Arylation of Halogenated Pyrimidines via a Suzuki Coupling Reaction

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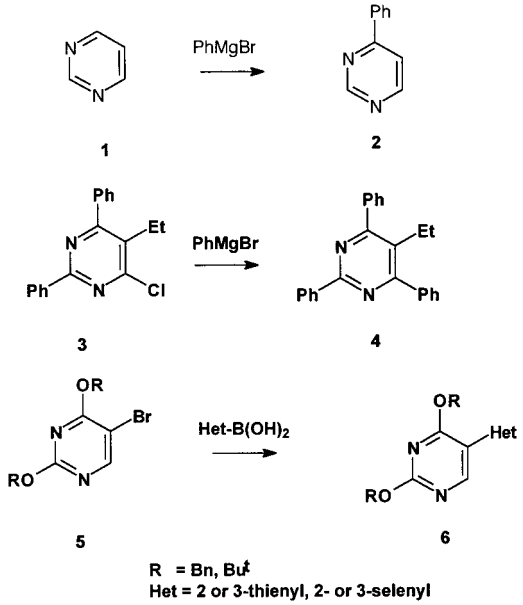
The Suzuki coupling reaction has been used extensively for the synthesis of a wide variety of unsymmetrical biaryl compounds. We have extended this reaction to demonstrate the utility of preparing monophenyl-, diphenyl-, or triphenylpyrimidine depending on the reaction conditions. Further, it has been shown that chloropyrimidine substrates are preferable over iodo-, bromo-, or fluoropyrimidines.

Introduction

There have been relatively few methods available to produce C-aryl derivatives of pyrimidine. Perhaps the most practical of these methods involves the primary synthesis in which the pyrimidine ring is constructed by condensation of two components bearing the desired aryl groups in appropriate locations. An example of this approach has been described by Pinner[1] to produce 4,6-dimethyl-2-phenylpyrimidine from benzamidine and acetylacetone. Likewise 2,4,6-triphenylpyrimidine can be prepared in analogous fashion.[2] Recently a modification of this approach has been described,[3] utilizing a three component coupling-isomerization sequence, catalyzed by a palladium complex to produce 2,4,6-tri(hetero)aryl-substituted pyrimidines.

The direct arylation of pyrimidines is a simpler approach that does not involve the preparation of product-specific intermediates. However, examples of this chemistry are quite limited. The reaction of a phenyl Grignard reagent combining with a suitable pyrimidine is one of the earlier methods described. Thus, phenylmagnesium bromide is reported to react with unsubstituted pyrimidine **1** to afford 4-phenylpyrimidine **2**[4] (Scheme 1), and with 4-chloro-5-ethyl-2,6-diphenylpyrimidine **3** to give the corresponding triphenyl derivative **4**.[5] In related chemistry, a Negishi coupling of 2,4-pyrimidinyl triflate with p-anisylzinc bromide affords 2,4-dianisylpyrimidine.[6] Directed ortho metalation of many nitrogen heterocycles, including pyrimidines, is an alternate method for the introduction of aryl substituents.[7] Given our continuing interest in investigating the substitution reactions of 2,4,6-trichloropyrimidine,[8] we sought to examine the application of Suzuki coupling reactions with a variety of halogenated pyrimidines.

Scheme 1



The electron deficient nature of the pyrimidine ring makes this system far more reactive in Suzuki couplings compared to the analogous benzenoid halides. For example, although aryl chlorides are generally unreactive toward the oxidative addition of palladium without the use of specialized and expensive ligands, the reaction of 2-chloropyrimidine with 5-indoylboronic acid occurred smoothly using tetrakis(triphenylphosphine)palladium.[9] The use of Suzuki coupling conditions has also been employed with 5-halogenated pyrimidines. Treatment of 5-bromo-2,4-dialkoxypyrimidines **5** with thienyl- or selenylboronic acids led to the expected 5-heterosubstituted products **6**[10] (Scheme 1).

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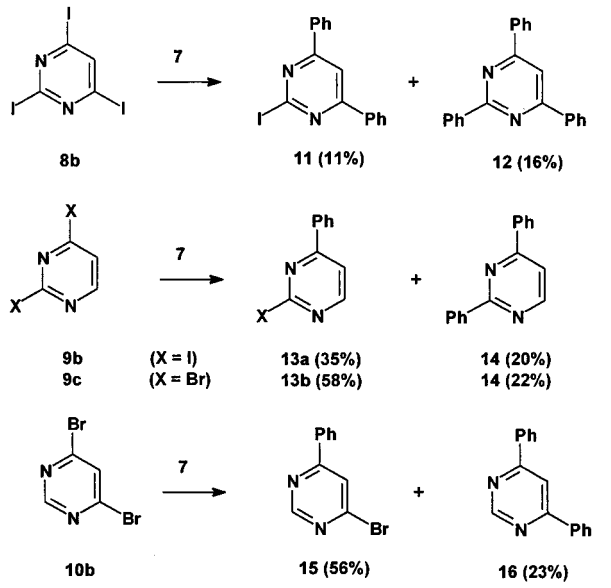
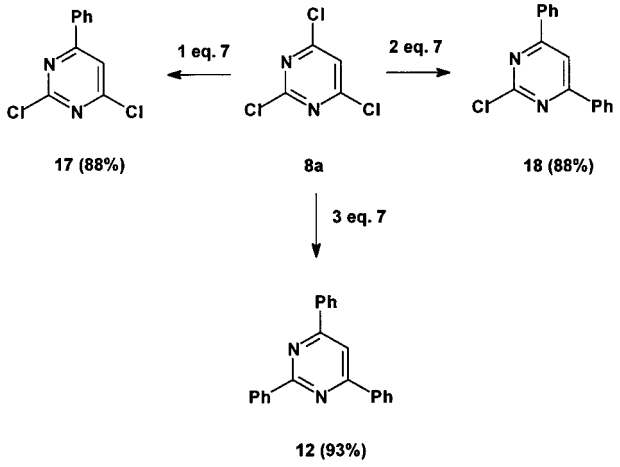
Scheme 2



Scheme 3



Results and Discussion

Unaware of any detailed study of the selectivity of Suzuki coupling at positions 2 or 4 of the pyrimidine ring, we have examined the reaction of phenylboronic acid **7** with three of the four possible 2,4,6-trihalopyrimidines **8** (**a** = Cl; **b** = I; **c** = F) as well as two 2,4-dihalopyrimidines **9** (**b** = I; **c** = Br) and 4,6-dibromopyrimidine **10b** (Schemes 2 and 3). Our two main objectives in this study were (1) to determine which of the four halogens would provide the best result and (2) to ascertain whether a Suzuki coupling reaction would occur preferentially at either of the nucleophilic sites (positions 2 or 4/6).

Halogenated Pyrimidines. Since oxidative addition of palladium into a carbon−halogen bond occurs in the order I > Br ≫ Cl ≫ F, based mainly on the strength of the C-halogen bond, we sought to include representative compounds containing each of the halogen atoms in our studies. The precursors for the iodo-, bromo-, and fluoropyrimidines were the corresponding commercially available chloro compounds.

Thus, 2,4,6-trichloropyrimidine **8a** was treated with aqueous HI to give the previously unknown 2,4,6-triiodopyrimidine **8b** in 90% yield. 2,4,6-Tribromopyrimidine is not commercially available and the literature procedures for its preparation are not easily reproduced.[11] Consequently we opted to examine two isomeric dibromopyrimidines instead. (see below) 2,4,6-Trifluoropyrimidine **8c** is readily obtained in 56% yield from **8a** using KF and 18-crown-6, as catalyst, in sulfolane. This method is simpler than previously reported syntheses of **8c** using AgF[12a] and KF in a sealed tube.[12b]

2,4-Diiodopyrimidine **9b** was formed in 91% yield upon treatment of the corresponding dichloropyrimidine **9a** with aqueous HI. Bromination of **9a** with PBr_3 under reflux afforded 2,4-dibromopyrimidine **9c** in 32% yield. It is worth noting that similar treatment of the trichloropyrimidine **8a** failed to provide the corresponding tribromopyrimidine.

Bromination of 4,6-dichloropyrimidine **10a** under conditions comparable to those above led to the formation of the dibromo compound **10b** in 41% yield.

Suzuki Coupling Reactions. Reaction of **8b** with one equivalent of phenylboronic acid **7**, catalytic amounts of palladium acetate and triphenylphosphine, and excess Na_2CO_3 in a water/ethanol/benzene solvent system at 70 °C led to low yields of coupled products, as determined by the ^{1}H NMR spectrum of the reaction mixture, accompanied by a substantial quantity of impurities. The same reaction conditions in a glyme/water mixture provided low, but improved, yields of a mixture of coupled products. Even though the initial stoichiometry was chosen to obtain the isomeric monosubstituted products, neither of these compounds could be isolated. Instead, only the 4,6-disubstituted product **11** (11%) and triphenylpyrimidine **12** (16%) were obtained. (Scheme 2) There was no indication of the formation of the isomeric 2,4-disubstituted compound. Despite the individual low yields, considering that **7** turned out to be the limiting reagent, the mass conversion was ∼70%. Clearly the iodo groups proved to be so reactive that no selectivity could be achieved. Even the use of a less active catalyst, tetrakis(triphenylphosphine)palladium, gave the same results. A 4-fold excess of **8b** gave neither of the monosubstituted products**,** and when the reaction was carried out at room temperature no reaction occurred.

In an effort to limit the sites of reaction and, therefore, improve the selectivity, 2,4-diiodopyrimidine **9b** was considered. Suzuki coupling of **9b** with **7** gave a mixture of the 4-substituted product **13a** in 35% yield and the disubstituted product **14** in 20% yield. Even though the major product was monosubstituted, the selectivity was not synthetically appealing.

The reaction of **9c** with one equivalent of **7** under Suzuki coupling conditions led to a mixture of 2-bromo-4-phenylpyrimidine **13b** (58%) and 2,4-diphenylpyrimidine **14** (22%) with no evidence of any appreciable quantity of the 2-phenyl derivative, a possible intermediate in the formation of **14**. Again the mass balance is quite good, but the bromo groups are also too reactive to give good selectivity. Similar results are observed when 4,6-dibromopyrimidine **10b** was treated under the same conditions affording a mixture of the monosubstituted compound **15** and the disubstituted pyrimidine **16**.

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The trichloropyrimidine **8a** was treated with one equivalent of **7** in the glyme/water solvent system using $Pd(OAc)_2/PPh_3$ as catalyst. (Scheme 3) A dramatic improvement in selectivity was achieved as 2,4-dichloro-6-phenylpyrimidine **17** was isolated in 88% yield, accompanied by small amounts of the di- and trisubstituted products. Interestingly, the selectivity of the coupling led almost exclusively to the 4-substituted isomer. ^{13}C NMR could readily confirm the position of substitution, where the spectrum showed four distinct carbons for the pyrimidine ring indicative of an unsymmetrical substitution pattern. The 2-phenyl derivative would exhibit only three signals in the ^{13}C NMR spectrum for the pyrimidine ring.

When **8a** was treated with 2 equiv of **7** under similar conditions only the 4,6-disubstituted product **18** was isolated in high yield (88%). This product arises by a subsequent substitution of the 4-phenyl derivative **17** at position 6 rather than at position 2. This result, in addition to our earlier report with substitution of chlorine by phenoxide anions,[8b] continues a growing list of unusual substitution patterns. Previous work by us[8a] and others[13] describes a more statistical ratio of 4-substitution vs 2-substitution when small anionic or neutral nucleophiles are employed.

Treatment of **8a** with a slight excess of 3 equiv of **7** under identical conditions afforded the triphenyl derivative **12** in 93% yield.

Although aryl fluorides are very unreactive toward oxidative addition of palladium, we were curious as to whether the electron-deficient pyrimidine ring coupled with the strong electron-withdrawing effect of fluorine would allow 2,4,6-trifluoropyrimidine **8c** to function as a suitable partner in a Suzuki coupling process. Unfortunately, when **8c** was treated in a manner similar to the other halogenated pyrimidines no arylation was observed. The major reaction appeared to be hydrolysis of one or more of the fluorine substituents under the relatively forcing conditions employed. We did not pursue further attempts to obtain the desired Suzuki coupled products since the chloro compound gave a satisfactory synthetic method for arylation of the pyrimidine ring.

Conclusions

We have synthesized or purchased a series of halogenated pyrimidines and subjected them to the conditions normally employed for Suzuki coupling reactions and obtained C-phenyl pyrimidines. Due to the electron-deficient nature of the pyrimidine ring, the typical iodo and bromo substrates proved to be too reactive to exhibit good selectivity where two or more halogens are present on the pyrimidine. The fluorinated pyrimidine, on the other hand, was completely unreactive toward coupling under comparable conditions. The observations that the halogen atoms (I, Br, Cl) attached at C-2 were replaced last provides a clear order of reactivity, namely position 4 > position 6 > position 2. The chloro pyrimidines proved to be excellent precursors for the synthesis of specific C-aryl pyrimidines in very good yields. Furthermore, since chloro compounds tend to be more available commercially, as well as less costly, this pathway is quite desirable. We are currently examining the scope of the Suzuki coupling reaction using substituted phenylboronic acids.

Experimental Section

General. Melting points were measured in open capillary tubes and are uncorrected. Proton and carbon magnetic resonance spectra were recorded at 300 MHz for ^1H NMR and 75 MHz for ^{13}C NMR using DMSO-d_6 or $CDCl_3$ containing tetramethylsilane as an internal standard. Reactions were monitored by thin-layer chromatography on silica gel containing fluorescent indicator using various combinations of hexane/ethyl acetate or chloroform/methanol as eluant. The plates used were Eastman Kodak. All mass spectral data were obtained by means of direct insertion probe (DIP) methods. Elemental analyses were performed by Galbraith Laboratories of Knoxville, Tennessee. Chemicals and reagents were purchased from Fisher or Aldrich Chemical Companies and were used without further purification.

2,4,6-Triiodopyrimidine (8b). A 100 mL round-bottom flask was charged with 2,4,6-trichloropyrimidine **8a** (5.0 g, 27.3 mmol) and 40 mL of HI as a 57% solution in water. The orange-colored bi-phasic system eventually changed to a thick, light orange slurry. After stirring overnight, the slurry was diluted with water, cooled in an ice/water bath and filtered. The resulting solid was washed well with cold water and dried to yield the crude product (11.3 g, 24.7 mmol, 90% yield) as a cream solid. The crude material was recrystallized from hexane to yield pure **8b** as ivory-colored needles, mp 203−205 °C (7.9 g, 70% recovery, 63% yield); ^1H NMR (DMSO-d_6) δ 8.3 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 127.2, 130.1, 141.6; MS (DIP) m/z 458 (M^+, 100), 331 (M-127, 80). Anal. Calcd for $C_4HN_2I_3$: C, 10.50; H, 0.22; N, 6.12. Found: C, 10.59; H, <0.5; N, 6.13.

2,4,6-Triphenylpyrimidine (12) and 4,6-diphenyl-2-iodopyrimidine (11). To a solution of 1.0 g (2.2 mmol) of 2,4,6-triiodopyrimidine **8b** in glyme was added phenylboronic acid **7** (0.28 g, 2.3 mmol) and aqueous sodium carbonate (0.72 g, 6.8 mmol). Palladium acetate (2.5 mol %) and triphenylphosphine (5.0 mol %) were used to generate the catalyst. The reaction was heated to reflux for 48 h. Following workup, the residue was chromatographed using a hexane/ethyl acetate gradient as the mobile phase. The first fraction (110.3 mg, 16%) was **12**; mp 184−186 °C.[14]

The second fraction was identified as **11** (87.0 mg, 11%); mp 148−150 °C; ^1H NMR ($CDCl_3$) δ 7.5 (m, 6H), 8.0 (s, 1H), 8.1 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 111.7, 127.3, 128.3, 131.5, 135.5, 166.3, 167.6; MS (DIP) m/z 358 (M+, 30), 231 (M-127, 100). Anal.Calcd. for $C_{16}H_{11}N_2I$: C, 53.65; H, 3.10; N, 7.82. Found: C, 54.08; H, 3.22; N, 7.74.

The reaction was repeated using the less active $Pd(PPh_3)_4$ catalyst. Two fractions were obtained using the same workup as described above. The first fraction (109.8 mg, 16%) was again **12**. The second fraction (83.5 mg, 11%) was **11**.

2,4-Diiodopyrimidine (9b). A 25 mL round-bottom flask was charged with 0.50 g (3.34 mmol) of 2,4-dichloropyrimidine **9a**. Hydrogen iodide (15 mL as a 57% solution in water) was added and the slurry stirred overnight at room temperature. The reaction mixture was neutralized carefully with cooling using 10% sodium hydroxide. The resulting gold-colored solid was filtered and washed with cold water (0.91 g, 82% yield). A second crop (0.10 g, 9% yield) was also obtained. mp 125−126 °C.[15]

2-Iodo-4-phenylpyrimidine (13a) and 2,4-Diphenylpyrimidine (14). A 25 mL round-bottom flask was charged with 321.8 mg (0.97 mmol) of 2,4-diiodopyrimidine **9b**, 130.0 mg (1.07 mmol, 1.1 equivalent) of phenylboronic acid **7**, 318.0 mg

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of sodium carbonate (3.1 equiv dissolved in 1.5 mL water), 3 mL benzene and 0.3 mL ethanol. The flask was covered with aluminum foil and tetrakis(triphenylphosphino)palladium (33.6 mg, 3 mol %) was added. The reaction was heated to reflux for 54 h and the solvents removed by rotary evaporation. The product was extracted into methylene chloride and the organics washed 3× with water. The organics were dried over anhydrous Na_2SO_4 and the methylene chloride evaporated under reduced pressure. The residue was purified by column chromatography (hexane/ethyl acetate) to yield a fraction (44.1 mg, 19.6% yield) that was shown to be 2,4-diphenylpyrimidine **14** by proton NMR; mp 63−65 °C;[16] ^{1}H NMR ($CDCl_3$) δ 7.5 (m, 6H), 7.6 (s, 1H), 8.2 (dd, 2H), 8.6 (dd, 2H), 8.85 (d, 1H); ^{13}C NMR ($CDCl_3$) δ 114.5, 127.2, 128.6, 130.6, 130.9, 136.9, 137.9, 157.8, 163.8, 164.3; MS (DIP) *m*/*z* 232 (M+, 100). The next fraction (96.2 mg, 35% yield) was identified as **13a**.[17]

4,6-Dibromopyrimidine (10b). A 25 mL round-bottom flask was charged with 0.25 g (1.68 mmol) of 2,4-dichloropyrimidine **10a** and 10 mL of phosphorus tribromide. The reaction was heated to reflux for 6 h, and the remaining PBr_3 distilled under vacuum. The residue was quenched carefully with cold water and the resulting white solid filtered and dried to yield 0.16 g (41% yield) of product, mp 48−50 °C.[18]

2,4-Dibromopyrimidine (9c). The title compound was synthesized from **9a** in the manner indicated above to give a white solid in 32% yield; mp 65−67 °C.[10a]

2-Bromo-4-phenylpyrimidine (13b) and 2,4-Diphenylpyrimidine (14). To a solution of 2,4-dibromopyrimidine **9c** (0.22 g, 0.92 mmol) in glyme was added phenylboronic acid **7** (0.11 g, 0.92 mmol), aqueous sodium carbonate (0.30 g, 2.85 mmol), and tetrakis(triphenylphosphino)palladium (33.6 mg, 3 mol %). The reaction was heated to reflux for 32 h and the solvents removed by rotary evaporation. The product was taken up in methylene chloride and the organics washed 3× with an equal volume of water. The organics were dried over magnesium sulfate and the methylene chloride evaporated under reduced pressure. The residue was purified by column chromatography (hexane/ethyl acetate) to yield two fractions. The first fraction (48.9 mg, 22% yield) was 2,4-diphenylpyrimidine **14**; mp 62−65 °C.[16] The second fraction (126.3 mg, 58%) was 2-bromo-4-phenylpyrimidine **13b**, mp 85−87 °C.[19]

2,4-Dichloro-6-phenylpyrimidine (17). A 100 mL round-bottom flask was charged with 1.0 g (5.5 mmol) of 2,4,6-trichloropyrimidine **8a**, 0.67 g (5.5 mmol, 1.0 equiv) of phenylboronic acid **7**, sodium carbonate (3.1 equiv dissolved in a minimum amount of water), and 50 mL of glyme. The flask was covered with aluminum foil and palladium acetate (61.2 mg, 5 mol %) and triphenylphosphine (143.0 mg, 10 mol %) were added. The reaction was heated to reflux for 18 h and the solvents removed by rotary evaporation. The product was extracted into methylene chloride and the organics washed 3× with water. The organics were dried over magnesium sulfate and the methylene chloride evaporated under reduced pressure. The residue was purified by column chromatography (hexane/ethyl acetate) to yield **17** (1.08 g, 88% yield). The material was further purified by column chromatography to yield an analytical sample, mp 85−86 °C.[20]

2-Chloro-4,6-diphenylpyrimidine (18). To a solution of 2,4,6-trichloropyrimidine **8a** (0.5 g, 2.7 mmol) in glyme was added phenylboronic acid **7** (0.7 g, 5.4 mmol, 2.0 equiv) and aqueous sodium carbonate (1.8 g, 16.7 mmol, 6.2 equiv). The active catalyst was generated by the addition of palladium acetate (2.5 mol %) and triphenylphosphine (5 mol %) to the reaction mixture. The reaction was heated to 70 °C for 24 h and following workup, was purified using column chromatography to give **18** as a white, fluffy solid in 88% yield; mp 113−115 °C.[21]

2,4,6-Triphenylpyrimidine (12). To a solution of **8a** (0.5 g, 2.7 mmol) in glyme was added phenylboronic acid **7** (8.9 mmol, 3.3 equiv) and aqueous sodium carbonate (25.1 mmol, 9.3 equiv). The active catalyst was generated by the addition of palladium acetate (2.5 mol %) and triphenylphosphine (5 mol %) to the reaction mixture. The reaction was heated to reflux for 24 h and following workup, was purified using column chromatography to give **12** in 93% yield; mp 185−186 °C.[14]

2,4,6-Trifluoropyrimidine (8c). A 250 mL, three-necked round-bottom flask equipped with a distillation head, vacuum adapter, and thermometer was charged with 10.4 g of spray-dried KF and 150 mL of sulfolane. Approximately 10 vol % was distilled from the mixture in order to remove residual water. After allowing the slurry to cool, 10 g (54.5 mmol) of 2,4,6-trichloropyrimidine **8a** and 0.72 g (5 mol %, 2.7 mmol) of 18-crown-6 were added and the reaction heated to 150 °C for 3.5 h. The title compound was obtained by distillation (4.1 g; 56% yield) as a water-white liquid, bp 98−101 °C.[12] The material was used in subsequent reactions without further purification.

Acknowledgment. We are indebted to the Research Excellence Fund of the State of Michigan for partial support of this work.

Supporting Information Available: Selected data (^{1}H NMR, ^{13}C NMR, mass spectra, and elemental analysis) for compounds **8c**, **9b**, **9c**, **10b**, **12**, **13a**, **13b**, **14**, **17**, and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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