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One-Pot Synthesis of 2,5-Disubstituted Pyrimidines from Nitriles

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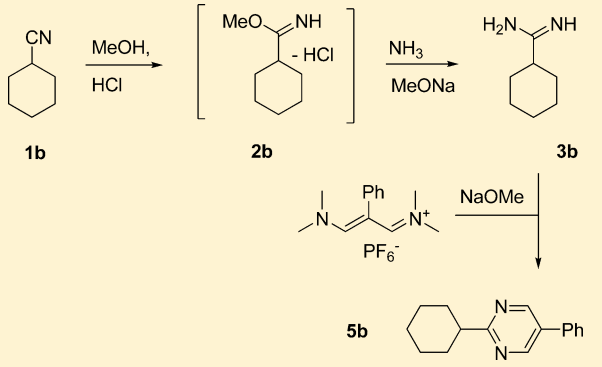
Supporting Information

ABSTRACT: A practical, one-step process for the synthesis of 2,5-disubstituted pyrimidines is presented. The protocol proved to be general for the synthesis of a variety of pyrimidine-containing compounds bearing an assortment of functional groups.

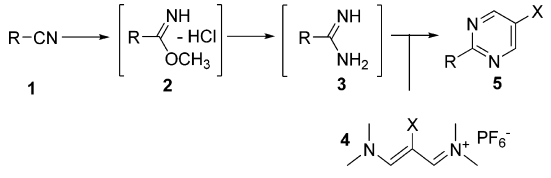


Substituted pyrimidines[1] are a diverse class of heterocycles found not only in a wide variety of natural products[2] but also as building blocks for a number of active pharmaceutical ingredients (APIs) present in prominent commercial drugs such as Crestor, Gleevec, and Aggrenox. Not surprisingly, our own interest in the development of 2,5-disubstituted pyrimidine-containing small molecules as possible therapeutic agents prompted our investigation toward a straightforward and scalable methodology for the synthesis of these compounds. A review of current literature procedures for the synthesis of pyrimidines yielded a vast number of existing methodologies,[3−6] and although some were very elegant and efficient, few were both amenable to the large-scale synthesis of 2,5-disubstituted pyrimidines and compatible with an assortment of functional groups.

An attractive and well-known approach to access 2,5-disubstituted pyrimidines involves the condensation of malondialdehydes or their equivalents, such as vinamidinium salts, with amidines.[7] In particular, the condensation of thermally stable vinamidinium hexafluorophosphate salts[8,9] with amidines promised to be an efficient and versatile strategy since a variety of these species are now commercially available, even in bulk. Accordingly, amidines[10] are usually made by adding ammonia to imidates (imino esters),[11] which in turn are usually synthesized from nitriles by means of a Pinner reaction under acidic[12] or basic reaction conditions.[13] In the majority of literature procedures utilizing the Pinner reaction, nitriles are treated with anhydrous hydrochloric acid and an alcohol in ethereal solvents and allowed to stand over a prolonged period of time until the product precipitates and is collected by filtration.[14] Yields are often modest for many substrates and the resulting imidate hydrochloride salts tend to be highly hygroscopic. Amidines can also be obtained with a modified Pinner reaction, in which nitriles are treated with thiols to give thio-imido intermediates which are then treated with ammonia.[15] Alternatively, amidines can be obtained by direct amination of nitriles with reagents like alkylchloroaluminum amides or CuCl.[16]

Although widely used, the existing protocols for the synthesis of pyrimidines were labor intensive and oftentimes impractical, inefficient, or incompatible with a number of functional groups. Therefore, the possibility of synthesizing 2,5-disubstituted pyrimidines from nitriles without isolation of the intermediate imidates and amidines, by reacting them directly with vinamidinium salts, was investigated (Scheme 1).

Scheme 1. One-Pot Synthesis of Pyrimidines from Nitriles



One-pot processes for the direct synthesis of pyrimidines from nitriles, to the best of our knowledge, have not been reported.[17] This is likely because the multistep transformations involved are often performed under quite different reaction conditions (acidic vs basic), and telescoping them in a compatible fashion is challenging. Reagents and impurities carried through from one transformation to the next can either lead to side reactions or even completely divert the reaction

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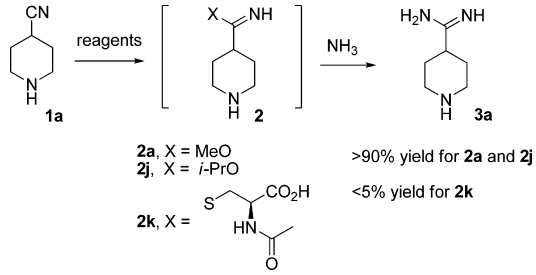
pathway. Nucleophilic functional groups, such as amines and alcohols, present in the substrates, could represent competing reactive sites, which may further complicate the chemistry and limit the scope of reaction.

To develop a streamlined and practical process, the synthesis of amidine **3a** from nitrile **1a** was first explored (Scheme 2).

Scheme 2. Initial Investigations for the Direct Synthesis of Amidines from Nitriles

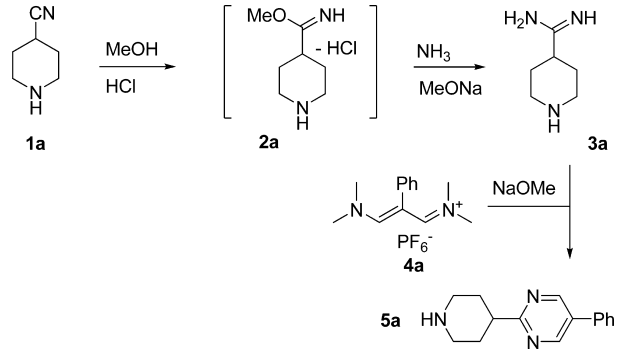


Accordingly, a methoxide-catalyzed imidate formation was first investigated, but it was found to be very slow even at 55 °C, and no significant product was observed after 24 h. This was most likely associated with the steric hindrance and the electron-donating effect of the branched alkyl substituent. Alternatively, the reaction of **1a** with *N*-acetylcysteine led to the formation of the corresponding thio-imidate intermediate **2k** in moderate (30−40%) yield. Reaction with ammonium chloride, however, failed to give the desired amidine **3a** even under reflux in methanol. Attention thus was turned to an HCl-catalyzed reaction. While reaction of **1a** with 1.25 M HCl in methanol gave a low conversion to the imidate, reactions with both methanol and 4.0 M HCl in dioxane and 6.0 M HCl in *i*-PrOH led to very clean formation of the imidates **2a** and **2j**, which could be subsequently converted to the amidines by the addition of ammonia with or without prior evaporation of the remaining HCl. It is likely that formation of the imidates is facilitated by the precipitation of the imidate salts from the reaction mixture in less polar solvents or solvent mixtures. The alkylaluminum-catalyzed direct ammonia addition to **1a** was not pursued due to economics and concerns about the generation of aluminum salts.

Optimization studies revealed that treatment of nitrile **1a** with 3 equiv of methanol and 3 equiv of HCl in dioxane (4 M solution) for 16 h at room temperature resulted in complete conversion to the imidate. In order to minimize the use of ammonia, 1 equiv of NaOMe was added to quench the excess amount of HCl. In this case, 2.2 equiv of ammonia[18] was found to be sufficient to effect the full conversion from the imidate to the amidine. Several methods such as RAMAN, ReactIR and LC/MS were evaluated as tools to monitor the formation of the imidates and subsequent conversion to their corresponding amidines, but it was ultimately found that analyzing aliquots by NMR was the most general and straightforward method.

Having optimized the amidine synthesis, attention was focused on obtaining general conditions for the in situ condensation of the amidine with a malondialdehyde or a vinamidinium salt equivalent. To accomplish this, once formation of the amidine **3a** was deemed complete,[19] an additional 1.2 equiv of NaOMe was added followed by addition of vinamidinium salt **4a**. The desired pyrimidine product **5a** was obtained after 1 h in 78% yield (Scheme 3).

Scheme 3. Synthesis of 5a



The scope of the one-pot process and its suitability for the synthesis of pyrimidine-bearing compounds containing other functional groups was then investigated. The synthesis of additional pyrimidine-containing compounds that incorporated a basic amine as described above was a challenge for three different reasons. First, the hydrochloride salt of the amine formed under the acidic conditions necessary for the initial formation of the imidate had to be at least partially soluble in the reaction medium to be able to react with methanol and give rise to the imidate (**2**, Scheme 1). Moreover, the additional amine functionality could in principle compete with ammonia during the formation of the amidine (**3**) from the imidate (**2**), and finally, the amine could potentially interfere in a competitive way with the reaction of the amidine (**3**) with the vinamidinium salt (**4**) in the last stage of the process. Fortunately, as shown in Table 1, a number of nitriles containing amine functionalities (**1a**, **1c**, **1e**, and **1g**) proved to be adequate substrates for the process and gave the corresponding pyrimidines (**5a**, **5c**, **5e**, and **5g**) when submitted to the new one-pot protocol. Similarly, the process was found to be suitable for the synthesis of pyrimidine compounds containing phenol (**1i**), nitro (**1d**), 2-chloropyridine (**1e**), and ether functional groups (**1f** and **1h**) as shown in Table 1.

In conclusion, a practical, robust and general one-pot process for the direct synthesis of pyrimidines from nitriles was demonstrated. The protocol proved to be general for the synthesis of 2,5-disubstituted pyrimidine compounds bearing a variety of functional groups in good yields using common, inexpensive reagents.

EXPERIMENTAL SECTION

Unless otherwise specified, all reactions were carried out in oven-dried glassware under an atmosphere of nitrogen. NMR spectra were recorded on a 400 MHz NMR spectrometer. Shifts are reported in ppm relative to tetramethylsilane; coupling constants (*J*) are reported in hertz, referred to as apparent peak multiplicities, and may not necessarily reflect true coupling constants. High-resolution mass spectral data were acquired using a LC/MSD TOF (time-of-flight) mass spectrometer in an electrospray positive ionization mode via flow injection. The commercially available starting materials were used as received without further purification and all solvents were dried by standard methods prior to use.

General Experimental Procedure for the Synthesis of Pyrimidines 5a−i. *Synthesis of 5-Chloro-2-cyclohexylpyrimidine (**5b**).* HCl (4 M) in dioxane (75.0 mmol) was charged to a round-bottom flask equipped with a temperature probe, stirrer, and nitrogen line. The solution was cooled to 0 °C, and cyclohexane carbonitrile **1b** (2.73g, 25.0 mmol) was charged as a solution in MeOH (3.04 mL, 75 mmol) over 30 min while keeping the temperature below 10 °C. The

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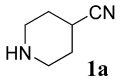
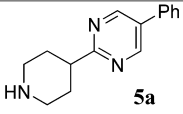
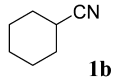
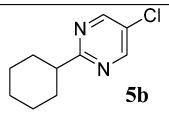
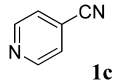
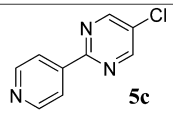
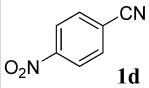
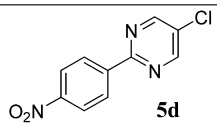
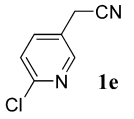
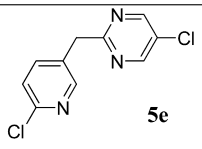
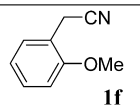
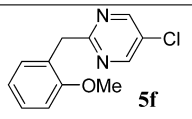
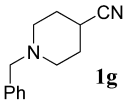
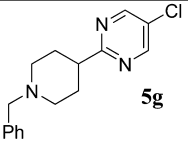
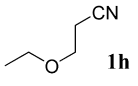
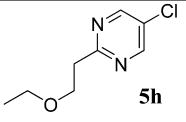
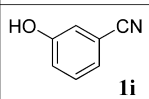
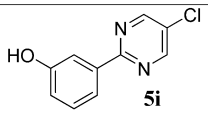
Table 1. Direct Synthesis of Pyrimidines from Nitriles

Entry	Nitrile	X (4)	Product	Yield
1	 **1a**	Ph	 **5a**	85%
2	 **1b**	Cl	 **5b**	86%
3	 **1c**	Cl	 **5c**	66%
4	 **1d**	Cl	 **5d**	77%
5	 **1e**	Cl	 **5e**	85%
6	 **1f**	Cl	 **5f**	84%
7	 **1g**	Cl	 **5g**	72%
8	 **1h**	Cl	 **5h**	68%
9	 **1i**	Cl	 **5i**	84%

temperature was then adjusted to 22 °C, and the mixture was stirred for 6−8 h at ambient temperature. The mixture was cooled to 5 °C, and 25 wt % NaOMe in MeOH (11.4 mL, 50 mmol) was charged while maintaining the temperature below 15 °C. The mixture was then stirred for 10−15 min at 15 °C. Ammonia in MeOH (7.0 N, 5.36 mL, 37.5 mmol) was charged, and the resulting mixture was stirred for 2 h at ambient temperature. The mixture was concentrated under reduced pressure at 50 °C (approximately 130 Torr) to a volume of approximately 25 mL (to remove excess ammonia). The resulting heterogeneous mixture containing the crude amidine (**3b**) was cooled to 20 °C and 25 wt % NaOMe in MeOH (14.3 mL, 63.5 mmol) was charged. The mixture was then stirred for 30 min, and (Z)-*N*-(2-chloro-3-(dimethylamino)allylidene)-*N*-methylmethanaminium hexafluorophosphate(V)[8,20] (8.09 g, 90% w/w, 23.8 mmol) was charged to the above mixture in two portions at ambient temperature over approximately 30 min. The mixture was stirred for 3 h at ambient temperature and then concentrated under reduced pressure at 60 °C to a minimum stirrable volume (approximately 20 mL). 2-Methyltetrahydrofuran (40.7 mL) was charged, and the mixture was concentrated further to a volume of approximately 20 mL under reduced pressure at 60 °C. 2-Methyltetrahydrofuran (41 mL) was charged, the mixture was cooled to ∼20 °C, water (20.4 mL) was charged, and the mixture was stirred for 5 min. The layers were separated, and the organic layer was collected. The aqueous layer was extracted with Me-THF (20.4 mL). The combined organic layers were washed with 30% aq NaOH (3 equiv of NaOH), and the layers were separated. The organic layer was dried with $MgSO_4$ and concentrated under reduced pressure.

Flash chromatography (hexane/ethyl acetate, 9:1 to 3:1 gradient) afforded 4.21 g (86% yield) of product **5b** as a colorless oil that solidified upon standing: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21−1.34 (m,1H), 1,35−1.47 (m, 2H), 1.59 (dddd, J = 3.2, 12.4, 12.4, 12.4 Hz, 2H), 1.75 (br d, J = 12.4 Hz, 1H), 1.86 (ddd, J = 3.2, 3.2, 12.4 Hz, 2H), 1.98 (br d, J = 12.4 Hz, 2H), 2.87 (m, 1H), 8.62 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.8, 26.1, 31.8, 46.8, 128.5, 155.3, 172.6; HRMS calcd for $[C_{10}H_{14}ClN_2]^+$ 197.0840, found 197.0827.

5-Phenyl-2-(piperidin-4-yl)pyrimidine (***5a***): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.84 (dddd, J = 4.0, 12.4, 12.4, 12.4 Hz, 2H), 2.06 (br d, J = 12.4 Hz, 2H), 2.81 (dt, J = 2.4, 12.4 Hz, 2H), 3.08 (m, 1H), 3.24 (br d, J = 12.4 Hz, 2H), 7.44−7.58 (m, 5H), 8.89 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.3, 45.5, 46.7, 126.9, 128.6, 129.4, 131.4, 134.7, 155.1, 172.2; HRMS calcd for $[C_{15}H_{18}N_3]^+$ 240.1495, found 240.1486.

5-Chloro-2-(pyridin-4-yl)pyrimidine (***5c***): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (dd, J = 1.6, 4.4 Hz, 2H), 8.78 (dd, J = 1.6, 4.4 Hz, 2H), 8.81 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 121.9, 131.0, 143.6, 150.7, 156.0, 160.6; HRMS calcd for $[C_9H_7ClN_3]^+$ 192.0323, found 192.0318.

5-Chloro-2-(4-nitrophenyl)pyrimidine (***5d***): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.391 (d, J = 8.2 Hz, 2H), 8.59 (d, J = 8.2 Hz, 2H), 9.13 (2, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 124.1, 129.0, 130.3, 141.8, 149.0, 156.5, 159.6; HRMS calcd for $[C_{10}H_7ClN_3O_2]^+$ 236.0221, found 236.0218.

5-Chloro-2-((6-chloropyridin-3-yl)methyl)pyrimidine (***5e***): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.25 (s, 2H), 7.27 (d, J = 8.4 Hz, 1H), 7.66 (dd, J = 2, 8.4 Hz, 1H), 8.39 (d, J = 2 Hz, 1H), 8.63 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.4, 124.0, 129.6, 132.1, 139.5, 150.0, 150.1, 155.9, 166.2; HRMS calcd for $[C_{10}H_8Cl_2N_3]^+$ 240.0090, found 240.0077.

5-Chloro-2-(2-methoxybenzyl)pyrimidine (***5f***): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (s, 3H), 4.30 (s, 2H), 6.86 (d, J = 8.0 Hz, 1H), 6,91 (ddd, J = 0.8, 7.6, 7.6 Hz, 1H), 7.19−7.25 (m, 2H), 8.59 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.3, 55.3, 110.5, 120.4, 126.3, 128.1, 128.6, 130.7, 155.4, 157.3, 168.1; HRMS calcd for $[C_{12}H_{12}ClN_2O]^+$ 235.0633, found 235.0627.

2-(1-Benzylpiperidin-4-yl)-5-chloropyrimidine (***5g***): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.93−1.98 (m, 4H), 2.05−2.16 (m, 2H), 2.82−2.92 (m, 1H), 3.00 (m, 2H), 3.54 (s, 2H) 7.22−7.37 (m, 5H), 8.61 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.0, 44.7, 53.5, 63.3, 126.9, 128.1, 128.8, 129.0, 138.7, 155.4, 171.5; HRMS calcd for $[C_{16}H_{19}ClN_3]^+$ 288.1262, found 288.1248.

5-Chloro-2-(2-ethoxyethyl)pyrimidine (***5h***): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (t, J = 7.2 Hz, 3H), 3.23 (t, J = 6.8 Hz, 2H), 3.52 (q, J = 7.2 Hz, 2H), 3.91 (t, J = 6.8 Hz, 2H), 8.63 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.0, 39.0, 66.2, 68.4, 129.0, 155.4, 166.8; HRMS calcd for $[C_8H_{12}ClN_2O]^+$ 187.0633, found 187.0626.

3-(5-Chloropyrimidn-2-yl)phenol (***5i***): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.21 (br, 1H), 7.00 (dd, J = 2.8, 8.4 Hz, 1H), 7.37 (dd, J = 8.0, 8.0 Hz, 1H), 7.88 (m, 1H), 7.99 (d, 8.0 Hz), 8.74 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 114.9, 118.3, 120.8, 129.5, 130.1, 138.0, 155.7, 156.0, 162.2; HRMS calcd for $[C_{10}H_8ClN_2O]^+$ 207.0320, found 207.0322.

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■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectral data for compounds **5a−i** are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) For a review on pyrimidine chemistry see: Brown, D. J.; Evans, R. F.; Cowden, W. B.; Fenn, M. D. *The Pyrimidines*; John Wiley & Sons: Montreal, 1994.
(2) Lagoja, I. M. *Chemistry Biodiversity* **2005**, *2*, 1.
(3) Sasada, T.; Kobayashi, F.; Sakai, N.; Konokahara, T. *Org. Lett.* **2009**, *11*, 2161.
(4) Zhichkin, P.; Fairfax, D. J.; Eisenbeis, S. A. *Synthesis* **2002**, 720.
(5) Movassaghi, M.; Hill, M. D. *J. Am. Chem. Soc.* **2006**, *128*, 14254.
(6) Dousson, C. B.; Heon, N. M.; Hill, G. B. *Synthesis* **2005**, *11*, 1817.
(7) (a) Reichardt, C.; Ferwanah, A.-R.; Pressler, W.; Yun, K.-Y. *Liebigs Ann. Chem.* **1984**, *4*, 649−679. (b) Stolle, W. A. W.; Marcelis, A. T. M.; Koetsier, A.; van der Plas, H. C. *Tetrahedron* **1989**, *45*, 6511. (c) Frissen, A. E.; Marcelis, A. T. M.; Melger, W. C.; van der Plas, H. C. *Tetrahedron* **1989**, *45*, 6891. (d) Reichardt, C.; Halbritter, K. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 86.
(8) Davies, I. W.; Marcoux, J.-F.; Xu, J.; Paluci, M.; Corley, E. G.; Robbins, M. A.; Tsou, N.; Ball, R. G.; Dormer, P.; Larsen, R. D.; Reider, P. J. *J. Org. Chem.* **2000**, *65*, 4571.
(9) Davies, I. W.; Taylor, M.; Marcoux, J.-F.; Wu, J.; Dormer, P. G.; Hughes, D.; Reider, P. J. *J. Org. Chem.* **2001**, *66*, 251.
(10) For a review, see: Aly, A. A.; Nour-El-Din, A. M. *ARKIVOC* **2008**, *i*, 153−194.
(11) For a review, see: Roger, R.; Nelson, D. G. *Chem. Rev.* **1961**, *61*, 179.
(12) Roger, R.; Neilson, D. G. *Chem. Rev.* **1961**, *61*, 179.
(13) Shaefer, F. C.; Peters, G. A. *J. Org. Chem.* **1961**, *26*, 412.
(14) (a) Barker, P. L.; Gendler, P. L.; Rapoport, H. *J. Org. Chem.* **1981**, *46*, 2455. (b) Ueno, H.; Maruyama, A.; Miyake, M.; Nakao, E.; Nakao, K.; Umezu, K.; Nitta, I. *J. Med. Chem.* **1991**, *34*, 2468 and references cited therein. (c) Chiba, T.; Takahashi, T.; Sakaki, J.-i.; Kaneko, C. *Chem. Pharm. Bull.* **1985**, *33*, 3046.
(15) (a) Schnur, R. C. *J. Org. Chem.* **1979**, *44*, 3726. (b) Lange, U. E. W.; Schaefer, B.; Baucke, D.; Buschmann, E.; Mack, H. *Tetrahedron Lett.* **1999**, *40*, 7067.
(16) (a) Garigipati, R. S. *Tetrahedron Lett.* **1990**, *31*, 1969. (b) Rousselet, G.; Capdevielle, P.; Maumy, M. *Tetrahedron Lett.* **1993**, *34*, 6395. (c) Frutos, R. P; Gallou, I.; Reeves, D.; Xu, Y.; Krishnamurthy, D.; Senanayake, C. H. *Tetrahedron Lett.* **2005**, *46*, 8369.
(17) For early examples of the synthesis of pyrimidines from preformed, isolated amidines, see refs 7c and 7d.
(18) For some substrates, 1.5 equiv of ammonia was enough to complete imidine formation.
(19) At this stage, the reaction mixture is at nearly neutral pH.
(20) In their report on the "Preparation of 2-chloro-1,3-bis(dimethylamino)trimethinium hexafluorophosphate" Davies et al. include the following comment: "Caution: The salt is a skin and eye irritant and was positive in the Ames mutagenesis assay. It should be handled in a hood with adequate personal protective equipment." Davies, I.W.; et al. *Organic Syntheses* **2003**, *80*, 200.