The Synthesis of Substituted Phenylpyrimidines via Suzuki Coupling Reactions

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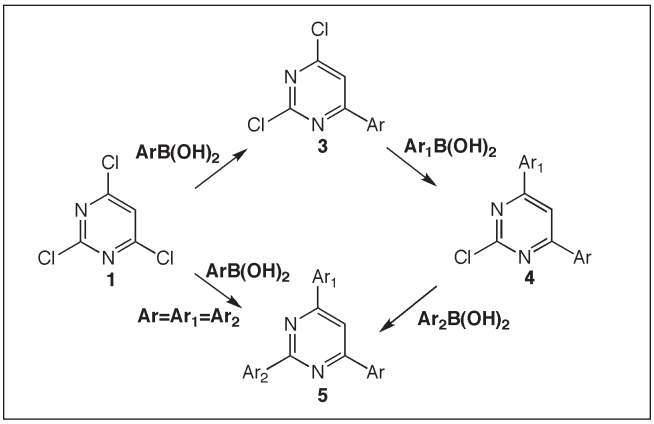

This paper describes the mon-, di-, and triarylation of the pyrimidine ring. It is possible to introduce one or more aryl rings in generally good yields and in a specific order, namely first in position 4, second in position 6, followed by position 2. A study of solvent and catalyst requirements has also been conducted.

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Introduction.

The direct arylation of the pyrimidine ring has been the subject of a limited number of approaches [1-4]. One of the more interesting arylation applications using Suzuki coupling involves resin-supported chloropyrimidines [5]. We recently described a convenient arylation of 2,4,6-trichloropyrimidine (**1**), using phenylboronic acid (**2a**) under Suzuki coupling conditions [6]. In this report the sequential displacement of the chlorines in very good yields was achieved. The selectivity for substitution was also very good following the pattern of position 4 > position 6 > position 2, suggesting that controlled multiple substitutions would be practical.

In this paper we report on our further investigations into the scope of this reaction, with emphasis on solvent, catalyst, and a variety of substituted phenylboronic acids. Much work has recently been devoted to exploring improvements in solvent systems and modified catalysts [7,8].

Results and Discussion.

Solvent.

In the previous report we identified a glyme/water medium as a suitable solvent system in order to obtain good yields of mono-, di-, and triphenyl-substituted pyrimidines [6]. Since glyme is a solvent that is prone to peroxide formation as well as being a suspected teratogen [9], we wished to explore other solvent systems. Polar protic solvents, such as methanol and ethanol, whose anions can function as good nucleophiles gave poor results in the reaction of (**1**) with phenylboronic acid (**2a**) due largely to the tendency to form ether by-products under the basic conditions required for the reaction. However use of the non-nucleophilic *t*-butyl alcohol solvent gave results comparable to those from the glyme/water solvent system.

Polar aprotic solvents such as acetonitrile, acetone, and tetrahydrofuran, as well as the halogenated polar solvents chloroform and methylene chloride, all performed well in the reactions, although the latter two solvents have their own toxicity issues associated with them. Non-polar solvents such as hexane (slow reaction), toluene, or benzene gave more by-product formation and increased amounts of the 2-substituted isomer. Higher boiling aprotic solvents such as dimethylformamide and dimethylsulfoxide were also not effective.

Catalyst.

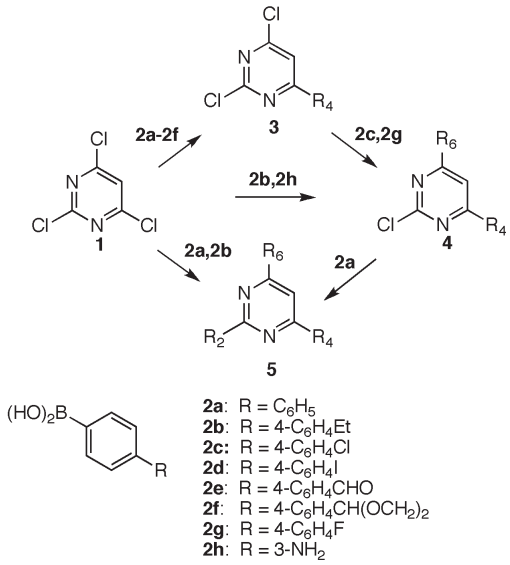
In the initial study catalytic amounts of palladium II acetate and triphenylphosphine were adopted as the standard methodology. In an effort to ascertain the optimum parameters we explored several alternatives. Palladium acetate alone functioned as an effective catalyst initially, but appeared to gradually decompose to palladium black over time as evidenced by a darkening of the reaction mixture and the appearance of fine black particles. This behavior was not observed when triphenylphosphine was used as the ligand. Palladium-on-carbon (10%) slowly catalyzed the Suzuki coupling but also led to reductive dehalogenation. Palladium acetate with 1,1'-bis(diphenylphosphino)-

ferrocene (dppf) or 1,3-bis(diphenylphosphino)propane (dppp) as ligands gave slower rates of reaction when the reaction was conducted at room temperature, but rates similar to those of palladium II acetate/triphenylphosphine when heated to reflux temperature. Consequently, we conclude that the initial choice of catalyst provides the best result.

Having established the nature of the catalyst for our further studies, we examined the quantity of catalyst required for optimum yields. Initially we used 2.5-5.0 mol % of palladium II acetate and twice this amount of triphenylphosphine. The palladium II acetate could be reduced to 0.5 mol % and still have reaction completion within 12 h.

The utilization of a variety of starting materials to produce mono-, di-, and trisubstituted arylpyrimidines is outlined in Scheme 1.

Scheme 1



Monosubstitution.

Monosubstitution of (**1**) using phenylboronic acid (**2a**) previously afforded the 4-substituted pyrimidine (**3a**) in high yield [6] (Entry 1, Table 1). By using a short series of substituted phenylboronic acids we were able to ascertain the influence substituents had on the efficiency of the reaction. Both the ethyl- (**2b**) and chloro- (**2c**) phenylboronic acids gave good yields of the monosubstituted products (**3b**) and (**3c**) (Entries 2 and 3). However neither the iodo- (**2d**) nor formyl (**2e**) reagents led to any significant yields of (**3d**) or (**3e**), respectively. In the case of the iodo compound it is likely that this halogen participated in a self-coupling reaction rather than the cross-coupling reaction with the chlorine in (**1**.) However when the formyl group was protected with ethylene glycol (**2f**) a 48 % yield of (**3f**) was obtained (Entry 4, Table 1).

Table

Entry	Reactants	Product	% Yield
1	**2a + 1**	**3a**	84[6]
2	**2b + 1**	**3b**	94
3	**2c + 1**	**3c**	82
4	**2f + 1**	**3f**	48
5	**2a + 1**	**4a**	88[6]
6	**2b + 1**	**4b**	88
7	**2c + 3b**	**4c**	48
8	**2g + 3b**	**4d**	38
9	**2g + 3a**	**4e**	54
10	**2h + 1**	**4f**	32
11	**2a + 4c**	**5b**	75
12	**2b + 1 + 2a**	**5c**	83
13	**2a + 1 + 2b**	**5d**	83
14	**2b + 1**	**5e**	Quant.

Disubstitution.

In our previous report [6] disubstitution leading to (**4a**) using phenylboronic acid (**2a**) was accomplished in 88 % yield (Entry 5). The results described above for monosubstitution suggested that the order of various substituted phenylboronic acids might be important in order to achieve good results. First, however, two equivalents of 4-ethylphenylboronic acid (**2b**) were used to confirm the 4,6-disubstitution pattern observed previously [6]. Thus, (**4b**) was prepared in 88 % yield (Entry 6). To determine unequivocally the order of substitution (**3b**) was prepared as previously mentioned and then treated with one equivalent of 4-chlorophenylboronic acid (**2c**). Compound (**4c**) was obtained in 48 % yield using this addition sequence (Entry 7).

Similarly, (**3b**) was converted into (**4d**) by using **2g** as the second reagent. The yield was somewhat poorer, though (38%) (Entry 8). Some improvement was realized when (**3a**) was treated with (**2g**) to give (**4e**) in 54 % yield (Entry 9). Finally, we wished to explore the utility of more polar groups in these reactions. Thus (**1**) was allowed to react with two equivalents of (**2h**) which provided the disubstituted derivative (**4f**) (Entry 10). This use of two equivalents of (**2**) in the same flask in the preparation of both (**4b**) and (**4f**) suggested that sequential formation of trisubstituted pyrimidines could be accomplished without isolation of intermediates. See below for an example of this methodology.

Trisubstitution.

Based on the high degree of success with both monosubstitution and disubstitution, we felt confident that we could introduce substituted phenyl rings in any order. Our first efforts in preparing triphenyl-substituted pyrimidines (**5**) began with the corresponding disubstitutedpyrimidine (**4**). Thus, (**4c**) was treated under the usual conditions with phenylboronic acid (**2a**). In this manner (**5b**) was obtained in 75 % yield (Entry 11). Additional triphenylsubstitutedpyrimidines (**5c**, **5d**) (Entries 12, 13) were obtained using

the one pot methodology by choosing the appropriate order of addition of various examples of (**2**). The preparation of (**5c**) illustrates this approach quite well.

The reaction flask was initially charged with (**1**), glyme, aqueous sodium carbonate, a phenylboronic acid (**2b**), 2.5 mol % palladium II acetate and 5.0 mol % triphenylphosphine. When it was determined (by tlc) that all of the phenylboronic acid had reacted, a different 4-substituted phenylboronic acid (**2a**) was added along with additional base, but no additional catalyst. Again, upon completion of this reaction a final charge of this reaction sequence was one equivalent of **2a**. This resulted in an 83 % yield of (**5c**). (See Table 1) The formation of (**5d**) was accomplished in a similar manner, though with one less step due to the use of two equivalents of (**2a**) in the first step. Subsequent reaction, without workup, with (**2a**) gave (**5d**) in 83 % yield. Finally (**5e**) was prepared from (**1**) using three equivalents of (**2b**), in quantitative yield (Entry 14).

EXPERIMENTAL

^{1}H and ^{13}C Nmr spectra were obtained using a Varian Inova (500 MHz) spectrometer. Deuteriochloroform and dimethylsulfoxide-d_6 with tetramethylsilane as the internal standard were the solvents of choice. A hexane/ethyl acetate solvent mixture was used to monitor the reaction by tlc. A Hewlett Packard Model 5995A GC/MS instrument was used to obtain all of the molecular weight information. Both GC and direct insertion probes (DIP) were used. A dry nitrogen environment was used in all reactions to ensure an inert atmosphere. Galbraith Analytical Laboratories of Knoxville, TN performed elemental analyses. High resolution mass spectra were obtained through the Michigan State University facilities. Sigma-Aldrich and Acros chemicals were utilized without further purification.

2,4-Dichloro-6-(4'-ethylphenyl)pyrimidine (**3b**).

To a solution of (**1**) (0.25 g, 1.36 mmol) in glyme was added 4-ethylphenylboronic acid (**2b**) (0.22 g, 1.47 mmol), aqueous sodium carbonate (4.22 mmol), palladium II acetate (2.5 mol %), and triphenylphosphine (5 mol %). The reaction was stirred at 70° for 24 h. The glyme was removed under reduced pressure and the residue partitioned between dichloromethane and water. After completion of the work up the residue was purified by column chromatography to yield **3b** in 94 % yield as a white solid (hexanes), mp 65.0-66.5°; ^{1}H nmr (deuteriochloroform): δ 1.29 (t, J = 2.5 Hz, 3H), 2.77 (q, J = 2.5 Hz, 2H), 7.36 (d, J = 3.0 Hz, 2H), 7.60 (s, 1H), 8.00 (d, J = 3.0 Hz, 2H); ^{13}C nmr (deuteriochloroform): δ 15.1, 28.8, 114.7, 127.5, 129.3, 131.3, 149.5, 160.7, 162.6, 168.0; ms: m/z 253 (M+, 41) 252 (M-1, 100).

Anal. Calcd. for $C_{12}H_{10}N_2Cl_2$: C, 56.94; H, 3.98; N, 11.07. Found: C, 57.13; H, 4.06; N, 10.99.

2,4-Dichloro-6-(4'-chlorophenyl)pyrimidine (**3c**).

This compound was obtained as a white solid (82 %), mp 127 – 9°; ^{1}H nmr (deuteriochloroform): δ 7.49 (d, J = 1.5 Hz, 2H), 7.65 (s, 1H), 8.09 (d, J = 1.4 Hz, 2H); ^{13}C nmr (deuteriochloroform): δ 115.1, 128.8, 129.5, 132.5, 138.9, 161.0, 163.1, 166.8; ms: m/z 259 (M+, 100).

Anal. Calcd. for $C_{10}H_5N_2Cl_3$: C, 46.28; H, 1.94; N, 10.79. Found: C, 46.01; H, 2.05; N, 10.73.

2,4-Dichloro-6-(4'-(1,3-dioxyanyl)phenyl)pyrimidine (**3f**).

This compound was obtained as a white solid (48 %), mp 132 – 4°; ^{1}H nmr (deuteriochloroform): δ 1.47-1.59 (t of d, J = 2.0 Hz, 1H), 2.18-2.35 (m, J = 2.0 Hz, 1H), 3.99-4.08 (t of d, J = 4.0 Hz, 2H), 4.29-4.37 (m, J = 6.0 Hz, 2H), 5.58 (s, 1H), 7.64-7.71 (s and d, J = 4.0 Hz, 3H), 8.10 (d, J = 4.0 Hz, 2H); ^{13}C nmr (deuteriochloroform): δ 25.7, 67.5, 100.6, 115.4, 126.9, 127.7, 134.2, 142.9, 160.9, 162.9, 167.7; MS m/z 311 (M+, 26) 251 (M-60, 99).

Anal. Calcd. for $C_{14}H_{12}N_2Cl_2$: C, 54.04; H, 3.89; N, 9.00. Found: C, 53.81; H, 4.01; N, 8.78.

2-Chloro-4,6-bis-(4'-ethylphenyl)pyrimidine (**4b**).

To a solution of (**1**) (0.50 g, 2.7 mmol) in glyme was added 4-ethylphenylboronic acid (**2b**) (5.9 mmol), aqueous sodium carbonate (16.7 mmol), palladium II acetate (2.5 mol %), and triphenylphosphine (5 mol %). The reaction was stirred at 70° for 24 h. The glyme was removed under reduced pressure and the residue partitioned between dichloromethane and water. After completion of the work up the residue was purified by column chromatography to yield (**4b**) (88 %) as a white solid (hexanes), mp 59-63°; ^{1}H nmr (deuteriochloroform): δ 1.29 (t, J = 3.0 Hz, 3H), 2.73 (q, J = 4.0 Hz, 2H), 7.37 (d, J = 3.0 Hz, 4H), 7.92 (s, 1H), 8.06 (d, J = 5.0 Hz, 4H); ^{13}C nmr (deuteriochloroform): δ 15.3, 28.8, 110.1, 127.8, 128.5, 133.0, 148.3, 161.9, 167.3; ms: m/z 322 (M+, 100).

Anal. Calcd. for $C_{20}H_{19}N_2Cl$: C, 74.41; H, 5.93; N, 8.68. Found: C, 74.39; H, 6.09; N, 8.68.

2-Chloro-4-(4'chlorophenyl)-6-(4'-ethylphenyl)pyrimidine (**4c**).

A mixture of palladium II acetate (0.060 g, 0.245 mmol), triphenylphosphine (0.128 g, 0.490 mmol), and glyme (50 mL) was allowed to stir under a nitrogen atmosphere for 10 min (turns red in color). To this mixture was added (**2c**) (0.768 g, 4.91 mmol) dropwise and allowed to stir for an additional 10 min upon completion of the addition at which time **3b** (1.13 g; 4.46 mmol) dissolved in glyme (90 mL) was added to the reaction mixture all at once and stirred a further 10 min. Sodium carbonate (1.61 g, 15.2 mmol) in water (20 mL) was added to the reaction flask and the whole heated to 70° for 27 h. The glyme was removed under reduced pressure and the residue taken up in ethyl acetate (150 mL). The organic solution was washed with water (5 x 100 mL), dried over anhydrous sodium sulfate, and purified by column chromatography. The resulting yellow solid was recrystallized twice from absolute ethanol to give pure (**4c**) (0.71 g, 48 %), mp 77-9 °; ^{1}H nmr (deuteriochloroform): δ 1.29 (t, J = 4.0 Hz, 3H), 2.75 (q, J = 3.0 Hz, 2H), 7.35 (q, J = 3.0 Hz, 2H), 7.48-7.57 (m, J = 3.0 Hz, 3H), 7.93 (s, 1H), 8.07 (t, J = 4.0 Hz, 2H), 8.18 (t, J = 4.0 Hz, 2H); ^{13}C nmr (deuteriochloroform): δ 15.4, 28.8, 110.2, 127.4, 128.0, 129.7, 132.8, 134.5, 136.8, 137.8, 147.7, 148.7, 162.0, 164.9, 167.8; ms: m/z 329 (M+, 72), 328 (M-1, 100). Hrms (EI): m/z calcd. for $C_{18}H_{14}Cl_2N_2$ = 328.0534; found: m/z = 328.0533.

2-Chloro-4-(4'-ethylphenyl)-6-(4'fluorophenyl)pyrimidine (**4d**).

This compound was prepared in a manner analogous to that for (**4c**), from (**3b**) and (**2g**). Colorless crystals of (**4d**) (38 %), mp 111-3° were obtained; ^{1}H nmr (deuteriochloroform): δ 1.29 (t, J =

1.6 Hz, 3H), 2.74 (q, J = 1.6 Hz, 2H), 7.21 (t, J = 2.5 Hz, 2H), 7.35 (d, J = 1.7 Hz, 2H), 7.92 (s, 1H), 8.05 (d, J = 1.4 Hz, 2H), 8.13-8.16 (dd, J = 1.0 Hz, 2H); ^{13}C nmr (deuteriochloroform): δ 15.3, 28.8, 110.1, 116.1, 116.2, 127.4, 128.6, 129.5, 129.6, 131.9, 132.9, 148.6, 161.9, 163.9, 166.2, 167.6; ms: m/z 312 (M+, 100), 297 (M-15, 57). Hrms (EI): m/z calcd. for $C_{18}H_{14}ClFN_2$ = 312.0830; found: m/z = 312.0822.

2-Chloro-4-(4'-fluorophenyl)-6-phenylpyrimidine (**4e**).

This compound was prepared in a manner analogous to that for (**4c**), from (**3a**) and (**2g**) using tetrahydrofuran as solvent. Colorless crystals of (**4e**) (54 %), mp 114-7° were obtained; ^{1}H nmr (deuteriochloroform): δ 7.20 (t, J = 4.0 Hz, 2H), 7.53 (t, J = 5.0 Hz, 3H), 7.94 (s, 1H), 8.14-8.18 (m, J = 5.0 Hz, 6H); ^{13}C nmr (deuteriochloroform): δ 110.1, 116.2, 127.4, 128.6, 129.5, 131.8, 132.9, 148.6, 161.9, 163.9, 166.2, 167.6; ms: m/z 284 (M+, 100), 249 (M-35, 85). Hrms (EI): m/z calcd. for $C_{16}H_{10}ClFN_2$ = 284.0517;found: m/z = 284.0519

2-Chloro-4,6-bis-(3'-aminophenyl)pyrimidine (**4f**).

This compound was prepared using the method for (**4b**) except that 2,2-dimethoxypropane was the solvent. The crude product was recrystallized from absolute ethanol to give deep yellow crystals (32 %), no mp below 250°; ^{1}H nmr (dimethylsulfoxide-d_6): δ 1.58 (s, 1H), 3.85 (s, 3H), 6.86 (s, 2H), 7.26-7.32 (m, J = 2.5 Hz, 2H), 7.44 (d, J = 2.6 Hz, 2H), 7.50 (d, J = 1.0 Hz, 2H), 7.92 (s, 1H); ^{13}C nmr (dimethylsulfoxide-d_6): δ 113.6, 117.4, 118.1, 129.8, 136.6, 147.1, 161.7, 170.6; ms: m/z 296 (M+, 100). Hrms (EI): m/z calcd. for $C_{16}H_{13}ClN_4$ = 296.0829; found: m/z = 296.0827.

4-(4'-Chlorophenyl)-6-(4'-ethylphenyl)-2-phenylpyrimidine (**5b**).

A mixture of palladium II acetate (0.023 g, 0.103 mmol), triphenylphosphine (0.054 g, 0.205 mmol), and tetrahydrofuran (50 mL) was allowed to stir under a nitrogen atmosphere for 10 min (turns red in color). To this mixture was added (**2a**) (0.25 g, 0.205 mmol) in tetrahydrofuran (90 mL) dropwise and allowed to stir for an additional 10 min upon completion of the addition. (**4c**) (0.675 g, 0.205 mmol) dissolved in tetrahydrofuran (50 mL) was added to the reaction mixture all at once and stirred a further 10 min. Sodium carbonate (0.652 g, 6.15 mmol) in water (20 mL) was added to the reaction flask and the whole heated to reflux for 27 h. The solvent was removed under reduced pressure and the residue taken up in ethyl acetate (150 mL). The organic solution was washed with water (5 x 100 mL), dried over anhydrous sodium sulfate, and purified by column chromatography. The resulting yellow solid was recrystallized from absolute ethanol to give pure (**5b**) as a white solid (0.057 g, 75 %), mp 115-7 °; ^{1}H nmr (deuteriochloroform): δ 1.28 (t, J = 3.0 Hz, 3H), 2.72 (q, J = 2.7 Hz, 2H), 7.41 (d, J = 5.0 Hz, 2H), 7.49-7.55 (m, J = 9.0 Hz, 5H), 7.86 (s, 1H), 8.20-8.24 (m, J = 5.0 Hz, 4H), 8.73 (d, J = 3.0 Hz, 1H); ^{13}C nmr (deuteriochloroform): δ 15.3, 28.8, 110.1, 116.0, 116.2, 127.4, 128.6, 129.5, 129.6, 131.8, 123.9, 148.6, 162.0, 163.9, 166.2, 167.6; ms: m/z 370 (M+, 100). Hrms (EI): m/z calcd. for $C_{24}H_{19}ClN_2$ = 370.1237; found: m/z = 370.1236.

2,4-Diphenyl-6-(4'-ethylphenyl)pyrimidine (**5c**).

To a solution of (**1**) (2.7 mmol) in glyme was added (**2a**) (2.7 mmol), aqueous sodium bicarbonate (8.4 mmol), palladium II acetate (2.5 mol %), and triphenylphosphine (5 mol %). The reaction mixture was stirred at 70° for 24 h. A solution of (**2b**) (2.7 mmol) in glyme and an additional quantity of aqueous sodium carbonate (8.4 mmol) was added and the reaction mixture heated for a further 24 h. Finally, another portion of (**2a**) (2.7 mmol) in glyme and aqueous sodium carbonate (8.4 mmol) was added and heating continued for 24 h. After workup the product was purified by column chromatography to afford **5c** as a white solid (83 %), mp 85.0-6.5°; ^{1}H nmr (deuteriochloroform): δ 1.39 (t, J = 4.0 Hz, 3H), 2.31 (q, J = 4.0 Hz, 2H), 7.43 (d, J = 3.0 Hz, 2H), 7.58-7.69 (overlapping signals, J = 4.0 Hz, 6H), 7.98 (s, 1H), 8.31 (d, J = 8.0 Hz, 4H), 8.80 (d, J = 7.0 Hz, 2H); ^{13}C nmr (deuteriochloroform): δ 15.3, 28.6, 109.6, 127.0, 127.1, 128.1, 128.2, 128.4, 128.7, 130.3, 130.4, 134.7, 137.3, 138.1, 147.1, 164.0, 164.1, 164.3; ms: m/z 336 (M+, 100). *Anal*. calcd. for $C_{24}H_{20}N_2$: C, 85.68; H, 5.99; N, 8.33. Found: C, 85.76; H, 6.21; N, 8.28.

4,6-Diphenyl-2-(4'-ethylphenyl)pyrimidine (**5d**).

To a solution of (**1**) (2.7 mmol) in glyme was added (**2a**) (5.4 mmol), aqueous sodium bicarbonate (8.4 mmol), palladium II acetate (2.5 mol %), and triphenylphosphine (5 mol %). The reaction mixture was stirred at 70° for 24 h. A solution of (**2b**) (2.7 mmol) in glyme and an additional quantity of aqueous sodium carbonate (8.4 mmol) was added and the reaction mixture heated for a further 24 h. After workup the product was purified by column chromatography to afford (**5d**) as a white solid (83 %), mp 95-98°; ^{1}H nmr (deuteriochloroform): δ 1.42 (t, J = 2.0 Hz, 3H), 2.89 (q, J = 3.0 Hz, 2H), 7.53 (d, J = 3.0 Hz, 2H), 7.59-7.70 (overlapping signals, J = 2.0 Hz, 6H), 7.96 (s, 1H), 8.45 (d, J = 4.0 Hz, 4H), 8.85 (d, J = 3.0 Hz, 2H); ^{13}C nmr (deuteriochloroform): δ 15.7, 29.1, 110.0, 127.4, 128.1, 125.8, 128.9, 130.8, 136.0, 137.6, 147.2, 164.5; MS m/z 336 (M+, 100).

Anal. Calcd. for $C_{24}H_{20}N_2$: C, 85.68; H, 5.99; N, 8.33. Found: C, 85.64; H, 5.95; N, 8.43.

2,4,6-Tris-(4'-Ethylphenyl)pyrimidine (**5e**).

To a solution of (**1**) (1.4 mmol) in glyme was added (**2b**) (4.3 mmol), aqueous sodium carbonate (13.0 mmol), palladium II acetate (2.5 mol %), and triphenylphosphine (5 mol %). The reaction was stirred at 70° for 24 h. Following workup the residue was purified by column chromatography to give (**5e**) as a white solid (quant. yield), mp ~ rt; ^{1}H nmr (deuteriochloroform): δ 1.38-1.48 (2 overlapping t, J = 3.0 Hz, 9H), 2.80-2.94 (2 overlapping q, J = 5.0 Hz, 6H), 7.51 (2 d in a ratio of 2:1, J = 3.0 Hz, 6H), 8.00 (s, 1H), 8.33 (d, J = 4.0 Hz, 4H), 8.83 (d, J = 3.0 Hz, 2H); ^{13}C nmr (deuteriochloroform): δ 15.6, 15.7, 28.9, 29.0, 109.4, 127.3, 128.0, 128.4, 128.6, 135.2, 136.1, 147.0, 147.2, 164.4, 164.5; MS m/z 356 (M+, 100).

Anal. Calcd. for $C_{25}H_{28}N_2$: C, 85.67; H, 7.19; N, 7.14. Found: C, 85.28; H, 7.39; N, 7.11.

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REFERENCES AND NOTES

[1] D. J. Brown, The Pyrimidines, Interscience Publishers, New York, NY, 1994, p. 15.

[2] W. Traube, *Ber*., **26**, 2551 (1893).

[3] A. Turck, N. Ple, A. Lepretre-Gaguere, and G. Queguiner, *Heterocycles* **49**, 205 (1998).

[4] A. Turck, N. Ple, Mongin,and G. Queguiner, *Tetrahedron*, **57**, 4489 (2001).

[5] J. V. Wade and C. A. Krueger, *J. Comb. Chem*., **5**, 267 (2003).

[6] J. M. Schomaker, and T. J. Delia, *J. Org. Chem*., **66**, 1725 (2001).

[7] R. Franzen and Y Xu, *Can. J. Chem*., **83**, 266 (2005).

[8] S. Schroter, C. Stock and T. Bach, *Tetrahedron*, **61**, 2245 (2005) and references cited therein.

[9] http://ecb.jrc.it/classlab/1503 F 1,2-dioxyethane.doc (accessed June 2005).