Synthesis of 2-Chloro-4,6-di(heteroaryl)pyrimidines

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A practical method for the preparation of 2-chloro-4,6-di(heteroaryl)pyrimidines and their 5-methyl homologues from readily available 2-chloropyrimidine and 2-chloro-5-methylpyrimidine, respectively, is described. The method is based on the addition reactions of heteroaryllithium reagents with chloropyrimidines followed by dehydrogenation of the resultant substituted dihydropyrimidines. The use of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone as the dehydrogenation agent gives the best results. Side reactions in the addition step are discussed.

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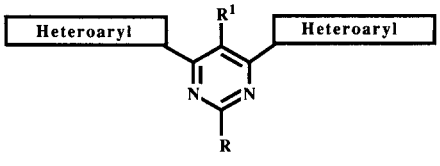
4,6-Di(heteroaryl)pyrimidines of a general structure **1** exhibit interesting properties which are strongly dependent on the type of heteroaryl groups and substituents R and R^1. For example, some compounds **1** with a cationic substituent R in combination with the anticancer drug bleomycin strongly enhance the bleomycin-mediated degradation of DNA [1], the reaction believed to be responsible for the anticancer properties of the drug. Other derivatives **1** containing a hydroxyalkyl group R are active against human immunodeficiency virus (HIV-1) *in vitro* [2]. Mechanisms of action of these bleomycin potentiators and anti-HIV-1 agents apparently involve interaction with nucleic acids [1-3]. Additional studies have suggested that new molecular probes for DNA conformation and dynamics can be developed within this class of compounds [3,4]. A limited number of available 2-chloropyrimidines **1** (R = Cl, R^1 = H) have systematically been screened for useful agricultural properties and found to be mild insecticides [5]. All these deravatives have been prepared in this laboratory by classical methods that require either a multistep synthesis or harsh conditions for the introduction of a substituent R at position 2 of the pyrimidine [3,6].



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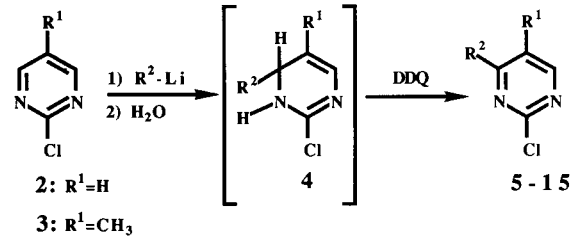
In this paper we report a facile and efficient preparation of 2-chloro-4,6-di(heteroaryl)pyrimidines **1** (R = Cl, R^1 = H or CH_3). Overall, twenty such derivatives have been obtained, with the structures **17-36** assigned to the particular compounds in the following text. Since the chlorine atom in 2-chloropyrimidines is easily replaced by common nucleophiles [7], this work provides an efficient entry into a large variety of substituted pyrimidines [8].

The method is based on previous observations that organolithium reagents tend to undergo an addition reaction to the N1 = C6 bond of a pyrimidine ring and the resultant adducts can be dehydrogenated to give 4-substituted pyrimidines. With 2-chloropyrimidine (**2**) the corresponding 4-substituted derivatives can be obtained [9-12]. However, this rather straightforward chemistry has not been used extensively because of severe experimental difficulties, especially in the dehydrogenation and isolation steps. We now present a general and experimentally simple synthetic route to substituted 2-chloropyrimidines which is based on the addition/dehydrogenation approach [12].

As shown in Scheme I, 2-chloropyrimidine (**2**) is reacted with lithium reagents R^2-Li to give the corresponding dihydropyrimidines **4**. 2-Chloro-5-methylpyrimidine (**3**) also undergoes similar addition reactions. These reactions are best conducted in ether. Adducts **4** thus obtained are dehydrogenated, without isolation, by treatment with 2,3-di-

Scheme I



2: R^1=H

3: R^1=CH_3

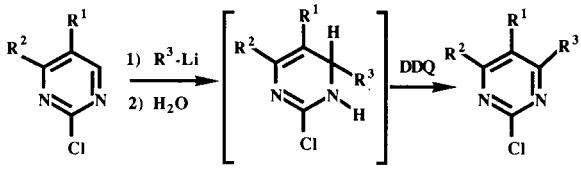
4

5 - 15

5 - 15	R^1	R^2
5	H	2-thiazolyl
6	H	1-methyl-2-pyrrolyl
7	H	2-benzo[b]furanyl
8	H	2-furanyl
9	CH_3	2-furanyl
10	H	3-furanyl
11	H	2-benzo[b]thienyl
12	H	2-thienyl
13	CH_3	2-thienyl
14	H	5-bromo-2-thienyl
15	H	3-thienyl

chloro-5,6-dicyano-1,4-benzoquinone (DDQ) to give the corresponding 2-chloro-4-heteroarylpyrimidines **5-15** in 32-91% yields [13]. Compounds **5-15** still contain one unsubstituted C=N bond and, as such, undergo the addition reaction with lithium reagents (Scheme II). Again, the resultant adducts **16** are treated, without isolation, with DDQ to give the desired 2-chloro-4,6-di(heteroaryl)pyrimidines **17-36**. With the single exception of **19** which was obtained in a disappointingly low yield of 5%, the remaining products were prepared with the efficiency of 38-92% under optimized conditions.

Scheme II



5-13, 15 16 17-36

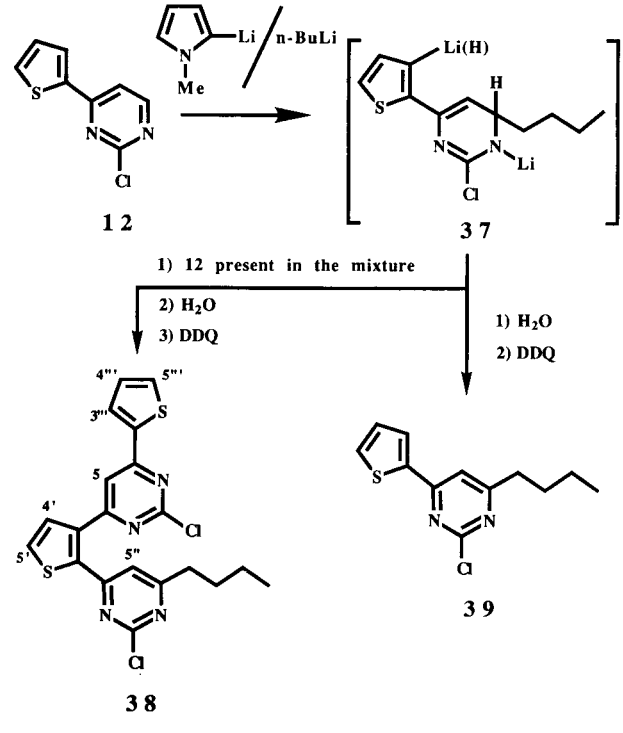
17-36	R1	R2	R3
17	H	2-thiazolyl	2-thiazolyl
18	H	2-thiazolyl	2-thienyl
19	H	1-methyl-2-pyrrolyl	1-methyl-2-pyrrolyl
20	H	1-methyl-2-pyrrolyl	2-benzo[b]furanyl
21	H	1-methyl-2-pyrrolyl	2-furanyl
22	H	1-methyl-2-pyrrolyl	2-benzo[b]thienyl
23	H	1-methyl-2-pyrrolyl	2-thienyl
24	H	2-benzo[b]furanyl	2-furanyl
25	H	2-benzo[b]furanyl	2-thienyl
26	H	2-furanyl	2-furanyl
27	CH_3	2-furanyl	2-furanyl
28	H	2-furanyl	2-benzo[b]thienyl
29	H	2-furanyl	2-thienyl
30	CH_3	2-furanyl	2-thienyl
31	H	3-furanyl	3-furanyl
32	H	3-furanyl	2-benzo[b]thienyl
33	H	2-benzo[b]thienyl	2-thienyl
34	H	2-thienyl	2-thienyl
35	CH_3	2-thienyl	2-thienyl
36	H	3-thienyl	3-thienyl

A solution of potassium permanganate in a large volume of anhydrous acetone has been used previously in the preparation of **5** and **12** from the corresponding crude adducts **4** [11]. Although the use of either permanganate or DDQ give similar results in the preparation of **12**, the application of DDQ in the synthesis of **5** is far superior to the classical oxidation method. The workup procedure is also simpler with DDQ than with permanganate as the oxidation agent. Moreover, compound **19** (Scheme II) could not be prepared when permanganate was used in the oxidation step. We have found that the dehydrogenation reactions can be conducted efficiently with DDQ replaced by 3,4,5,6-tetrachloro-1,2-benzoquinone or 2,3,5,6-tetrachloro-1,4-benzoquinone. The use of these tetrachlorobenzoquinones is not recommended, however, because of their limited solubility. DDQ, thus, is a reagent of choice to effect dehydrogenation of 2-chlorodihydropyrimidines [14].

This conclusion is strongly supported by the following studies. Thus, as a departure from our normal procedure, selected intermediate dihydropyrimidines **4** were isolated, purified by chromatography, and the purified products were treated with DDQ. These dehydrogenation reactions were virtually quantitative. The same results were obtained for aromatizations of purified dihydropyrimidines **16** with DDQ. These results demonstrate that it is the first addition step in the preparation of **5-15** and **17-36** which is accompanied by side reactions.

To understand side processes that accompany the addition reaction of lithium reagents with pyrimidines, 1-methyl-2-pyrrolyllithium was allowed to react with 2-chloro-4-(2′-thienyl)pyrimidine **12**, then the mixture was treated with DDQ and analyzed. This preparation was chosen because it produced the desired product **23** in a modest yield only. The same problem was encountered in most other syntheses with 1-methyl-2-pyrrolyllithium. It was hoped, therefore, that study of this model reaction would allow a general understanding of side reactions that compete with and/or follow the addition reaction of the lithium reagent with a pyrimidine ring.

Scheme III



Analysis of the reaction products revealed, in addition to **23**, a complicated mixture of polymeric materials. This

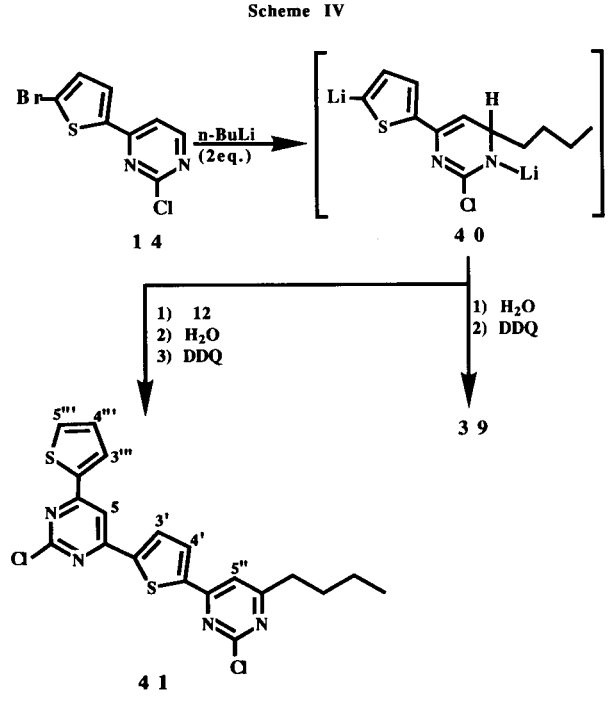
mixture could not be separated into components by chromatography. It appeared to us that the formation of polymeric materials could be a result of secondary lithiation reactions of compounds present in the mixture followed by the addition reactions of these lithiated compounds with pyrimidines. The result of the subsequent experiment conducted with a mixture of **12**, 1-methyl-2-pyrrolyllithium, and *n*-butyllithium is consistent with this hypothesis (Scheme III). After a usual workup, in addition to **23**, two new major products **38** and **39** were isolated by chromatography. While **39** is the expected alkyl analog of **23**, the structure of **38** is quite unusual but fully confirmed by low- and high-resolution mass spectrometry and high-field proton nmr including nOe and decoupling experiments. When the mixture was allowed to react for a relatively short period of time before quenching and subsequent treatment with DDQ, compound **39** was the major low molecular product. Substitution of deuterium oxide for water in this experiment resulted in **39** partly deuterated at position 3′ of the thiophene, as shown by proton nmr spectroscopy.

These results can be explained as follows. An addition of *n*-butyllithium with the pyrimidine ring of **12** and a lithiation reaction of the thiophene portion at position 3′ produce initially a dilithio derivative **37**, a precursor to **39**. The intermediate product **37** may also undergo the addition reaction with **12**. The resultant adduct is then dehydrogenated upon treatment with DDQ to furnish the tetracyclic product **38**. An important role of the butyl substituent is that it cannot be lithiated. This lack of reactivity greatly reduces further transformations of intermediate butyl-substituted dihydropyrimidines. Moreover, the presence of a hydrophobic butyl group in the aromatized product **38** facilitates chromatographic separation of **38** from more polar polycyclic products.

The formation of the intemediate 3′-thienyllithium derivative **37** is quite interesting because thiophene itself is regioselectively lithiated at position 2(5). Apparently, the N3 of the pyrimidine in **12** or N3 of the dihydropyrimidine in the butylated adduct of **12** form initially a complex with a lithium reagent, thus allowing a regioselective lithium transfer to the 3′ position of the adjacent thiophene. The resultant 3′-thienyllithium derivative **37** is also expected to be stabilized by interaction with the N3 of the dihydropyrimidine. A related regioselective nitrogen atom-mediated lithiation reaction has been reported by Kauffmann [15].

The isomeric 5′-thienyllithium derivative **40** was generated from 4-(5′-bromo-2′-thienyl)-2-chloropyrimidine **14** and *n*-butyllithium (Scheme IV). The reagent **40** was allowed to react with 2-chloro-4-(2′-thienyl)pyrimidine **12** before quenching the mixture and subsequent treatment with DDQ to give a butyl derivative **39** and a new tetracyclic compound **41** as the major, low molecular products. Compound **41** was fully characterized by spectral methods, as discussed for its isomer **38**.

Scheme IV



14 40 39 41

With the two isomers in hand we have shown using chromatography that compound **41**, synthesized according to Scheme IV, is not produced under the conditions of Scheme III. This result, in turn, demonstrates high regioselectivity of the lithiation reaction at position 3′ of the 2-thienyl substituent.

We, thus, believe that lithium-transfer reactions from 1-methyl-2-pyrrolyllithium to the position 3′ of **6**, **7**, **8**, **11** and **12**, and then followed by addition reactions of the resultant secondary reagents with pyrimidines are responsible for the relatively inefficient preparations of the corresponding pyrrolylpyrimidines **19**, **20**, **21**, **22** and **23**. It is reasonable to assume that other heteroaryllithium reagents used in this work can also promote similar side reactions [16]. The data given in the Experimental are consistent with the extent of such secondary lithium-transfer reactions and subsequent addition reactions being dependent on the structures of heteroarylpyrimidines **5-15** and heteroaryllithium reagents used in the preparation of **17-36**.

EXPERIMENTAL

2-Chloropyrimidine **2** (Aldrich) and 2-chloro-5-methylpyrimidine **3** [17] were crystallized from hexanes/dichloromethane (8:2) before use. All reactions with organolithium reagents were conducted in ether or ether/tetrahydrofuran under static pressure of nitrogen. These solvents were distilled from sodium benzophenone ketyl immediately before use. The glassware was dried at

140°, assembled hot, and cooled in a stream of nitrogen. The liquids were transferred with syringes. Hetarenes for preparation of their lithium derivatives were dried with freshly activated (250°/1 mm Hg) molecular sieves 3A. 2-Thiazolyllithium, 3-furanyllithium, 5-bromo-2-thienyllithium, and 3-thienyllithium in ether (25 ml) were generated in the bromine-lithium exchange reaction of 2-bromothiazole, 3-bromofuran, 2,5-dibromothiophene, and 3-bromothiophene (13 mmoles), respectively, with *n*-butyllithium (Aldrich, 2.6 *M* in hexanes, 5 ml, 13 mmoles) at −45° [11, 12, 18]. 2-Benzo[*b*]thienyllithium and 2-thienyllithium in ether (25 ml) were generated by treatment of benzo[*b*]thiophene or thiophene (25 mmoles), respectively, with *n*-butyllithium (5 ml, 13 mmoles) at 0° for 15 minutes [11, 12, 18]. Similar lithiation reactions of benzo[*b*]furan and furan (50 mmoles) with *n*-butyllithium (13 mmoles) were successful when the mixtures in ether/tetrahydrofuran (2:1, 25 ml) were allowed to react at −5° for 1 hour [15]. The lithiation reaction of 1-methylpyrrole (5 ml, 68 mmoles) with *n*-butyllithium (13 mmoles) to produce 1-methyl-2-pyrrolyllithium reagent was conducted in ether/tetrahydrofuran (2:1, 25 ml) at −10° for 2 hours. The large excess of 1-methylpyrrole is essential to ensure complete consumption of *n*-butyllithium. 1-Methylpyrrole was also lithiated in ether in the presence of *N,N,N',N'*-tetramethylethylenediamine [19]. These two methods gave essentially the same results in the prepration of compound **6**.

Melting points (Pyrex capillary) are uncorrected. Mass spectra (70 eV) were recorded on a Varian MAT spectrometer. Unless stated otherwise, ^{1}H nmr spectra were obtained on a Varian VXR-400 (400 MHz) spectrometer at 25°. The spectra were taken in deuteriochloroform solutions (0.05 *M*) with tetramethylsilane as an internal standard. The nOe and decoupling experiments for proton assignments were also conducted on this spectrometer.

The proton assignments using nOe were facilitated by our previous observations [19-21] that 4-(2'-thienyl)pyrimidine and 4-(1'-methyl-2'-pyrrolyl)pyrimidine systems exist in *s-cis* equilibrium conformation in solution. For all compounds containing these unfused systems, irradiation of H5 of the pyrimidine resulted in a strong nOe at H3' of the five-membered heterocycle. In the same way irradiation of H3' resulted in strong nOe's to H4' of the same ring and H5 of the pyrimidine. Similar effects were observed for compounds comprised of 5-methyl-4-(2'-thienyl)pyrimidine [21] or 4-(2'-benzo[*b*]thienyl)pyrimidine. 2'-Furanyl and 2'-benzo[*b*]furanyl derivatives, which apparently do not favor the s-cis equilibrium conformation [20], gave weaker but also unambiguous nOe enhancements for the H5-H3' interactions.

General Procedure for Preparation of 2-Chloro-4-(heteroaryl)pyrimidines **5-15**.

A solution of a heteroaryllithium reagent R^2-Li, prepared with 13 mmoles of *n*-butyllithium as described above, was treated dropwise at −30° with a solution of **2** or **3** (12 mmoles) in ether (30 ml) and the resultant mixture was stirred at −30° for 30 minutes. Then the temperature was allowed to rise to 0° during 1 hour, within which time the progress of the reaction was monitored by tlc on silica gel (hexanes/dichloromethane, 1:1). As soon as **2** or **3** was consumed, the mixture was quenched with water (0.27 ml, 15 mmoles) in tetrahydrofuran (3 ml), and treated with a solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 3 g, 13 mmoles) in tetrahydrofuran (15 ml) to effect aromatization of intermediate dihydropyrimidine **4**. The mixture was stirred at 25° for 15 minutes, cooled to 0°, treated with hexanes (10 ml) and then with a cold aqueous solution of sodium hydroxide (3 *M*, 10 ml, 30 mmoles), and stirred at 0° for 5 minutes. The organic layer was dried with anhydrous sodium sulfate and then concentrated to give a crystalline residue of **5-15**. Products **5-15** were purified on a short chromatography column (a standard glass filter) packed with dry silica gel (15 g) with hexanes/dichloromethane (1:4) as an eluent. Final crystallization from hexanes/dichloromethane or hexanes/toluene furnished analytically pure **5-15**.

2-Chloro-4-(2'-thiazolyl)pyrimidine, **5**.

This compound had mp 153-155° (reported [11] mp 153-155°), yield 83%.

2-Chloro-4-(1'-methyl-2'-pyrrolyl)pyrimidine, **6**.

This compound had mp 110-112°, yield 67%, ^{1}H nmr: δ 4.08 (s, Me), 6.22 [dd, H4', H(3'-4') = 4.0 Hz, J(4'-5') = 2.4 Hz], 6.85 [dd, H5', J(3'-5') = 1.6 Hz, J(4'-5') = 2.4 Hz], 6.90 [dd, H3', J(3'-4') = 4.0 Hz, J(3'-5') = 1.6 Hz], 7.35 [d, H5, J(5-6) = 5.6 Hz], 8.38 [d, H6, J(5-6) = 5.6 Hz]; ms: m/e 192 (100), 193 (68, M$^+$), 194 (39), 195 (22, M$^+$).

Anal. Calcd. for $C_9H_8ClN_3$: C, 55.83; H, 4.16. Found: C, 55.94; H, 4.12.

4-(2'-Benzo[*b*]furanyl)-2-chloropyrimidine, **7**.

This compound had mp 192-193°, yield 38%; ^{1}H nmr: δ 7.32 [t, H6', J(5'-6') = J(6'-7') = 7.6 Hz], 7.44 (dd, H5', J(4'-5') = 8.0 Hz, J(5'-6') = 7.6 Hz], 7.58 [d, H4', J(4'-5') = 8.0 Hz], 7.71 (d, H7', J(6'-7') = 7.6 Hz], 7.74 [d, H5, J(5-6) = 5.2 Hz], 7.76 (s, H3'), 8.68 [d, H6, J(5-6) = 5.2 Hz]; ms: m/e 230 (100, M$^+$), 231 (15), 232 (34, M$^+$).

Anal. Calcd. for $C_{12}H_7ClN_2O$: C, 62.48; H, 3.06. Found: C, 62.36; H, 3.09.

2-Chloro-4-(2'-furanyl)pyrimidine, **8**.

This compound had mp 102-104°, yield 91%; ^{1}H nmr: δ 6.61 [dd, H4', J(3'-4') = 3.6 Hz, J(4'-5') = 1.8 Hz], 7.39 [d, H3', J(3'-4') = 3.6 Hz], 7.53 [d, H5, J(5-6) = 5.4 Hz], 7.63 [d, H5', J(4'-5') = 1.8 Hz], 8.59 [d, H6, J(5-6) = 5.4 Hz]; ms: m/e 180 (100, M$^+$), 181 (19), 182 (33, M$^+$).

Anal. Calcd. for $C_8H_5ClN_2O$: C, 53.20; H, 2.79. Found: C, 53.30; H, 2.76.

2-Chloro-4-(2'-furanyl)-5-methylpyrimidine, **9**.

This compound had mp 88-90°, yield 63%; ^{1}H nmr: δ 2.54 (s, Me), 6.62 [dd, H4', J(3'-4') = 3.6 Hz, J(4'-5') = 1.6 Hz], 7.36 [d, H3', J(3'-4') = 3.6 Hz], 7.70 [d, H5', J(4'-5') = 1.6 Hz], 8.41 (s, H6); ms: m/e 194 (100, M$^+$), 195 (17), 196 (35, M$^+$).

Anal. Calcd. for $C_9H_7ClN_2O$: C, 55.54; H, 3.63. Found: C, 55.63; H, 3.68.

2-Chloro-4-(3'-furanyl)pyrimidine, **10**.

This compound had mp 87-89°, yield 67%; ^{1}H nmr: δ 6.90 [d, H4', J(4'-5') = 1.6 Hz], 7.30 [d, H5, J(5-6) = 5.2 Hz], 7.53 [d, H5', J(4'-5') = 1.6 Hz], 8.21 (s, H2'), 8.54 [d, H6, J(5-6) = 5.2 Hz]; ms: m/e 180 (100, M$^+$), 181 (32), 182 (35, M$^+$).

Anal. Calcd. for $C_8H_5ClN_2O$: C, 53.20; H, 2.79. Found: C, 53.01; H, 2.86.

4-(2'-Benzo[*b*]thienyl)-2-chloropyrimidine, **11**.

This compound had mp 203-205°, yield 32%; ^{1}H nmr: δ 7.43

(m, 2H), 7.59 [d, H5, J(5-6) = 5.2 Hz], 7.88 (m, 2H), 8.12 (s, H3'), 8.60 [d, H6, J(5-6) = 5.2 Hz]; ms: m/e 246 (100, M⁺), 247 (19), 248 (43, M⁺).

Anal. Calcd. for $C_{12}H_7ClN_2S$: C, 58.42; H, 2.86. Found: C, 58.56; H, 2.90.

2-Chloro-4-(2'-thienyl)pyrimidine, **12**.

This compound had mp 128-129° (reported [11] mp 125-127°), yield 79%.

2-Chloro-5-methyl-4-(2'-thienyl)pyrimidine, **13**.

This compound had mp 99-100°, yield 74%; ^{1}H nmr: δ 2.55 (s, Me), 7.21 [dd, H4', J(3'-4') = 3.6 Hz, J(4'-5') = 5.2 Hz], 7.62 [d, H5', J(4'-5') = 5.2 Hz], 7.80 [d, H3', J(3'-4') = 3.6 Hz], 8.41 (s, H6); ms: m/e 209 (100), 210 (94, M⁺), 211 (46), 212 (36, M⁺).

Anal. Calcd. for $C_9H_7ClN_2S$: C, 51.31; H, 3.35. Found: C, 51.24; H, 3.39.

4-(5'-Bromo-2'-thienyl)-2-chloropyrimidine, **14**.

This compound had mp 143-144°, yield 58%; ^{1}H nmr: δ 7.14 [d, H4', J(3'-4') = 4.0 Hz], 7.39 [d, H5, J(5-6) = 5.2 Hz], 7.56 [d, H3', J(3'-4') = 4.0 Hz], 8.55 [d, H6, J(5-6) = 5.2 Hz]; ms: m/e 195 (100, M⁺-Br), 197 (37, M⁺-Br), 274 (65, M⁺), 276 (86, M⁺), 278 (25, M⁺).

Anal. Calcd. for $C_8H_4BrClN_2S$: C, 34.87; H, 1.46. Found: C, 35.01; H, 1.50.

2-Chloro-4-(3'-thienyl)pyrimidine, **15**.

This compound had mp 92-93°, yield 87%; ^{1}H nmr: δ 7.45 [dd, H5', J(2'-5') = 3.2 Hz, J(4'-5') = 5.2 Hz], 7.48 [d, H5, J(5-6) = 5.4 Hz], 7.69 [dd, H4', J(2'-4') = 1.2 Hz, J(4'-5') = 5.2 Hz], 8.22 [dd, H2', J(2'-4') = 1.2 Hz, J(2'-5') = 3.2 Hz], 8.59 [d, H6, J(5-6) = 5.4 Hz]; ms: m/e 161 (33), 195 (16), 196 (100, M⁺), 197 (15), 198 (36, M⁺).

Anal. Calcd. for $C_8H_5ClN_2S$: C, 48.85; H, 2.56. Found: C, 49.00; H, 2.51.

Preparation of 2-Chloro-4,6-di(heteroaryl)pyrimidines **17-36**.

The addition reactions of lithium reagents R^3-Li with pyrimidines **5-15**, the subsequent dehydrogenation reactions with DDQ, and purification of the resultant products **17-36** were conducted as described above for the preparation of **5-15**.

2-Chloro-4,6-di(2'-thiazolyl)pyrimidine, **17**.

This compound had mp 232-234°, yield 68%; ^{1}H nmr (60 MHz): δ 7.67 [d, H5', J(4'-5') = 3.0 Hz], 8.10 [d, H4', J(4'-5') = 3.0 Hz], 8.87 (s, H5); ms: m/e 280 (100, M⁺), 281 (35), 282 (41, M⁺).

Anal. Calcd. for $C_{10}H_5ClN_4S_2$: C, 42.78; H, 1.80. Found: C, 42.90; H, 1.84.

2-Chloro-4-(2'-thiazolyl)-6-(2"-thienyl)pyrimidine, **18**.

This compound had mp 206-207°, yield 75% (**5** and 2-thienyllithium), yield 47% (**12** and 2-thiazolyllithium); ^{1}H nmr: δ 7.19 [dd, H4", J(3"-4") = 3.9 Hz, J(4"-5") = 5.4 Hz], 7.61 [dd, H5", J(3"-5") = 1.0 Hz, J(4"-5") = 5.4 Hz], 7.62 [d, H5', J(4'-5') = 2.9 Hz], 7.95 [dd, H3", J(3"-4") = 3.9 Hz, J(3"-5") = 1.0 Hz], 8.04 [d, H4', J(4'-5') = 2.9 Hz], 8.27 (s, H5); ms: m/e 279 (100, M⁺), 280 (21), 281 (41, M⁺).

Anal. Calcd. for $C_{11}H_6ClN_3S_2$: C, 47.22; H, 2.16. Found: C, 47.33; H, 2.12.

2-Chloro-4,6-bis(1'-methyl-2'-pyrrolyl)pyrimidine, **19**.

This compound was obtained as an oil, yield 5%; ^{1}H nmr: δ 4.07 (s, Me), 6.20 [dd, H4', J(3'-4') = 4.0 Hz, J(4'-5') = 2.44 Hz], 6.81 [dd, H5', J(3'-5') = 1.6 Hz, J(4'-5') = 2.4 Hz), 6.84 [dd, H3', J(3'-4') = 4.0 Hz, J(3'-5') = 1.6 Hz], 7.49 (s, H5); ms: m/e 271 (100), 272 (75, M⁺), 273 (44), 274 (25, M⁺).

High resolution ms. Calcd. for $C_{14}H_{13}{}^{35}ClN_4$: m/e 272.0829. Found: m/e 272.0832.

Anal. Calcd. for $C_{14}H_{13}ClN_4$: C, 61.65; H, 4.80. Found: C, 61.40; H, 4.71.

6-(2"-Benzo[*b*]furanyl)-2-chloro-4-(1'-methyl-2'-pyrrolyl)pyrimidine, **20**.

This compound had mp 162-163°, yield 53% (**6** and 2-benzo[*b*]furanyllithium), yield 15% (**7** and 1-methyl-2-pyrrollithium); ^{1}H nmr: δ 4.12 (s, Me), 6.26 [dd, H4', J(3'-4') = 4.0 Hz, J(4'-5') = 2.4 Hz], 6.88 [dd, H5', J(3'-5') = 1.6 Hz, J(4'-5') = 2.4 Hz], 7.07 [dd, H3', J(3'-4') = 4.0 Hz, J(3'-5') = 1.6 Hz], 7.30 (m, H6"), 7.42 (m, H5"), 7.59 (m, H4"), 7.69 [d, H3", J(3"-4') = 0.8 Hz], 7.70 (m, H7"), 7.87 (s, H5); ms: m/e 308 (100), 309 (72, M⁺), 310 (49), 311 (25, M⁺).

Anal. Calcd. for $C_{17}H_{12}ClN_3O$: C, 65.92; H, 3.91. Found: C, 65.83; H, 3.95.

2-Chloro-6-(2"-furanyl)-4-(1'-methyl-2'-pyrrolyl)pyrimidine, **21**.

This compound had mp 126-128°, yield 38% (**8** and 1-methyl-2-pyrrolyllithium), yield 11% (**6** and 2-furanyllithium); ^{1}H nmr: δ 4.09 (s, Me), 6.23 [dd, H4', J(3'-4') = 4.0 Hz, J(4'-5') = 2.4 Hz], 6.59 [dd, H4", J(3"-4") = 3.6 Hz, J(4"-5") = 1.6 Hz], 6.85 [dd, H5', J(3'-5') = 1.8 Hz, J(4'-5') = 2.4 Hz], 6.97 [dd, H3', J(3'-4') = 4.0 Hz, J(3'-5') = 1.8 Hz], 7.31 [dd, H3", J(3"-4") = 3.6 Hz, J(3"-5") = 0.8 Hz], 7.61 [dd, H5", J(3"-5") = 0.8 Hz, J(4"-5") = 1.6 Hz], 7.66 (s, H5); ms: m/e 258 (100), 259 (55, M⁺), 260 (39), 261 (18, M⁺).

Anal. Calcd. for $C_{13}H_{10}ClN_3O$: C, 60.12; H, 3.88. Found: C, 60.01; H, 3.92.

6-(2"-Benzo[*b*]thienyl)-2-chloro-4-(1'-methyl-2'-pyrrolyl)pyrimidine, **22**.

This compound had mp 169-171°, yield 48% (**6** and 2-benzo[*b*]thienyllithium), yield 14% (**11** and 1-methyl-2-pyrrollithium); ^{1}H nmr (60 MHz): δ 4.08 (s, Me), 6.27 (m, H4'), 6.88 (m, H5'), 7.00 (m, H3'), 7.40 (m, 3H), 7.70 (s, H5), 7.85 (m, 2H), 8.12 (s, H3"); ms: m/e 324 (100), 325 (66, M⁺), 326 (48), 327 (24, M⁺).

Anal. Calcd. for $C_{17}H_{12}ClN_3S$: C, 62.67; H, 3.71. Found: C, 62.55; H, 3.75.

2-Chloro-4-(1'-methyl-2'-pyrrolyl)-6-(2"-thienyl)pyrimidine, **23**.

This compound had mp 108-109°, yield 40% (**6** and 2-thienyllithium), yield 19% (**12** and 1-methyl-2-pyrrollithium); ^{1}H nmr: δ 4.09 (s, Me), 6.23 [dd, H4', J(3'-4') = 4.0 Hz, J(4'-5') = 2.4 Hz], 6.85 [dd, H5', J(3'-5') = 1.6 Hz, J(4'-5') = 2.4 Hz], 6.94 [dd, H3', J(3'-4') = 4.0 Hz, J(3'-5') = 1.6 Hz], 7.17 [dd, H4", J(3"-4") = 3.8 Hz, J(4"-5") = 5.2 Hz], 7.54 [dd, H5", J(3"-5") = 1.2 Hz, J(4"-5") = 5.2 Hz], 7.58 (s, H5), 7.82 [dd, H3", J(3"-4") = 3.8 Hz, J(3"-5") = 1.2 Hz].

Anal. Calcd. for $C_{13}H_{10}ClN_3S$: C, 56.62; H, 3.66. Found: C, 56.51; H, 3.69.

4-(2'-Benzo[*b*]furanyl)-2-chloro-6-(2"-furanyl)pyrimidine, **24**.

This compound had mp 188-189°, yield 80% (**7** and 2-furanyllithium), yield 56% (**8** and 2-benzo[*b*]furanyllithium); ^{1}H nmr: δ 6,.64 [dd, H4", J(3"-4") = 3.6 Hz, J(4"-5") = 1.5 Hz], 7.32 (m,

H6'), 7.43 [m, H5' and H3"), 7.60 [d, H4', J(4'-5') = 8.4 Hz), 7.68 [d, H5", J(4"-5") = 1.5 Hz], 7.70 [d, H7', J(6'-7') = 8.0 Hz], 7.75 (s, H3'), 8.03 (s, H5); ms: m/e 268 (11, M⁺-CO), 296 (100, M⁺), 297 (20), 298 (34, M⁺).

Anal. Calcd. for $C_{16}H_9ClN_2O_2$: C, 64.99; H, 3.07. Found: C, 64.84; H, 3.05.

4-(2'-Benzo[*b*]furanyl)-2-chloro-6-(2"-thienyl)pyrimidine, **25**.

This compound had mp 123-124°, yield 91% (**7** and 2-thienyllithium), yield 26% (**12** and 2-benzo[*b*]furanyllithium); ^{1}H nmr: δ 7.21 [dd, H4", J(3"-4") = 3.8 Hz, J(4"-5") = 5.0 Hz], 7.32 (m, H6'), 7.44 (m, H5'), 7.61 (m, H4' and H5"), 7.70 (m, H7'), 7.75 [d, H3', J(3'-4') = 1.2 Hz], 7.96 (s, H5), 7.97 [dd, H3", J(3"-4") = 3.8 Hz, J(3"-5") = 1.2 Hz]; ms: m/e 312 (100, M⁺), 313 (20), 314 (38, M⁺).

Anal. Calcd. for $C_{16}H_9ClN_2OS$: C, 61.44; H, 2.90. Found: C, 61.35; H, 2.93.

2-Chloro-4,6-di(2'-furanyl)pyrimidine, **26**.

This compound had mp 187-188°, yield 67%; ^{1}H nmr: δ 6.61 [dd, H4', J(3'-4') = 3.6 Hz, J(4'-5') = 1.8 Hz], 7.38 [dd, H3', J(3'-4') = 3.6 Hz, J(3'-5') = 0.8 Hz], 7.64 [dd, H5', J(3'-5') = 0.8 Hz, J(4'-5') = 1.8 Hz], 7.82 (s, H5); ms: m/e 218 (19, M⁺-CO), 245 (30), 246 (100, M⁺), 247 (27), 248 (41, M⁺).

Anal. Calcd. for $C_{12}H_7ClN_2O_2$: C, 58.43; H, 2.86. Found: C, 58.35; H, 2.89.

2-Chloro-4,6-di(2'-furanyl)-5-methylpyrimidine, **27**.

This compound had mp 122-123°, yield 77%; ^{1}H nmr: δ 2.75 (s, Me), 6.62 [dd, H4', J(3'-4') = 3.6 Hz, J(4'-5') = 1.8 Hz], 7.29 [dd, H3', J(3'-4') = 3.6 Hz, J(3'-5') = 0.8 Hz], 7.70 [dd, H5', J(3'-5') = 0.8 Hz, J(4'-5') = 1.8 Hz]; ms: m/e 203 (29, M⁺-H-2CO), 205 (13, M⁺-H-2CO), 231 (41, M⁺-H-CO), 233 (15, M⁺-H-CO), 259 (19), 260 (100, M⁺), 261 (30), 262 (45, M⁺).

Anal. Calcd. for $C_{13}H_9ClN_2O_2$: C, 59.90; H, 3.48. Found: C, 60.03; H, 3.52.

6-(2"-Benzo[*b*]thienyl)-2-chloro-4-(2'-furanyl)pyrimidine, **28**.

This compound had mp 194-196°, yield 84% (**8** and 2-benzo[*b*]-thienyllithium), yield 84% (**11** and 2-furanyllithium); ^{1}H nmr: δ 6.63 [dd, H4', J(3'-4') = 3.6 Hz, J(4'-5') = 1.8 Hz], 7.42 (m, 3H), 7.66 [dd, H5', J(3'-5') = 0.8 Hz, J(4'-5') = 1.8 Hz], 7.86 (s, H5), 7.88 (m, 2H), 8.17 (s, H3"); ms: m/e 312 (100, M⁺), 313 (21), 314 (38, M⁺).

Anal. Calcd. for $C_{16}H_9ClN_2OS$: C, 61.44; H, 2.90. Found: C, 61.52; H, 2.94.

2-Chloro-4-(2'-furanyl)-6-(2"-thienyl)pyrimidine, **29**.

This compound had mp 169-171°, yield 85% (**8** and 2-thienyllithium), yield 75% (**12** and 2-furanyllithium); ^{1}H nmr: δ 6.62 [dd, H4', J(3'-4') = 3.6 Hz, J(4'-5') = 1.6 Hz], 7.19 [dd, H4", J(3"-4") = 3.6 Hz, J(4"-5") = 5.2 Hz], 7.39 [dd, H3', J(3'-4') = 3.6 Hz, J(3'-5') = 0.8 Hz], 7.59 [dd, H5", J(3"-5") = 1.2 Hz, J(4"-5") = 5.2 Hz], 7.64 [dd, H5', J(3'-5') = 0.8 Hz, J(4'-5') = 1.6 Hz], 7.76 (s, H5), 7.89 [dd, H3", J(3"-4") = 3.6 Hz, J(3"-5") = 1.2 Hz]; ms: m/e 227 (14, M⁺-Cl), 234 (12, M⁺-CO), 261 (18), 262 (100, M⁺), 263 (24), 264 (45, M⁺).

Anal. Calcd. for $C_{12}H_7ClN_2OS$: C, 55.08; H, 2.70. Found: C, 54.84; H, 2.73.

2-Chloro-4-(2'-furanyl)-5-methyl-6-(2"-thienyl)pyrimidine, **30**.

This compound had mp 92-93°, yield 65% (**13** and 2-furanyllithium), yield 42% (**8** and 2-thienyllithium); ^{1}H nmr: δ 2.75 (s, Me), 6.62 [dd, H4', J(3'-4') = 3.6 Hz, J(4'-5') = 1.6 Hz], 7.19 [dd, H4", J(3"-4") = 3.8 Hz, J(4"-5") = 5.2 Hz], 7.30 [dd, H3', J(3'-4') = 3.6 Hz, J(3'-5') = 0.8 Hz], 7.59 [dd, H5", J(3"-5") = 1.0 Hz, J(4"-5") = 5.2 Hz], 7.67 [dd, H3", J(3"-4") = 3.8 Hz, J(3"-5") = 1.0 Hz], 7.69 [dd, H5', J(3'-5') = 0.8 Hz, J(4'-5') = 1.6 Hz]; ms: m/e 247 (20, M⁺-H-CO), 275 (80), 276 (100, M⁺), 277 (44), 278 (38, M⁺).

Anal. Calcd. for $C_{13}H_9ClN_2OS$: C, 56.42; H, 3.28. Found: C, 56.57; H, 3.31.

2-Chloro-4,6-di(3'-furanyl)pyrimidine, **31**.

This compound had mp 146-148°, yield 91%; ^{1}H nmr: δ 6.93 [dd, H4', J(2'-4') = 0.8 Hz, J(4'-5') = 2.0 Hz], 7.35 (s, H5), 7.55 [dd, H5', J(2'-5') = 1.6 Hz, J(4'-5') = 2.0 Hz], 8.24 [dd, H2', J(2'-5') = 1.6 Hz, J(2'-4') = 0.8 Hz]; ms: m/e 218 (36, M⁺-CO), 220 (12, M⁺-CO), 246 (100, M⁺), 247 (17), 248 (37, M⁺).

Anal. Calcd. for $C_{12}H_7ClN_2O_2$: C, 58.43; H, 2.86. Found: C, 58.32; H, 2.90.

6-(2"-Benzo[*b*]thienyl)-2-chloro-4-(3'-furanyl)pyrimidine, **32**.

This compound had mp 160-162°, yield 90% (**11** and 3-furanyllithium), yield 85% (**10** and 2-benzo[*b*]thienyllithium); ^{1}H nmr: δ 6.97 [dd, H4', J(2'-4') = 1.0 Hz, J(4'-5') = 1.8 Hz], 7.43 (m, H5" and H6"), 7.57 [dd, H5', J(2'-5') = 1.5 Hz, J(4'-5') = 1.8 Hz], 7.61 (s, H5), 7.87 (m, H4"), 7.89 (m, H7"), 8.16 [d, H3", J(3"-4") = 0.6 Hz], 8.28 [dd, H2', J(2'-4') = 1.0 Hz, J(2'-5') = 1.5 Hz]; ms: m/e 312 (100, M⁺), 313 (21), 314 (39, M⁺).

Anal. Calcd. for $C_{16}H_9ClN_2OS$: C, 61.44; H, 2.90. Found: C, 61.31; H, 2.92.

4-(2'-Benzo[*b*]thienyl)-2-chloro-6-(2"-thienyl)pyrimidine, **33**.

This compound had mp 188-189°, yield 87% (**11** and 2-thienyllithium), yield 53% (**12** and 2-benzo[*b*]thienyllithium); ^{1}H nmr: δ 7.21 [dd, H4", J(3"-4") = 3.8 Hz, J(4"-5") = 5.0 Hz], 7.43 (m, H5' and H6'), 7.61 [dd, H5", J(3"-5") = 1.2 Hz, J(4"-5") = 5.0 Hz], 7.78 (s, H5), 7.89 (m, H4' and H7'), 7.92 [dd, H3", J(3"-4") = 3.8 Hz, J(3"-5") = 1.2 Hz], 8.17 (s, H3'); ms: m/e 293 (13, M⁺-Cl), 328 (100, M⁺), 329 (21), 330 (44, M⁺).

Anal. Calcd. for $C_{16}H_9ClN_2S_2$: C, 58.44; H, 2.76. Found: C, 58.50; H, 2.81.

2-Chloro-4,6-di(2'-thienyl)pyrimidine, **34**.

This compound had mp 195-196°, yield 72%; ^{1}H nmr: δ 7.19 [dd, H4', J(3'-4') = 3.8 Hz, J(4'-5') = 5.2 Hz], 7.59 [dd, H5', J(3'-5') = 1.2 Hz, J(4'-5') = 5.2 Hz], 7.67 (s, H5), 7.88 [dd, H3', J(3'-4') = 3.8 Hz, J(3'-5') = 1.2 Hz]; ms: m/e 243 (30, M⁺-Cl), 278 (100, M⁺), 279 (21), 280 (47, M⁺).

Anal. Calcd. for $C_{12}H_7ClN_2S_2$: C, 51.70; H, 2.53. Found: C, 51.81; H, 2.55.

2-Chloro-5-methyl-4,6-di(2'-thienyl)pyrimidine, **35**.

This compound had mp 120-122°, yield 75%; ^{1}H nmr: δ 2.76 (s, Me), 7.20 [dd, H4', J(3'-4') = 3.8 Hz, J(4'-5') = 5.2 Hz], 7.60 [dd, H5', J(3'-5') = 1.2 Hz, J(4'-5') = 5.2 Hz], 7.68 [dd, H3', J(3'-4') = 3.8 Hz, J(3'-5') = 1.2 Hz]; ms: m/e 291 (100), 292 (100, M⁺), 293 (57), 294 (43, M⁺).

Anal. Calcd. for $C_{13}H_9ClN_2S_2$: C, 53.30; H, 3.09. Found: C, 53.38; H, 3.09.

2-Chloro-4,6-di(3'-thienyl)pyrimidine, **36**.

This compound had mp 143-144°, yield 92%; ^{1}H nmr: δ 7.44 [dd, H5', J(2'-5') = 2.8 Hz, J(4'-5') = 5.2 Hz], 7.65 (s, H5), 7.70 [dd, H4', J(2'-4') = 1.2 Hz, J(4'-5') = 5.2 Hz], 8.21 [dd, H2', J(2'-4') = 1.2 Hz, J(2'-5') = 2.8 Hz]; ms: m/e 243 (37, M$^+$-Cl), 277 (17), 278 (100, M$^+$), 279 (21), 280 (42, M$^+$).

Anal. Calcd. for $C_{12}H_7ClN_2S_2$: C, 51.70; H, 2.53. Found: C, 51.62; H, 2.56.

Preparation of Compounds **38** and **39**.

A mixture of 1-methylpyrrole and *n*-butyllithium was allwoed to react under standard conditions but only for 30 minutes before treatment with **12** and then with DDQ. A standard workup as described above was followed by chromatography on silica gel (hexanes/dichloromethane, 7:3) to give, in order of elution, **39**, **23** (8%), and **38**.

4-[2'-(6"-Butyl-2"-chloro-4"-pyrimidinyl)-3'-thienyl]-2-chloro-6-(2'''-thienyl)pyrimidine, **38**.

This compound had mp 110-112°, yield 10%; ^{1}H nmr: δ 0.83 (t, Me, J = 7.2 Hz), 1.29 (sext., CH_2, J = 7.2 Hz), 1.55 (m, CH_2), 2.67 (t, CH_2, J = 7.6 Hz), 7.17 [dd, H4''', J(3'''-4''') = 4.0 Hz, J(4'''-5''') = 5.0 Hz], 7.20 (s, H5"), 7.46 [d, H5', J(4'-5') = 5.2 Hz], 7.60 [dd, H5''', J(3'''-5''') = 1.2 Hz, J(4'''-5''') = 5.0 Hz], 7.60 (s, H5), 7.62 [d, H4', J(4'-5) = 5.2 Hz], 7.78 [dd, H3''', J(3'''-4''') = 4.0 Hz, J(3'''-5''') = 1.2 Hz]; ms: m/e 369 (25), 371 (11), 404 (100, M$^+$-C_3H_6), 405 (23), 406 (75, M$^+$-C_3H_6), 407 (16), 408 (17, M$^+$-C_3H_6), 446 (12, M$^+$), 448 (8, M$^+$), 450 (2, M$^+$).

High resolution ms. Calcd. for $C_{20}H_{16}{}^{35}Cl_2N_4S_2$: m/e 446.0193. Found: m/e 446.0199.

Anal. Calcd. for $C_{20}H_{16}Cl_2N_4S_2$: C, 53.69; H, 3.61. Found: C, 53.38; H, 3.72.

4-Butyl-2-chloro-6-(2'-thienyl)pyrimidine, **39**.

This compound was obtained as an oil, yield 9%; ^{1}H nmr (60 MHz): δ 0.95 (t, Me, J = 7 Hz), 1.15-2.0 (m, CH_2CH_2), 2.80 (t, CH_2, J = 7 Hz), 7.20 [dd, H4', J(3'-4') = 3.8 Hz, J(4'-5') = 5.2 Hz], 7.32 (s, H5), 7.60 [dd, H5', J(3'-5') = 1.2 Hz, J(4'-5') = 5.2 Hz], 7.86 [dd, H3', J(3'-4') = 3.8 Hz, J(3'-5') = 1.2 Hz].

Anal. Calcd. for $C_{12}H_{13}ClN_2S$: C, 57.02; H, 5.18. Found: C, 57.21; H, 5.23.

Preparation of 4-[5'-(6"-Butyl-2"-chloro-4"-pyrimidinyl)-2'-thienyl]-2-chloro-6-(2'''-thienyl)pyrimidine, **41**.

Compound **14** and *n*-butyllithium (1.9 molar equivalents) were allowed to react under the general conditions for bromine-lithium exchange reactions given above. The mixture was treated with a solution of **12** in ether, then with DDQ, and worked-up using a standard procedure. Chromatographic separation on silica gel (hexanes/dichloromethane, 6:4) gave **39** (13%) and **41**. Compound **39** was the major low molecular product when the mixture was oxidized without prior treatment with **12**.

Product **41** had mp 245-246°, yield 22%; ^{1}H nmr: δ 0.97 (t, Me, J = 7.2 Hz), 1.45 (sext. CH_2, J = 7.2 Hz), 1.75 (m, CH_2), 2.80 (t, CH_2, J = 7.6 Hz), 7.21 [dd, H4''', J(3'''-4''') = 3.8 Hz, J(4'''-5''') = 5.2 Hz], 7.39 (s, H5"), 7.62 [dd, H5''', J(3'''-5''') = 1.2 Hz, J(4'''-5''') = 5.2 Hz], 7.72 (s, H5), 7.88 [d, H4', J(3'-4') = 4.0 Hz], 7.90 [dd, H3''', J(3'''-4''') = 3.8 Hz, J(3'''-5''') = 1.2 Hz], 7.93 [d, H3', J(3'-4') = 4.0 Hz]; ms: m/e 404 (100, M$^+$-C_3H_6), 405 (24), 406 (77, M$^+$-C_3H_6), 407 (17), 408 (20, M$^+$-C_3H_6), 446 (2, M$^+$), 448 (1.6, M$^+$), 450 (0.4, M$^+$).

High resolution ms. Calcd. for $C_{20}H_{16}{}^{35}Cl_2N_4S_2$: m/e 446.0193. Found: m/e 446.0186.

Anal. Calcd. for $C_{20}H_{16}Cl_2N_4S_2$: C, 53.69; H, 3.61. Found: C, 53.69; H, 3.66.

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