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Synthesis of *N,N*-Diaryl-(pyridin-3-yl)pyrimidin-2-amine Derivatives and Their Photochemical Properties

Ibrahim Mustafa El-Deeb* · So-Ha Lee†

†*Life Sciences Research Division, Korea Institute of Science and Technology, P.O.Box 131, Cheongryang, Seoul 130-650, Korea*
**Department of Biomolecular Science, University of Science and Technology, 113 Gwahangno, Yuseong-gu, Daejeon 305-333, Korea*
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Abstract : Although the pyrimidine derivatives were obtained in low yields ranging from 8% to 20%, we reported the successful preparation of *N,N*-diaryl-pyrimidin-2-amine derivatives starting from the corresponding 2-aminopyrimidines (1a-1c), by direct palladium-catalyzed arylation using different arylbromides. The reasons of low yields are thought to be the electronic and steric effects by the neighboring aromatic systems. The absorption spectra and photoluminescent spectra of compounds (3a–3g and 4a-4c) were measured using dichloromethane on the concentration of 25 mM by UV–vis spectroscopy and luminescent spectroscopy. Pyrimidine derivatives 4a, 4b, and 4c showed moderate emission maxima at 474 nm, 481 nm, and 367 nm, respectively, while other compounds showed very weak photoluminescence or no photoluminescence at all.

Keywords: Palladium catalyst, N,N-diarylation, 2-aminopyrimidine, phosphine ligand.

1. Introduction

The formation of aryl-nitrogen bond is an important chemical step in the synthesis of a large number of pharmaceuticals[1] and luminescence interest[2]. Because of the importance of this step, the synthetic procedure for *N*-arylation using various aryl halides has been extensively studied. The Ullmann C-N coupling has been a powerful method for the coupling of aryl halides with amines[3]. However, the Ullmann reaction is limited to electron deficient aryl halides and requires harsh reaction conditions. Recently, the palladium-catalyzed *N*-arylation has gained a great attention as a synthetically powerful tool due to the milder reaction conditions and the higher efficiency of the catalytic system[4-12]. A series of modifications and improvements have been made on the palladium-catalyzed *N*-arylation by Buchwald and his group[4-9], and by others[10-13] in order to extend its application to a large variety of amines. The reaction was successful in the arylation of both primary and secondary amines in aromatic and

† Corresponding author
(e-mail : LSH62112kist.re.kr)

heteroaromatic ring systems, using aryl iodides[11], bromides[6], chloride[4] and even triflates[10]. Contrasting for Ullmann reaction, the palladium-catalyzed arylation of amines could be achieved using both electron deficient and electron rich aryl halides[6,14].

We have reported previously the successful *N*-arylation of 2-aminopyrimidine derivatives using both electron rich and electron deficient aryl bromides[14]. However, the diarylation of 2-aminopyrimidines using aryl halides has not been reported yet, which is probably due to the highly electron deficient nature of the amino group of the pyrimidine-2-amines. The only reported synthesis of *N,N*-diaryl-2-aminopyrimidine derivatives was achieved by the reaction of the corresponding 2-chloropyrimidines with secondary aromatic amines[15].

In this work, we succeed in the preparation of *N,N*-diaryl-2-aminopyrimidine derivatives using different 2-aminopyrimidines, and also report the preliminary photoluminescent properties of the synthesized pyrimidine derivatives.

2. Experimental

2.1. General

^{1}H-NMR (300 MHz) was recorded on a Bruker Avance 300 spectrometer with TMS as an internal reference. The IR spectra were recorded on Perkin Elmer Spectrum GX spectrometer. UV-visible absorbance spectra and luminescence spectra were recorded on S-2130 spectroscopy and RF-5301-PC luminescent spectroscopy, respectively. Melting points were taken on a Thomas-Hoover capillary melting apparatus and were uncorrected. Column chromatography was performed on Merck silica gel 60 (230-400 mesh). TLC was carried out using glass sheets precoated with silica gel 60 F254 prepared by E. Merck. All the commercially available reagents were obtained from Aldrich and Tokyo Kasei Chemical and generally used without further purification.

2.2. General procedure for the synthesis of compounds 2a-2c.

A mixture of the appropriate 4-(6-substituted pyridin-3-yl)pyrimidin-2-amine (0.40 mmol), 2-bromonaphthalene (90 mg, 0.44 mmol), dichlorobis(triphenylphosphine) palladium(II) (28 mg, 0.04 mmol), Xantphos (23 mg, 0.04 mmol), and NaO*t*-Bu (58 mg, 0.60 mmol) was refluxed in toluene (5 mL) under N_2 atmosphere for 8 h. The reaction mixture was cooled at ice bath to allow the solid product. The product was filtered, washed with cold toluene, then with water.

2.2.1. 4-(Pyridine-3-yl)pyrimidine-2 -amine (2a)

The synthetic procedure of the compound 2a is explained in literatre[14].

2.2.2. *N*-(Naphthalen-2-yl)-4-(6-phenylpyridin-3-yl)pyrimidin-2-amine (2b).

It was obtained as yellowish green crystals. 126 mg (84%); m.p. 210-211 °C; IR (KBr) υ /cm^{-1}: 3351, 1573, 1455, 813; ^{1}H-NMR (DMSO-d_6) δ 7.36 (t, *J* = 7.8 Hz, 1H), 7.45-7.57 (m, 4H), 7.62 (d, *J* = 5.4 Hz, 1H), 7.81-7.89 (m, 4H), 8.21 (d, *J* = 8.4 Hz, 3H), 8.57 (s, 1H), 8.64-8.70 (m, 2H), 9.49 (d, *J* = 1.8 Hz, 1H), 10.04 (s, 1H, NH).

2.2.3. *N*-(Naphthalen-2-yl)-4-(6-(pyridin-3-yl)pyridin-3-yl)-pyrimidin-2-amine (2c).

It was obtained as yellow crystals. 119 mg (79%). m.p. 215-216 °C; IR (KBr) υ/cm^{-1}: 3260, 1571, 1454, 802; ^{1}H-NMR (DMSO-d_6): δ 7.36 (t, *J* = 7.2 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.58 (dd, *J* = 3.3, 4.8 Hz, 1H), 7.63 (d, *J* = 5.1 Hz, 1H), 7.80-7.89 (m, 4H), 8.31 (d, *J* = 8.4 Hz, 1H), 8.55-8.57 (m, 2H), 8.69-8.71 (m, 3H), 9.38 (d, *J* = 1.2 Hz, 1H), 9.52 (d, *J* = 1.5 Hz, 1H), 10.02 (s, 1H, NH).

2.3. General procedure for the synthesis of compounds 3a-3g.

A mixture of the appropriate *N*-(naphthalen-2-yl)pyrimidin-2-amine (2a-2c) (0.168 mmol), the appropriate aryl bromide (0.20 mmol), dichlorobis (triphenylphosphine) palladium(II) (24 mg, 0.034 mmol), Xantphos (20 mg, 0.034 mmol), and NaO^{t}Bu (32 mg, 0.34 mmol) was refluxed in toluene (3 mL) under N_2 atmosphere for 24 h. The reaction mixture was filtered off while hot. The filtrate was concentrated, and then purified by column chromatography in compounds 3a-3g (silica gel, ethyl acetate-hexane, 1:1 for 3a-3g, ethyl acetate-hexane, 1:3 for 3d-3g).

2.3.1. *N*-(Naphthalen-2-yl)-N-phenyl-4-(pyridin-3-yl)pyrimidin-2-amine (3a).

It was obtained as yellow powder. 8 mg (13%); m.p. 83-85°C; IR (KBr) υ/cm^{-1}: 1565, 1415, 1262, 1098, 1024, 802; ^{1}H-NMR ($CDCl_3$): δ 7.21 (d, *J* = 5.3 Hz, 1H), 7.40-7.48 (m, 8H), 7.55 (d, *J* = 8.3 Hz, 1H), 7.69-7.73 (m, 2H), 7.86-7.90 (m, 2H), 8.28 (d, *J* = 7.2 Hz, 1H), 8.53 (d, *J* = 5.1 Hz, 1H), 8.68 (d, *J* = 4.7, Hz), 9.13 (s, 1H).

2.3.2. *N,N*-bis(Naphthalen-2-yl)-4-(pyridin-3-yl)pyrimidin-2-amine (3b).

It was obtained as brown powder. 13 mg (18%); m.p. 103-105°C; IR (KBr) υ/cm^{-1}: 1565, 1413, 1262, 1097, 1024 (C-N), 802; ^{1}H-NMR ($CDCl_3$): δ 7.25 (d, *J* = 5.1 Hz, 1H), 7.35-7.50 (m, 5H), 7.60 (dd, *J* = 1.8, 6.9 Hz, 2H), 7.70-7.92 (m, 8H), 8.23 (d, *J* = 8.1 Hz, 1H), 8.54 (d, *J* = 5.2 Hz, 1H), 8.66 (d, *J* = 3.3 Hz, 1H), 9.14 (s, 1H).

2.3.3. *N*-(Naphthalen-2-yl)-*N*-(4-biphenyl)-4-(pyridin-3-yl)pyrimidin-2-amine (3c).

It was obtained as pink powder. 14 mg (19%); m.p. 254-255°C; IR (KBr) υ/cm^{-1}: 1561, 1450, 1262, 1095, 1024, 806; ^{1}H-NMR ($CDCl_3$): δ 7.31-7.95 (m, 18H), 8.67 (d, *J* = 7.7 Hz, 1H), 8.81-8.83 (m, 2H), 9.30 (s, 1H); PL λ_{max} = 410 nm (CH_2Cl_2, 25 μM).

2.3.4. *N*-(Naphthalen-2-yl)-*N*-phenyl-4-(6-phenylpyridin-3-yl)pyrimidin-2-amine (3d).

It was obtained as yellow powder. 6 mg (11%); m.p. 175-176°C; IR (KBr) υ/cm^{-1}: 1565, 1416, 1262, 1097, 1022, 802; ^{1}H-NMR ($CDCl_3$): δ 7.42-7.60 (m, 12H), 7.71-7.75 (m, 2H), 7.85-7.92 (m, 3H), 8.08 (d, *J* = 5.7 Hz, 2H), 8.38 (d, *J* = 9.0 Hz, 1H), 8.55 (d, *J* = 5.1 Hz, 1H), 9.26 (s, 1H); PL λ_{max} = 464 nm (CH_2Cl_2, 25 μM).

2.3.5. *N,N*-bis(Naphthalen-2-yl)-4-(6-phenylpyridin-3-yl)pyrimidin-2-amine (3e).

It was obtained as yellow powder. 11 mg (17%); m.p. 206-207°C; IR (KBr) υ/cm^{-1}: 1574, 1454, 812; ^{1}H-NMR ($CDCl_3$): δ 7.26-7.55 (m, 12H), 7.69 (dd, *J* = 2.1, 6.6 Hz, 1H), 7.81-7.97 (m, 5H), 8.11 (d, *J* = 6.6 Hz, 2H), 8.40 (s, 1H), 8.51 (dd, *J* = 2.1, 6.3 Hz, 1H), 8.59 (d, *J* = 5.1 Hz, 1H), 9.42 (s, 1H); PL λ_{max} = 499 nm (CH_2Cl_2, 25 μM).

2.3.6. *N,N*-bis(Naphthalen-2-yl)-4-(6-(pyridin-3-yl)pyridin-3-yl)-pyrimidin-2-amine (3f).

It was obtained as yellowish brown powder. 5 mg (8%); m.p. 210-212°C; IR (KBr) υ/cm^{-1}: 1565, 1419, 801; ^{1}H-NMR ($CDCl_3$): δ 7.30 (d, *J*= 5.1 Hz, 1H), 7.45 (t, *J* = 5.1 Hz, 4H), 7.61 (dd, *J* = 2.1, 6.6 Hz, 3H), 7.71-7.75 (m, 4H), 7.81 (d, *J* = 8.4 Hz, 1H), 7.87-7.93 (m, 4H), 8.30 (dd, *J* = 2.4, 6.3 Hz, 1H), 8.56 (d, *J* = 5.1 Hz, 1H), 8.61 (d, *J* = 8.1 Hz, 1H), 8.70 (d, *J* = 2.4 Hz, 1H), 9.24 (s, 1H), 9.30 (s, 1H).

2.3.7. *N*-(Naphthalen-2-yl)-*N*-(4-biphenyl)-4-(6-(pyridin-3-yl)-pyridin-3-yl)pyrimidin-2-amine (3g).

It was obtained as yellow powder. 4 mg

(6%); m.p. 172-174°C; IR (KBr) υ/cm^{-1}: 1568, 1420, 807; ^{1}H-NMR ($CDCl_3$): δ 7.27 (d, *J*= 2.7 Hz, 2H), 7.28-7.94 (m, 17H), 8.28 (d, *J*= 6.9 Hz, 1H), 8.43 (d, *J* = 7.8 Hz, 1H), 8.56 (d, *J* = 5.0 Hz, 1H), 8.68 (d, *J* = 2.1 Hz, 1H), 9.24 (s, 2H).

2.4. General procedure for the synthesis of compounds 4a-4c.

A mixture of the appropriate 4-(6-substituted pyridin-3-yl)pyrimidin-2-amine (**1a-1b**) (0.29 mmol), the appropriate aryl bromide (0.87 mmol), dichlorobis (triphenylphosphine) palladium(II) (61 mg, 0.087 mmol), Xantphos (50 mg, 0.087 mmol), and $CsCO_3$ (280 mg, 0.87 mmol) was heated in DMF (3 mL) under N_2 atmosphere for 10 h. The reaction mixture was left to cool, and then poured over crushed ice while stirring. The aqueous solution was extracted with dichloromethane (100 mL x 2). The organic layer was separated, dried over anhydrous $MgSO_4$, and then evaporated under vacuum to yield the crude product, which was crystallized from ethanol to yield the pure target compounds.

2.4.1. *N,N*-Diphenyl-4-(pyridin-3-yl)pyrimidin-2-amine (4a).

It was obtained as yellow crystals. 12 mg (13%); m.p. 121-122°C; IR (KBr) υ/cm^{-1}: 1582, 1447, 1303, 1095, 1025 (C-N), 807; ^{1}H-NMR ($CDCl_3$): δ 7.06-7.77 (m, 12H), 8.38 (d, *J* = 7.8 Hz, 1H), 8.53 (d, *J* = 5.1 Hz, 1H), 8.74 (d, *J* = 4.2 Hz, 1H), 9.31 (s, 1H); PL λ_{max} = 474 nm (CH_2Cl_2, 25 μM).

2.4.2. *N,N*-Diphenyl-4-(6-phenylpyridin-3-yl)pyrimidin-2-amine (4b).

It was obtained as yellowish brown powder. 10 mg (8%); m.p. 170-171°C; IR (KBr) υ/cm^{-1}: 1576, 1448, 1297, 1072, 1018, 808; ^{1}H-NMR ($CDCl_3$): δ 7.10 (t, *J*= 7.2 Hz, 1H), 7.23 – 7.56 (m, 11H), 7.74 (d, *J*= 8.1 Hz, 2H), 7.90 (d, *J* = 8.3 Hz, 1H), 8.10 (d, *J* = 7.4 Hz, 2H), 8.45 (d, *J* = 7.8 Hz, 1H), 8.54 (d, *J* = 5.1 Hz, 1H), 9.40 (s, 1H); PL λ_{max} = 481 nm (CH_2Cl_2, 25 μM).

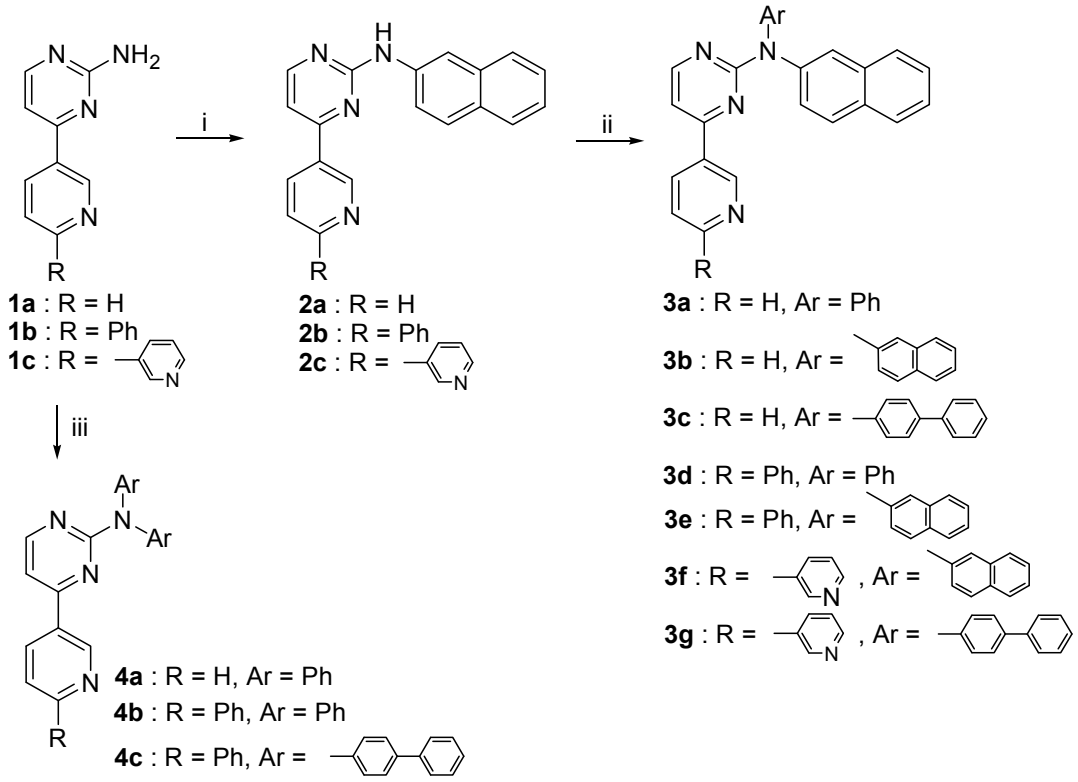
2.4.3. *N,N*-bis(4-Biphenyl)-4-(6-phenylpyridin-3-yl)pyrimidin-2-amine (4c).

It was obtained as yellow fluffy plates. 32 mg (20%); m.p. 216-217°C; IR (KBr) υ/cm^{-1}: 1578, 1422, 1296, 1074, 1018, 826; ^{1}H-NMR ($CDCl_3$): δ 7.25-7.74 (m, 20H), 7.81 (d, *J* = 8.1 Hz, 2H), 7.92 (d, *J* = 8.4 Hz, 1H), 8.10 (d, *J* = 7.5 Hz, 2H), 8.48 (d, *J* = 8.1 Hz, 1H), 8.55 (d, *J* = 5.7 Hz, 1H), 9.42 (s, 1H); PL λ_{max} = 367 nm (CH_2Cl_2, 25 μM).

3. Results and Discussion

Three different pyrimidine-2-amines (1a-1c) were used as substrates for *N,N*-diarylation. These amines were prepared according to the reported literature procedures [16] and the procedures used in our laboratory [14]. The starting amines (1a-1c) were refluxed with 2-bromonaphthalene in toluene under nitrogen atmosphere, using dichlorobis (triphenylphosphine)Pd(II) as a catalyst, Xantphos as a phosphine ligand, and sodium *tert*-butoxide as a base. The required *N*-arylamines 2a, 2b and 2c were obtained in moderate yields of 56%, 48% and 79%, respectively (Scheme 1).

The reaction of *N*-(naphtalen-2-yl) pyrimidin-2-amine derivatives (2a-2c) with various aryl bromides to yield *N,N*-diarylpyrimidin-2-amines (3a-3g) failed to proceed in good yields, in spite of a large number of reaction trials using palladium catalyst. However, the optimum condition for preparation of compounds 3a-3g required the use of double the amount of the palladium catalyst and ligand used for the preparation of the mono-aryl derivatives. Further increase in the amount of palladium catalyst (over 20 mol%) in attempts to increase the product yield resulted in the production of numerous oxidation-reduction side products. Switching



Reaction conditions and yields: i) 2-bromonaphthalene, dichlorobis (triphenylphosphine)Pd(II), Xantphos, NaO^{t}Bu, toluene, N_2, reflux, 8h, 56% (2a), 48% (2b), 79% (2c), ii) Ar-Br, dichlorobis(triphenylphosphine)Pd(II), Xantphos, NaO^{t}Bu, toluene, N_2, reflux, 24h, iii) Ar-Br, dichlorobis(triphenyl phosphine)Pd(II), Xantphos, $CsCO_3$, DMF, N_2, reflux, 10h.

Scheme 1. Synthesis of *N,N*-diarylpyrimidine derivatives

the solvent to other aromatic hydrocarbons (benzene or xylene) or other solvents such as dioxane and THF was found to either decrease the yield or block the reaction completely. Replacement of sodium *tert*-butoxide by other bases such as K_2CO_3 or $CsCO_3$ was also accompanied by hindrance of the reaction.

The low product yield might be owed to two major factors. The first one is the electronic effect caused by the two aromatic systems attached to the secondary amino group which makes it to be highly electron deficient, and therefore inert towards nucleophilic substitution reactions. The second factor is probably the steric effect caused by the bulky groups attached to the secondary amine NH, which makes the approach of the aryl halide to the NH group very difficult.

N,N-Diaryl-2-aminopyrimidines 4a-4c were prepared starting from the amine in one step without the isolation of the mono-aryl amine. Amines 1a and 1b were allowed to react with three equivalents of the appropriate aryl bromide in DMF under nitrogen atmosphere, using dichlorobis(triphenylphosphine)Pd(II) and

Xantphos, while replacing sodium *tert*-butoxide with $CsCO_3$, The target compounds 4a, 4b and 4c were obtained in low yields of 13%, 8% and 20%, respectively. The reaction conditions and yields for the synthesis of the compounds 3a-4c is explained in Table 1.

The IR and ^{1}H-NMR spectra of the target compounds (3a-3g and 4a-4c) were consistent with the assigned structures. The highly deshielded NH-proton ($\delta \approx 10$ ppm) of the mono-aryl derivatives was found to disappear in the ^{1}H-NMR spectra of *N,N*-diaryl derivatives. Also in the IR spectra, the characteristic NH-band in the range of 3200–3400 cm^{-1} was found to disappear in the IR

Table 1. Reaction conditions and yields of *N.N*-diarylation products 3a-4c.

compound no.	R	Ar	Reaction conditions	yield (%)
3a	H	phenyl	compound 2a, phenylbromide, dichlorobis (triphenylphosphine)palladium (II), NaO^{t}Bu, Xantphos, toluene	13
3b	H	2-naphthyl	compound 2a, 2-naphthylbromide, dichlorobis(triphenylphosphine)palladium (II), NaO^{t}Bu, Xantphos, toluene	18
3c	H	4-biphenyl	compound 2a, 4-biphenylbromide, dichlorobis(triphenylphosphine)palladium (II), NaO^{t}Bu, Xantphos, toluene	19
3d	phenyl	phenyl	compound 2b, phenylbromide, dichlorobis (triphenylphosphine)palladium (II), NaO^{t}Bu, Xantphos, toluene	11
3e	phenyl	2-naphthyl	compound 2b, 2-naphthylbromide, dichlorobis(triphenylphosphine)palladium (II), NaO^{t}Bu, Xantphos, toluene	17
3f	3-pyridinyl	2-naphthyl	compound 2c, 2-naphthylbromide, dichlorobis(triphenylphosphine)palladium (II), NaO^{t}Bu, Xantphos, toluene	8
3g	3-pyridinyl	4-biphenyl	compound 2c, 4-biphenylbromide, dichlorobis(triphenylphosphine)palladium (II), NaO^{t}Bu, Xantphos, toluene	7
4a	H	phenyl	compound 1a, phenylbromide, dichlorobis (triphenylphosphine)palladium (II), $CsCO_3$, Xantphos, DMF	13
4b	phenyl	phenyl	compound 1b, phenylbromide, dichlorobis (triphenylphosphine)palladium (II), $CsCO_3$, Xantphos, DMF	8
4c	phenyl	4-biphenyl	compound 1b, 4-biphenylbromide, dichlorobis(triphenylphosphine)palladium (II), $CsCO_3$, Xantphos, DMF	20

spectra of the diaryl products. The remaining protons of the target compounds were observed in the expected regions of ^{1}H-NMR spectra.

The absorption spectra and photoluminescent spectra of the compounds (3a–3g and 4a-4c) were measured using dichloromethane on the concentration of 25 mM by UV–vis. spectroscopy and luminescent spectroscopy. The pyrimidine derivatives 3a, 3b, 3f, and 3g did not show emission maxima at all, contrary to our expectation. Compounds 3c, 3d, and 3f showed very weak emission maxima at 410 nm, 464 nm, and 499 nm, respectively, while compounds 4a, 4b, and 4c showed moderate emission maxima at 474 nm, 481 nm, and 367 nm, respectively.

4. Conclusion

Although the pyrimidine derivatives were obtained in low yields ranging from 8% to 20%, we reported the successful preparation of *N,N*-diaryl-2-aminopyrimidine derivatives starting from the corresponding 2-aminopyrimidines (1a-1c), by direct palladium-catalyzed arylation using different arylbromides. We think that the first reason of low yield is the electronic effect caused by the two aromatic systems attached to the secondary amino group which makes it to be highly electron deficient, and therefore inert towards nucleophilic substitution reactions. The second reason of low yield is thought to be probably the steric effect caused by the bulky groups attached to the secondary amine NH, which makes the approach of the aryl halide to the NH group very difficult. Compounds 4a, 4b, and 4c showed moderate emission maxima at 474 nm, 481 nm, and 367 nm, respectively, while other compounds showed very weak photoluminescence or no photoluminescence at all.

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