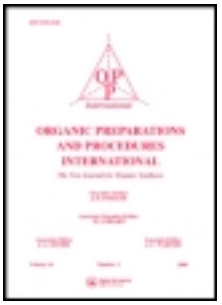

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AN IMPROVED PREPARATION OF 4-AMINOPYRIMIDINES-5-CARBOXALDEHYDE

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OPPI BRIEFS

AN IMPROVED PREPARATION OF 4-AMINOPYRIMIDINE-5-CARBOXALDEHYDE

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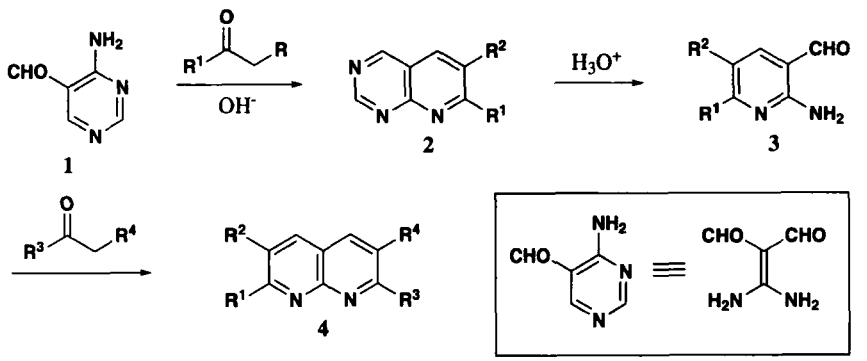
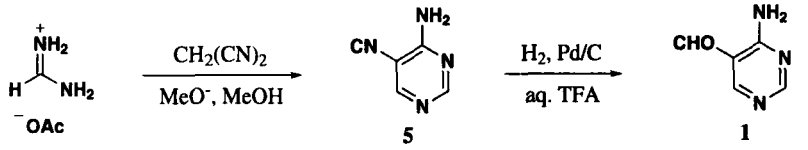
4-Aminopyrimidine-5-carboxaldehyde (**1**) is of general utility in the Friedländer reaction with ketones[1] to give pyrido[2,3-d]pyrimidines (**2**) which may be hydrolyzed to 2-aminonicotinaldehydes (**3**). Since these compounds upon condensation with ketones afford 1,8-naphthyridines (**4**), **1** may be regarded as a synthetic equivalent of (diaminomethylene)malonaldehyde (*Eq. 1*).[1-4]



(1)

Aminoaldehyde **1** has been used extensively for the synthesis of polycyclic metal ligands[1c,d,5,6] and artificial receptors for hydrogen-bonded complexation of organic molecules.[7,8] This article describes the most efficient and reliable known synthesis of **1**.

This two-step preparation of 4-aminopyrimidine-5-carboxaldehyde incorporates important improvements of previous methods (*Eq. 2*).[9,10] The first step, originally conducted with formamidine

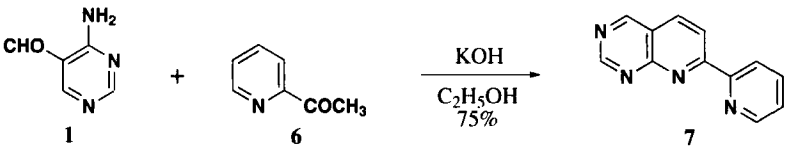


(2)

hydrochloride in ethanol (45% yield),[9] was performed with formamidine acetate and methanol instead and makes the current procedure less expensive, easier to carry out (the product precipitates) and more efficient. 4-Aminopyrimidine-5-carbonitrile (**5**) has also been prepared by reaction of 4-chloro-5-cyanopyrimidine with ammonia[10] and by hydrogenolysis of 4-amino-2-chloro-5-cyanopyrimidine.[12] Both methods not only require *three* steps from commercially available starting materials, but offer no advantage in yield over the current procedure. An alternative reaction that proceeds in comparable yield is the condensation of malononitrile with *s*-triazine,[13,14] albeit an expensive starting material.

The catalytic hydrogenation of 4-aminopyrimidine-5-carbonitrile (**5**)[10] is known to be unpredictable[1d] with respect to duration of reaction, product yield and purity. It was suspected that the catalyst was poisoned by variable quantities of a side-product formed in the first step. Indeed, 4-aminopyrimido[4,5-d]pyrimidine[11] was identified as a 6-8% impurity in crude 4-aminopyrimidine-5-carbonitrile, and does poison the Pd/C catalyst. However, when this side-product was removed by recrystallization of the crude product from acidified water, as in the current procedure, the hydrogenation step in aqueous hydrochloric acid as the solvent still showed poor reproducibility.[10] The problem proved to be the low solubility of the hydrochloride salt of 4-aminopyrimidine-5-carbonitrile (**5**). Preparative scale reactions necessitate hydrogenation of an aqueous *suspension* of the nitrile, and momentary cooling of the reaction mixture causes precipitation on the catalyst, resulting in deactivation. In the current procedure, this problem is avoided by using trifluoroacetic acid and by adding the catalyst after exchanging the air atmosphere for hydrogen in the apparatus.

Friedländer condensations of 4-aminopyrimidine-5-carboxaldehyde with ketones (usually cyclic) are typically carried out by adding methanolic potassium hydroxide to a solution of the two reactants in methanol[2,7,8f] or ethanol[3,5,6] and heating the reaction mixture under reflux (yields, 64-95%).[2,3,5-7,8f] Experimental details for the reaction with 2-acetylpyridine (**6**) are included here as an example (*Eq. 3*).



1 6 7 (3)

EXPERIMENTAL SECTION

Formamidine acetate (99%, Aldrich Chemical Company, Inc.) was recrystallized from absolute ethanol, yielding white crystals, mp. 158-161°. Malononitrile (99%, Aldrich Chemical Company, Inc.) was recrystallized from *t*-butyl methyl ether and decolorized with charcoal (Norit), yielding white crystals, mp. 32-34°. Sodium methoxide solution was prepared by adding 500 mL of absolute methanol to a 1-L, three-necked, round-bottomed flask equipped with a magnetic stirring bar, two glass stoppers, a reflux condenser, and a nitrogen gas inlet tube attached to a mineral oil bubbler. The apparatus was placed behind a safety shield and flushed with nitrogen, then the flask was immersed in an ice bath. A lump of sodium (23 g, 1.0 mol) cut into small pieces was added gradually to the cold, rapidly stirred methanol.

4-Aminopyrimidine-5-carbonitrile (5).- A 2-L, single-necked, round-bottomed flask was equipped with a magnetic stirring bar and a 1-L pressure-equalizing dropping funnel fitted with a nitrogen gas inlet tube attached to a mineral oil bubbler. The flask was flushed with nitrogen and then charged with 94.0 g (0.9 mol) of formamidine acetate, 30.5 g (0.46 mol) of malononitrile and 500 mL of anhydrous methanol. The addition funnel was charged with 500 mL of a 2 M solution of sodium methoxide in methanol, which was added dropwise over a 6-hr period to the vigorously stirred reaction mixture. The resulting solution was stirred under nitrogen at room temperature for 48 hr and then cooled by means of an ice bath for 1 hr. The yellow precipitate was collected, washed with 30 mL of ice-cold methanol and dried under vacuum (0.1 mm). The crude product (38-42 g, 69-76%) was recrystallized from 1.7 L of 10% aqueous acetic acid. The golden-yellow crystals formed at 5° were collected, washed with 40 mL of cold water and dried under vacuum (0.1 mm) to give 28-32 g (51-58%) of 4-aminopyrimidine-5-carbonitrile (**5**), mp. 254-256°, *lit.*[9,13,10] 250°, 255-256°, 256-258°. The product is by pure thin-layer chromatographic analysis (silica gel, $CHCl_3$/MeOH (4/1, v/v), R_f = 0.63); ^1H NMR (300 MHz, DMSO-d_6): δ 7.91 (br. s, 2 H, NH_2), 8.53 (s, ^1H, H2), 8.59 (s, 1 H, H6); ^{13}C NMR (75 MHz, DMSO-d_6): δ 89.7, 115.3, 160.7, 161.1, 162.4.

Anal. Calcd for $C_5H_4N_4$: C, 50.00; H, 3.36; N, 46.64. Found: C, 49.74; H, 3.30; N, 46.47

If the side-product, 4-aminopyrimido[4,5-d]pyrimidine, is detected by tlc (R_f = 0.36; $CHCl_3$/MeOH (4/2, v/v)) or ^1H NMR (δ 8.62 s, 9.30 s, 9.70 s), then the product should be recrystallized again from 10% aqueous acetic acid.

4-Aminopyrimidine-5-carboxaldehyde (1).- A 1-L, two-necked, Morton flask, equipped with a magnetic stirring bar, solid addition bulb and reflux condenser (*Fig. 1*), was charged with 20.0 g (0. 17 mol) of 4-aminopyrimidine-5-carbonitrile (**5**), 200 mL of water and 66 mL of trifluoroacetic acid (99%, Aldrich Chemical Company, Inc.). The solid addition bulb was charged with 2.0 g of palladium-on-carbon catalyst (10% Pd, Aldrich Chemical Company, Inc., or Acros Organics) and 30 mL of water. ***Water should not be omitted from the solid addition bulb because exposure of the dry catalyst to hydrogen can cause an explosion!***

The flask was then attached to a gas manifold connected to a water aspirator, bubbler, hydrogen source and gas buret (1-2 L).[15] The entire system was evacuated (30-40 mm), filled with hydrogen gas and the evacuation/filling procedure was repeated three more times. ***An electrical pump should not be used for evacuation because of danger of explosion of hydrogen gas.*** The reaction flask was immersed in an oil bath at 60° and the contents were stirred until a homogeneous solution was formed. The temperature of the oil bath should never drop below 55° to avoid precipitation of the reactant salt on the catalyst. Then the solid addition

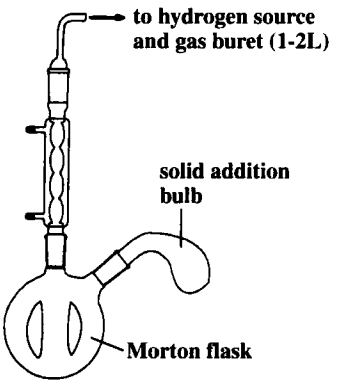


Fig. 1
Apparatus for Atmospheric Hydrogenation of 4-Aminopyrimidine-5-carbonitrile

bulb was rotated 180° to transfer the catalyst suspension into the reaction flask and the contents were stirred vigorously. Over a period of 20 hr, 5.2 L (0.19 mol, 25°, 655 mm) of hydrogen was consumed. Since the rate of hydrogenation is highly dependent on stirring rate and catalyst quality, it is thus advisable to follow the progress of the reaction by the volume of consumed hydrogen. Best results are obtained when the reaction is stopped after 1.10-1.15 equivalents of hydrogen are consumed, according to calculation based on the Ideal Gas Law. A slight excess of hydrogen should be consumed to avoid contamination of the product by starting material, which is difficult to remove by recrystallization. Over-hydrogenation reduces the yield of the desired product. The catalyst was removed by vacuum filtration and washed with 10 mL of water. The combined filtrates were cooled (0°) and neutralized to pH 7 by slow addition of potassium hydroxide pellets (ca. 41 g), such that the internal temperature does not exceed 5°. A pale yellow precipitate of 4-aminopyrimidine-5-carboxaldehyde formed during neutralization and the resulting mixture was refrigerated at 5° overnight. The precipitate was collected, washed with cold water (2 x 10 mL) and dried under vacuum (0.1 mm). The crude, pale yellow product (14-15 g) was dissolved in 90 mL of boiling water and the solution was allowed to cool to room temperature, then refrigerated at 5° overnight. The resulting pale yellow crystals were collected, washed with cold water (10 mL) and dried under vacuum (0.1 mm) to give 12.3-13.2 g (60-64%) of 4-aminopyrimidine-5-carboxaldehyde (**1**), mp. 191-193°, *lit.*[10] 179-181°; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.96 br. s, 1 H, NH), 8.26 (br. s, 1 H, NH), 8.52 (s, 1 H, H2), 8.70 (s, 1 H, H6), 9.84 (s, 1 H, CHO); ^{13}C NMR (75 MHz, DMSO-d_6): δ 112.1, 160.7, 161.5, 163.8, 193.1.

7-(2-Pyridyl)pyrido[2,3-d]pyrimidine (7)[2].- A 250-mL, single-necked, round-bottomed flask was equipped with magnetic stirring bar and a condenser fitted with a nitrogen gas inlet tube. The flask was charged with 5.0 g (0.04 mol) of 4-aminopyrimidine-5-carboxaldehyde (**1**), 4.9 g (0.04 mol) of 2-acetylpyridine (99+%, Aldrich Chemical Company, Inc.) and 150 mL of absolute ethanol, then flushed with nitrogen. The solution was heated to boiling and 0.15 mL of a solution of 15% (w/v) potassium hydroxide in methanol was added. The reaction mixture was heated under reflux for 24 hr, then cooled (0°) for 1 hr. The resulting precipitate was collected and dried under vacuum (0.1 mm) to yield 6.9 g (83%) of a tan solid. A solution of crude product in 300 mL of $CHCl_3$ was boiled and CH_3OH was added slowly to maintain the volume of the hot solution until it became cloudy. The resulting mixture was allowed to cool, then refrigerated at 0° for 12 hr. The product was collected, washed with 20 mL of cold CH_3OH and dried under vacuum (0.1 mm), yielding 6.0 g (72%) of **7** as a light yellow, microanalytically pure, crystalline solid, mp. 190-192°, *lit.*[2] 200°; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45 (m, 1 H, H5′), 7.93 (m, 1 H, H4′), 8.44 (d, 1 H, H5, J = 8.4 Hz), 8.76 (d, 1 H, H3′, J = 4.2 Hz), 8.87 (d, 1 H, H6′, J = 9.3 Hz), 8.90 (d, 1 H, H6, J = 8.4 Hz), 9.50 (s, 1 H, H2), 9.55 (s, 1 H, H4); ^{13}C NMR (75 MHz, DMSO-d_6): δ 120.4, 122.3, 123.8, 126.1, 137.6, 137.9, 150.0, 155.0, 158.5, 159.5, 162.0, 164.4.

Anal. Calcd for $C_{12}H_8N_4$: C, 69.22; H, 3.87; N, 26.91. Found: C, 69.23; H, 3.62; N, 26.92

REFERENCES

1. (a) P. Caluwe, *Tetrahedron*, **36**, 2359 (1980); (b) C.-C. Cheng and S.-J. Yan, *Org. Reactions*, **28**, 37 (1982); (c) R. P. Thummel, *Tetrahedron*, **47**, 6851 (1991); (d) R. P. Thummel, *Synlett*, **1** (1992).

2. G. Evens and P. Caluwe, *J. Org. Chem.*, **40**, 1438 (1975).

3. P. Caluwe and T. G. Majewicz, *J. Org. Chem.* **40**, 2566 (1975).

4. T. G. Majewicz and P. Caluwe, *J. Org. Chem.*, **44**, 531 (1979).

5. R. P. Thummel, D. Williamson and C. Hery, *Inorg. Chem.*, **32**, 1587 (1993).

6. R. P. Thummel, F. Lefoulon, D. Williamson, and M. Chavan, *Inorg. Chem.*, **25**, 1675 (1986).

7. T. W. Bell and J. Liu, *J. Am. Chem. Soc.*, **110**, 3673 (1988).

8. (a) T. W. Bell and J. Liu, *Angew. Chem. Int. Ed.*, **29**, 923 (1990); D. L. Beckles, J. Maioriello, V. J. Santora, T. W. Bell, E. Chapoteau, B. Czech and A. Kumar, *Tetrahedron*, **51**, 363 (1995); (c) T. W. Bell, Z. Hou, S. C. Zimmerman and P. A. Thiessen, *Angew. Chem. Int. Ed.*, **34**, 2163 (1995); (d) T. W. Bell and Z. Hou, *Angew. Chem. Int. Ed.*, **36**, 1536 (1997); (e) T. W. Bell and Z. Hou, *Chemosensors of Ion and Molecule Recognition* (A. Czarnik and J.P. Desvergne, Eds.), p. 121, Kluwer, Dordrecht, The Netherlands, 1997; (f) T. W. Bell, A. B. Khasanov, M. G. B. Drew, A. Filikov and T. L. James, *Angew. Chem. Int. Ed.*, **38**, 2543 (1999).

9. J. Baddiley, B. Lythgoe and A. R. Todd, *J. Chem. Soc.*, 386 (**1943**).

10. H. Bredereck, G. Simchen and H. Traut, *Chem. Ber.*, **100**, 3664 (1967).

11. E. C. Taylor, R. J. Knopf, R. F. Meyer, A. Holmes and M. L. Hoefle, *J. Am. Chem. Soc.*, **82**, 5711 (1960).

12. H. W. Schmidt, G. Koitz and H. Junek, *J. Heterocyclic Chem.*, **24**, 1305 (1987).

13. A. Kreutzberger and C. Grundmann, *J. Org. Chem.*, **26**, 1121 (1961).

14. K. R. Huffman, F. C. Schaefer and G. A. Peters, *J. Org. Chem.*, **27**, 551 (1962).

15. B. S. Furniss, A. J. Hannaford, V. Rogers, P. W. G. Smith and A. R. Tatchell, "*Vogel's Textbook of Practical Organic Chemistry*," 4th edition, pp. 65-67, Longman Group Limited, London, 1978.