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Synthesis of 4,6-disubstituted pyrimidines via Suzuki and Kumada coupling reaction of 4,6-dichloropyrimidine

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Abstract

A series of 4,6-disubstituted pyrimidines were synthesized via Suzuki and Kumada coupling reaction of 4,6-dichloropyrimidine.

Keywords: Pyrimidines; Cross-coupling; Perfluorocyclobutyl (PFCB)

1. Introduction

The realization of the biochemical importance of nucleic acids has occasioned a great revival of interest in the chemistry of pyrimidines. Among them, substituted pyrimidines have become increasingly important as biologically interesting compounds, materials and ligands in molecular recognition [1]. The traditional methods for the synthesis of substituted pyrimidines were based on the condensation reactions of 1,3-dicarbonyl compounds (and synthetic equivalents) with amidines or amidinium salts [1,2]. The cross-coupling reaction of halopyrimidines with arylboric acid is a simpler approach to substituted pyrimidines that does not involve the preparation of product-specific intermediates [3]. Recently, a new type of polymer containing the perfluorocyclobutyl (PFCB) unit, which is prepared by the free-radical thermal cyclodimerization of aryl trifluorovinyl ether monomers, has received considerable attention (Scheme 1) [4], since PFCB polymers exhibit a wide range of complementary properties, including excellent processability, compared to traditional perfluorinated materials [5]. During our ongoing projects involving the synthesis of PFCB polymers, we required 4,6-di-(4-trifluorovinyloxyphenyl)pyrimidine **2a** (Scheme 1). We envisaged the preparation of such 2,6-disubstituted pyrimidine via the Kumada or Suzuki coupling reaction of 4,6-dichloropyrimidine.

Initial attempts to synthesize 4,6-di-(4-trifluorovinyloxyphenyl)pyrimidine **2a** by the cross-coupling of 4-(trifluorovinyloxy)phenylmagnesium bromide [4] with 4,6-dichloropyrimidine upon catalysis under $Ni(dppp)Cl_2$ (Kumada reaction) [6] failed, although the reaction of phenylmagnesium bromide with chloropyrimidine was one of the earlier methods used for the synthesis of C-aryl derivatives of pyrimidine [7]. Fortunately, treatment of 4,6-dichloropyrimidine with 4-(trifluorovinyloxy)phenylboronic acid [8] in the presence of $Pd(PPh_3)_4$ [9] provide **2a** in high yield. This difference between these two coupling reactions prompted us to investigate the cross-coupling of 4,6-dichloropyrimidine with various Grignard reagent and boronic acids. We selected 4-(trifluorovinyloxy)bromobenzene, 4-fluorobromobenzene, bromobenzene and 1-bromobutane for the conversion of the Grignard reagent and boronic acids, respectively.

As shown in Scheme 2 and Table 1, the reaction of 4,6-dichloropyrimidine with 2.0 equiv. of other three Grignard reagents (entries 2-4) in the presence of $[Ni(dppp)Cl_2]$ occurred smoothly. Although the 4,6-disubstituted pyrimidines were obtained in moderate yield, it was observed that the homo-coupling of Grignard reagents occurred. In addition, we also tried the reaction of **1a** and **1b** with 4,6-dichloropyrimidine without the catalysis of $[Ni(dppp)Cl_2]$. There was no reaction for **1a**. In the case of **1b**, **2b**, 4-chloro-6-phenylpyrimidine and biphenyl were isolated. Biphenyl was the major product.

Treatment of 4,6-dichloropyrimidine with two equivalent of boronic acids under Suzuki coupling conditions led to the

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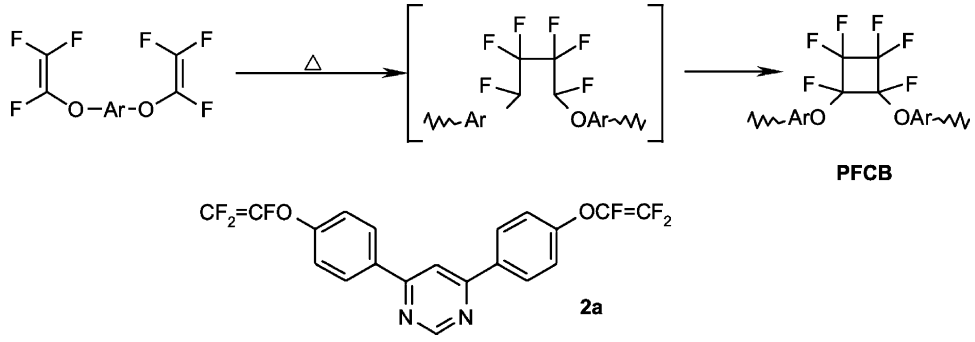
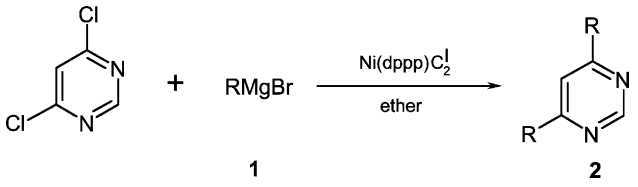
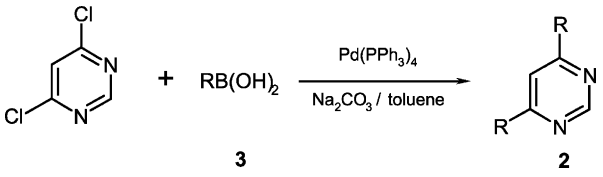


Scheme 1.



Scheme 2.



Scheme 3.

expected 4,6-disubstituted pyrimidines in high yield (Scheme 3 and Table 2). No evidence for the homo-coupling of boronic acids was observed. Recently, 4,6-diphenylpyrimidine (**2b**) has also been prepared through the Suzuki cross-coupling of 4,6-dibromopyrimidine with phenylboronic acid [3c]. It is noteworthy that the isolated yield of 4,6-disubstituted pyrimidines in the Suzuki reaction was higher than in the Kumada reaction. Aryl chlorides, an attractive class of substrates due to their low cost and ready availability, were generally not suitable coupling partners in palladium-catalyzed Suzuki reactions [10]. During the past few years, this deficiency has been remedied through the use of special ligands such as electron-rich, sterically hindered phosphines [11], carbenes [12] and ferrocene-derived triarylphosphine [13]. The palladium-catalyzed Suzuki cross-coupling of 4,6-dichloropyrimidine in the presence of palladium(0) can be accomplished, because 4,6-dichloropyrimidine is a very activated aryl chloride.

In conclusion, we have described two routes to 4,6-disbstituted pyrimidines via the Suzuki and Kumada cross-coupling reaction of 2,6-dichloropyrimidine. The Suzuki reaction was more general, versatile and resulted in high yield than the Kumada reaction for the synthesis of 2,6-disbstituted pyrimidines.

Table 1
The cross-coupling of 4,6-dichloropyrimidine with Grignard reagents in the presence of $Ni(dppp)Cl_2$

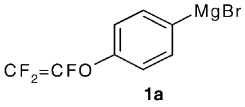
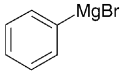
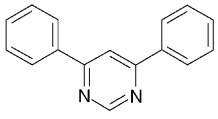
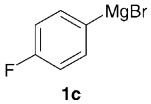
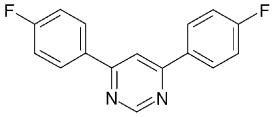
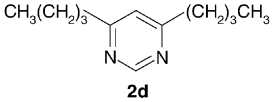
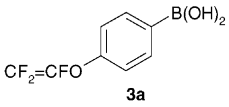
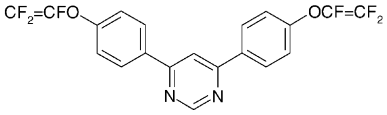
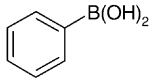
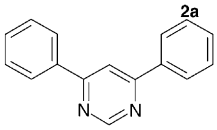
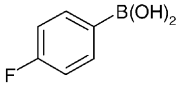
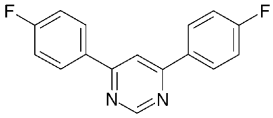
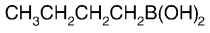
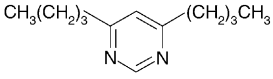
Entry	Grignard reagent **1**	Disubstituted pyrimidine **2**	Isolated yield (%)
1	 **1a**	No reaction	
2	 **1b**	 **2b**	70
3	 **1c**	 **2c**	63
4	$CH_3CH_2CH_2CH_2MgBr$ **1d**	 **2d**	67

Table 2
The cross-coupling of 4,6-dichloropyrimidine with boronic acids in the presence of $Pd(PPh_3)_4$

Entry	Boronic acid **3**	Disubstituted pyrimidine **2**	Isolated yield (%)
1	 **3a**	 **2a**	76
2	 **3b**	 **2b**	86
3	 **3c**	 **2c**	79
4	 **3d**	 **2d**	82

2. Experimental

^{1}H NMR spectra were recorded on a Bruker AMX-300 (300 MHz) spectrometer in $CDCl_3$ with $CHCl_3$ as an internal standard. ^{19}F NMR spectra were obtained on a Bruker AMX-300 (282 MHz) spectrometer in $CDCl_3$ with $CFCl_3$ as an external standard, downfield shifts being designated as negative. All chemical shifts (δ) are expressed in ppm. Coupling constants (J) are given in Hz. Mass spectra were recorded on a Finnigan-MAT-8430 instrument using EI ionization at 70 eV. IR spectra were recorded on a Shimadzu IR-440 spectrometer.

2.1. Representative procedure for the preparation of Grignard reagents (*1a–1d*) and boronic acids (*3a–3d*)

A solution of 4-(trifluorovinyloxy)bromobenzene [4] (25.3 g, 0.10 mol) in THF (50 ml) was added dropwise at 15 °C to the mixture of magnesium (2.94 g, 0.12 mol) and THF (100 ml). Then the reaction mixture was stirred at reflux for 6 h to give the Grignard reagent **1a**.

Under a nitrogen atmosphere at −65 °C, a solution of trimethylborate (10.4 g, 0.1 mol) in THF (30 ml) was added dropwise to the Grignard reagent prepared above. After the addition of trimethylborate, the reaction mixture was stirred for 15 h at room temperature. Concentrated sulfuric acid (20 ml) was added to the mixture. The reaction mixture was extracted with CH_2Cl_2 and washed with 10% aqueous Na_2CO_3. The product was concentrated in vacuo as a brown waxy solid, which was recrystallized from toluene to give boronic acid **3a**.

2.2. Representative procedure for the Kumada cross-coupling reaction

The Grignard reagent **1c** (10 mmol) was added dropwise at 5 °C to a solution of 4,6-dichloropyrimidine (0.74 g, 5 mmol) and Ni(dppp)Cl_2 (0.02 g, 0.037 mmol) in THF (6 ml), after the addition of the Grignard reagent, the reaction mixture was stirred at reflux for 10 h. Then 2 M HCl (20 ml) and Et_2O (20 ml) were added at 0 °C. The aqueous layer was extracted with Et_2O (3× 10 ml). The combined organic phases were washed with water and brine and dried over anhydrous Na_2SO_4. After removal of the solvent in vacuo, the residue was purified by flash chromatography to provide **2c** (63%) as a white solid.

2.3. Representative procedure for the Suzuki cross-coupling reaction

A solution of 4,6-dichloropyrimidine (0.41 g, 2.75 mmol), boronic acid **3a** (1.2 g, 5.5 mmol), $Pd(PPh_3)_4$ (0.11 g, 0.1 mmol) toluene (20 ml) and 2 M Na_2CO_3 (8 ml) was stirred at 100 °C for 12 h. Then the reaction mixture was extracted with CH_2Cl_2 (3× 30 ml). The combined organic phases were washed with water and brine, and dried over $MgSO_4$. After removal of the solvent in vacuo, the residue was purified by flash chromatography to provide **2a** (76%) as a white solid.

2.4. 4,6-Di-(4-trifluorovinyloxyphenyl)pyrimidine *2a*

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 (d, J = 8.8 Hz, 4H), 8.02 (s, 1H), 8.18 (d, J = 8.8 Hz, 4H), 9.28 (s, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −119.5 (dd, J = 85.3, 60.9 Hz, 1F),

−126.1 (dd, $J = 110.0$, 85.3 Hz,1F), −134.6 (dd, $J = 110.0$, 60.9 Hz, 1F); IR (KBr): 1838, 1596, 1519, 1321, 1276, 1137, 834, 772, 522 cm^{-1}; MS *m/z* (%): 424 (100), 396 (10), 327 (59), 230 (72), 203 (11). Anal. Calc. for $C_{20}H_{10}F_6N_2O_2$: C, 56.61; H, 2.38; N, 6.60. Found: C, 56.84; H, 2.54; N, 6.47.

2.5. 4,6-Diphenyl pyrimidine **2b**

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 (m, 6H), 8.12 (s, 1H), 8.18 (m, 4H), 9.32 (s, 1H); MS *m/z* (%): 232 (100), 204 (70), 102 (35), 77 (11), 51 (11).

2.6. 4,6-Di(4-fluorophenyl)pyrimidine **2c**

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19–7.25 (m, 4H), 8.00 (1H, s), 8.13–8.18 (m, 4H), 9.27 (1H, s); IR (KBr) 3044, 1601, 1582, 1509, 1460, 1365, 1224, 1158, 837 cm^{-1}; MS *m/z* (%): 268 (100), 241 (62), 214 (14), 120(31), 91(12). Anal. Calc. for $C_{16}H_{10}F_2N_2$: C, 71.63; H, 3.76; N, 10.45. Found: C, 71.86; H, 3.92; N, 10.48.

2.7. 4,6-Dibutylpyrimidine **2d**

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94 (t, $J = 7.0$ Hz, 6H), 1.35–1.43 (m, 4H), 1.67–1.75 (m, 4H), 2.77 (t, $J = 7.0$ Hz, 4H); MS *m/z* (%): 191 (82), 109 (34), 98 (46), 81 (100), 70 (21), 53 (21), 41 (14). Anal. Calc. for $C_{12}H_{20}N_2$: C, 74.95; H, 10.48; N, 14.57. Found: C, 74.45; H, 9.54; N, 14.66.

Acknowledgements

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