S. Tumkevicius,* J. Dodonova, I. Baskirova, and A. Voitechovicius

Department of Organic Chemistry, Vilnius University, Naugarduko 24, Vilnius LT-03225, Lithuania
*E-mail: sigitas.tumkevicius@chf.vu.lt

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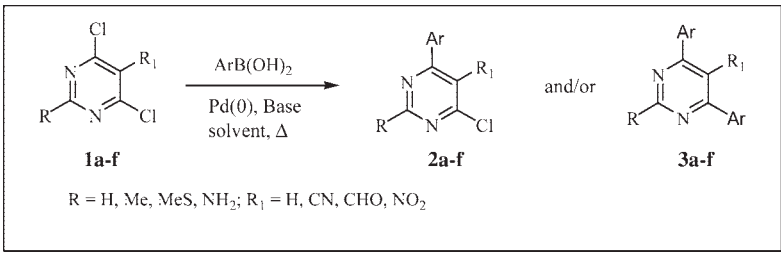

The Suzuki-Miyaura reaction of some 4,6-dichloropyrimidines bearing methylthio-, methyl-, amino-, cyano-, formyl-, and nitro groups in positions 2 and/or 5 of the pyrimidine ring with arylboronic acids has been investigated. Influence of palladium catalyst, ligand, base, and solvent on the reaction outcome was studied. The reaction was found to give the corresponding 4,6-diarylpyrimidines in reasonable yields using $Pd(OAc)_2/PPh_3/K_3PO_4$ or $Pd(PPh_3)_2Cl_2/K_3PO_4$ as catalyst systems.

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INTRODUCTION

In the past two decades, the Suzuki-Miyaura cross-coupling reaction has evolved into one of the most widely used carbon-carbon bond forming processes [1,2]. Its impact on organic synthesis is largely attributed to the fact that it provides an applicable method for the preparation of biaryls. Aryl- and heteroarylpyrimidine derivatives have found applications in many contemporary areas of chemistry, such as, ligands for coordination to metal ions [3], components for molecular recognition studies involving hydrogen bonding and π–π interactions [4], compounds with therapeutic and agrochemical properties [5], fluorophores and electron-transporting compounds in organic light-emitting devices [6]. Although the direct arylation of simple chloropyrimidines is well documented [7], arylation of chloropyrimidines containing various reactive groups and application of the Suzuki-Miyaura reaction for the synthesis of densely substituted arylpyrimidines is explored insufficiently. Continuing our studies on the synthesis of pyrimidine derivatives and related heterocycles [8] in this communication, we present the results of investigation of the palladium-catalyzed cross-coupling reaction of some 4,6-dichloropyrimidines (**1a–f**) bearing methylthio-, methyl-, amino-, cyano-, formyl-, and nitro groups in positions 2 and/or 5 of the pyrimidine ring with selected arylboronic acids.

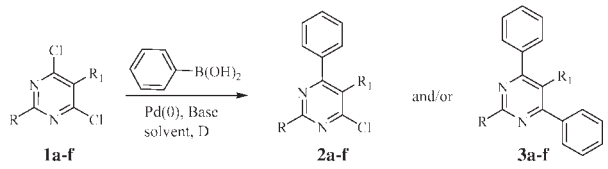
RESULTS AND DISCUSSION

Our investigation started with the cross-coupling of 4,6-dichloropyrimidines **1a–f** with phenylboronic acid (Scheme 1).

Initially, compound **1a** [9] was coupled with a slight excess of phenylboronic acid using $Pd(OAc)_2/PPh_3/Na_2CO_3$ (aqueous 1*M* solution) as a catalyst system in tetrahydrofurane. However, conversion of **1a** was very slow and led to a complex mixture of products from which any product was isolated (Table 1, entry 1). Almost the same result was obtained when Cs_2CO_3 was used as a base instead Na_2CO_3. Change of $Pd(OAc)_2$ to $Pd_2(dba)_3$ did not give the desirable result again—a mixture of **2a** and **3a** with the latter compound as major product was isolated in negligible amount.

It should be mentioned that in spite of the fact that equivalent amount of phenylboronic acid was used both chlorine groups of compound **1a** took part in the coupling reaction (entries 2 and 3). When 2.16 equiv. of phenylboronic acid was used in the reaction the corresponding 4,6-diphenylpyrimidine **3a** was isolated in 29% low yield (entry 4). We decided that a reason of such poor reaction course can be due to the presence of water in the reaction mixture. Chlorine groups in positions 4 and 6 of the pyrimidine ring are very reactive toward various nucleophiles [11]. Thus, in addition to other possible side reactions, such as, dehalogenation, homocoupling, etc., hydrolysis of chlorine groups under the alkaline reaction conditions could also occur to give several side products. Therefore, for further study, K_3PO_4/anhydrous dioxane was chosen as a base/solvent system. Using $Pd(OAc)_2/PPh_3/K_3PO_4$ as a catalyst system, the reaction of **1a** with 1.08 equiv. of phenylboronic acid gave a complex mixture of products from which compound **2a** was isolated in 26% yield (entry 5). When the coupling was carried out with 2.16 equiv. of phenylboronic acid in an

Scheme 1



a: R = SMe, R_1 = CN; **b**: R = SMe, R_1 = CHO; **c**: R = NH_2, R_1 = CHO; **d**: R = NH_2, R_1 = H; **e**: R = Me; R_1 = H; **f**: R = H, R_1 = NO_2

anhydrous dioxane with K_3PO_4 as a base twofold coupling occurred to give compound **3a** in 51% yield (entry 6).

The cross-coupling reaction of 4,6-dichloro-2-methylthiopyrimidine-5-carbaldehyde (**1b**) [9] with 1.08 equiv. phenylboronic acid using $Pd(OAc)_2/PPh_3/K_3PO_4$ in dioxane at 70°C furnished 4-chloro-2-methylthio-6-phenylpyrimidine-5-carbaldehyde (**2b**) in 34% yield (entry 7). A slightly better yield of **2b** (42%) was obtained when $Pd_2(dba)_3$ was used as a catalyst and when the reaction was carried out at room temperature (entry 8). In the reaction of **1b** with 2.16 equiv. of phenylboronic acid at the reflux temperature of dioxane, the corresponding 4,6-diphenylpyrimidine **3b** was obtained in 62% yield (entry 9). Compounds **1c,d** [12,13] bearing strong electron-donating and capable to form complexes with palladium species amino group [14] in the position 2 of the pyrimidine ring reacted with phenylboronic acid only at elevated temperatures. Moreover, possibly due to decreased reactivity of chlorine groups, the cross-coupling reaction with 1.08 equiv. phenylboronic acid did not give monophenyl derivatives **2c,d**. With both substrates **1c,d**, the side reactions competed with the cross-coupling reaction and, at best, formation of both monophenyl and diphenyl derivatives were observed. However, performing the reaction of **1c,d** with double amount of phenylboronic acids using $Pd(OAc)_2/PPh_3/K_3PO_4$ gave **3c,d** in 68% and 59% yields, respectively (entries 10 and 15). To increase the yield of the cross-coupling product **3c** bidentate ligand—1,4-di(triphenylphosphino)butane (dppb) and more electron rich and sterically hindered ligands—tri(*o*-tolyl)phosphane and (2-biphenyl)dicyclohexylphosphine were used in the reaction. However, the side reactions competed again and complex mixtures of products were formed (entries 11 and 12) or no reaction was observed (entry 13). It was found that using $Pd(PPh_3)_2Cl_2$ instead $Pd(OAc)_2$ sometimes gives better results (entries 14 and 16) and there is no necessity to add an additional amount of ligand when $Pd(PPh_3)_2Cl_2$ is used as a catalyst. Under these conditions, 4,6-diphenyl-2-methylpyrimidine (**3e**) was obtained in 73% yield (Table 1, entry 17). The cross-coupling of 4,6-dichloro-5-nitropyrimidine (**1f**) [15] with phenylboronic acid proceeded ambiguously. Nitro group due to its electron-withdrawing nature activates chlorine groups in the positions 4 and 6 of the pyrimidine ring, but this, perhaps, increases chances of side reactions to take place. Thus, after 2 h substrate **1f**

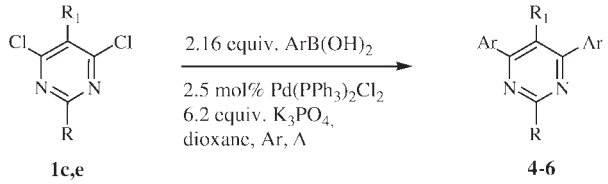
Table 1

Results of the Suzuki-Miyaura reaction of compounds **1a–f** with phenylboronic acid.

Entry	Compd.	$PhB(OH)_2$ Equiv.	Catalyst/ligand	Base/solvent	Reaction temp. (°C)/duration (h)	Product (yield, %)[a]
1	**1a**	1.08	$Pd(OAc)_2/PPh_3$	$Na_2CO_3/H_2O/THF$	Δ/35	ND
2	**1a**	1.08	$Pd(OAc)_2/PPh_3$	$Cs_2CO_3/H_2O/THF$	Δ/33	**2a** + **3a** (traces)[b]
3	**1a**	1.08	$Pd_2(dba)_3/PPh_3$	$Cs_2CO_3/H_2O/THF$	Δ/28	**2a:3a** = 1:3[b]
4	**1a**	2.16	$Pd(OAc)_2/PPh_3$	$Cs_2CO_3/H_2O/THF$	Δ/11	**3a** (29)
5	**1a**	1.08	$Pd(OAc)_2/PPh_3$	K_3PO_4/dioxane	70°C/25	**2a** (26)
6	**1a**	2.16	$Pd(OAc)_2/PPh_3$	K_3PO_4/dioxane	Δ/2.7	**3a** (51)
7	**1b**	1.08	$Pd(OAc)_2/PPh_3$	K_3PO_4/dioxane	70°C/35	**2b** (34)
8	**1b**	1.08	$Pd_2(dba)_3/PPh_3$	K_3PO_4/dioxane	r.t./72	**2b** (42)
9	**1b**	2.16	$Pd(OAc)_2/PPh_3$	K_3PO_4/dioxane	Δ/2.75	**3b** (62)
10	**1c**	2.16	$Pd(OAc)_2/PPh_3$	K_3PO_4/dioxane	Δ/13	**3c** (68)
11	**1c**	2.16	$Pd(OAc)_2$/dppb	K_3PO_4/dioxane	Δ/3	ND
12	**1c**	2.16	$Pd(OAc)_2/P(o\text{-tol})_3$	K_3PO_4/dioxane	Δ/13	ND
13	**1c**	2.16	$Pd(OAc)_2$/(2-biPh)PCy_2	K_3PO_4/dioxane	Δ/5	Recovered **1c**
14	**1c**	2.16	$Pd(PPh_3)_2Cl_2$	K_3PO_4/dioxane	Δ/7	**3c** (85)
15	**1d**	2.16	$Pd(OAc)_2/PPh_3$	K_3PO_4/dioxane	Δ/25	**3d** (59)[c]
16	**1d**	2.16	$Pd(PPh_3)_2Cl_2$	K_3PO_4/dioxane	Δ/3.5	**3d** (51)
17	**1e**	2.16	$Pd(PPh_3)_2Cl_2$	K_3PO_4/dioxane	Δ/3	**3e** (73)[c]
18	**1f**	2.16	$Pd(OAc)_2/PPh_3$	K_3PO_4/dioxane	Δ/2	**3f** (21)

[a] The yields reported are after isolation and purification by the column chromatography.
[b] Determined by ^1H NMR spectra.
[c] Physical properties of compounds **3d,e** corresponded the reported data [10] where they were synthesized from acyclic precursors by cyclocondensation reactions.

Scheme 2



1c,e **4-6**

disappeared from the reaction mixture (TLC data), but the desirable 4,6-diphenyl-5-nitropyrimidine (**3f**) was isolated only in 21% yield (Table 1, entry 18).

Taking into account, the results of the cross-coupling reactions of **1a–e** with phenylboronic acid some 4,6-diarylpyrimidines **4–6** using $Pd(PPh_3)_2Cl_2/K_3PO_4$ as a catalyst system were synthesized (Scheme 2, Table 2).

In conclusion, the performed investigation showed that the synthesis of 6-aryl-4-chloropyrimidines bearing various substituents in the second and fifth positions of the pyrimidine ring by the Suzuki-Miyaura cross-coupling reaction is problematic. The reaction proceeds with the formation of mixtures of mono- and di-arylpyrimidines. Otherwise, the Suzuki-Miyaura cross-coupling reaction of the corresponding 4,6-dichloropyrimidines with double amount of arylboronic acids using $Pd(OAc)_2/PPh_3/K_3PO_4$ or $Pd(PPh_3)_2Cl_2/K_3PO_4$ as catalyst systems in dioxane furnishes the corresponding 2- and/or 5-substituted 4,6-diarylpyrimidines in reasonable yields.

EXPERIMENTAL

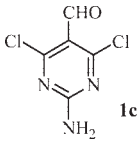
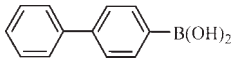
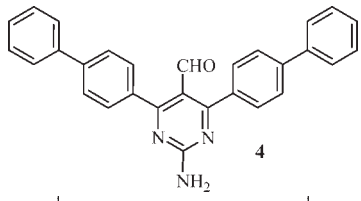
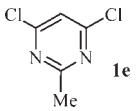
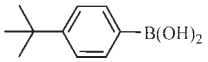
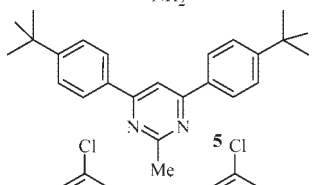
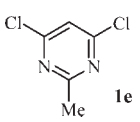
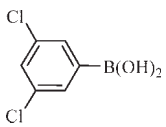
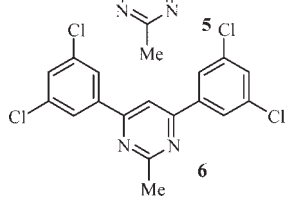
Melting points were determined in open capillaries and are uncorrected. UV spectra were obtained on a PerkinElmer UV-vis spectrophotometer Lambda 20 in ethanol solutions. IR spectra were run on a PerkinElmer FTIR spectrophotometer Spectrum BX II in nujol. ^1H and ^{13}C NMR spectra were recorded on a Varian INOVA spectrometer (300 MHz and 75 MHz, respectively). Chemical shifts are reported in ppm relative to tetramethylsilane. Mass spectrum was obtained on a mass spectrometer Kratos 115-30 (70 eV) by direct insertion probe. Elemental analysis (C and H) were found to be in good agreement (±0.4%) with the calculated values. Column chromatography was performed using Silica gel 60 (0.040–0.063 mm) (Merck). All reactions and purity of the synthesized compounds were monitored by TLC using Silica gel 60 F_{254} aluminum plates (Merck). Visualization was accomplished by UV light.

Typical procedure for the synthesis of compounds 2a,b and 3a–d,f using $Pd(OAc)_2/PPh_3/K_3PO_4$. A solution of compound **1a–d,f** (0.45 mmol) in anhydrous dioxane (20 mL) was flushed with argon and K_3PO_4 (0.61 g, 2.9 mmol), phenylboronic acid (0.118 g, 0.97 mmol) (in case of synthesis **2a,b** 0.3 g, 1.47 mmol K_3PO_4, and 0.06 g, 0.49 mmol phenylboronic acid was used), 2.5 mol % $Pd(OAc)_2$ and 5 mol % PPh_3 were added under stirring and argon flow. The reaction mixture was stirred under argon at a temperature indicated in Table 1. Then dioxane was evaporated under reduced pressure to dryness. To dissolve inorganic salts the residue was treated with water (5 mL) and stirred for 0.5 h. The obtained solution was extracted with chloroform (3 × 25 mL), organic layer was dried with Na_2SO_4, chloroform removed by distillation under reduced pressure, and the solid was purified by column chromatography to give compounds **2a,b**, and **3a–d,f**.

Typical procedure for the synthesis of compounds 3c–e, 4–6 using $Pd(PPh_3)_2Cl_2/K_3PO_4$. A suspension of compounds **1c–e** (0.51 mmol) in dioxane (25 mL) was flushed with argon. Then, K_3PO_4 (3.16 mmol), arylboronic acid (1.1 mmol), 2.5 mol % $Pd(PPh_3)_2Cl_2$ were added under stirring and argon flow. The reaction mixture was refluxed under stirring and argon until compounds **1c–e** consumed (TLC control). Then

Table 2

Coupling of compounds **1c,e** with arylboronic acids.

Compound	Arylboronic acid	Duration (h)	Product	Yield (%)
 **1c**		2	 **4**	50
 **1e**		4	 **5**	65
 **1e**		7	 **6**	50

dioxane was evaporated under reduced pressure. To dissolve inorganic salts, the residue was treated with water (5 mL) and stirred for 0.5 h. The solid obtained was filtered off and purified by crystallization or column chromatography.

4-Chloro-2-methylthio-6-phenylpyrimidine-5-carbonitrile (2a). Compound **2a** was purified by column chromatography using benzene, yield 26%, mp 95–96°C. ^{1}H NMR (deuteriochloroform): δ 2.69 (s, 3H, SCH_3), 7.59–7.63 (m, 3H, 3′,4′,5′-H), 8.08–8.11 (m, 2H, 2′, 6′-H). ^{13}C NMR (deuteriochloroform): δ 14.99, 101.0, 114.9, 129.0, 129.6, 131.9, 134.5, 163.8, 168.8, 176.7. Anal. Calcd. for $C_{12}H_8ClN_3S$: C, 55.07; H, 3.08. Found: C, 55.42; H, 3.01.

4-Chloro-2-methylthio-6-phenylpyrimidine-5-carbaldehyde (2b). Compound **2b** was synthesized by the typical procedure using $Pd(OAc)_2$ (yield 34%) or by analogous procedure using 2.5 mol % $Pd_2(dba)_3$ under conditions presented in Table 1 (yield 42%). Compound **2b** was purified by column chromatography using benzene. mp 140–141°C. UV: λ_{max} 266 (ε 17,000), 287 (ε 15,000). IR: 1694 cm^{-1} (CHO). ^{1}H NMR (deuteriochloroform): δ 2.69 (s, 3H, SCH_3), 7.57–7.62 (m, 5H, C_6H_5), 10.09 (s, 1H, CHO). ^{13}C NMR (deuteriochloroform): δ 14.85, 120.7, 129.0, 130.5, 131.6, 135.2, 160.9, 170.1, 176.2, 188.2. Anal. Calcd. for $C_{12}H_9ClN_2OS$: C, 54.44; H, 3.43. Found: C, 54.78; H, 3.64.

2-Methylthio-4,6-diphenylpyrimidine-5-carbonitrile (3a). Compound **3a** was purified by column chromatography using benzene. Yield 29%, mp 220–221°C. UV: λ_{max} 277 (ε 30,000), 339 (ε 2500). IR: 2220 cm^{-1} (CN). ^{1}H NMR (deuteriochloroform): δ, 2.73 (s, 3H, SCH_3), 7.59–7.62 (m, 6H, 2 × 3′,4′,5′-H), 8.07–8.10 (m, 4H, 2 × 2′,6′-H). ^{13}C NMR (deuteriochloroform), δ, ppm: 14.8, 98.4, 117.7, 129.0, 129.6, 131.96, 135.8, 169.4, 175.9. Anal. Calcd. for $C_{18}H_{13}N_3S$: C, 71.26; H, 4.32. Found: C, 71.17; H, 4.55.

2-Methylthio-4,6-diphenylpyrimidine-5-carbaldehyde (3b). Compound **3b** was purified by column chromatography using benzene. Yield 62%, mp 112–113°C. UV: λ_{max} 275 (ε 20,000). IR: 1697 cm^{-1} (CHO). ^{1}H NMR (deuteriochloroform): δ 2.73 (s, 3H, SCH_3), 7.54–7.57 (m, 6H, 3′,4′,5′-H), 7.68–7.71 (m, 4H, 2′,6′-H), 10.05 (s, 1H, CHO). ^{13}C NMR (deuteriochloroform): δ 14.73, 121.8, 128.7, 130.4, 130.9, 136.8, 168.8, 175.1, 190.6. Anal. Calcd. for $C_{18}H_{14}N_2OS$: C, 70.56; H, 4.61. Found: C, 70.79; H, 4.49.

2-Amino-4,6-diphenylpyrimidine-5-carbaldehyde (3c). Yield 85% using $Pd(PPh_3)_2Cl_2$ and 68% using $Pd(OAc)_2/PPh_3$, mp 149–150°C (dec.) (from 2-propanol). UV: λ_{max} 259 (ε 22,000), 276 sh. (ε 21,000), 314 sh. (ε 11,000). IR: 3468, 3380 sh, 3277 (NH_2), 1687 cm^{-1} (C=O). ^{1}H NMR (deuteriochloroform): δ 5.96 (s, 2H, NH_2), 7.50–7.63 (m, 10H, 2× C_6H_5), 9.89 (s, 1H, CHO). ^{13}C NMR (deuteriochloroform): δ 117.9, 128.6, 129.5, 130.4, 137.5, 162.4, 172.5, 189.2. Anal. Calcd. for $C_{17}H_{13}N_3O$: C, 74.17; H, 5.11. Found: C, 74.00; H, 4.95.

5-Nitro-4,6-diphenylpyrimidine (3f). Compound **3f** was purified by column chromatography using benzene. Yield 21%, mp 117°C. UV: λ_{max} 257 sh. (ε 17,000); 271 (ε 18,000). ^{1}H NMR (deuteriochloroform): δ 7.52–7.60 (m, 6H, 2×[3′,4′,5′-H]), 7.73–7.76 (m, 4H, 2×[2′,6′-H]), 9.41 (s, 1H, 2-H). ^{13}C NMR (deuteriochloroform): δ 128.1, 129.3, 131.5, 133.6, 143.99, 158.3, 158.4. ms (ESI): *m/z* (%) 278 (100) (M +1). Anal. Calcd. for $C_{16}H_{11}N_3O_2$: C, 69.31; H, 4.00. Found: C, 69.22; H, 4.08.

2-Amino-4,6-di(4-biphenyl)pyrimidine-5-carbaldehyde (4). Compound **4** was purified by column chromatography using chloroform. Yield 50%, mp 248–251°C (from chloroform). UV: λ_{max} 204 (ε 67,000), 287 (ε 42,000). IR: 3492, 3400 sh., 3290 (NH_2), 1688 cm^{-1} (C=O). ^{1}H NMR (deuteriochloroform): δ 6.10 (s, 2H, NH_2), 7.44–7.46 (m, 2H, 2 × 4″-H), 7.50–7.55 (m, 4H, 2 × 3″,5″-H), 7.68–7.71 (m, 4H, 2 × 2″,6″-H), 7.77 (s, 8H, 2 × 2′,3′,5′,6′-H), 10.01 (s, 1H, CHO). ^{13}C NMR (dimethyl sulfoxide-d_6): δ 116.99, 126.8, 127.6, 128.6, 129.8, 131.1, 137.5, 140.1, 142.0, 163.4, 171.6, 188.9. ms (ESI): *m/z* (%) 428 (100) (M +1). Anal. Calcd. for $C_{29}H_{21}N_3O$: C, 81.48; H, 4.95. Found: C, 81.64; H, 5.04.

4,6-Di(4-tert-butylphenyl)-2-methylpyrimidine (5). Compound **6** was purified by column chromatography using chloroform. Yield 65%, mp 110–111°C. UV: λ_{max} 206 (ε 34,000), 255 (ε 25,000), 283 sh. (ε 21,000), 297 sh. (ε 24,000), 306 (ε 27,000). ^{1}H NMR (deuteriochloroform): δ 1.41 [s, 18H, 2× $C(CH_3)_3$], 2.88 (s, 3H, 2-CH_3), 7.58 (d, J = 8.7 Hz, 4H, 2 × 3′,5′-H), 7.88 (s, 1H, 5-H), 8.08 (d, J = 8.7 Hz, 4H, 2 × 2′,6′-H). ^{13}C NMR (deuteriochloroform): δ 26.72, 31.50, 35.13, 109.91, 126.17, 127.29, 135.00, 154.33, 164.97, 168.63. Anal. Calcd. for $C_{25}H_{30}N_2$: C, 83.75; H, 8.43. Found: C, 84.06; H, 8.62.

4,6-Bis(3,5-dichlorophenyl)-2-methylpyrimidine (6). Yield 50%, mp 230–231°C (from toluene). UV: λ_{max} 219 (ε 29,000), 247 (ε 12,000), 260 sh. (ε 8100), 295 (ε 12,000), 318 (ε 4600). ^{1}H NMR (deuteriochloroform): δ 2.91 (s, 3H, 2-CH_3), 7.56 (t, ^4J = 1.8 Hz, 2H, 2 × 4′-H), 7.82 (s, 1H, 5-H), 8.07 (d, ^4J = 1.8 Hz, 4H, 2 × 2′,6′-H). ^{13}C NMR (deuteriochloroform): δ 26.6, 110.2, 126.0, 131.0, 136.1, 140.2, 162.9, 169.50. ms (ESI): *m/z* (%) 384 (100) (M^+). Anal. Calcd. for $C_{17}H_{10}Cl_4N_2$: C, 53.16; H. 2,62. Found: C, 53.23; H, 2.57.

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