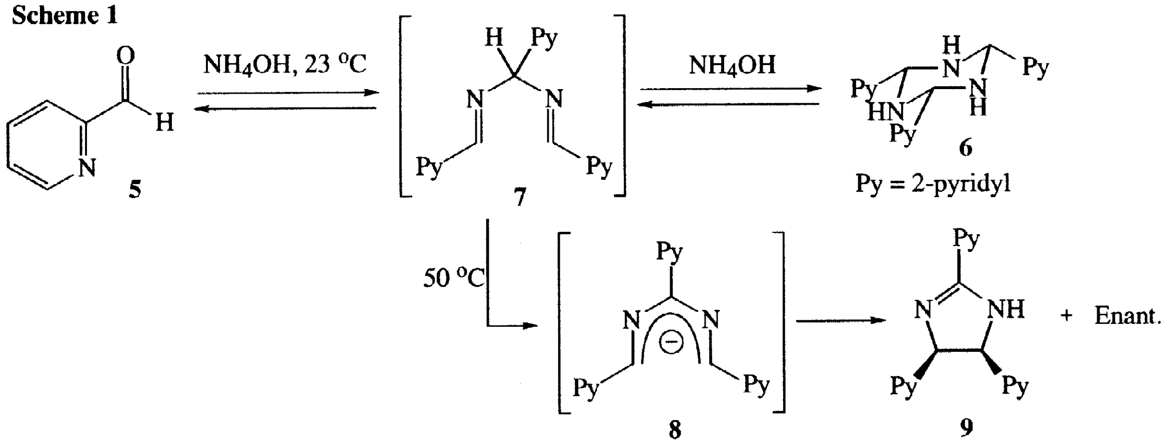
0040-4039/98/$19.00 © 1998 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(98)00957-5

Our results are outlined in Scheme 1 and Equation 2. In general, addition of aromatic aldehydes to ammonium hydroxide solutions produce 2,4-diazapentadienes. However, aldehydes with electron withdrawing substituents favor formation of 1,3,5-triazenes.[15,16] In agreement with previous reports,[17] addition of 2-pyridinecarboxyladehyde to concentrated ammonium hydroxide results in precipitation of the 1,3,5-triazine (**6**). The formation of **6** is clean and isolation is performed by filtration in 89 % yield.[18] The structure was assigned by NMR spectrometry and verified by X-ray crystallography (Figure 1).[19]

Conditions were varied in an effort to the favor formation of the 2,4-diazapentadiene (**7**). We found that slow addition of two equivalents of ammonium hydroxide to three equivalents of the aldehyde in THF at 23 °C resulted in the formation of a mixture of two products in a ratio of 1.5 to 1 (^{1}H NMR) along with remaining aldehyde. The minor product was the 1,3,5-triazine **6**. The major product was determined to be imidazoline **9** (Scheme 1). Under these conditions, the ratio of **6** and **9** did not change with time. We rationalized that if **6** could be formed reversibly, the equilibrium would be driven to the cyclized product **9**. Reaction of the aldehyde **5** with 5 equivalents of ammonium hydroxide in THF led to initial formation of the triazine **6**. Gentle heating of the solution to 50 °C resulted in complete conversion of the triazine to the desired cyclized product **9** over 24 h in 84 % yield.[18] The assignment of the *cis* geometry was based on the derivatization of the imidazoline with benzoyl chloride. The inequivalent methine hydrogens in the derivatized product are coupled in the ^{1}H NMR with J = 8 Hz. This coupling constant is consistent with a *cis* geometry of the 4,5-pyridyl groups.[14] This geometry was further supported by an X-ray structure determination (Figure 1).

Apparently, cyclization of the transient 2,4-diazapentadiene **7** occurs readily at room temperature with dilute ammonium hydroxide. Reports of cyclization of 2,4-diazapentadienes derived from 4-chloro- and 4-cyanobenzaldehyde indicate that the cyclization takes place at 50 °C in low yield (45%) in concentrated ammonium hydroxide. However, high temperatures (120 °C) or strong bases have generally been used to deprotonate and cyclize the 2,4-diazapentadiene **1** (Equation 1).

Scheme 1



Catalytic conversion of the *cis* imidazoline **9** to the *trans* **10** was also accomplished under remarkably mild conditions. The use of 5 mol % potassium *tert*-butoxide resulted in the clean formation of the *trans* product **10** (92 % yield).[18] These conditions can be contrasted with high temperature reported for conversion of the *cis* imidazoline to the *trans* outlined in Equation 1. The facile conversion of **9** to **10** is most likely a result of the increased acidity of the C-H alpha to the pyridyl ring and the directing effect of the nitrogen lone pair of the pyridyl group. The X-ray crystal structure of **10**, illustrated in Figure 1, clearly shows the *trans* nature of the 4,5-pyridyl groups.

Equation 2

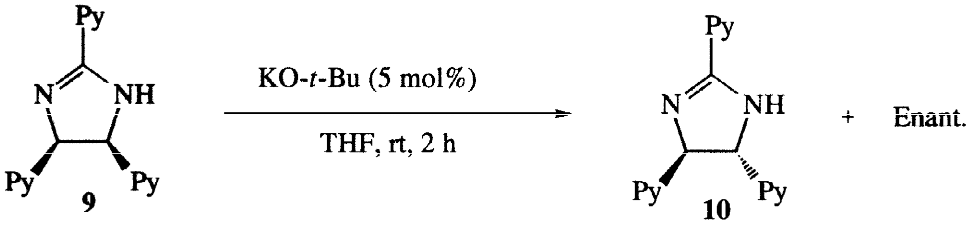
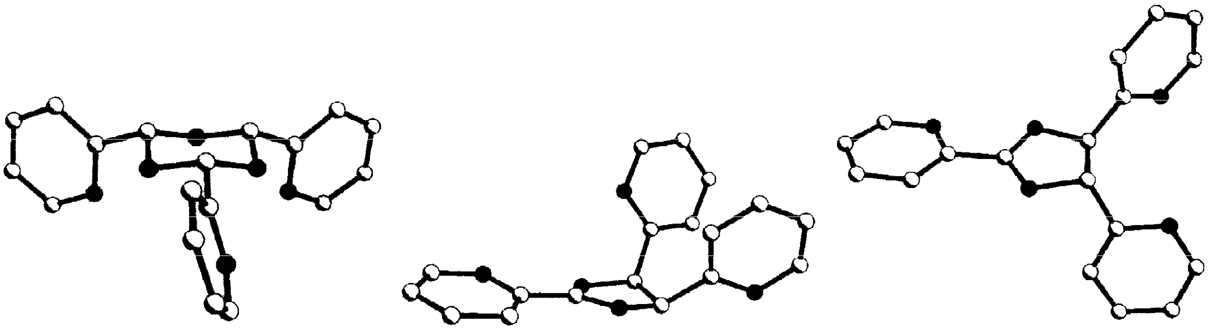


Figure 1. X-ray structures of **6**, **9**, and **10**. Black spheres are nitrogen, white spheres are carbon,. Hydrogens have been omitted for clarity.


6 **9** **10**

In summary, we have described the reactions of 2-pyridinecarboxyaldehyde with ammonium hydroxide to provide the *cis*-imidazoline **9**. This product is catalytically isomerized to the *trans* derivative **10** by potassium *tert*-butoxide at room temperature. We are currently exploring the utility of **9** and **10** as ligands for the synthesis of novel transition metal complexes and the asymmetric isomerization of **9** to give non-racemic **10**.

Acknowledgments: This work was supported by San Diego State University. We would like to thank the National Science Foundation for funding of a 500 MHz NMR spectrometer (CHE-9413802) for SDSU and CONACYT Proyecto Infraestructura (F264-E9207) for funding of an X-ray diffractometer for Instituto Tecnológico de Tijuana.

Notes and References

1) Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; John Wiley and Sons: New York, 1995.
2) Morrison, J. D., Ed. *Asymmetric Synthesis*; Academic Press: New York, 1983.
3) Bosnich, B., Ed. *Asymmetric Catalysis*; Martinus Nijhoff Publishers: Dodrect, The Netherlands, 1986.

4) **Whitesell, J. K.** *Chem. Rev.* **1989**, *89*, 1581-1615.
5) **Brunner, H.; Zettlmeier, W., Eds** *Handbook of Enantioselective Catalysis*; **VCH: New York, 1993.**
6) **Ojima, I., Ed.** *Catalytic Asymmetric Synthesis*; VCH: New York, 1993.
7) **Noyori, R.** *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994.
8) **Bennani, Y. L.; Hanessian, S.** *Chem. Rev.* **1997**, *97*, 3161-3195.
9) **Galsbøl, F.; Steenbøl, P.;** Sørensen, B. S. *Acta. Chem. Scand.* **1972**, *26*, 3605-3611.
10) Larrow, J. F.; Jacobsen, E. N.; Gao, Y.; Hong, Y.; Nie, X.; Zepp, C. M. *J. Org. Chem.* **1994**, *59*, 1939-1942.
11) Corey, E. J.; Kühnle, F. *Tetrahedron Lett.* **1997**, *38*, 8631-8634.
12) Oi, R.; Sharpless, K. B. *Tetrahedron Lett.* **1991**, *32*, 999-1002.
13) Sprung, M. M. *Chem. Rev.* **1940**, *26*, 297-338.
14) Hunter, D. H.; Sim, S. K. *Can. J. Chem.* **1972**, *50*, 669-677.
15) Nielsen, A. T.; Atkins, R. L.; Moore, D. W.; Scott, R.; Mallory, D.; LaBerge, J. M. *J. Org. Chem.* **1973**, *38*, 3288-3295.
16) Quirke, J. M. E. *1,3,5-Triazines*; Katritzky, A. R. and Rees, C. W., Ed.; Pergamon Press: Oxford, 1984; Vol. 3, pp 457-530.
17) Harries, C.; Lénárt, G. H. *Justus Liebigs An. Chem.* **1915**, *410*, 95-116.
18) Data for **6**, **9** and **10**. Synthesis of **6**: 2-Pyridinecarboxyaldehyde (2 g, 18.6 mmol) was added to ammonium hydroxide (30%, 16 mL, 124 mmol, 6.7 eq) and solution was stirred for 2 h at 23 °C. During this time, a pale yellow precipitate formed. The precipitate was removed by filtration, dried, and crystallized from CH_2Cl_2/diethyl ether by gas phase diffusion giving **6** as pale yellow crystals (1.78 g, 5.6 mmol, 89%); mp 137-139 °C; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.56 (d, J = 4.6 Hz, 3H), 7.63 (dt, J = 1.6 Hz, J = 7.7 Hz, 3H), 7.42 (d, J = 7.7 Hz, 3H), 7.16 (t, J = 7.5 Hz, 3H), 5.33 (s, 3H), 2.77 (s, 1H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 50 MHz) δ 158.8, 149.6, 136.9, 123.2, 122.2, 73.4 ppm; Synthesis of **9**: To a stirring solution of 2-pyridinecarboxyaldehyde (10 g, 93.3 mmol) in THF (75 mL) at 23 °C was added ammonium hydroxide (30%, 20 mL, 77.8 mmol, 1.7 eq.). The solution was then heated to 50 ∞C for 48 h, extracted with 20 mL CH_2Cl_2, and washed with 3X30 mL water. The organic layer was dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The remaining solid was crystallized from CH_2Cl_2/diethyl ether by gas phase diffusion providing **9** as pale yellow crystals (8.4 g, 27.9 mmol, 84%); mp 141-143 °C; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.68 (d, J = 5.7 Hz, 1H), 8.33 (m, 3H), 7.84 (dt, J = 1.8 Hz, J = 7.7 Hz, 1H), 7.43 (m, 3H), 7.09 (d, J = 7.7 Hz, 1H), 6.91 (m, 3H), 6.68 (s 1H), 6.05 (d, J = 11.1 Hz, 1H), 5.58 (d, J= 11.1 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 50 MHz) δ 165.0, 158.9, 148.8, 148.6, 148.5, 136.5, 135.6, 125.3, 122.8, 121.9, 121.4, 66.2 ppm; MS (EI) 301 (M^+), 195 (base); Synthesis of **10**: Powder **9** (1 g, 3.32 mmol) was dissolved in 4 mL of dry THF. The solution was mixed with potassium *tert*-butoxide (18.6 mg, 0.17 mmol, 0.05 eq). On addition of the potassium *tert*-butoxide, the solution became dark brown and slowly turned to amber. The reaction was stirred for an additional 2 h at 23 °C. CH_2Cl_2 was added to the reaction mixture and it was washed with 3X10 mL water. The organic layer was dried over $MgSO_4$, filtered and the solvent removed under reduced pressure yielding **10** (920 mg, 3.1 mmol, 92%); mp 129-131 °C; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.61 (m, 3H), 8.31 (d, J = 7.9 Hz, 1H), 7.79 (dt, J = 1.6 Hz, J = 7.7 Hz, 1H), 7.68 (dt, J = 1.8 Hz, J = 6.5 Hz, 2H), 7.49 (d, J = 7.7 Hz, 2H), 7.38 (m, 1H), 7.22 (m, 2H), 6.80 (s(br), 1H), 5.54 (s, 2H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 50 MHz) δ 163.2, 161.7, 149.6, 148.8, 147.9, 136.8, 136.6, 125.5, 123.1, 122.4, 121.5, 73.5 ppm; MS (EI) 301 (M^+), 223 (base).
19) Lund, E. W. *Acta Chem. Scand.* **1951**, *5*, 679-680.