and nitrogen inlet was charged with a solution of **11** (24.26 g, 137.8 mmol) in dry tetrahydrofuran (300 mL). The solution was cooled to 4 °C, and then a solution of borane (1 M in tetrahydrofuran, 142 mL) was added dropwise over 20 min such that the internal temperature did not exceed 5 °C during the addition. The cooling bath was removed, and the reaction mixture was allowed to warm to room temperature and stir for 2.5 h. The reaction was then quenched by the dropwise addition of water (9.5 mL) followed (after hydrogen evolution was complete) by the addition of 2.5 N NaOH (280 mL). Hydrogen peroxide (30% aqueous solution, 16 mL) was carefully added dropwise such that the reaction temperature was 45 °C upon completion of the addition. An oil bath was added and the reaction mixture maintained at 45–50 °C for 1 h. The reaction mixture was allowed to cool and then diluted with 20% NaCl (500 mL). The layers were separated, and the aqueous layer was extracted with an additional portion of tetrahydrofuran (300 mL). The combined organic extracts were washed with 20% NaCl (500 mL), dried ($MgSO_4$), and concentrated. Trituration with hexane afforded 11.65 g of **12**. The mother liquors were chromatographed (Waters Prep500A) with 10% ethyl acetate in hexane as eluant to afford an additional 10.20 g (total yield 82%) of **12**: mp 81–83 °C; ^1H NMR δ 7.24 (m, 1 H, H-2), 6.23 (d, 1 H, J = 1.6 Hz, H-3), 4.23 (br, m, 1 H, $W_{0.5}$ = 8.8 Hz, H-5), 2.68–2.55 (m, 2 H, H-7,7′), 2.43 (br s, 1 H, $W_{0.5}$ = 4.4 Hz, H-4), 2.04–1.92 (m, 2 H, H-6,6′), 0.99 (s, 9 H, $C(CH_3)_3$); IR ($CHCl_3$) 3570, 3420 cm^{-1}; LRMS, m/e 194 (M), 137 (base). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.21; H, 9.34. Found: C, 73.92; H, 9.11.

4-*tert*-Butyl-4,5,6,7-tetrahydro-5-benzofuranone (13). A 1000-mL three-neck flask fitted with a 250-mL dropping funnel, mechanical stirrer, and an internal thermometer was flame-dried, then charged with a solution of oxalyl chloride (13.4 mL, 19.5 g, 130 mmol) in methylene chloride (240 mL), and cooled to −78 °C with a dry ice/acetone bath. A solution of dimethyl sulfoxide (21.3 mL, 23.5 g, 300 mmol) in methylene chloride (55 mL) was added dropwise over 15 min while the reaction temperature was maintained below −70 °C. The mixture was allowed to stir for an additional 20 min, and then a solution of **12** (21.85 g, 112.5 mmol) was added dropwise over about 15 min. The mixture was stirred at −78 °C for 1 h, and then triethylamine (freshly distilled from CaH_2, 87 mL, 625 mmol) was added dropwise over about 20 min. During the addition the reaction temperature increased to −50 °C. The cooling bath was removed and the white suspension allowed to warm to room temperature over 1 h. The reaction was then poured into water (900 mL), and the layers were separated. The aqueous layer was reextracted with methylene chloride (300 mL), and the combined organic layers were extracted sequentially with 2 N HCl (500 mL), 5% $NaHCO_3$ (1000 mL) and 20% NaCl (1000 mL), dried ($MgSO_4$), and concentrated to a dark oil. Chromatography (Waters Prep 500A) with 10% ethyl acetate in hexane as eluant afforded **13** (17.70 g, 81.8%) as a pale yellow oil, which slowly darkened upon prolonged standing. **13**: bp 100–105 °C (0.2 mmHg); ^1H NMR δ 7.35 (d, 1 H, J = 1.8 Hz, H-2), 6.27 (d, 1 H, J = 1.8 Hz, H-3), 3.22–2.52 (m, 5 H, H-4,6,6′,7,7′), 1.02 (s, 9 H, $C(CH_3)_3$); IR ($CHCl_3$) 1710 cm^{-1}; LRMS, m/e 192 (M), 136 (base). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.98; H, 8.39. Found C, 75.01; H, 8.55.

4-*tert*-Butyl-5-benzofuranol (1). A mixture of **13** (1.00 g, 5.2 mmol) and sulfur (0.167 g, 1 equiv) in a sealable tube was flushed with nitrogen, sealed, and heated to 225 °C for 30 min. An additional portion of sulfur (0.030 g) was then added and the mixture heated an additional 15 min. After cooling the total reaction mixture was taken up in a small portion of methylene chloride and applied directly to a flash silica gel column. Elution with 5% ethyl acetate in hexane gave **1** (0.520 g, 52%). An analytical sample was prepared by sublimation at 55 °C and 0.2 mmHg. **1**: mp 53–56 °C; ^1H NMR δ 7.52 (d, 1 H, J = 2.1 Hz, H-2), 7.20 (dd, 1 H, J = 8.5, 1.0 Hz, H-7), 7.10 (dd, 1 H, J = 2.1, 1.0 Hz, H-3), 6.65 (d, 1H, J = 8.5 Hz, H-6), 4.69 (s, 1 H, OH), 1.59 (s, 9 H, $C(CH_3)_3$); IR (CCl_4) 3530 cm^{-1}; LRMS, m/e 190 (M), 175 (base), 147. Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.42; H, 7.71.

4-*tert*-Butyl-2,3-dihydro-5-benzofuranol (2). To a solution of **1** (0.660 g, 3.47 mmol) in acetic acid (20 mL) was added 10% palladium-on-carbon (0.130 g) and the mixture hydrogenated overnight at 40 psi. The reaction mixture was taken up in ether (25 mL) and filtered through a bed of Celite to remove the catalyst. The filtrate and washings were diluted with water (100 mL) and ether (50 mL) and the layers separated. The aqueous layer was washed with an additional portion of ether (50 mL), and the combined extracts were washed sequentially with 5% $NaHCO_3$ (3 × 50 mL), water (50 mL), and 20% NaCl (50 mL), and then dried ($MgSO_4$), and concentrated. Purification by flash chromatography with 5% ethyl acetate in hexane as eluant gave pure **2** (0.515 g, 77%): mp 184–185 °C; ^1H NMR δ 6.52 (d, 1 H, J = 8.2 Hz, H-6(7)), 6.46 (d, 1 H, J = 8.2 Hz, H-7(6)), 4.43 (t, 2 H, J = 8.5 Hz, H-2,2′), 4.40 (s, 1 H, OH), 3.44 (t, 2 H, J = 8.5 Hz, H-3,3′), 1.48 (9 H, s, $C(CH_3)_3$); IR ($CHCl_3$) 3600, 3500–3250 cm^{-1}; LRMS, m/e 192 (M), 177 (base), 150, 149, 135. Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.05; H, 8.42.

4-*tert*-Butyl-5-benzofuranol-6-carboxaldehyde (9). To a solution of ethyl formate (28.8 g, 389 mmol) in toluene (185 mL) was added sodium hydride (97%, 4.66 g, 194 mmol), and to the resulting suspension was added dropwise a solution of **13** (12.5 g, 65.0 mmol) over 30 min (gas evolution). The mixture was allowed to stir at room temperature for 90 min and then quenched by the dropwise addition of 5% H_2SO_4 (160 mL). The mixture was diluted with ether (200 mL), and the layers were separated. The aqueous layer was extracted with ether (2 × 100 mL), and the combined organic layers were washed with 20% NaCl (500 mL), dried ($MgSO_4$), and concentrated to a dark oil. The residue was taken up in benzene (240 mL) and DDQ (15.79 g, 69.55 mmol) was added in portions. The mixture was allowed to stir for 45 min at room temperature at which point a precipitate had separated. The reaction mixture was filtered and concentrated to a black tar. The tar was taken up in chloroform (50 mL) and diluted with hexane (100 mL). The tarry solid which separated was removed by filtration and the filtrate concentrated and chromatographed (Waters Prep 500A, 5% ethyl acetate in hexane as eluant) to afford **9** as a yellow solid (9.4 g, 66%): mp 77–78 °C; ^1H NMR δ 11.65 (s, 1 H, OH), 9.88 (s, 1 H, CHO), 7.72 (d, 1 H, J = 2.4 Hz, H-2), 7.52 (d, 1 H, J = 0.8 Hz, H-7), 7.21 (dd, 1 H, J = 2.4, 0.8 Hz, H-3), 1.63 (s, 9 H, $C(CH_3)_3$); IR ($CHCl_3$) 3080, 1645, 1625 cm^{-1}; LRMS, m/e 218 (M), 203 (base), 175, 147, 136, 108. Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.56; H, 6.47. Found: C, 71.32; H, 6.49.

Addition and Substitution Reactions of Chloropyrimidines with Lithium Reagents

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Pyrimidines bearing halogeno substituents at activated positions 2, 4, and 6 are a cornerstone to diverse modifications of the pyrimidine ring. The polyhalogenated compounds undergo regioselective and stepwise substitutions with common nucleophiles such as hydroxide ion, alkoxides, mercaptides, and amines.[1] These reactions have produced many biologically active derivatives including compounds, synthesized in this laboratory, that enhance the activity of known anticancer agents.[2]

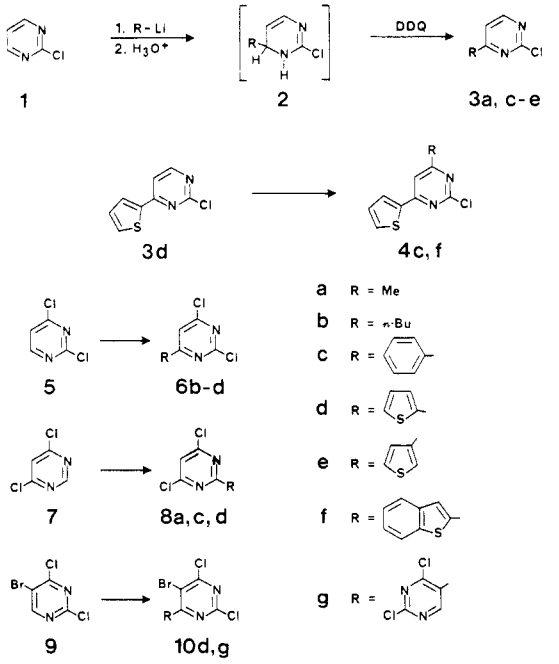
Halogenopyrimidines are normally obtained from hydroxypyrimidines; several other less convenient methods are also known.[1a] Few studies have been devoted to the synthesis of substituted halogenopyrimidines via the dis-

(1) (a) For an excellent review, see: Brown, D. J. *The Pyrimidines*; Interscience: New York, 1985. (b) Strekowski, L. *Roczn. Chem.* **1975**, *49*, 1017.

(2) (a) Strekowski, L.; Mokrosz, J. L.; Tanious, F. A.; Watson, R. A.; Harden, D.; Mokrosz, M.; Edwards, W. D.; Wilson, W. D. *J. Med. Chem.* **1988**, *31*, 1231. (b) Strekowski, L.; Chandrasekaran, S. Wang, Y.-H.; Edwards, W. D.; Wilson, W. D. *J. Med. Chem.* **1986**, *29*, 1311.

0022-3263/88/1953-4137$01.50/0

Scheme I

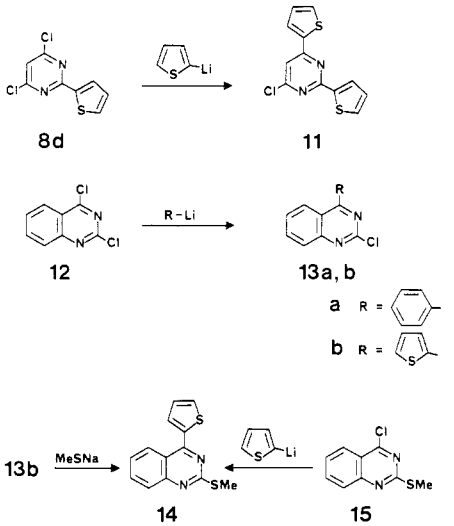


placement of hydrogen[3] or one of the halogens in readily available simple 2-, 4-, and 6-halogenopyrimidines by the action of organometallic reagents. The reactions with Grignard reagents proved to be of no synthetic value. The nickel-catalyzed reactions of the Grignard reagents gave extensive coupling in most cases studied.[4] (2-Thienyl)lithium was reacted with 2-bromo- and 2-chloropyrimidine[5] to give an addition product to the N1=C6 bond of the pyrimidine. These dihydro derivatives were aromatized in low yield by treatment with potassium permanganate in acetone.

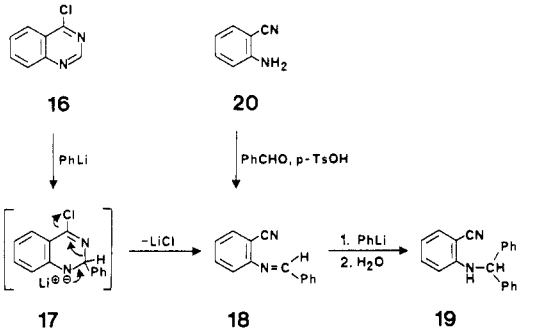
We wish to report that the reactions of organolithium reagents with chloropyrimidines provide a basis for a simple and highly efficient method for modification of the pyrimidine ring. In general, the addition of the nucleophilic group to the formal azomethine moiety occurs if the C=N bond bears no substituent. The nucleophilic addition to the activated position bearing the chlorine followed by the elimination of the chlorine takes place only if all azomethine bonds are substituted. Selected examples of the many successful reactions conducted in this laboratory and the scope and limitations of the method are discussed below.

The addition reactions are illustrated in Scheme I. In a typical preparation, the reaction mixture of 2-chloropyrimidine (**1**) with a lithium reagent is quenched with 1 molar equiv of acetic acid and the resultant dihydro product **2**, without isolation, is treated immediately with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ). The dehydrogenation step is completed within 5 min at room temperature, and the yields of isolated pure products **3** are high (79–84%). Products **3** without a substituent at position 6 can be substituted further in a similar way, as exemplified by the synthesis of **4c** and **4f** from **3d**. A similar sequence of addition–oxidation reactions with 2,4-dichloropyrimidine (**5**) produced 6-substituted derivatives **6** in exceptionally high yields of 85–93%. 4,6-Dichloropyrimidine (**7**) undergoes the addition of a nucleophilic group at position 2 to yield 2-substituted products **8**.[6] The addition of (2-thienyl)lithium to 5-bromo-2,4-dichloropyrimidine (**9**) followed by oxidation of the intermediate dihydro product with DDQ gave **10d** as expected. However, treatment of **9** with 1 molar equiv of (*n*-butyl)lithium followed by quenching of the mixture with acetic acid gave 2,4-dichloropyrimidine (**5**) in a 95% yield. This result indicates that the competitive bromine–lithium exchange reaction between **9** and (*n*-butyl)lithium is faster than the additionof the nucleophile to the azomethine bond in **9**. When **9** is treated with 0.5 equiv of (*n*-butyl)lithium, the resultant 5-lithio derivative undergoes a smooth addition to **9** to give, after oxidation, the bipyrimidine **10g** in an 83% yield.

Scheme II



Scheme III



A selective substitution of the chlorine atom at position 4(6) takes place with 2,4,6-trisubstituted pyrimidines (Scheme II). Thus, the reaction of (2-thienyl)lithium with 1 equiv of **8d** gave monosubstituted product **11** in a 70% yield. A disubstituted product was not found. Apparently, the increased electron density in the pyrimidine ring of **11** in comparison to that of **8d** renders the former com-

(3) The substitution of hydrogen in electron-deficient azaaromatics by the action of nucleophilic agents can formally be regarded as a hydride ion replacement. In the vast majority of cases these reactions proceed via a two-stage mechanism involving addition and elimination promoted by an oxidizing agent. For a recent review, see: Chupakin, O. N.; Charushin, V. N.; van der Plas, H. C. *Tetrahedron* **1988**, *44*, 1.

(4) (a) Elmoghayar, M. R. H.; Groth, P.; Undheim, K. *Acta Chem. Scand., Ser. B* **1983**, *B37*, 109. (b) Elmoghayar, M. R. H.; Undheim, K. *Acta Chem. Scand., Ser. B* **1983**, *B37*, 160. (c) Yamanaka, H.; Edo, K.; Shoji, F.; Konno, S.; Sakamoto, T.; Mizugaki, M. *Chem. Pharm. Bull.* **1978**, *26*, 2160.

(5) (a) Gronowitz, S.; Roe, J. *Acta Chem. Scand.* **1965**, *19*, 1741. (b) Brown, D. J.; Cowden, W. B.; Strekowski, L. *Aust. J. Chem.* **1982**, *35*, 1209.

(6) Regioselectivity of the nucleophilic addition to N1=C6 vs N1=C2 in 4-chloropyrimidine could not be studied because this derivative is highly unstable and decomposes completely within a few minutes after liberation from the hydrochloride: Boarland, M. P. V.; McOmie, J. F. W. *J. Chem. Soc.* **1951**, 1218. Pyrimidine itself undergoes a regioselective addition to N1=C6; for a review, see ref 7.

pound less reactive toward a nucleophilic attack.[7] The reaction of organolithium reagents with 2,4-dichloroquinazoline (**12**) is regioselective, resulting in the predominant substitution of the chlorine at position 4. The yields of products **13a** and **13b** were 69% and 76%, respectively. Careful analysis of the reaction mixtures revealed the absence of the corresponding 4-chloro isomers. This result can be explained in terms of a competitive ring opening in the σ-complex resulting from the nucleophilic attack at position 2 as in **17** (see below). The structure of **13b** was proven by its transformation to **14** and independent synthesis of **14** from the known derivative **15**.[8]

In contrast to the successful addition and coupling reactions discussed above, the reaction of 4-chloroquinazoline (**16**) with phenyllithium resulted in ring opening to give 2-[(benzylidene)amino]benzonitrile (**18**) and 2-[(diphenylmethyl)amino]benzonitrile (**19**) as the minor and major product, respectively (Scheme III). The structure of **18** was proven by independent synthesis from 2-aminobenzonitrile (**20**) and benzaldehyde.[9] Treatment of **18** with phenyllithium gave **19** in a 92% yield,[10] identical in all respects with the major product of the reaction of 4-chloroquinazoline. It appears, therefore, that **18** is the precursor for the formation of **19** in the reaction of 4-chloroquinazoline with phenyllithium.[11] Compound **18** may be formed by ring opening in the σ-complex **17**, which results from the attack of the lithium reagent at position 2 in 4-chloroquinazoline. We have thus shown that the addition of a lithium reagent to the unsubstituted position 2 is preferred over substitution of chlorine at position 4 in the pyrimidine ring of quinazoline.

In quinazoline chemistry a similar ring opening[11] has been observed in the reactions of 4-chloroquinazoline with lithium piperidide in piperidine and potassium amide in liquid ammonia,[12] and in the reactions of 4-(alkylthio)-quinazolines with alkali.[13] In the latter cases, however, ring opening occurs only when an electron-withdrawing substituent is present in position 6 or 8, which stabilizes the intermediate formed by the attack of hydroxide ion at position 2.[13a] A ring opening has also been observed in the reaction of 1-methyl-4-(methylthio)quinazolinium iodide with sodium hydroxide.[13b]

Experimental Section

2-Chloropyrimidine (**1**), 2,4-dichloropyrimidine (**5**), and 4,6-dichloropyrimidine (**7**) were obtained from Aldrich. 5-Bromo-2,4-dichloropyrimidine[14] (**9**), 2,4-dichloroquinazoline[15] (**12**), 4-chloro-2-(methylthio)quinazoline[16] (**15**), and 4-chloroquinazoline[17] (**16**) were prepared as described. Methyllithium (1.4 M in ether), (*n*-butyl)lithium (2.6 M in hexanes), and phenyllithium (1.8 M in cyclohexane/ether) were obtained from Aldrich. (2-Benzo[*b*]thienyl)lithium and (2-thienyl)lithium in ether were generated from benzo[*b*]thiophene (6.05 g, 45 mmol) and thiophene (3.6 mL, 45 mmol), respectively, by treatment with (*n*-butyl)lithium (10 mL, 26 mmol) at 0 °C for 15 min.[5b] (3-Thienyl)lithium in ether (50 mL) was generated from 3-bromothiophene (2.4 mL, 25 mmol) and (*n*-butyl)lithium (10 mL, 26 mmol) at −30 °C. Ether was distilled from sodium benzophenone ketyl immediately before use. All air-sensitive reactions were conducted under an atmosphere of high-purity nitrogen. ^{1}H NMR spectra were recorded on a Varian EM360 (60 MHz) spectrometer in a $CDCl_3$ solution with Me_4Si as an internal standard.

General Procedure for the Preparation of 3, 4, 6, and 8. A solution of 2-chloropyrimidine (**1**), 2-chloro-4-(2-thienyl)pyrimidine (**3d**), 2,4-dichloropyrimidine (**5**), or 4,6-dichloropyrimidine (**7**) (25 mmol) in ether (75 mL) was cooled to −30 °C and treated dropwise with methyllithium, (*n*-butyl)lithium, or phenyllithium (26 mmol). Alternatively, a solution of (2-benzo[*b*]thienyl)lithium, (2-thienyl)lithium, or (3-thienyl)lithium was treated at −30 °C with a solution of the respective chloropyrimidine. The resultant mixture was stirred at −30 °C for 30 min and then at 0 °C for 30 min, quenched with a solution of acetic acid (1.6 mL, 26 mmol) and water (0.25 mL, 14 mmol) in tetrahydrofuran (5 mL), and treated with a solution of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ, 5.9 g, 26 mmol) in tetrahydrofuran (25 mL). The mixture was stirred at room temperature for 5 min, cooled to 0 °C, treated with a cold aqueous solution of sodium hydroxide (3 M, 10 mL, 30 mmol), and stirred at 0 °C for 5 min. The organic layer was dried over anhydrous sodium sulfate, decolorized with charcoal or silica gel, and concentrated to give a crystalline residue (**3c–e**, **4c,f**, **6c,d**, and **8a,c,d**) or an oil (**3a** and **6b**). The solid products were crystallized from hexane or hexane/toluene (8:2).

2-Chloro-4-methylpyrimidine (3a; from **1** and methyllithium): yield 84%; bp 65 °C/0.01 mmHg (lit.[18] bp 101 °C/23 mmHg).

2-Chloro-4-phenylpyrimidine (3c; from **1** and phenyllithium): yield 82%; mp 84–86 °C (lit.[18] mp 87–89 °C).

2-Chloro-4-(2-thienyl)pyrimidine (3d; from **1** and (2-thienyl)lithium): yield 79%; mp 128–129 °C (lit.[5b] mp 125–127 °C).

2-Chloro-4-(3-thienyl)pyrimidine (3e; from **1** and (3-thienyl)lithium): yield 80%; mp 127–129 °C; NMR δ 7.28 (t, 1 H, J = 4 Hz), 7.92 (d, 1 H, J = 4 Hz), 8.0 (d, 1 H, J = 5 Hz), 8.13 (d, 1 H, J = 4 Hz), 8.72 (d, 1 H, J = 5 Hz). Anal. Calcd for $C_8H_5ClN_2S$: C, 48.85; H, 2.56; N, 14.24. Found: C, 49.00; H, 2.51; N, 14.40.

2-Chloro-4-phenyl-6-(2-thienyl)pyrimidine (4c; from **3d** and phenyllithium): yield 70%; mp 129–131 °C; NMR δ 7.05 (t, 1 H, J = 4 Hz), 7.4 (m, 4 H), 7.67 (s, 1 H), 7.87 (d, 1 H, J = 4 Hz), 7.90 (m, 2 H). Anal. Calcd for $C_{14}H_9ClN_2S$: C, 61.63; H, 3.33; N, 10.27. Found: C, 61.81; H, 3.25; N, 10.35.

2-Chloro-6-(2-benzo[*b*]thienyl)-4-(2-thienyl)pyrimidine (4f; from **3d** and (2-benzo[*b*]thienyl)lithium): yield 53%; mp 188–189 °C; NMR δ 7.33 (m, 5 H), 7.63 (s, 1 H), 7.77 (m, 2 H), 8.07 (s, 1 H). Anal. Calcd for $C_{16}H_9ClN_2S_2$: C, 58.44; H, 2.76; N, 8.52. Found: C, 58.36; H, 2.77; N, 8.40.

6-(*n*-Butyl)-2,4-dichloropyrimidine (6b; from **5** and (*n*-butyl)lithium): yield 93%; bp 80 °C/0.1 mmHg; NMR δ 0.9 (t, 3 H, J = 7 Hz), 1.5 (m, 4 H), 2.7 (t, 2 H, J = 6 Hz), 7.17 (s, 1 H). Anal. Calcd for $C_8H_{10}Cl_2N_2$: C, 46.90; H, 4.91; N, 13.66. Found: C, 46.98; H, 4.94; N, 13.70.

2,4-Dichloro-6-phenylpyrimidine (6c; from **5** and phenyllithium): yield 92%; mp 85–86 °C (lit.[4a] mp 83–86 °C).

2,4-Dichloro-6-(2-thienyl)pyrimidine (6d; from **5** and (2-thienyl)lithium): yield 85%; mp 107–108 °C; NMR δ 7.03 (t, 1

(7) Unfused heterocyclic systems composed of electron-deficient and electron-excessive aromatics are extensively polarized with the electron density transferred from the π-excessive to π-deficient subunit: Kaufmann, T. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 1.

(8) The halogen atom in **13a** or **13b** is also replaced by alkoxide ions and amines to produce the respective 2-substituted quinazolines in 60–80% yields. In contrast, the reaction of **13a** with 1 equiv of phenyllithium (25 °C, 1 h) gave a complicated mixture of products. 2,4-Diphenylquinazoline was not formed, as shown by comparison of the authentic sample[10] with the mixture using TLC and NMR. The ^{1}H NMR spectrum of the mixture gave no absorption in the region δ 7.5–8.5 characteristic for the quinazoline system, indicating opening and/or saturation of the pyrimidine ring. 2,4-Disubstituted quinazolines are conveniently prepared from anthranilonitrile.[10]

(9) Bergman, J.; Brynolf, A.; Vuorinen, E. *Tetrahedron* **1986**, *42*, 3689.

(10) Careful analysis of the reaction mixture revealed absence of products that might be formed from a nucleophilic addition to the nitrile moiety in **18**. The complete chemoselectivity of this reaction is remarkable. It has been reported that phenylmagnesium bromide adds to the nitrile moiety in **18**: Bergman, J.; Brynolf, A.; Elman, B.; Vuorinen, E. *Tetrahedron* **1986**, *42*, 3697.

(11) Compound **18** was also obtained in a 98% yield in the reaction of **16** with 1 equiv of phenylmagnesium bromide in ethyl ether (35 °C, 2 h).

(12) De Valk, J.; van der Plas, H. C.; Jansen, F.; Koudijs, A. *Recl. Trav. Chim. Pays-Bas* **1973**, *92*, 460.

(13) (a) Taylor, E. C.; Knopf, R. J.f Cogliano, J. A.; Barton, J. W.; Pfeiderer, W. *J. Am. Chem. Soc.* **1960**, *82*, 6058. (b) Fry, D. J.; Kendall, J. D.; Morgan, A. J. *J. Chem. Soc.* **1960**, 5062.

(14) Mulvey, D. M.; Babson, R. D.; Zawoiski, S.; Ryder, M. A. *J. Heterocycl. Chem.* **1973**, *10*, 79.

(15) Butler, K.; Partridge, M. W. *J. Chem. Soc.* **1959**, 1512.

(16) Seth, M.; Khomma, N. M. *Indian J. Chem., Sect. B.* **1976**, *14B*, 536.

(17) Endicott, M. M.; Wick, E.; Mercury, M. L.; Sherrill, M. L. *J. Am. Chem. Soc.* **1946**, *68*, 1299.

(18) Matsukawa, T.; Ohta, B. *J. Phram. Soc. Japn.* **1950**, *70*, 134.

H, J = 5 Hz), 7.33 (s, 1 H), 7.5 (d, 1 H, J = 5 Hz), 7.67 (d, 1 H, J = 5 Hz). Anal. Calcd for $C_8H_4Cl_2N_2S$: C, 41.57; H, 1.74; N, 12.12. Found: C, 41.71; H, 1.80; N, 12.08.

4,6-Dichloro-2-methylpyrimidine (**8a**; from **7** and methyllithium): yield 85%; mp 45–46 °C (lit.[19] mp 45–45.5 °C).

4,6-Dichloro-2-phenylpyrimidine (**8c**; from **7** and phenyllithium): yield 68%; mp 95–97 °C (lit.[20] mp 97–98 °C).

4,6-Dichloro-2-(2-thienyl)pyrimidine[21] (**8d**; from **7** and (2-thienyl)lithium): yield 77%; mp 129–130 °C; NMR δ 7.1 (s, 1 H), 7.15 (t, 1 H, J = 4 Hz), 7.5 (d, 1 H, J = 4 Hz), 8.0 (d, 1 H, J = 4 Hz).

5-Bromo-2,4-dichloro-6-(2-thienyl)pyrimidine (10d). A solution of (2-thienyl)lithium (26 mmol) in ether (75 mL) was cooled to −45 °C and treated dropwise with a solution of 5-bromo-2,4-dichloropyrimidine (**9**, 5.7 g, 25 mmol) in ether (10 mL). The mixture was stirred at −40 °C for 1 h, quenched at −20 °C with a mixture of acetic acid (1.5 mL, 26 mmol) and methanol (1.2 mL, 30 mmol), and then treated at −20 °C with a solution of DDQ (5.9 g, 26 mmol). Workup as described above gave 5.81 g of **10d** (75%): mp 123–124 °C; NMR δ 7.13 (t, 1 H, J = 4 Hz), 7.57 (d, 1 H, J = 4 Hz), 8.35 (d, 1 H, J = 4 Hz). Anal. Calcd for $C_8H_3BrCl_2N_2S$: C, 30.99; H, 0.98; N, 9.04. Found: C, 31.08; H, 1.04; N, 8.99.

5-Bromo-2,2′,4′,6-tetrachloro-4,5′-bipyrimidine (10g). (*n*-Butyl)lithium (5 mL, 13 mmol) was added dropwise within 5 min to a solution of 5-bromo-2,4-dichloropyrimidine (**9**, 5.3 g, 26 mmol) in ether (125 mL), maintained at −70 °C and stirred. The mixture, containing a yellow precipitate, was then stirred at −45 °C for 30 min, quenched at −45 °C with a mixture of acetic acid (0.75 mL, 13 mmol) and methanol (0.7 mL, 17 mmol), stirred at −45 °C until the yellow precipitate disappeared (5–10 min), and treated at −45 °C with a solution of DDQ (2.95 g, 13 mmol) in tetrahydrofuran (100 mL). Treatment of the mixture with aqueous sodium hydroxide (3 M, 5 mL, 15 mmol) at 0 °C was followed by workup as described above to give 4.04 g (83%) at **10g**: mp 136–138 °C; NMR δ 8.66 (s, H-5). Anal. Calcd for $C_8HBrCl_4N_4$: C, 25.63; H, 0.27; N, 14.95. Found: C, 25.72; H, 0.35; N, 15.01.

General Procedure for the Preparation of 11, 13a,b, and 14. A solution of 4,6-dichloro-2-(2-thienyl)pyrimidine (**8d**), 2,4-dichloroquinazoline (**12**), or 4-chloro-2-(methylthio)quinazoline (**15**) (25 mmol) in ether (10 mL) was added dropwise to a solution of the respective lithium reagent (26 mmol) in ether (50 mL) at 0 °C. The resultant mixture was stirred at room temperature for 1 h, quenched with water (0.5 mL, 28 mmol), dried over anhydrous sodium sulfate, and decolorized by passing through a short column (10 cm) packed with charcoal or silica gel. Evaporation of the ether was followed by crystallization of the residue from hexanes or hexanes/CH_2Cl_2 (8:2).

6-Chloro-2,4-di(2-thienyl)pyrimidine (**11**; from **8d** and (2-thienyl)lithium): yield 70%; mp 86–88 °C; NMR δ 7.12 (t, 2 H, J = 4 Hz), 7.29 (s, 1 H), 7.50 (m, 2 H), 7.75 (d, 1 H, J = 4 Hz), 8.03 (d, 1 H, J = 4 Hz). Anal. Calcd for $C_{12}H_7ClN_2S_2$: C, 51.70; H, 2.53. Found: C, 51.54; H, 2.58.

2-Chloro-4-phenylquinazoline (**13a**; from **12** and phenyllithium): yield 69%; mp 112–114 °C (lit.[22] mp 114–115 °C.

2-Chloro-4-(2-thienyl)quinazoline (**13b**; from **12** and (2-thienyl)lithium): yield 76%; mp 107–108 °C; NMR δ 7.23 (t, 1 H, J = 4 Hz), 7.67 (m, 2 H), 7.90 (m, 3 H), 8.47 (d, 1 H, J = 8 Hz). Anal. Calcd for $C_{12}H_7ClN_2S$: C, 58.40; H, 2.86; N, 11.35. Found: C, 58.33; H, 2.89; N, 11.28.

2-(Methylthio)-4-(2-thienyl)quinazoline (14). A. From **15** and 2-[(benzylidene)amino]benzonitrile[9] yield 62%; mp 83–84 °C; NMR δ 2.67 (s, 3 H), 7.20 (t, 1 H, J = 4 Hz), 7.57 (m, 2 H), 7.80 (m, 3 H), 8.35 (d, 1 H, J = 8 Hz). Anal. Calcd for $C_{13}H_{10}N_2S_2$: C, 60.43; H, 3.90; N, 10.84. Found: C, 60.54; H, 3.90; N, 10.81.

B. 2-Chloro-4-(2-thienyl)quinazoline (**13b**) was reacted with sodium methyl mercaptide according to a general procedure[23] to give a 75% yield of **14**, identical with the sample obtained in the reaction of **15** with (2-thienyl)lithium, as described above.

2-[(Diphenylmethyl)amino]benzonitrile (19). A. A solution of 2-[(benzylidene)amino]benzonitrile[9] (**18**, 0.75 g, 3.63 mmol) in ether (50 mL) was treated with phenyllithium (4.0 mmol) at 0 °C, and the resultant mixture was stirred at 0 °C for 1.0 h. Quenching with water and the usual workup gave 0.95 g (92%) of **19**: mp 112–114 °C (from hexanes); IR 2220 cm^{-1} (C≡N); NMR δ 5.1 (d 1 H, J = 4 Hz, N–H, exchangeable with D_2O), 5.6 (d, 1 H, J = 4 Hz), 6.5 (d, 1 H, J = 8 Hz), 6.7 (t, 1 H, J = 8 Hz), 7.25 (t, 1 H, J = 8 Hz), 7.33 (m, 10 H), 7.45 (d, 1 H, J = 8 Hz). Anal. Calcd for $C_{20}H_{16}N_2$: C, 84.48; H, 5.67; N, 9.85. Found: C, 84.36; H, 5.75; N, 10.01.

B. Phenyllithium (21 mmol) was added dropwise at 0 °C to a solution of 4-chloroquinazoline (**16**, 3.15 g, 10 mmol) in ether (50 mL). The mixture was stirred at 0 °C for 1 h, then quenched with water, and dried over anhydrous sodium sulfate. Chromatography on silica gel (CH_2Cl_2) afforded **19** (1.54 g, 54%) and **18** (0.1 g, 5%) in order of elution.

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(19) Yanagida, S.; Ohoko, M.; Okahama, M.; Komoni, S. *J. Org. Chem.* **1969**, *34*, 2972.
(20) Yamagida, S.; Yokoe, M.; Ohoka, M.; Komoni, S. *Bull. Chem. Soc. Japn.* **1971**, *44*, 2182.
(21) For another synthesis of **8d**, see: Decroix, B.; Morel, J. *C. R. Hebd. Seances, Ser. C* **1975**, *281*, 39. The melting point is not given in this work.
(22) Schofield, K. *J. Chem. Soc.* **1952**, 1927.
(23) Windus, W.; Shildneck, P. R. *Organic Syntheses*; Wiley: New York, 1943; Collect. Vol. 2, p 345.

Synthesis of *N,N*-Dimethylnitramine by Nitrodephosphorylation of Hexamethylphosphoramide

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The large-scale synthesis of *N,N*-dimethylnitramine[1,2] poses serious safety problems resulting primarily from the formation of nitrosamine byproduct and the use of potentially explosive mixtures of nitric acid and acetic or trifluoroacetic anhydride.[3,4] In addition, the use of the highly oxidizable amide, dimethylformamide, increases the changes of thermal runaway during the nitration process. In our search for a safe, pilot-plant-scale synthesis of this material (not currently available commercially), we examined the ostensibly exothermic metathesis of a phosphoryl amine with nitric acid—in this case hexamethylphosphoramide (HMPA)—to give dimethylnitramine and phosphoric acid (eq 1). This approach utilizes amides of

$$[(CH_3)_2N]_3P{=}O + 3HONO_2 \rightarrow (HO)_3P{=}O + 3(CH_3)_2NNO_2 \quad (1)$$

phosphoric acid, rather than formic acid, thus circumventing some of the potential oxidative side reactions of *N,N*-dimethylformamide and similar carboxylic acid amides under typical nitration conditions.

This synthesis has proved viable in practice. We isolated a 200% yield of *N,N*-dimethylnitramine and only a small amount (12%) of the carcinogenic *N,N*-dimethylnitrosamine impurity when the reaction was run on roughly a half-mole scale, based on starting HMPA. The reaction was run between 0 and 10 °C; ice-bath cooling was required. The products were isolated by neutralization with

(1) Robson, J. H.; Reinhart, J. *J. Am. Chem. Soc.* **1955**, *77*, 2453.
(2) Robson, J. H.; Reinhart, J. *J. Am. Chem. Soc.* **1955**, *77*, 107.
(3) Bedford, C. D. *Chem. Eng. News* **1980**, *58*(35), 33 and 43.
(4) Coon, C. Lawrence Livermore National Laboratory, 1987 (personal communication).

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