SUZUKI-MIYaura CROSS-COUPLING REACTION OF DICHLORO-HETEROAROMATICS: SYNTHESIS OF FUNCTIONALIZED DINUCLEOPHILIC FRAGMENTS

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ABSTRACT

The Suzuki-Miyaura cross-coupling reaction has successfully been applied for the synthesis of 4,4'-[6-(diethylamino)-1,3,5-triazine-2,4-diyl]diphenol (**4a**), 4,4'-(pyrimidine-4,6-diyl)diphenol (**4b**), 4,4'-(pyridine-2,6-diyl)diphenol (**4c**). The reaction of 4,6-dichloro-*N,N*-diethyl-1,3,5-triazine-2-amine (**1a**), 4,6-dichloropyrimidine (**1b**) and 2,6-dichloropyridine (**1c**) with *p*-methoxyphenylboronic acid (**2**) in the presence of palladium catalyst followed by demethylation reaction furnished the desired products in good to excellent yields. To test the reactivity of these nucleophiles, the compound **4a** was further reacted with cyanuric chloride to get trimeric fragment (**5a**). All the compounds were characterized by their physical, spectral (¹H and ¹³C NMR and Mass) and microanalytical data. These dinucleophilic fragments (**4a-4c**) having triazine, pyrimidine and pyridine rings, respectively, are excellent future candidates for the construction of large functional hetero-atom bridged macrocycles for diverse applications in host-guest chemistry, supramolecular catalysis, self-assembly and other related fields of supramolecular chemistry in addition to their potential in medicinal chemistry.

Keywords: dichloroheteroaryls, Suzuki-Miyaura cross-coupling, demethylation, dinucleophiles.

INTRODUCTION

Dinucleophilic fragments along with dielectrophiles are important building blocks in the construction of hetero-atom bridged calixaromatics; a new generation macrocyclic host molecules in supramolecular chemistry [1-8]. The size and electronic features of the cavity of such macrocycles is very crucial for their applications and both these factors are in turn directly related to these building blocks. Due to this reason, design and synthesis of such fragments can be considered as an important contribution in the field of supramolecular and material chemistry. Interesting recent applications of giant cavity macrocycle such as sensors, delivery vehicles, gas storage and separation materials [9-15] has opened up a need for large, rigid, reactive and functionalized building blocks required for the construction of related macrocycles.

Carbon-carbon bond forming methods have immense importance in chemistry and among them Suzuki-Miyaura cross-coupling reaction comes out to be the most widely employed, powerful and versatile method [16-24]. The importance of this cross-coupling reaction is not only due to the growing availability of the air and moisture stable boronic acids, but also due to their excellent compatibility with a large variety of functional groups. It is now a general, convenient and applicable method for the formation of various biologically active compounds [25-27], polymers [28], ligands [29] and other useful materials [30]. Apart from these advantages, it is generally thought that when nitrogen heterocycles are employed as one or both of the coupling partners, its efficiency is not as good as for aryl-aryl bond formation [31-33]. However, with the availability of various catalytic systems, this limitation has been largely controlled.

It is now well established that the presence of heteroaromatic moieties such as triazine, pyrimidine, and pyridine impart special properties to the macrocycles by virtue of which they can interact with the anions through anion- π interactions [34, 35], and with metal cations through coordination [1, 8, 36-38] in addition to providing hydrogen bond driven self-assemblies [39-44]. Therefore, we thought it worthwhile to incorporate such important heteroaromatic moieties in nucleophilic and electrophilic fragments needed for the construction of such macrocycles.

Herein, as continuation of our previous study [45], we report the synthesis of dinucleophilic fragments through Suzuki-Miyaura cross coupling reaction. The new functionalized dinucleophilic fragments (**4a-4c**) are therefore attractive candidates for the construction of functionalized giant macrocycles for their possible applications in hydrogen bond and/or coordination driven self assemblies and other related fields of supramolecular and material chemistry. In addition, these reactive dinucleophiles having medicinally important functionalities installed can also be an important intermediates in the synthesis of organic compounds of medicinal interest.

EXPERIMENTAL

General

NMR spectra were recorded at 300 MHz (Bruker) and chemical shifts

are reported in ppm versus tetramethylsilane with either tetramethylsilane or the residual solvent resonance used as an internal standard. Melting points are uncorrected. Solvents were dried according to standard procedures prior to use. All other major chemicals were obtained from commercial sources and used without further purification.

General Procedure for the synthesis of 3

4-Methoxyphenyl-boronic acid (1.3 g, 8.8 mmol), corresponding dichloroheteroaryl compound (4 mmol), Pd(PPh₃)₂Cl₂ (84 mg, 0.12 mmol), and Cs₂CO₃ (4.43 g, 13.6 mmol) were added to a 50 mL round-bottom flask equipped with a stirring bar. The flask was evacuated and refilled with argon four to five times. 1,4-Dioxane (30 mL) was then injected through syringe and heated the reaction mixture under reflux for 3 h with continuous stirring. The reaction mixture was then cooled to room temperature and 50 mL water was added to it. Afterwards, it was extracted with CHCl₃ (4 × 40 mL). The combined extracts were dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was chromatographed on a silica gel column (100-200) with a mixture of petroleum ether and CHCl₃ as the mobile phase (7:1) to give pure **3** as white solid.

4,6-bis(4-methoxyphenyl)-*N,N*-dimethyl-1,3,5-triazine-2-amine (**3a**)

Yield: 88%; m.p. 182–183 °C; ¹H NMR (300 MHz, CDCl₃) δ = 7.83 (d, *J* = 8.7 Hz, 4H, C(3,5)H-phenyl), 7.09 (d, *J* = 8.7 Hz, 4H, C(2,6)H-phenyl), 3.96 (s, 6H, OCH₃), 3.49-3.46 (m, 4H, CH₂-diethylamino), 1.06 (t, *J* = 6.9 Hz, 6H, CH₃-diethylamino); ¹³C NMR (75 MHz, CDCl₃) 174.3, 169.8 (triazine), 157.5 (C₄-phenyl), 136.6, 127.4, 121.2 (C₁, C_{2,6}, C_{3,5}-phenyl), 57.8 (methoxy), 41.2, 12.6 (diethylamino); MS (ESI) *m/z* 365.2 [M+ H] (100%), 366.2 (29), 367.2 (3). Anal. Calcd for C₂₁H₂₄N₄O₂: C, 69.21; H, 6.64; N, 15.37. Found: C, 69.38; H, 6.59; N, 15.43.

4,6-bis(4-methoxyphenyl)pyrimidine (**3b**)

Yield: 85%; m.p. 166–167 °C; ¹H NMR (300 MHz, CDCl₃) δ = 8.96 (s, 1H, pyrimidinyl), 7.73 (s, 1H, pyrimidinyl), 7.72 (d, *J* = 8.7 Hz, 4H, C(3,5)H-phenyl), 7.07 (d, *J* = 8.7 Hz, 4H, C(2,6)H-phenyl), 3.91 (s, 6H, methoxy); ¹³C NMR (75 MHz, CDCl₃) 163.3, 161.2, 156.9 (pyrimidinyl), 153.2 (C₄-phenyl), 136.4, 126.9, 120.8 (C₁, C_{2,6}, C_{3,5}-phenyl), 56.5 (methoxy); MS (ESI) *m/z* 293.2 [M+ H] (100%), 294.1 (26), 295.2 (3). Anal. Calcd for C₁₈H₁₆N₂O₂: C, 73.95; H, 5.52; N, 9.58. Found: C, 73.83; H, 6.73; N, 9.45.

2,6-bis(4-methoxyphenyl)pyridine (**3c**)

Yield: 79%; m.p. 158–159 °C; ¹H NMR (300 MHz, CDCl₃) δ = 8.74 (d, *J* = 1.9 Hz, 2H, pyridinyl), 7.96 (t, *J* = 2.1, 1H, pyridinyl), 7.58 (d, *J* = 8.7 Hz, 4H, C(3,5)H-phenyl), 7.03 (d, *J* = 8.7 Hz, 4H, C(2,6)H-phenyl), 3.87 (s, 6H, methoxy); ¹³C NMR (75 MHz, CDCl₃) 159.9 (C₂, C₆-pyridinyl), 146.0 (C₄-phenyl), 136.2, 131.9, 130.3, 128.3, 114.6 (C_{3,5}, C₄-pyridinyl & C₁, C_{2,6}, C_{3,5}-phenyl), 55.4 (methoxy); MS (ESI) *m/z* 292.2 [M+ H] (100%), 293.2 (23), 367.2 (2). Anal. Calcd for C₁₉H₁₇N₂O₂: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.27; H, 6.02; N, 4.79.

General Procedure for the synthesis of 4

Method A: In a 100 mL round bottom flask containing 50 mL of dry CH₂Cl₂ and 5 mmol of the respective compound **3**, BBr₃ (20 mmol) was carefully added at room temperature with stirring. The reaction mixture was refluxed for 2 h before cooling it to room temperature. Water (50 mL) was then

slowly added to the flask and the mixture was extracted with ethyl acetate (4 x 50 mL), dried (Na₂SO₄) and purified further by column chromatography using petroleum ether and acetone (5:1) to obtain pure **4** as white solid:

Method B: In a 100 mL round bottom flask containing 50 mL of acetic acid, the respective compound **3** (5 mmol) was added while stirring and heated the mixture till reflux. Aqueous HBr (48%) (35 mmol) was then added dropwise. After 30 h of refluxing, the reaction mixture was concentrated on rotary evaporator to a small volume and then added to it 100 mL of water. Precipitates thus formed were filtered and washed thoroughly with water. The residue was then chromatographed on a silica gel column (100-200) with a mixture of petroleum ether and acetone (5:1) as the mobile phase to give pure **4** as white solid.

4,4'-[6-(diethylamino)-1,3,5-triazine-2,4-diyl]diphenol (**4a**)

Yield: 83%; m.p. 243–244 °C; ¹H NMR (300 MHz, Acetone) δ = 8.44 (s, 2H, hydroxy), 7.79 (d, *J* = 8.7 Hz, 4H, C(3,5)H-phenyl), 7.06 (d, *J* = 8.7 Hz, 4H, C(2,6)H-phenyl), 3.48–3.45 (m, 4H, CH₂-diethylamino), 1.05 (t, *J* = 6.9 Hz, 6H, CH₃-diethylamino); ¹³C NMR (75 MHz, Acetone) 173.9, 169.6 (triazinyl), 153.2 (C₄phenyl), 134.3, 127.3, 120.9 (C₁, C_{2,6}, C_{3,5}-phenyl), 41.1, 12.5 (diethylamino); MS (ESI) *m/z* 337.1 [M+ H] (100%), 338.1 (24), 339.2 (2). Anal. Calcd for C₁₉H₂₀N₄O₂: C, 67.84; H, 5.99; N, 16.66. Found: C, 67.77; H, 6.08; N, 16.56.

4,4'-pyrimidine-4,6-diyl]diphenol (**4b**)

Yield: 80%; m.p. 227–228 °C; ¹H NMR (300 MHz, Acetone) δ = 8.39 (s, 2H, hydroxy), 8.93 (s, 1H, pyrimidinyl), 7.71 (s, 1H, pyrimidinyl), 7.67 (d, *J* = 8.7 Hz, 4H, C(3,5)H-phenyl), 7.04 (d, *J* = 8.7 Hz, 4H, C(2,6)H-phenyl); ¹³C NMR (75 MHz, Acetone) 162.9, 160.8, 156.7 (pyrimidinyl), 148.5 (C₄phenyl), 135.3, 125.4, 120.5 (C₁, C_{2,6}, C_{3,5}-phenyl); MS (ESI) *m/z* 265.1 [M+ H] (100%), 266.1 (20), 267.1 (1). Anal. Calcd for C₁₆H₁₂N₂O₂: C, 72.72; H, 4.58; N, 10.60. Found: C, 72.93; H, 4.61; N, 10.49.

4,4'-(pyridine-2,6-diyl)diphenol (**4c**)

Yield: 78%; m.p. 217–218 °C; ¹H NMR (300 MHz, Acetone) δ = 8.36 (s, 2H, hydroxy), 8.73 (d, *J* = 1.9 Hz, 2H, pyridinyl), 7.95 (t, *J* = 2.1, 1H, pyridinyl), 7.53 (d, *J* = 8.7 Hz, 4H, C(3,5)H-phenyl), 7.01 (d, *J* = 8.7 Hz, 4H, C(2,6)H-phenyl); ¹³C NMR (75 MHz, Acetone) 159.7 (C₂, C₆-pyridinyl), 142.0 (C₄-phenyl), 135.7, 130.9, 130.1, 127.8, 114.5 (C_{3,5}, C₄-pyridinyl & C₁, C_{2,6}, C_{3,5}-phenyl); MS (ESI) *m/z* 264.1 [M+ H] (100%), 265.1 (19), 266.1 (2). Anal. Calcd for C₁₇H₁₃N₂O₂: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.49; H, 4.77; N, 5.28.

Synthesis of trimeric fragment **5a**

To an ice-bath cooled solution of cyanuric chloride (0.41 g, 2.2 mmol) in acetone (20 mL) containing K₂CO₃ (finely ground) (0.42 g, 3 mmol), was added dropwise solution of **4a** (0.34 g, 1 mmol) in acetone (30 mL) at room temperature during 1 h. The reaction mixture was stirred for another 6 h, filtered and solvent was removed through a rotary evaporator. The residue was chromatographed on a silica gel column (100-200) with a mixture of petroleum ether and chloroform (6:1) as the mobile phase to give pure **5a** (0.46 g, 73%) as a white solid.

4,6-bis[4-[(4,6-dichloro-1,3,5-triazin-2-yl)oxy]phenyl]-*N,N*-dimethyl-1,3,5-triazin-2-amine (**5a**) m.p. 268–269 °C; δ = 7.91 (d, *J* = 8.7 Hz, 4H, C(3,5)H-phenyl), 7.18 (d, *J* = 8.7 Hz, 4H, C(2,6)H-phenyl), 3.51–3.47 (m, 4H, CH₂-diethylamino), 1.07 (t, *J* = 6.9 Hz, 6H, CH₃-diethylamino); ¹³C NMR (75 MHz, CDCl₃) 175.4, 173.3, 170.1, 169.8 (triazinyl), 159.1 (C₄phenyl), 137.1, 127.3, 120.8 (C₁, C_{2,6}, C_{3,5}-phenyl), 41.5, 12.9 (diethylamino); MS (EI) *m/z* 630 (77), 632 (100), 634 (48). Anal. Calcd for C₂₅H₁₈Cl₄N₁₀O₂: C, 47.49; H, 2.87; N, 22.15. Found: C, 47.53; H, 3.06; N, 22.10.

RESULTS AND DISCUSSION

We initiated our synthesis by reacting 4,6-dichloro-*N,N*-diethyl-1,3,5-triazin-2-amine (**1a**) with 4-methoxyphenylboronic acid (**2**) in the presence of Pd₂(dba)₃/PCy₃, K₃PO₄ and 1,4-Dioxane/H₂O as catalyst, base and reaction solvent, respectively at 100°C for 6 hours (Scheme 1) [45]. However, the reaction provided very low yield of the desired coupled product (entry 1, table 1). Quenching the reaction after 3h, when one of the reactant was completely consumed, the product **3a** was isolated in slightly higher 36% yield (entry 2, table 1). The change of catalyst from Pd₂(dba)₃/PCy₃ to Pd(PPh₃)₄ and Pd(PPh₃)₂Cl₂ while keeping other conditions constant resulted in an increased yield (41% and 62%, respectively) with decreased amount of reaction time (entry 3 and 4, table 1). However, PdCl₂dppf as catalyst provided decreased yield (40%) with increased reaction time (entry 5, table 1). Keeping in view, the reactive nature of dichloro of **1a** with nucleophiles under basic conditions at highly temperatures, it was thought good to avoid aqueous conditions. Therefore, anhydrous 1,4-dioxane was used instead of 1,4-dioxane: water

mixture. As expected, the reaction yield was considerably improved to 70% with Pd(PPh₃)₂Cl₂ catalyst, although, the reaction time was increased from two to twelve hours (entry 6, table 1). Interestingly, the change of base from K₃PO₄ to K₂CO₃ led to increased amount of the product **3a** (77%) with decreased reaction time whereas the use of Cs₂CO₃ further improved the yield (82%) with more reduction in the reaction time (entry 7 and 8, table 1). This improvement may be attributed to the different solubility characteristics of three bases in 1,4-dioxane solvent. This was further supported by slow reaction in toluene solvent most probably due to the poor solubility of Cs₂CO₃ (entry 9, table 1). The reaction in low boiling ether solvents such as DME and THF also resulted in diminished yield with increased reaction time. (entry 10 and 11, table 1). Furthermore, increased catalyst loading from 2 to 3 mol% led to further increase in the yield from 82 to 88% respectively. It is very interesting to mention here that none of the mono-coupled product was obtained in any of the tested reaction conditions. This may be due to the very low reactivity difference in the two chloro groups present in **1a**. The optimized reaction conditions were then used to prepare pyrimidine-core (**3b**) and pyridine-core (**3c**) fragments in 85% and 79% yields, respectively (Scheme 2).

Scheme 1. Synthesis of triazine-core fragment (**3a**) through Suzuki-Miyaura cross-coupling reaction.

Table 1. Optimization of catalyst, base and solvent for the synthesis of **3a**.

No.	Catalyst	Base	Solvent	Temp. (°C)	Time (h)	3 (%) ^b
1	Pd ₂ (dba) ₃ /PCy ₃	K ₃ PO ₄	1,4-Dioxane/H ₂ O	100	06	28
2	Pd ₂ (dba) ₃ /PCy ₃	K ₃ PO ₄	1,4-Dioxane/H ₂ O	100	03	36
3	Pd(PPh ₃) ₄	K ₃ PO ₄	1,4-Dioxane/H ₂ O	100	03	41
4	Pd(PPh ₃) ₂ Cl ₂	K ₃ PO ₄	1,4-Dioxane/H ₂ O	100	02	62
5	PdCl ₂ dppf	K ₃ PO ₄	1,4-Dioxane/H ₂ O	100	04	40
6	Pd(PPh ₃) ₂ Cl ₂	K ₃ PO ₄	1,4-Dioxane	reflux	12	70
7	Pd(PPh ₃) ₂ Cl ₂	K ₂ CO ₃	1,4-Dioxane	reflux	07	77
8	Pd(PPh ₃) ₂ Cl ₂	Cs ₂ CO ₃	1,4-Dioxane	reflux	03	82
9	Pd(PPh ₃) ₂ Cl ₂	Cs ₂ CO ₃	Toluene	reflux	20	80
10	Pd(PPh ₃) ₂ Cl ₂	Cs ₂ CO ₃	DME	reflux	04	80
11	Pd(PPh ₃) ₂ Cl ₂	Cs ₂ CO ₃	THF	reflux	09	74
12 ^a	Pd(PPh ₃) ₂ Cl ₂	Cs ₂ CO ₃	1,4-Dioxane	reflux	03	88

Entries 1–11; catalyst = 2 mol%. ^aCatalyst = 3 mol%. ^bIsolated yields, 4,6-dichloro-*N,N*-diethyl-1,3,5-triazin-2-amine (**1**) (1 equiv.), 4-methoxyphenyl boronic acid (**2**) (2.2 equiv.), base (3.4 equiv.).

Scheme 2. Synthesis of pyrimidine-core (**3b**) and pyridine-core (**3c**) fragments.

After successful synthesis of heteroaryl-centred fragments (**3a-3c**) in good yields, our next target was to demethylate these fragments to get reactive and functionalized dinucleophiles (Scheme 3). For this purpose, we used two different methods. In method A, we used BBr_3 as Lewis acid in dichloromethane solvent which provided us our desired products in 93-95% yield in just 2 hours reaction time while method B where HBr was used in acetic acid solvent furnished dinucleophilic fragments (**4a-4c**) in 78-83% yield after refluxing for 30 hours. Both the methods have their own advantages and disadvantages. BBr_3 is slightly expensive other than handling and work-up problems used in method A. However, it is more convenient to use method B, where there are no such issues despite having long reaction time and slightly less reaction yield.

Scheme 3. Demethylation of **3a-3c** and synthesis of functionalized nucleophilic fragments **4a-4c**.

To test the nucleophilic ability of the synthesized dinucleophiles (**4a-4c**), **4a** having the most electron deficient triazine ring at its centre was selected and reacted with cheap and readily available electrophilic fragment, cyanuric chloride, in the presence of K_2CO_3 as a base in acetone solvent at 0°C (Scheme 4). To our delight, reaction went smoothly providing our desired product in 73% yield. All the products, **3a-3c**, **4a-c** and **5a** were obtained as solids, and their composition and identity was deduced from elemental analysis and spectroscopic data. In ^1H NMR & ^{13}C NMR spectroscopy, all the protons and carbons due to central heteroaryl and phenyl rings were found in their expected chemical shift regions. The mass spectral data of all the synthesized compounds also clearly justified the formation of proposed structures.

Scheme 4. Synthesis of trimeric fragment (**5a**) from dinucleophile (**4a**)

CONCLUSION

In conclusion, we have used Suzuki-Miyaura cross-coupling reaction for the synthesis of functionalized dinucleophilic fragments by reacting dichloroheteroaryls and *p*-methoxyphenylboronic acid followed by demethylation reaction. All the coupling products were obtained in good yields when $\text{Pd}(\text{PPh}_3)_4$ and Cs_2CO_3 was used as catalyst and base, respectively in 1,4-dioxane solvent. The demethylation reaction performed in two different reaction conditions also provided good yields of the desired products. In addition, we have also shown the ability of these dinucleophilic fragments to undergo substitution reaction by treating **4a** with cyanuric chloride, with the production of desired product in good yield. The dinucleophiles having electron deficient triazine ring, pyrimidine and pyridine ring installed at their centres will provide a route to the construction of functionalized giant macromolecules, which may further prove useful host molecules for anion recognition and hydrogen bond/coordination driven self-assembled structures for relevant applications in supramolecular and material chemistry. In addition, these dinucleophiles having medicinally important functionalities and two reactive sites will allow the preparation of various new compounds of medicinal interest.

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