A New Preparation of 5-Hydroxypyrimidines Derived from Carboxylic Acids, Epichlorohydrin, and Ammonia[1]

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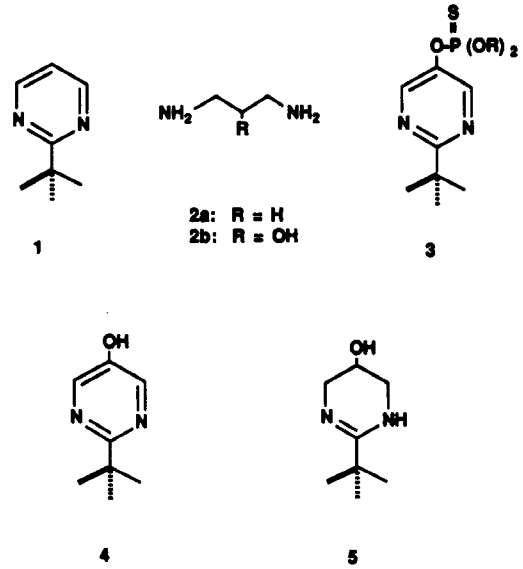
The preparation of high-value molecules from inexpensive and readily available starting materials with a minimal number of processing steps continues to be a critical challenge for industrial chemists. We recently reported[2] an improved preparation of 2-*tert*-butylpyrimidine 1 from diamine **2a** and pivalic acid using a simple vapor-phase catalytic reactor. Pyrimidine 1 is a precursor



to the active insecticides 2-*tert*-butylpyrimidinyl thiophosphates, **3**.[3] The conversion of 1 to **3** requires halogenation and hydrolysis steps to establish the 5-oxygen group.[3] Other methods of oxygenation of the 5-position of pyrimidines are also known.[4] An improvement of the synthetic procedure would involve a more direct preparation of 2-*tert*-butyl-5-hydroxypyrimidine (**4**), where placement of the 5-hydroxyl group occurs during assembly of the pyrimidine ring. We report here a method for the preparation of multigram quantities of 2-*tert*-butyl-5-hydroxy-1,4,5,6-tetrahydropyrimidine (**5**) from diamine **2b** and pivalic acid over an alumina catalyst bed and the subsequent dehydrogenation of **5** to **4** with manganese dioxide. During the course of our study, another group reported[5] the vapor-phase preparation of **5** over a titania catalyst.

Results and Discussion

Amidation and Cyclization. Tetrahydropyrimidines are advantageously prepared[2,5] in the vapor phase over a Lewis acid catalyst from diamines and carboxylic acids, which allows their preparation without the use of a large excess of diamine, as required in the condensed phase.[6] Tetrahydropyrimidine **5** was readily prepared by feeding a concentrated aqueous mixture of the pivalate salt of diamine **2b** in a nearly 1/1 molar ratio into a alumina catalyst bed[2,7] held at 275 °C. Thus, the amidation of **2b** with pivalic acid was effected, giving hydroxy amino amide **7** (Scheme I). Intermediate **7**, which was not isolated, can undergo dehydrative cyclization on the alumina catalyst to either oxazoline **8**[8] or pyrimidine **5**. The two cyclization reactions are equilibria between water, ring-opened **7**, and ring-closed forms **8**[8] and **5**.[2]

Interestingly, a direct equilibrium between oxazoline **8** and pyrimidine **5** also exists[9] which does not go through the ring-opened form **7**. This was demonstrated by heating a sample of pure **5** in the absence of water above 100 °C, using a solvent such as toluene. The insoluble crystalline pyrimidine gradually dissolved, and a mixture of **8** and **5** was observed by GC analysis. A sample of pure oxazoline **8** was recovered in this manner by cooling the solution and separating insoluble **5**. When heating to temperatures below 100 °C, conversion of **5** to **8** was found to be very slow.

Purified oxazoline **8** as a neat oil gradually solidified upon standing, even when stored at 0 °C. NMR analysis of the solid showed complete reversion to the pyrimidine **5**. Thus, although the crude product from the alumina catalyst bed consisted of approximately equal proportions of **8** and **5**, the product mixture could be shifted completely in favor of the desired pyrimidine **5**, which was easily purified due to its tendency to form stable insoluble crystals. The conversion of oxazoline to pyrimidine[9] was accelerated by heating. Thus, neat oxazoline oil obtained from the alumina bed reactor, after separation of the first crop of **5**, was heated to 80 °C overnight, after which the oil solidified and a second crop of **5** was obtained. This gave a 74% yield of **5** based on pivalic acid. The yield loss was due primarily to bis-amidation of **2b** and uncyclized hydroxy amino amide **7**. No attempt was made to isolate or characterize the bis-amidation product.

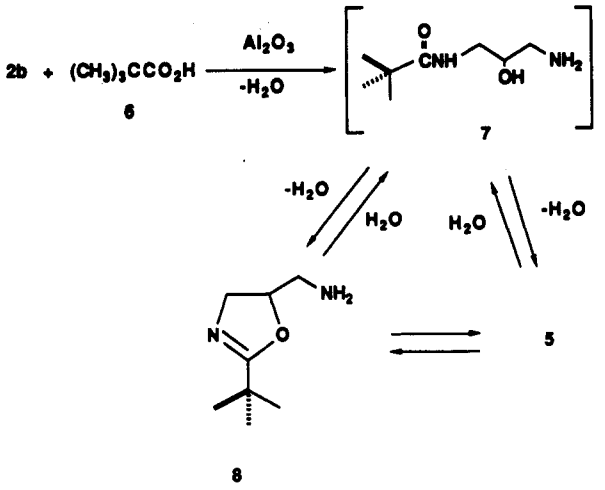
Although oxazoline **8** was not characterized by elemental analysis, this compound was sufficiently stable for characterization by ^1H and ^{13}C NMR. Compounds **5**, **7**, and **8** were readily distinguished by their NMR spectra. The spectra of **7** and **8** exhibited resonances corresponding to six distinct carbons while the spectrum of **5** showed five distinct resonances due to the degeneracy of carbons 4 and 6 in the pyrimidine ring. Oxazoline **8** gave a somewhat more complex ^1H NMR spectrum than **5** or **7** due to its unsymmetrical and 5-membered ring structure.[10]

Dehydrogenation. Unlike the direct vapor-phase dehydrogenation reaction which gives **1**,[2] the catalytic dehydrogenation of **5** to **4** could not be effected in the vapor phase. Due to the interconversion of oxazoline **8**

(1) Dedicated to the memory of Dr. Clinton Harrington.
(2) Hull, J. W., Jr.; Otterson, K. *J. Org. Chem.* **1992**, *57*, 2925.
(3) Pews, R. G. *Heterocycles* **1990**, *31*, 109.
(4) Hurst, D. T. *Aust. J. Chem.* **1983**, *36*, 1285.
(5) Teunissen, A. J. J. M.; Klop, W.; Delahaye, H. J. A. V. U.S. Pat. 4880929, 1989; *Chem. Abstr.* **1988**, *109*, 231056h.
(6) Pews, R. G. *Heterocycles* **1988**, *27*, 1867.
(7) The alumina catalyst designation of CSS-300 LDS 1/8"refers to 1/8-in. low-density catalyst substrate spheres with a surface area of 300 m^2/g, obtained from Alcoa Chemicals Division. It is a macroporous γ-alumina. See ref 2.
(8) For a review of the preparation and reactions of oxazolines, see: Frump, J. A. *Chem. Rev.* **1971**, *71*, 483.
(9) This facile transformation of an oxazoline to a pyrimidine appears to be somewhat unusual and is apparently enhanced by the aminomethyl appendage on 8. For an example of a similar transformation of an oxazole at high temperature, see ref 15.
(10) Weinberger, M. A.; Greenhalge, R. *Can. J. Chem.* **1963**, *41*, 1038.

0022-3263/93/1958-0520$04.00/0

Scheme I



and pyrimidine **5**, a low-temperature dehydrogenation was preferable. Additionally, a direct conversion of **5** to **4** was preferable in which no protecting groups are used for either the nitrogen or oxygen functional groups. Treatment of **5** with manganese dioxide[11] as a warm slurry in solvents such as toluene, chloroform, or *tert*-butyl alcohol gave the desired pyrimidinol **4** in modest yields as high as 41%. Monitoring of the reaction progress by HPLC indicated that the dehydrogenation reaction slowed dramatically at 50% conversion, probably due to the acid/base interaction of **4** and **5**.[12] Thus, the strong amidine base **5** deprotonated **4** as it was formed, giving the amidinium salt of **4**. Control experiments carried out with added acetic acid indicated that **5** in its protonated form was not readily dehydrogenated by MnO_2. The crude product obtained after workup as an aqueous solution of 4^-5^+ was treated with concentrated HCl, which gave crude **4** as an oil and left unreacted **5** in solution as the HCl salt.

The dehydrogenation reaction was carried out over the course of a few hours at reflux temperatures in solvents such as chloroform or *tert*-butyl alcohol, and 30% yields of **4** were obtained. A higher yield of 41% and a product of higher purity were obtained when the reaction was carried out at room temperature over a 1–2-week period.

Conclusion

Since hydroxy diamine **2b** can be prepared from epichlorohydrin and ammonia,[13] this route makes available the 5-hydroxypyrimidines in three synthetic steps from the inexpensive industrial feedstocks epichlorohydrin, ammonia, and carboxylic acids. The pyrimidine ring is first assembled from the diamine and carboxylic acid components over an alumina catalyst, and the oxidation level is subsequently adjusted with a dehydrogenation step.

Experimental section

General. 1,3-Diamino-2-hydroxypropane (**2b**) and pivalic acid (**6**) were obtained from Aldrich. Bulk quantities of **6** were obtained from Exxon. A purified sample of 2-*tert*-butyl-5-hydroxypyrimidine (**4**) used as a standard was prepared according to the method of Pews.[3] Activated grades of MnO_2 were obtained from Aldrich or Strem Chemicals, Inc., and gave similar results. GC and HPLC analytical methods used for internal standard analysis, as well as the alumina catalyst[7] and reactor used to carry out amidation reactions in the vapor phase, have been described previously.[2] Melting points are uncorrected unless otherwise noted; 300-MHz proton and 75-MHz carbon NMR spectra were obtained on a Bruker AC300 spectrometer.

2-*tert*-Butyl-5-hydroxy-1,4,5,6-tetrahydropyrimidine (5). The vapor-phase reactor and catalyst for amidation reactions have been described elsewhere.[2] The catalyst bed consisted of 73 g of alumina catalyst,[7] which comprised a 15-in. length in a 1-in.-diameter quartz tube, with the noncatalyst portions of the tube occupied by inert quartz chips. The feed solution was comprised of 41.4% pivalic acid, 43.9% 1,3-diamino-2-hydroxypropane, and 14.6% water, corresponding to a 1/1.2/2 molar ratio, and was kept warm on a hot plate stirrer and pumped through a heated line to the catalyst bed. Pivalic acid (167.4 g, 1.64 mol), 1,3-diamino-2-hydroxypropane (177.5 g, 1.97 mol), and water (59.0 g, 3.28 mol) were pumped as a single feed to the alumina bed held at 275 °C, at a rate of 1.5 g/min. A preheater tube held at 250 °C served to vaporize the feed components. A nitrogen flow rate of 210 mL/min was applied to the reactor during the run. The reactor effluent was condensed with a hot water condenser to prevent crystallization. The product consisted of an orange oil containing crystalline solid and was stripped on a rotary evaporator to remove water. A roughly equal volume of acetonitrile was added, the slurry was cooled to 0 °C, and crystalline **5** was collected on a filter and dried in a vacuum oven at 60 °C to give 139.2 g of **5** as a first crop. The mother liquor was reduced in volume to give an orange oil and placed in an oven at 80 °C overnight. After addition of acetonitrile to the resulting solid and filtration as above, an additional 60.1 g of solid was obtained, which consisted of 84% **5** and 15% uncyclized **7** by GC analysis, to give a total of 189.7 g of **5**, representing a 74% isolated yield based on pivalic acid and a 62% yield based on diamine **2b**. A pure sample of **5** was prepared by recrystallization from warm CH_3CN: mp 212–214 °C (corrected) dec; ^1H NMR (D_2O/CD_3CN) δ 3.9 (m, 1 H), 3.1 (apparent dt, 2 H), 2.9 (apparent dd, 2 H), 1.0 ppm (s, 9 H); ^{13}C NMR {^1H} (D_2O/CD_3CN) δ 168.7 (1 C), 60.0 (1 C), 47.0 (2 C), 37.0 (1 C), 27.7 ppm (3 C). Anal. Calcd for $C_8H_{16}N_2O$: C, 61.50; H, 10.32; N, 17.93. Found: C, 61.57; H, 10.50; N, 18.01.

2-*tert*-Butyl-5-(aminomethyl)oxazoline (8). Solid **5** (2.55 g, 1.63 mmol) was heated to reflux in 100 mL of toluene for 22 h. The solution was cooled to 25 °C, and the slurry was filtered to remove 0.91 g of unconverted **5** after drying. The toluene filtrate was evaporated to give 1.17 g of **8** as an oil: ^1H NMR ($CDCl_3$) δ 4.5 (m, 1 H), 3.8 (apparent dd, 1 H), 3.5 (apparent dd, 1 H), 2.8 (apparent dq, 2 H), 1.2 ppm (s, 9 H); ^{13}C NMR {^1H} ($CDCl_3$) δ 173.3 (1 C), 80.1 (1 C), 56.4 (1 C), 45.3 (1 C), 32.5 (1 C), 27.1 ppm (3 C).

The neat oil gradually solidified over a number of days, even at 0 °C, reverting back to pyrimidine **5**.

(3-Amino-2-hydroxypropyl)pivalamide (7). An aqueous solution of pyrimidine **5** was stirred overnight at 25 °C. The water was evaporated and **7** was obtained in quantitative yield and was recrystallized from warm CH_3CN: mp 115.5 °C (corrected); ^1H NMR (CD_3CN/D_2O) δ 3.5 (m, 1 H), 3.1 (apparent dq, 2 H), 2.5 (apparent dq, 2 H), 1.1 ppm (s, 9 H); ^{13}C NMR {^1H} (CD_3CN/D_2O) δ 181.7 (1 C), 72.1 (1 C), 45.1 (1 C), 43.6 (1 C), 39.4 (1 C), 27.7 ppm (3 C). Anal. Calcd for $C_8N_{18}N_2O_2$: C, 55.15; H, 10.41; N, 16.08. Found: C, 54.81; H, 10.52; N, 16.07.

2-*tert*-Butyl-5-hydroxypyrimidine (4). Pyrimidine **5** (40.25 g, 0.26 mol) and activated MnO_2 (201.75 g, 2.32 mol) were placed into a 2-L 3-necked round-bottom flask fitted with an overhead stirrer. The reactor was purged with argon, and 600 mL of *tert*-butyl alcohol was added. The slurry was stirred at 25 °C for 15 days, diluted with about 200 mL of CH_3OH, and filtered through Celite on a glass filter, rinsing the filter cake with excess CH_3OH. The filtrate was evaporated to give 46.9 g of solid residue, which is a mixture of **5** and **4**. This product was dissolved in 200 mL of H_2O and the pH reduced to 5.0 with 37% HCl, resulting in the

(11) Fatiadi, J. *Synthesis* **1976**, 65.
(12) The pK_a's of **4** and **5** are approximately 7.0 and 11.5, respectively. See ref 14.
(13) (a) Indian Pat. IN 148638, 1981; *Chem. Abstr.* **1982**, *96*, 103639b. (b) Enders, H.; Pusch, G. U.S. Pat. 3432553, 1969; *Chem. Abstr.* **1969**, *70*, 105943h.
(14) (a) Brown, D. J. *The Pyrimidines*; John Wiley and Sons: New York, 1962; p 466. (b) Brown, D. J. *The Pyrimidines, Supplement I*; John Wiley and Sons: New York, 1970; p 355.
(15) Dornow, A.; Hell, H. *Chem. Ber.* **1960**, *93*, 1998.

precipitation of 4 as an oil. This mixture was extracted with CH_2Cl_2, and the organic phase was evaporated to give 16.41 g of 4 as a tan crystalline solid, mp 126–129 °C (lit.[3] mp, 130–132 °C), GC assay 100%, for a yield of 41%: ^{13}C NMR {^1H} ($CDCl_3$) δ 168.5 (1 C), 149.7 (1 C), 144.2 (2 C), 38.8 (1 C), 29.7 ppm (3 C). The ^1H NMR spectrum has been reported.[3]

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