A Convenient Method for the Preparation of Highly Substituted Pyrimidines: Synthesis of Tri- and Tetra-Subsituted Pyrimidines from 1,3-Dicarbonyl Compounds and *N*,*N*,*N*'-Tris-(Trimethylsilyl)amidines.

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A modification of the Pinner pyrimidine synthesis has been developed that utilizes trimethylsilyl amidines and results in greatly improved yield of highly substituted pyrimidines.

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Introduction.

The biological importance of pyrimidine compounds is well known [1], and, as a consequence, considerable attention has been devoted to developing practical syntheses of variously substituted pyrimidines [2,3]. Among the possible disconnection strategies, the condensation of a three-carbon unit (typically a 1,3-dione or enone) with an N-C=N fragment (typically an amidine) is widely used for the direct preparation of the pyrimidine nucleus (the Pinner method) [4]. However, this method works best for the synthesis of pyrimidines having relatively low degrees of substitution. In the case of highly substituted pyrimidines, use of the Pinner method generally requires longer reaction time and often results in poor yields [5-7].

We have been interested in the development of novel ligands for the estrogen receptor that are chemically simple and amenable to combinatorial synthesis. In the process of our work in this area, we sought to prepare a number of highly substituted diazenes, including some tetrasubstituted pyridines [8]. We were able to prepare some of the pyrimidines of interest to us by the condensation of a ketone with two equivalents of an aryl nitrile in presence of trifluoromethanesulfonic anhydride [9], a method that shows good regioselectivity when the ketone component is enolizable in only one direction. This approach, however, is not suitable for the preparation of 2,4,5-tris-aryl- and 2,5-bis-aryl-pyrimidines. When we explored another known method involving the condensation of 1,3-dicarbonyl compounds with aromatic aldehydes in presence of ammonium acetate [10], a route which goes *via* a dihydropyrimidine intermediate, we obtained the desired pyrimidines, but only in unacceptably low yields. Therefore, we sought to develop a better, more general method for the synthesis of these highly substituted pyrimidines.

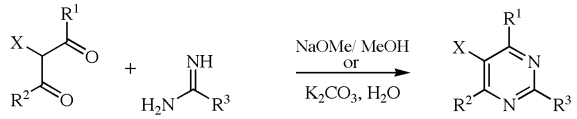
In this report, we describe our development of a modification of the Pinner pyridimine synthesis that uses silyl-substituted amidines in place of amidines. This method can be used in a convenient manner for the synthesis of various tri- and tetrasubstituted pyrimidines in good yields.

Results and Discussion.

In the Pinner pyrimidines synthesis [4,6,11] (Scheme 1a), an amidine is condensed with a 1,3-dicarbonyl compound. The rate-limiting step in this double condensation reaction is thought to be the dehydration of the various hydroxy-hydropyrimidine intermediates [12]. The substituted 1,3-dione precursors, we found, were often sensitive to the basic conditions typically used in this condensation [7]. Therefore, we sought to modify this reaction so that it would proceed under milder conditions and in a manner such that the dehydration steps would be facilitated. To reduce the need for base and to accelerate the dehydrations, we selected an *N*,*N*,*N*'-tris-(trimethylsilyl)amidines as an amidine equivalent (Scheme 1b). These silyl amidines, which are readily prepared by a known method (Scheme 1c) [13], are much less basic than unsubsituted amidines. Also, because the dehydration step with these

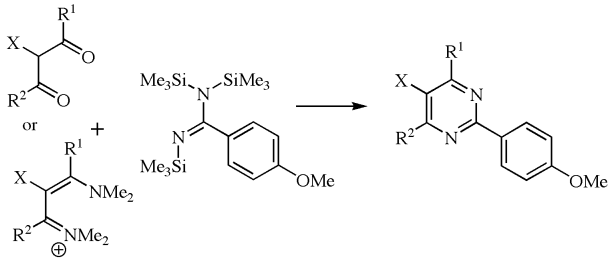
Scheme 1

a) Standard Pinner Pyrimide Synthesis

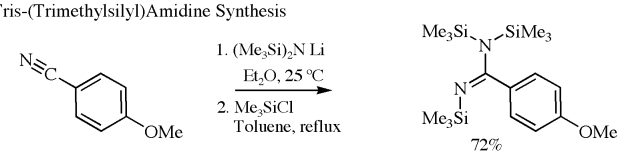


R^1	R^2	R^3	X	
Me	Me	Ph	H	poor yield
H	Me	Ph	H	no reaction
Me	Me	Me	Me	poor yield & long reaction time

b) Proposed Modification of the Pinner Synthesis



c) Tris-(Trimethylsilyl)Amidine Synthesis

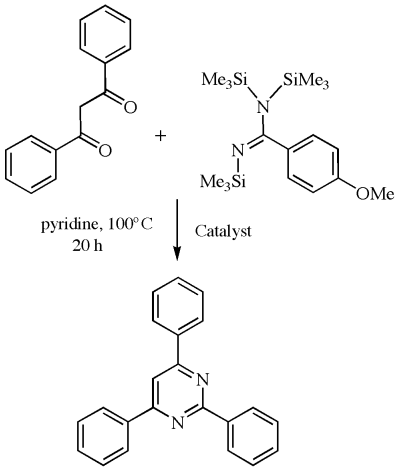


Methods for Pyrimidine Synthesis

N-trimethyl silyl analogs would produce hexamethyldisiloxane rather than water, we anticipated that the condensation reaction would be driven in the forward direction by the silyl substitution.

In our preliminary attempts with this modification of the Pinner method, we found that the reaction of dibenzoylmethane with an aryl *N*,*N*,*N*'-tris-(trimethylsilyl)benzamidine in the presence anhydrous KF [14], a catalyst selected to assist the silyl transfer process, did not give the required pyrimidine (Scheme 2, entry 1). However, when we replaced this anhydrous salt with other forms of KF (entries 2-4), yields increased. The yield with ammonium bifluoride (NH_4•HF_2) was 40% (entry 5). This result suggested that activation of the 1,3-dicarbonyl component might also be also required to facilitate this reaction.

Scheme 2

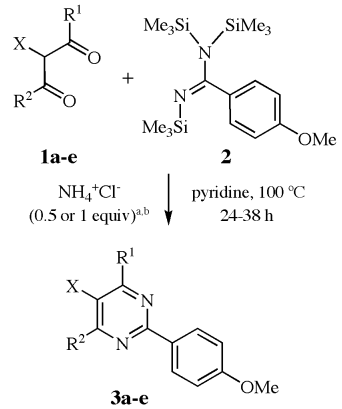


	Catalyst	Yield
1	KF (anhyd.)	<1%
2	KF (1.5% H_2O)	20%
3	KF (anhyd. + 1equiv. H_2O)	10%
4	HF•Pyridine	5%
5	NH_4•HF_2	40%
6	$MeNH_2$•HCl	85%
7	Me_2NH•HCl	90%

Reaction Conditions and Yields of Pyrimidine Synthesis from Dibenzoylmethane and N,N,N'-Tris-(trimethylsilyl)phenylamidine

On this basis, we the investigated amine salts, namely $MeNH_2$•HCl, Me_2NH•HCl, and NH_4Cl, and we found that the reaction proceeds well without the presence of fluoride ion (Scheme 2, entries 6-7). For the synthesis of tri-subsituted pyrimidines, all of these salts gave good yields, but for the tetra-subsituted pyrimidines, only NH_4Cl worked well, presumably because it is the least bulky. Accordingly, we chose NH_4Cl as being most general for the synthesis of pyrimidines. Using this salt with 1,3-diketones and *N*,*N*,*N*'-tris-(trimethylsilyl)benzamidines in pyridine under reflux for 24-38 hours, we obtained the corresponding pyrimidines in moderate to good yields (Scheme 3). We found that pyridine worked better as a solvent than DMF or acetonitile, and we also found that using half of an equivalent of the amine salt worked best for tri-substituted systems, whereas for the preparation of tetra-substituted pyrimidines, a full equivalent of salt was preferred. The yields for tri-substituted pyrimidines were 74-89%, and for tetra- substituted pyrimidines were 42-78%, depending on substituents.

Scheme 3



	R^1	R^2	X	Yield
a	Me	Me	H	89%[a]
b	Ph	Ph	H	83%[a]
c	Ar[c]	Ar	H	74%[a]
d	Ar	Ar	Pr	42%[b]
e	Ar	Pr	Ar	45%[b]
f	Me	Me	Et	78%[b]
g	Me	Pr	Ar	60%[b]

[a] 0.5 equiv $NH_4^+Cl^-$ was used for the trisbustituted pyrimidines.
[b] 1.0 equivalent $NH_4^+Cl^-$ was used for the tetrasubstituted pyrimidines.
[c] Ar = *p*-(OMe)-C_6H_4

Synthesis of pyrimidines according to the modified Pinner reaction.

Conclusion.

We have developed a general method for the synthesis of tri- and tetra-substituted pyrimidines in high yield, using 1,3-dicarbonyl compounds and *N*,*N*,*N*'-tris-(trimethylsilyl)amidines in place of amidines, which are typically used in the Pinner pyrimidine synthesis.

EXPERIMENTAL

All reaction using water or air sensitive reagents were conducted under dry inert gas atmosphere with dry solvents. Pyridine and hexane were distilled from CaH_2 under N_2 and stored over CaH_2 until used. THF, dichloromethane, diethyl ether and toluene were obtained dry from solvent delivery system designed by J.C. Meyer using activated neutral alumina under dry Argon. All the reagents purchased from Aldrich Chemicals and Lancaster were used without further purification. The 1,3-diones are prepared according to a literature procedure [8]. All reactions were monitored by TLC (Merck, 0.25 mm silica gel

glass plates containing F-254 indicator), which were visualized under UV light (254 nm), iodine vapor, or by using a phosphomolybdic acid indicator spray. Flash column chromatography [15] was performed using Woelm 32-63 μm silica gel packing.

^{1}H NMR and ^{13}C NMR spectra were recorded on Varian U400 or U500 spectrometers, and spectra chemical shifts (δ) are reported in parts per million (ppm) downfield from internal tetramethylsilane or by reference to proton resonances resulting from incomplete deuteration of the NMR solvent. Coupling constants are reported in Hertz. Electron ionization (EI) spectra were obtained using a Finnigan-MATCH5 spectrometer at 70 eV. Elemental analysis was performed by the Microanalytical Service Laboratory at the University of Illinois, Urbana-Champaign. Melting points (uncorrected) were recorded on a Thomas-Hoover Electrothermal Apparatus. All final compounds were obtained in chromatographically homogenous form.

General Method for Pyrimidine Synthesis.

The silylamidine, *N*,*N*,*N*'-tris-(trimethylsilyl)-4-methoxybenzamidine, was prepared according to a literature procedure [13], by the reaction of anisonitrile and $(Me_3Si)_2NLi\bullet OEt_2$ in ether to afford the adduct $Ar(NLi)N(SiMe_3)$, which was then heated with Me_3SiCl in toluene to give the product in 76% yield (Scheme 1c). This amidine (1.5 mmol) was then added dropwise at room temperature to a stirred solution of 1,3-diketone (1 mmol) and ammonium chloride (0.6-1 mmol) in dry pyridine (10 ml) under dry inert atmosphere. The reaction mixture was refluxed for 24-38 hours, and after completion of the conversion (as determined by TLC analysis), the reaction mixture was cooled and ice-water was added with stirring. The precipitate was collected by filtration, washed, and then dried, or the product was extracted with ethyl acetate (2x 10 ml). Extracts were washed with 2 *N* HCl (2 x 5 ml), brine (5 ml), and then dried over anhydrous Na_2SO_4. Solvents were removed under vacuum, and the products were purified by flash column chromatography over silica gel using hexane-ethyl acetate or by recrystallization.

4,6-Bis-methyl-2-(4'-methoxyphenyl)pyrimidine (**3a**).

This material was prepared, according to the general procedure, from pentane-2,4-dione **1a** (200 mg, 2 mmol), amidine **2** (1.1 g, 3 mmol), and dimethyl ammonium chloride (64 mg, 1.2 mmol) in dry pyridine (15 ml) with reflux for 24 hours. Isolation of the water-soluble product by extraction, furnished, after recrystallization from hexane-ethyl acetate, pyrimidine **3a** (382 mg, 89%); mp 91-92 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.42 (2H, AA'XX', J_{AX} = 9.00 & $J_{AA'}$ = 2.14 Hz), 7.00 (2H, AA'XX', J_{AX} = 9.00 & $J_{AA'}$ = 2.14 Hz), 6.87 (1H, s, HC(5) pyrimidine), 3.88 (3H, s, OMe) and 2.53 (6H, s, 2 CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.59, 163.88, 161.51, 130.78, 129.78, 117.25, 113.72, 55.28 and 24.12; MS (EI,70 eV) m/z 214 (M^+, 100%), 135 (41%), 199 (32%).

Anal. Calcd. for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.07. Found: C, 72.79; H, 6.60; N, 12.93.

4,6-Bis-phenyl-2-(4'-methoxyphenyl)pyrimidine (**3b**).

This material was prepared, according to the general procedure, from dibenzoylmethane **1b** (225 mg, 1 mmol), amidine **2** (550 mg, 1.5 mmol), and dimethyl ammonium chloride (32 mg, 0.6 mmol) in dry pyridine (10 ml), with reflux for 24 hours. After collection of the insoluble precipitate by filtration and crystallization from hexane-ethyl acetate, we obtained pyrimidine **3b** (281 mg, 83%). mp 140-141 °C (lit. [8] m.p. 135-136 °C); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.70 (2H, AA'XX', J_{AX} = 9.00 & $J_{AA'}$ = 2.14 Hz), 8.28 (4H, AA'XX', J_{AX} = 6.64 & $J_{AA'}$ = 2.14 Hz), 7.96 (1H, s, HC(5) pyrimidine), 7.58-7.50 (6H, m, (C4 &C6)-Ph), 7.05 (2H, AA'XX', J_{AX} = 9.00 & $J_{AA'}$ = 2.14 Hz) and 3.92 (3H, s, OMe); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 164.65, 164.26, 161.85, 137.65, 130.82, 130.71, 130.12, 128.89, 127.27, 113.73, 109.66 and 55.36. MS (EI, 70 eV) m/z 338 (M^+, 100%), 339 (29%), 102 (44%).

2,4,6-Tris-(4'-methoxyphenyl)pyrimidine (**3c**).

This material was prepared, according to the general procedure, from 1,3-(4'-methoxyphenyl)-1,3-dione **1c** (284 mg, 1 mmol), amidine **2** (550 mg, 1.5 mmol), and dimethyl ammonium chloride (32 mg, 0.6 mmol) in dry pyridine (10 ml), with reflux for 38 hours. After collection of the solid product by filtration and crystallization from hexane-ethyl acetate, we obtained pyrimidine **3c** (294 mg, 74%); mp 174-175 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.66 (2H, AA'XX', J_{AX} = 9.00 & $J_{AA'}$ = 2.14 Hz), 8.23 (4H, AA'XX', J_{AX} = 9.00 & $J_{AA'}$ = 2.14 Hz), 7.80 (1H, s, HC(5) pyrimidine), 7.04 (6H, AA'XX', J_{AX} = 9.00 & $J_{AA'}$ = 2.14 Hz), 3.89 (3H, s, OMe) and 3.89 (3H, s, 2 OMe); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 163.91, 163.76, 161.71, 161.64, 131.14, 130.19, 129.98, 128.66, 114.11, 113.63, 107.85, 55.36 and 55.31; MS (EI, 70 eV) m/z 398 (M^+, 100%), 132 (16%).

Anal. Calcd. for $C_{25}H_{22}N_2O_3$: C, 75.36; H, 5.57; N, 7.03. Found: C, 74.92; H, 5.51; N, 6.79.

5-Propyl-2,4,6-tris-(4'-methoxyphenyl)pyrimidine (**3d**).

This material was prepared, according to the general procedure, from 1,3-bis-(4'-methoxyphenyl)-2-propyl-1,3-dione **1d** (50 mg, 0.153 mmol), amidine **2** (85 mg, 0.23 mmol), and dimethyl ammonium chloride (7 mg, 0.15 mmol) in dry pyridine (5 ml), with reflux for 38 hours. After isolation of the solid product by filtration and recrystallization from ethanol, we obtained pyrimidine **3d** (28 mg, 42%); mp 139-140 °C (lit. [8] 135 °C); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.49 (2H, AA'XX', J_{AX} = 9.00 & $J_{AA'}$ = 2.19 Hz), 7.62 (4H, AA'XX', J_{AX} = 8.79 & $J_{AA'}$ = 2.19 Hz), 7.03 (4H, AA'XX', J_{AX} = 8,79 & $J_{AA'}$ = 2.19 Hz), 6.99 (2H, AA'XX', J_{AX} = 9.00 & $J_{AA'}$ = 2.14 Hz), 3.92 (3H, s, OMe), 3.89 (3H, s, OMe), 3.86 (3H, s, OMe), 2.84 (2H, t, J = 7.81 Hz, CH_2CH_2), 1.15 (2H, quint, J = 7.56 & 7.81 Hz, $CH_2CH_2CH_3$) and 0.59 (3H, t, J = 7.56 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.63, 163.09, 161.42, 160.74, 160.03, 132.39, 130.69, 130.34, 129.78, 129.10, 127.20, 113.84, 113.68, 113.58, 55.42, 55.33, 55.29, 30.45, 22.77 and 13.88; MS (EI, 70 eV) m/z 440 (M^+, 87%), 439 (49%), 133 (100%).

4-Propyl-2,5,6-tris-(4'-methoxyphenyl)pyrimidine (**3e**).

This material was prepared, according to the general procedure, from 1,2-bis-(4'-methoxyphenyl)-hexane-1,3-dione **1e** (30 mg, 0.092 mmol), amidine **2** (51 mg, 0.14 mmol), and dimethyl ammonium chloride (5 mg, 0.09 mmol) in dry pyridine (5 ml), with reflux for 38 hours. After isolation of the solid product by filtration and crystallization from ethanol, we obtained pyrimidine **3e** (18 mg, 45%); mp 129-130 °C (lit. [8] 130-131 °C); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.56 (2H, AA'XX', J_{AX} = 9.00 & $J_{AA'}$ = 1.93 Hz), 7.41 (2H, AA'XX', J_{AX} = 8.79 & $J_{AA'}$ = 1.94 Hz), 7.05 (2H, AA'XX', J_{AX} = 8,79 & $J_{AA'}$ = 2.14 Hz), 7.00 (2H, AA'XX', J_{AX} = 8.79 & $J_{AA'}$ = 1.93 Hz), 6.89 (2H, AA'XX', J_{AX} = 8.79 & $J_{AA'}$ = 1.95 Hz), 6.76 (2H, AA'XX', J_{AX} = 9.00 & $J_{AA'}$ =

2.14 Hz), 3.88 (3H, s, OMe), 3.86 (3H, s, OMe), 3.85 (3H, s, OMe), 2.65 (2H, t, J = 7.50 Hz, CH_2CH_2), 1.78 (2H, quint, J = 7.5 & 7.3 Hz, $CH_2CH_2CH_3$) and 0.91 (3H, t, J = 7.30 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.33, 162.91, 162.02, 161.49, 159.85, 158.78, 131.54, 131.47, 131.38, 131.06, 129.79, 129.41, 128.52, 113.98, 113.66, 113.10, 55.16, 55.13, 55.14, 37.33,21.90 and 14.05; MS (EI, 70 eV) m/z 440 (M^+, 56%), 439 (38%), 411 (100%).

4,6-Bis-methyl-5-ethyl-2-(4'-methoxyphenyl)pyrimidine (**3f**).

This material was prepared, according to the general procedure, from 3-ethyl-2,4-pentanedione **1f** (256 mg, 2 mmol), amidine **2** (1.1 g, 3 mmol), and ammonium chloride (108 mg, 2 mmol) in dry pyridine (15 ml), with reflux for 38 hours. After isolation of the water-soluble product by extraction and after purification by flash column chromatography, we obtained pyrimidine **3f** (377 mg, 78%). mp 80-81 °C (hexane-ethyl acetate); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.36 (2H, AA'XX', J_{AX} = 9.00 & $J_{AA'}$ = 2.14 Hz), 6.97 (2H, AA'XX', J_{AX} = 9.00 & $J_{AA'}$ = 2.14 Hz), 3.86 (3H, s, OMe), 2.67 (2H, q, J = 7.50 Hz, CH_2CH_3), 2.55 (6H, s, 2 CH_3) and 1.16 (3H, t, J = 7.50 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 164.23, 161.19, 160.86, 130.93, 129.85, 129.34, 113.68, 55.28, 21.89, 21.29 and 12.98. MS (EI, 70 eV) m/z 242 (M^+, 96%), 227 (100%), 134 (44%).

Anal. Calcd. for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.35; H, 7.55; N, 11.56.

2,5-Bis-(4'-methoxyphenyl)-6-methyl-4-propylpyrimidine (**3g**).

This material was prepared, according to the general procedure, from 2-(4'-methoxyphenyl)-hepane-2,4-dione **1g** (234 mg, 1 mmol), amidine **2** (550 mg, 1.5 mmol), and dimethyl ammonium chloride (54 mg, 1 mmol) in dry pyridine (10 ml), with reflux for 38 hours. After isolation of the solid product by filtration and crystallization from ethanol, we obtained pyrimidine **3g** (209 mg, 60%); mp 134-135 °C (lit [8] 135-136 °C); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.47 (2H, AA'XX', J_{AX} = 8.79 & $J_{AA'}$ = 1.93 Hz), 7.12 (2H, AA'XX', J_{AX} = 8.58 & $J_{AA'}$ = 1.93 Hz), 7.01 (4H, AA'XX', J_{AX} = 8.58 & $J_{AA'}$ = 2.14 Hz), 3.90 (3H, s, OMe), 3.89 (3H, s, OMe), 2.54 (2H, t, J = 7.50 Hz, $CH_2CH_2CH_3$), 2.34 (3H, s, CH_3), 1.74 (2H, quint, J = 7.50 Hz, $CH_2CH_2CH_3$) and 0.89 (3H, t, J = 7.50 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.79, 164.92, 162.01, 161.39, 158.98, 131.05, 130.41, 130.36, 129.66, 129.18, 114.10, 113.72, 55.31, 55.25, 37.15, 23.40, 21.84 and 14.00; MS (EI, 70 eV) m/z 348 (M^+ 38%), 347 (22%), 320 (89%), 319 (100%).

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REFERENCES AND NOTES

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