REGIOSELECTIVE SUBSTITUTION IN TRIFLYLOXYPYRIMIDINES AND CHLOROPYRIMIDINES USING ZINC AND TIN REAGENTS†

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Abstract - 2,4-Ditriflyloxy-6-methylpyrimidine has been synthesized and its ability to undergo palladium catalyzed coupling with both zinc and tin reagents studied. Similar coupling reactions with 2,4-dichloropyrimidine establish triflyloxypyrimidines as being more reactive than chloropyrimidines. NOE studies were undertaken to determine the position of the substituents. The arylzinc reagents reacted first and preferably in the 4-position of the pyrimidines.

Interest in introducing substituents into the pyrimidine nuclei often stems from their potential as physiologically active compounds, therefore methods for their synthesis have been extensively studied.[1] A technique of increasing importance in organic synthesis is carbon-carbon bond formation by the transition-metal catalyzed reaction between an organometallic reagent and an organic halide or similar electrophilic derivatives. The extension of this methodology to heterocyclic chemistry has been reviewed recently.[2,3] The use of trifluoromethanesulfonyloxy compounds (triflyloxy) in cross-coupling is gaining prominence since the pioneering work of Stille.[4] We have previously studied the synthesis of organostannylpyrimidines and their palladium-catalyzed cross-coupling reactions with organic halides.[5] More recently, we have made 2- and 4/6-trifluoromethanesulfonyloxypyrimidines (triflyloxypyrimidines) and examined their reactivity in palladium-catalyzed coupling with various organometallic compounds.[6] Examples of six-membered ring triflyloxy-heterocycles are limited and those of pyrimidines almost nonexistent. Those reported in the literature have the triflyloxy group in the benzenoid 5-position of the pyrimidine.[7] The challenge, successfully accomplished as reported here, has been to convert the very stable pyrimidine 2- and 4/6-oxo-substituents into the excellent triflyloxy leaving group. Since 2-,4- and 6-pyrimidinones can be looked upon as heteroaryl alcohols, in their tautomeric form, it was envisaged that they could be converted into triflyloxy compounds using methods similar to those for phenols.[8] Substituents could then be introduced into these positions via coupling reactions of the triflyloxy group with organometallic reagents.

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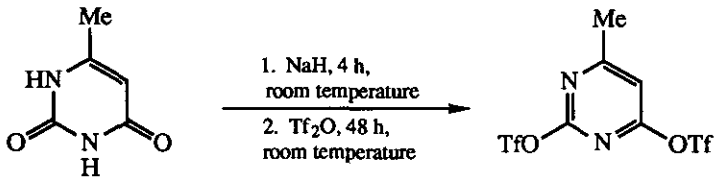
†Dedicated to Professor Edward C. Taylor on the occasion of his 70th birthday.

In the research described in this paper, 2,4-ditriflyloxy-6-methylpyrimidine (**2a**) and 2,4-dichloropyrimidine (**2b**) serve as models to discern the difference in reactivity between chloropyrimidines and the triflyloxy analogs. Discrimination between the 2- and the 4-position in each of these cases was also successfully attempted. It has previously been shown that coupling of organostannanes occurs more readily with the 4-halopyrimidines than with the 2-halocompounds.[9] Finally, the possibility of selectively introducing an organozinc reagent in one of the positions followed by an organostannyl reagent in the other, all done in a one-pot reaction, was explored.

RESULTS AND DISCUSSION

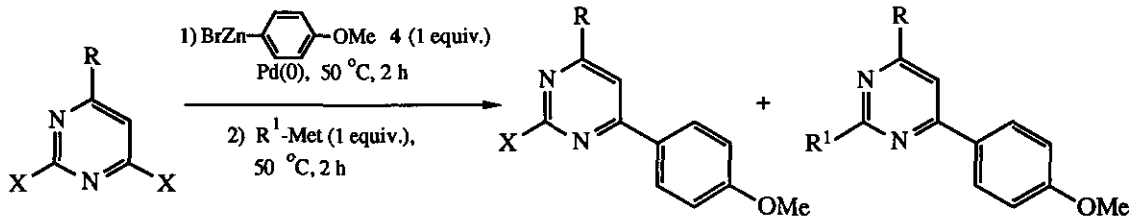
2-Triflyloxypyrimidines and 2-methylthio-4-triflyloxypyrimidine with a hydrogen present in the electron-deficient 4/6-position are unstable and are difficult to isolate in pure form.[6] Replacement of the protons in the 4/6-position with a methyl group however improved their stability and allowed isolation in almost pure form. 2,4-Ditriflyloxy-6-methylpyrimidine (**2a**) was synthesized from 6-methyluracil (**1**). Uracil derivatives are poorly soluble in methylene chloride, the solvent commonly used in triflyloxy synthesis. Despite these limitations, (**2a**) was successfully synthesized, albeit in modest yields, by first treating (**1**) with sodium hydride in methylene chloride at ambient temperature followed by triflic anhydride for 48 hours (Scheme 1).



1 **2a**

Scheme 1

The reagent p-anisylzinc bromide (**4**) was generated in situ by treating p-bromoanisole (**3**) with n-BuLi at -78 °C for one hour followed by transmetallation with zinc bromide at the same temperature for a further one hour. The results of the palladium catalyzed substitution reactions with **2a** and **2b** are summarized in Scheme 2 and Table 1.



2a: R = Me, X = OTf
b: R = H, X = Cl

5a - f **6a - f**

Scheme 2

Substrate	R^1-Met	Compd 5 (% Yield)	Compd 6 (% Yield)
2a	-	**5a** (0)	**6a** (80)[a]
2b	-	**5b** (65)	**6b** (0)[b]
2a	Thienyl-$SnBu_3$	**5a** (0)	**6c** (61)[b]
2b	Thienyl-$SnBu_3$	**5b** (41)	**6d** (48)
2a	n-BuZnBr	**5a** (0)	**6e** (71)[c]
2b	n-BuZnBr	**5b** (45)	**6f** (47)

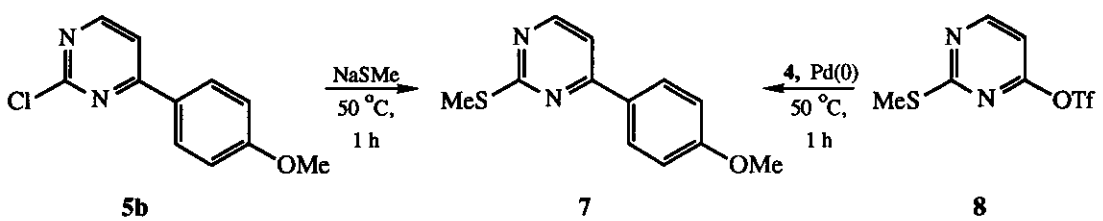
a) 2.5 equiv. of **4** were used, R^1=p-anisyl. b) Some 4-anisyl-2-butylpyrimidine (**6e**)/(**6f**) was also formed. c) Some **6a** was also formed.

Table 1

When compound (**2a**) was treated with two and a half molar equivalents of p-anisylzinc bromide (**4**), 2,4-di-anisylpyrimidine (**6a**) was obtained in 80% yield after chromatographic purification. The disubstituted molecule was the only product present as shown by a gcms analysis of the reaction mixture. Sequential treatment of the ditriflate (**2a**) with equimolar amounts of the p-anisylzinc reagent (**4**) and 2-tributylstannylthiophene gave 4-anisyl-thienylpyrimidine (**6c**) (61%) as the major product. The organo-zinc and tin reagents were added sequentially to avoid any complicating reactions between the two organometallic reagents.

Similarly sequential treatment of the 2,4-dichloropyrimidine (**2b**) with equimolar amounts of zinc and tin reagents gave the disubstituted product (**6d**). In order to compare the reactivity difference between **2a** and **2b** the reaction time was kept constant viz. 2 hours. For the chloride the thienylation was half completed as compared to full thienylation for the triflate. In the initial experiment only one equivalent of the anisylzinc reagent (**4**) was used with **2b** in which case 4-anisyl-2-chloropyrimidine (**5b**) was isolated in 65 % yield!

NOE experiments (vide infra) were performed to establish the positional identity of the product. The nmr analysis showed that the anisyl substituent in **5b** was situated in the 4-position and not in the 2-position. A further confirmation of this fact was obtained when **5b** was treated with sodium methanethiolate in dimethyl-formamide for one hour at 50 °C. The compound (**7**) thus obtained proved to be identical to a substance previously synthesized by palladium-catalyzed coupling between 2-methylthio-4-triflyloxypyrimidine (**8**) and p-anisylzinc bromide (**4**) (Scheme 3).[5]



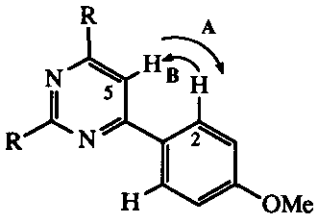
5b **7** **8**

Scheme 3

The anisylzinc reagent (**4**) was generated from 4-bromoanisole which was lithiated by butyllithium followed by metal exchange with zinc bromide. When lithiation of 4-bromoanisole had not gone to completion before addition of zinc bromide some butylzinc bromide was also present in the reaction mixture giving rise to 4-anisyl-2-butylpyrimidine as by-products as shown in Table 1 reactions 2 and 3 (vide supra). This showed that even an alkyl group could be introduced into the pyrimidine nucleus via the palladium-catalyzed reaction starting with triflyloxypyrimidines and organozinc reagents. This is a particularly interesting observation since previous attempts to introduce alkyl groups by palladium-catalyzed reactions of either alkylstannyl reagents with chloropyrimidines or the reverse, stannylpyrimidines with alkyl halides have not been very successful.[12] It is known that during the catalytic cycle, alkyl halides add to the palladium species in an oxidative addition step and, if a β-hydrogen is present, hydride elimination competes with transmetallation.[4,13] Furthermore, selective transfer of one alkyl group from a tetraalkylstannyl reagent is difficult to achieve as shown by Stille.[4] The use of alkylzinc reagents avoids the latter problem and their reaction with triflyloxypyrimidines was envisaged to provide an efficient method for the introduction of these substituents in pyrimidines. In order to test for possible differences in reactivity between the 2,4-ditriflyloxypyrimidine (**2a**) and 2,4-dichloropyrimidine (**2b**), the following experiments were performed. Each of the molecules (**2a**) and (**2b**) were treated with one molar equivalent of p-anisylzinc bromide (**4**) and one molar equivalent butylzinc bromide, both generated simultaneously and in situ from the respective lithium reagent and zinc bromide (Scheme 2). With 2,4-dichloropyrimidine (**2b**) almost equal amounts of 4-anisyl-2-chloropyrimidine (**5b**) and 4-anisyl-2-butylpyrimidine (**6f**) were formed, while 71% of 4-anisyl-2-butylpyrimidine (**6e**) and 19% 2,4-dianisylpyrimidine (**6a**) were formed from **2a**. These results clearly show that the arylzinc reagent is more reactive than the alkylzinc compound, and it couples preferentially in the more activated 4-position with both the triflyloxy- and the chloropyrimidines. While competition occurs between any excess aryl reagent and alkylzinc reagent for the 2-triflyloxy position, only the alkylzinc and not the arylzinc reacts partially with the 2-chloropyrimidine. This further emphasizes that the 2-chloro substituent is situated in the less reactive position and that any chloro substituent is less reactive than corresponding triflyloxy substituent.

In palladium-catalyzed triflyloxy-stannyl cross coupling reactions it is customary to add up to three equivalents of lithium chloride to the reaction mixture, the rationale being the need to undergo ligand exchange after oxidative addition of the triflyloxy group to the active palladium(0) catalyst.[14a,b] This was unnecessary in the above reactions, possibly because both lithium and bromide ions are found in the reaction mixture. Contrary evidence for reactions that require salts for product formation[14] and those where retardation occurs in the presence of salts[15] have been reported in the literature. In our case at least the existence of lithium and bromide ions was not detrimental.

NOE experiments on **5b** and **6a, c-f** were performed to establish the positional identity of the substituents.[11] The most diagnostic NOE effects observed were those between H-5 in the pyrimidine nucleus and H-2s in the anisyl substituent (Figure 1).[16] The large positive effects between these protons effectively proves that the anisyl substituent sits in the 4/6-position. Furthermore the NOE's of **6a** were 16% and 17% between H-5 and the H-2s in the 4-anisyl substituent, but there were no effects between H-5 and the H-2s in the 2-anisyl substituent, thus confirming the results obtained for **5a**.



NOE %,	A	B
5b	11	12
6a	17	16
6c	16	17
6d	14	6
6e	15	13
6f	11	1

Fig. 1

This synthetic study clearly illustrates that a chloro substituent in the 2-position of the pyrimidine nucleus is less reactive in coupling reactions than triflyloxy substituents and further that arylzinc reagents compete successfully with alkylzinc reagents in these reactions. In all cases, anisylzinc bromide (**4**) reacted in the 4-position and if an excess reagent remained after complete 4-substitution, the reagent then reacted further if there was an triflyloxy-substituent in the 2-position, but not with a 2-chloro substituent. The chloropyrimidine (**2b**) was found to be particularly sluggish in coupling reactions compared to the corresponding triflyloxypyrimidine (**2a**). By optimizing the conditions it is quite certain that complete selectivity can be obtained in these reactions. The high combined yields (61-92 %) in these reactions show that this methodology is a valuable addition to the existing preparative organometallic cross-coupling repertoire. In conclusion, we have successfully synthesized 2,4-ditriflyloxypyrimidine (**2a**) and shown that the 2-position of this compound is more reactive than the corresponding position of 2,4-dichloropyrimidine (**2b**) in palladium-catalyzed coupling reactions, with both zinc reagents and tin reagents.

EXPERIMENTAL

The one dimensional ^{1}H nmr spectra were recorded at 300 MHz with either a Varian XL-300 (manual) or at 200 MHz with a Varian Gemini 200 instrument. The ^{13}C nmr spectra were recorded at 75 or 50 MHz using the above mentioned spectrometers. The single (′) in the tabulation of ^{13}C nmr data refers to resonances belonging to the 4-substituent, numbering starting with the carbon attached to C-4. The (″) refers to resonances belonging to the 2-substituent, starting with the carbon attached to C-2. The difference nuclear Overhauser experiments were performed on the Varian XL-300 (manual) instrument equipped with a 5 mm ^{1}H/broad band switchable probe. The samples were dissolved in $CDCl_3$ and were deoxygenated with a flow of helium gas for several minutes, before being capped. The Overhauser experiments were run with a build-up time of 30 seconds to ensure close to steady state conditions. The relevant resonances were irradiated at low power for this period, the decoupler was then gated off, and due to instrument instability a delay (D2) of either 2 or 4 microseconds was introduced between the end of the selective irradiation and the ^{1}H broad band proton pulse, the ^{1}H broad band proton pulse was applied and followed by the FID acquisition. Between 64 and 160 FIDs were acquired. The process was repeated with the decoupler set at a frequency far from any resonance, and the FID resulting from the latter experiment was subtracted from the former. Mass spectra were recorded at 70 eV ionizing voltage. Isobutane or ammonia was used for chemical ionization (CI). Ms spectra are presented as m/z (% rel. int.). THF used in the reactions was dried by distillation over metallic sodium/benzophenone, dichloromethane was distilled over calcium hydride and DMF was first shaken with

NaOH pellets, then distilled over BaO. Zinc bromide was dried by heating at 125 °C under high vacuum for 2-4 h. Zinc bromide was weighed out and dissolved in dry THF to give a 1 M solution which was stored under nitrogen. All reactions were run under nitrogen. 6-Methyluracil (**1**), 2,4-dichloropyrimidine (**2b**), and p-bromoanisole are commercially available.[17] 2-Tributylstannylthiophene was made according to a literature procedure.[18]

2,4-Ditriflyloxy-6-methylpyrimidine[19] (**2a**). Sodium hydride (0.72g, 30 mmol) was added to a solution of 6-methyluracil (1.29 g, 10 mmol) in 50 ml CH_2Cl_2 and the resulting mixture was stirred at ambient temperature for 4 h. Triflic anhydride (5.64 g, 20 mmol) was then introduced and stirring was continued for 48 h. The reaction mixture was poured into cold saturated aqueous ammonium chloride solution, extracted with CH_2Cl_2 (2 x 50 ml), washed with water (2 x 50 ml), dried ($MgSO_4$) and further purified on a silica column using CH_2Cl_2 as the eluent. 1.21 g (31%) of the product was obtained after final bulb to bulb distillation at 125 °C / 0.005 mm Hg. ^{1}H Nmr ($CDCl_3$, 300 MHz); δ 7.13 (1H, H-5), 2.70 (3H, Me). ^{13}C Nmr ($CDCl_3$, 75 MHz); δ 177.27 (C-2), 164.30 (C-4), 156.90 (C-6), 118.87 (q, $J_{C,F}$ 118.8 Hz, CF_3), 110.93 (C-5), 25.26 (Me). Ms (EI): 390 (6, M^+), 257 (15), 176 (22), 165 (6), 108 (14), 47 (14), 83 (13), 71 (17), 69 (100).

General Procedure for Reaction with Zinc and Tin Reagents. n-Butyllithium (5 mmol) was added to a solution of p-bromoanisole (0.93 g 5 mmol) in THF (20 ml) at -78 °C under N_2. After 1 h, a solution of zinc bromide (5 ml, 1 M, 5 mmol) was added dropwise and the stirring was continued for 1 more hour at -78 °C at which time the cold bath was removed and the reaction mixture was allowed to reach room temperature. The pyrimidine substrate and tetrakis(triphenylphosphine)palladium (0.1 g, 2 mol %), both dissolved in dry THF (15 ml), were added and the resulting solution was heated at 50 °C for 2 h. The reaction mixture was cooled, and if applicable, the THF solution of tin reagent was introduced and the resulting solution was heated at 50 °C for a further 2 h. Saturated aqueous NH_4Cl (20 ml) was added and the solution was extracted with EtOAc (5 x 50 ml) and washed (H_2O, 2 x 50 ml), dried ($MgSO_4$), and evaporated. The product was purified on a silica column. If tin reagent was used then the reaction mixture was first diluted with EtOAc then treated with saturated aqueous KF solution and filtered through celite before the extraction.

2,4-Di-p-anisyl-6-methylpyrimidine (**6a**). To p-anisylzinc bromide (5 mmol), was added 2,4-ditriflyloxy-6-methylpyrimidine (**2a**) (0.78 g, 2 mmol). Hexane : EtOAc, 4 : 1 was used as eluent in the chromatographic separation. Yield 0.40 g (67 %). mp 112 °C (hexane). ^{1}H Nmr ($CDCl_3$, 200 MHz); δ 8.56 (d, J 8.99 Hz, 2H), 8.17 (J 8.99 Hz, 2H,), 7.32 (s, 1H, H-5), 7.03 (d, J 8.99 Hz, 2H), 7.02 (d, J 8.99 Hz, 2H), 3.88 (s, 3H, OMe), 3.87 (s, 3H, OMe), 2.68 (s, 3H, C_6-Me). ^{13}C Nmr ($CDCl_3$, 50 MHz); δ 167.13 (C-2), 163.84 (C-4), 163.03 (C-6), 161.73 (C-1′), 161.60 (C-1′′), 130.94 (C-4′, C-4′′), 129.87 (C-3′, C-5′), 128.59 (C-3′′, C-5′′), 114.10 (C-2′, C-6′), 113.67 (C-2′, C-6′), 112.29 (C-5), 55.30 (OMe), 24.49 (C-Me). Ms (EI): 306 (100, M^+), 291 (13), 173 (6), 158 (8), 132 (13). Anal. Calcd for $C_{19}H_{18}N_2O_2$: C 74.04, H 5.90. Found: C 74.34, H 5.85.

4-p-Anisyl-2-chloropyrimidine (**5b**). To p-anisylzinc bromide (**4**) (5 mmol) was added 2,4-dichloropyrimidine (**2b**) (0.70 g, 4.7 mmol). Hexane : EtOAc, 4 : 1 and 2 : 1 were used as eluents in the chromatographic

separation. Yield 0.68 g (65 %). mp 142 °C (hexane). ^{1}H Nmr ($CDCl_3$, 200 MHz); δ 8.55 (d, H-6, J 5.37 Hz, 1H), 8.06 (d, J 9.0 Hz, 2H), 7.56 (d, H-5, J 5.37 Hz, 1H), 7.00 (d, J 9.0 Hz, 2H), 3.88 (s, 3H, Me). ^{13}C Nmr ($CDCl_3$, 50 MHz); δ 167.10 (C-2), 163.31 (C-4), 162.23 (C-1′), 159.88 (C-6), 129.62 (C-3′, C-5′), 127.92 (C-4′), 114.97 (C-2′, C-6′), 114.62 (C-5), 55.97 (OMe). Ms (EI): 222/220 (29/100, M$^+$), 207 (7), 205 (14), 179 (8), 177 (20), 144 (1), 143 (3),142 (10), 141 (6), 116 (14), 114 (8), 89 (19), 77 (7). Anal. Calcd for $C_{11}H_9N_2OCl$: C 59.90, H 4.08. Found: C 60.07, H 4.23.

4-(p-Anisyl)-6-methyl-2-(2-thienyl)pyrimidine (**6c**). p-Anisylzinc bromide (**4**) (5 mmol) was mixed with 2,4-ditriflyloxy-6-methylpyrimidine (**2a**) (1.95 g, 5 mmol), tetrakis(triphenylphosphine)palladium, (0.1 g, 2 mol %) and the resulting solution was refluxed for 2 h. 2-Tributylstannylthiophene (1.87g, 5 mmol) was added and the reaction mixture was refluxed a further 2 h. After purification on a silica column with hexane : EtOAc 4 : 1 as eluent 2 products were isolated. 4-(p-Anisyl)-6-methyl-2-(2-thienyl)pyrimidine (**6c**) eluted first in 0.86 g (61%) yield. ^{1}H Nmr ($CDCl_3$, 200 MHz); δ 8.17 (d, J 9.0 Hz, 2H), 8.13 (dd, J 3.7 Hz, J 1.2 Hz, 1H), 7.50 (dd, J 5.0 Hz, J 1.26 Hz, 1H), 7.33 (s, 1H, H-5), 7.19 (dd, J 3.7 Hz, J 5.0 Hz, 1H), 7.04 (d, J 9.0 Hz, 2H), 3.91 (s, 3H, OMe), 2.60 (s, 3H, C_6Me). ^{13}C Nmr ($CDCl_3$, 50 MHz); δ 167.42 (C-2), 163.10 (C-4), 161.88 (C-1′), 161.03 (C-6′), 144.22 (C-2′′), 129.23 (C-3′′), 129.10 (C-4′), 128.63 (C-3′, C-5′), 128.53 (C-4′′), 127.97 (C-5′′), 114.15 (C-2′, C-6′), 112.50 (C-5), 55.35 (OMe), 24.40 (CMe). Ms (EI): 282 (100, M$^+$), 267 (7), 239(6), 173 (20), 133 (11), 132 (27), 117 (13), 109 (13) 89 (15). 4-(p-Anisyl)-2-methyl-6-butylpyrimidine (**6e**) eluted second, 24% yield (data see below).

4-(p-Anisyl)-2-(2-thienyl)pyrimidine (**6 d**). To p-anisylzinc bromide (**4**) (5 mmol) was added 2,4-dichloropyrimidine (**2b**) (0.82 g, 5.5 mmol). After 2 h, 2-tributylstannylthiophene (1.87 g, 5 mmol) was added and the solution was refluxed for a further 2 h. Two products were isolated on silica gel chromatography with hexane : EtOAc, 4 : 1. 4-(p-Anisyl)-2-(2-thienyl)pyrimidine (**6d**) eluted first, 0.64 g (48%) yield. ^{1}H Nmr ($CDCl_3$, 200 MHz); δ 8.61 (d, J 5.46 Hz, 1H, H-6), 8.12 (d, J 9.0 Hz, 2H), 8.09 (dd, J 3.26 Hz, J 1.5 Hz, 1H), 7.48 (dd, J 1.18 Hz, J 5.04 Hz, 1H), 7.36 (d, J 5.46 Hz, 1H, H-5), 7.16 (dd, J 3.19 Hz, J 5.04 Hz, 1H), 6.98 (d, J 8.95 Hz, 2H), 3.84 (s, 3H, OMe). ^{13}C Nmr ($CDCl_3$, 50 MHz); δ 163.16 (C-2), 162.03 (C-4), 161.18 (C-1′), 157.32 (C-6), 143.84 (C-2′′), 129.49 (C-3′′), 128.74 (C-4′), 128.66 (C-4′′), 128.59 (C-3′, C-5′), 128.06 (C-5′′), 114.13 (C-2′, C-6′), 112.93 (C-5), 55.26 (OMe). Ms (EI): 268 (100, M$^+$), 253 (8), 225 (6), 159 (13), 132 (35), 117 (11), 109 (17), 89 (17). The second product eluting was identified as 4-(p-anisyl)-2-chloropyrimidine (**5b**), 41% yield (spectroscopic data, see above).

4-(p-Anisyl)-2-butyl-6-methylpyrimidine (**6e**). p-Bromoanisole **3** (0.94 g, 5 mmol), n-BuLi (7 ml, 1.5 M in hexane, 10 mmol), zinc bromide (10 ml, 1 M, 10 mmol), 2,4-ditriflyloxy-6-methylpyrimidine (**2a**) (1.95 g, 5 mmol), and tetrakis(triphenylphosphine)palladium (0.1 g, 2 mol %) were reacted together as described above. Two products were obtained after separation on a silica column using CH_2Cl_2 and CH_2Cl_2 : EtOAc 4 : 1 as eluents. The first product eluting was 2,4-(p-anisyl)-6-methylpyrimidine (**6a**), 0.24 g (19%) yield. Data see above. 4-(p-Anisyl)-2-butyl-6-methylpyrimidine (**6e**) eluted second and was obtained in 0.72 g (71%) yield after bulb to bulb distillation at 180 °C/ 0.005 mm Hg. ^{1}H Nmr ($CDCl_3$, 200 MHz); δ 7.99 (d, J 9.0 Hz, 2H),

7.21 (s, 1H, H-5), 6.91 (d, J 9.0 Hz, 2H), 3.77 (s, 3H, OMe), 2.89 (br t, J 7.8 Hz, 2H, CH_2), 1.83 (m, 2H, CH_2), 1.40 (m, 2H, CH_2), 0.91 (br t, J 7.2 Hz, 3H, CH_3). ^{13}C Nmr ($CDCl_3$, 50 MHz); δ 170.98 (C-2), 166.68 (C-4), 163.07 (C-6), 161.7 (C-1′), 129.65 (C-4′), 128.49 (C-3′, C-5′), 114.02 (C-2′, C-6′), 112.28 (C-5), 55.17 (OMe), 39.34 (CH_2), 30.86 (CH_2), 24.21 (C_6-Me), 22.54 (CH_2), 13.87 (CH_3). Ms (CI): 257 (100, M+1), 256 (13, M^+), 255 (9), 227 (6), 214 (35), 184 (1), 133 (2), 124 (2). Anal. Calcd for $C_{16}H_{20}N_2O$: C 74.95, H 7.87. Found: C 74.56, H 7.63.

4-(p-Anisyl)-2-butylpyrimidine (**6f**). p-Bromoanisole (0.94 g, 5 mmol), n-BuLi (7 ml, 1.5 M in hexane, 10 mmol), zinc bromide (10 ml, 1 M, 10 mmol), 2,4-dichloropyrimidine (**2b**) (0.745 g, 5 mmol) and tetrakis(triphenylphosphine)palladium (0.1 g, 2 mol %) were reacted together as described above. Two products were obtained after silica column chromatography using CH_2Cl_2 and CH_2Cl_2 : EtOAc, 4 : 1 as eluents. 4-(p-Anisyl)-2-chloropyrimidine (**5f**) eluted first, 45% yield (spectroscopic data see above). 4-(p-Anisyl)-2-butylpyrimidine (**6f**) eluted second, 0.57 g (47%) yield. mp 246 °C (hexane). ^1H Nmr ($CDCl_3$, 200 MHz); δ 8.56 (d, J 5.41 Hz, 1H, H-6), 8.03 (d, J 8.87 Hz, 2H), 7.37 (d, J 5.38 Hz, 1H, H-5), 6.96 (d, J 9.03 Hz, 2H), 3.82 (s, 3H, OMe), 2.95 (m, 2H, CH_2), 1.82 (m, 2H, CH_2), 1.49 (m, 2H, CH_2), 0.93 (br t, J 7.3 Hz, 3H, CH_3) ^{13}C Nmr ($CDCl_3$, 50 MHz); δ 171.27 (C-2), 163.09 (C-4), 161.74 (C-1′), 156.90 (C-6), 129.32 (C-4′), 128.50 (C-3′, C-5′), 114.09 (C-2′, C-6′), 112.82 (C-5), 55.20 (OMe), 39.27 (CH_2), 30.62 (CH_2), 23.05 (CH_2), 13.86 (CH_3). Ms (CI): 243 (100, M+1), 242 (21, M^+), 241 (8), 227 (4), 223 (3), 213 (5), 200 (25), 185 (2), 167 (1), 133 (4), 110 (2). Anal. Calcd for $C_{15}H_{18}N_2O$: C 74.08, H 7.44. Found: C 73.78, H 7.29.

4-p-Anisyl-2-methylthiopyrimidine (**7**). 4-p-Anisyl-2-chloropyrimidine (**5b**) (0.22 g, 1 mmol) and sodium methanethiolate (0.07 g, 1 mmol) were dissolved in DMF (10 ml) and stirred at 50 °C for 1 h at which time no starting material remained as shown by tlc. After all the solvent was removed under high vacuum, the residue was partitioned between water and EtOAc, the organic layer was dried ($MgSO_4$) and the product was purified on silica with $CHCl_3$: EtOAc 9 : 1 as eluent to give 0.122 g (61%) of (**7**). mp 87 °C (hexane). ^1H Nmr ($CDCl_3$, 300 MHz); δ 8.53 (d, J 4.9 Hz, 1H, H-6), 8.06 (d, J 8.9 Hz, 2H), 7.27 (d, J 4.9 Hz, 1H, H-5), 6.98 (d, J 8.9 Hz, 2H), 3.86 (s, 3H, OMe), 2.63 (s, 3H, SMe). ^{13}C Nmr ($CDCl_3$, 75 MHz); δ 172.47 (C-2), 163.27 (C-4), 162.15 (C-1′), 157.29 (C-6), 128.71 (C-3′, C-5′), 114.21 (C-2′, C-6′), 110.94 (C-5), 55.40 (OMe), 14.15 (SMe). Ms (EI): 232 (100, M^+), 231 (34), 186 (30), 185 (30), 171 (25), 159 (5), 155 (6), 143 (5), 116 (6), 89 (11). Anal. Calcd for $C_{12}H_{12}N_2O$: C 71.98, H 6.04. Found: C 71.67, H 5.84.

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10. This product is formed presumably from the reaction with n-butyllithium or n-butylzinc bromide. The former was dismissed as unlikely since previous attempts by us to lithiate 2- and 4-halopyrimidines with n-BuLi have resulted in polymerization. Similar results have recently been reported; R. Radinov, C. Chanev, and M. Haimova, J. Org. Chem., 1991, 56, 4793.
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16. Long range NOE's were observed for **5b**. A negative NOE from H-5 via H'-2 to H'-3 and a small positive NOE to the methoxy group (relayed via 2 intervening nuclei) were observed, giving additional proof for the structure. Similar long range NOE's were observed for other members of this class of compounds. Other NOE's for **5b**: H-5 to H-6 (10 %), H-6 to H-5 (16 %), H'-2 to H'-3 (13 %), H'-3 to H'-2 (11 %), H'-3 to OMe (6 %). Similar effects were observed for **6a, c-f**. Compounds (**6e**) and (**6f**) showed no NOE's from the methylenes bound directly to the pyrimidines to any protons in the pyrimidine rings. Most relaxations in methyl and methylene chains take place within their own groups; c. f. ref. 10 pp. 81-85. In spite of this, small effects (less than 1 %) were observed on H-4 and H-5 from the methylene and the methyl groups at the end of the butyl chain indicating the possibility that the molecules might have preferred conformations (among others) which involves having the butyl chain

folded back on top of the flat pyrimidines. Normalized NOE percentages are reported here and in Figure 1. E. g. when saturating one proton and measuring the NOE effect on a group of equivalent protons, the observed effect is divided by the number of protons. When saturating two equivalent protons and observing the combined NOE on a single proton no data manipulation is performed since steady state is assumed. (Polarization of one proton arising from irradiation of one or several identical protons is assumed to result in the same NOE). The observation of small negative three nuclei effects and even the small positive four nuclei effect indicate that the assumption of steady state seems to be valid.

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