Pyrrolo[2,3-*d*]pyrimidine-Core-Extended π-Systems: Synthesis of 2,4,7-Triarylpyrrolo[2,3-*d*]pyrimidines

Sigitas Tumkevicius,* Jelena Dodonova

Vilnius University, Faculty of Chemistry, Department of Organic Chemistry, Naugarduko 24, 03225 Vilnius, Lithuania
Fax +370(5)2330987; E-mail: sigitas.tumkevicius@chf.vu.lt

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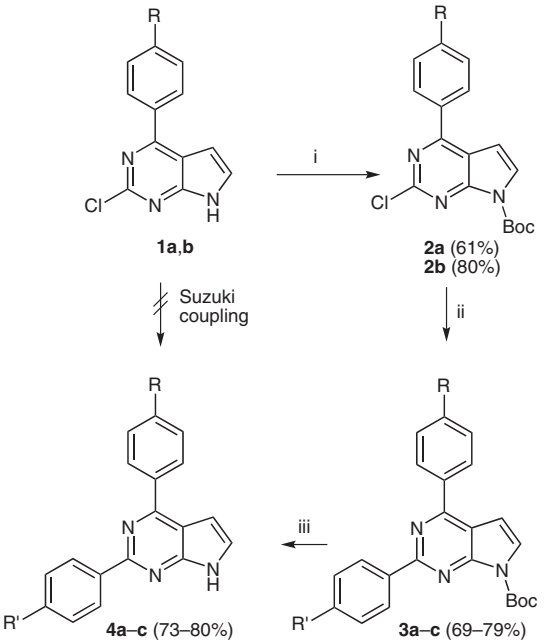
Abstract: A simple and facile synthesis of novel fluorescent pyrrolo[2,3-*d*]pyrimidines with various aryl and heteroaryl assemblies in positions 2, 4, and 7 of the heterocycle by combination of the Suzuki cross-coupling and copper(I) iodide N-arylation reactions of chloropyrrolo[2,3-*d*]pyrimidines with arylboronic acids and haloarenes is described.

Key words: pyrrolo[2,3-*d*]pyrimidine, oligoarylenes, Suzuki coupling, N-arylation, fluorescence

The introduction of a heteroaryl moiety into extended π-systems often brings about a number of interesting properties that are useful in the development of advanced electronic and photonic materials.[1] Owing to the light-emitting,[2] self-assembling,[3] and complex-forming[4] properties with metal ions or organic molecules such materials are of interest in biological, chemical, and materials science. Although the parent pyrrolo[2,3-*d*]pyrimidine is known to possess fluorescence properties[5] and some derivatives were demonstrated to be suitable for probing the structure of DNA,[6] exploitation of this heteroaromatic core in functional π-systems is insufficient. Only recently, pyrrolo[2,3-*d*]pyrimidine-core-based oligoarylenes have been synthesized and elucidated as blue-light emitters.[7] To develop more efficient fluorescent materials we report herein on the sequential assembly of π-systems, such as aryl groups, onto the pyrrolo[2,3-*d*]pyrimidine core as a useful method for the construction of more π-extended triarylpyrrolo[2,3-*d*]pyrimidines bearing various aryl branches in positions 2, 4, and 7 of the heterocycle. Introduction of different aryl functionalities at various positions of pyrrolo[2,3-*d*]pyrimidine was not only synthetically challenging but is also important for tuning of structure and photophysical properties of the pyrrolo[2,3-*d*]pyrimidine derivatives as well as for construction of biologically active pyrrolo[2,3-*d*]pyrimidine derivatives. Arylpyrrolo[2,3-*d*]pyrimidines were found to display a wide range of biological activities, such as antimicrobial,[8a] inhibition of protein kinases[8b–e] and dihydrofolate reductase,[8f] antagonist effects to receptors,[8g] and cytostatic effects.[8h]

Earlier we found that the Suzuki coupling of 2,4-dichloropyrrolo[2,3-*d*]pyrimidine with arylboronic acids depending on the amount of arylboronic acid and reaction conditions proceeded to give 4-aryl-2-chloro- (**1**) or 2,4-diarylpyrrolo[2,3-*d*]pyrimidines (**4**, R = R′)[7], respectively. However, attempts to synthesize 2,4-diarylpyrrolopyrimidines by the Suzuki coupling of **1** with arylboronic acids failed. Otherwise, we observed that Boc group at the position 7 of pyrrolo[2,3-*d*]pyrimidine increases reactivity of 2-chlorine group of pyrrolo[2,3-*d*]pyrimidine in the Suzuki coupling.[7] Therefore, for the synthesis of pyrrolo[2,3-*d*]pyrimidines **4** with different aryl groups in positions 2 and 4 from 4-aryl-2-chloropyrrolo[2,3-*d*]pyrimidines (**1**) we have developed a protocol consisting of *N*(7) protection with Boc group, Suzuki coupling, and *N*(7)-deprotection reactions (Scheme 1). Synthesis of *N*(7)-Boc derivatives **2** was carried out by the reaction of **1** with Boc_2O in CH_2Cl_2 in the presence of DMAP and DIPEA.[9] The Suzuki coupling of **2** with arylboronic acids using $Pd(OAc)_2$/P(2-biphenyl)Cy_2/K_3PO_4 as a catalyst system proceeded at reflux in dry 1,4-dioxane.[10] Deprotection of *N*(7) of **3** to give compounds **4** in good yields



Scheme 1 *Reagents and conditions*: i) Boc_2O, DMAP, DIPEA, CH_2Cl_2; ii) R′$C_6H_4B(OH)_2$, $Pd(OAc)_2$, P(2-biPh)Cy_2, K_3PO_4, 1,4-dioxane, reflux; iii) HCl, Me_2CO, reflux.

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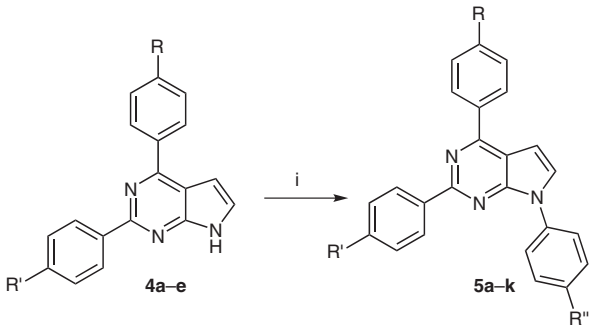
was achieved by reflux **3** with concentrated hydrochloric acid in acetone[11] or trifluoracetic acid in CH_2Cl_2.

Products **4a–c** thus obtained and pyrrolo[2,3-*d*]pyrimidines **4d**,**e**, prepared directly by the Suzuki coupling of 2,4-dichloro[2,3-*d*]pyrimidine with arylboronic acids as described previously,[7] were subjected to N-arylation (Scheme 2). The catalyst system CuI/*trans*-1,2-diaminocyclohexane/K_3PO_4 was used as the catalyst system of choice.[12] Employing other ligands and bases in the reaction gave worse results. For example, the reaction of **4e** with iodobenzene using CuI/1,10-phenanthroline/Cs_2CO_3 as a catalyst system furnished the target compound **5h** in only 49% yield, while using CuI/*trans*-1,2-diaminocyclohexane/K_3PO_4 as a catalyst system, compound **5h** was obtained in 85% yield (Table 1, entry 8).

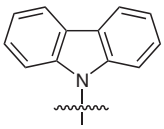
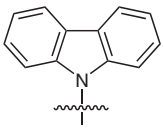
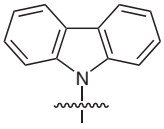
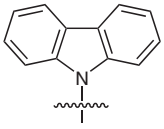
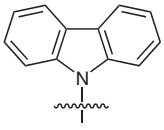
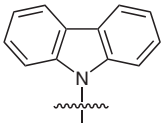
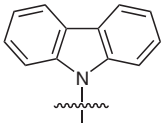
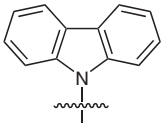
To achieve full conversion of compounds **4** in the N-arylation reaction an amount of CuI ranging from 3–10 mol% was used.[13] The reaction proceeded at reflux temperature of dioxane and worked well with aryl iodides and bromides bearing electron-donating or electron-withdrawing groups. The yields of 2,4,7-triarylpyrrolo[2,3-*d*]pyrimidines varied from good to excellent (Table 1). Lower yields of compounds **5i–k** (Table 1, entries 9–11) were obtained, presumably because of their more complex purification by column chromatography.



Scheme 2 *Reagents and conditions:* i) 4-R″C_6H_4I(Br), CuI, (±)-*trans*-1,2-diaminocyclohexane, K_3PO_4, 1,4-dioxane, reflux.

The synthesized 2,4,7-triarylpyrrolo[2,3-*d*]pyrimidines were subjected to optical absorption and fluorescence studies. The compounds in dilute THF solution exhibited strong absorption with their absorption maxima positioned in the range of 256–342 nm. The pyrrolo[2,3-*d*]pyrimidine derivatives in THF solution were found to exhibit fluorescence with emission maxima located in the range of 403–540 nm and fluorescence quantum yields ranging from 2% to 40%. The fluorescence lifetimes estimated in THF solutions span the range from 2.6 ns to 12.2 ns.

Table 1 Preparation of Compounds **5**

Entry	Compd **5**	R	R′	R″	CuI (mol%)	Reaction time (h)	Yield (%)
1	**5a**	H	OEt	CN	3	6	90
2	**5b**	H	Ph	CN	10	25	95
3	**5c**	H	Ph	OMe	5	11	93
4	**5d**	OMe	OEt	H	5	9.5	99
5	**5e**	H	H	OMe	5	12	92
6	**5f**	H	H	NPh_2	6	22	72
7	**5g**	H	H	CN	5	12	82
8	**5h**			H	5	10	85
9	**5i**			OMe	7	19	51
10	**5j**			CN	7	22	57
11	**5k**			NPh_2	8	29	59

In summary, we have developed a simple synthetic strategy that permits the assembly of aromatic π-systems onto a pyrrolo[2,3-*d*]pyrimidine core in a programmable and diversity-oriented format. A more detailed study of the photophysical properties of the synthesized compounds in various solvents and in a solid state and further variations of oligoarylene branches at the pyrrolo[2,3-*d*]pyrimidine framework are currently being carried out, and the results will be reported in due course.

Acknowledgment

Research Council of Lithuania is greatly acknowledged for financial support (project No. MIP-65/2010).

References and Notes

(1) (a) Hughes, G.; Bryce, M. R. *J. Mater. Chem.* **2005**, *15*, 94. (b) Wong, W. Y.; Zhou, G.-J.; Yu, X.-M.; Kwok, H.-S.; Lin, Z. *Adv. Funct. Mater.* **2007**, *17*, 315. (c) Tao, Y.; Wang, Q.; Yang, C.; Wang, Q.; Zhang, Z.; Zou, T.; Qin, J.; Ma, D. *Angew. Chem. Int. Ed.* **2008**, *47*, 8104.

(2) (a) Wong, K.-T.; Hung, T. S.; Lin, Y.; Wu, C.-C.; Lee, G.-H.; Peng, S.; Chou, C. H.; Su, Y. O. *Org. Lett.* **2002**, *4*, 513. (b) Wu, C. C.; Lin, Y. T.; Chiang, H. H.; Cho, T. Y.; Chen, C. W.; Wong, K. T.; Liao, Y. L.; Lee, G. H.; Peng, S. M. *Appl. Phys. Lett.* **2002**, *81*, 577. (c) Yamaguchi, Y.; Kobayashi, S.; Wakamiya, T.; Matsubara, Y.; Yoshida, Z. *Angew. Chem. Int. Ed.* **2005**, *44*, 7040. (d) Achelle, S.; Ramondenc, Y.; Marsais, F.; Ple, N. *Eur. J. Org. Chem.* **2008**, 3129. (e) Jaung, J.-Y. *Dyes Pigments* **2006**, *71*, 245.

(3) (a) Petitjean, A.; Khoury, R. G.; Kyritsakas, N.; Lehn, J.-M. *J. Am. Chem. Soc.* **2004**, *126*, 6637. (b) Schull, G.; Douillard, L.; Fiorini-Debuisschert, C.; Charra, F.; Mathevet, F.; Kreher, D.; Attias, A.-J. *Adv. Mater.* **2006**, *18*, 2954.

(4) (a) Bunzli, J.-C. G.; Piguet, C. *Chem. Soc. Rev.* **2005**, *34*, 1048. (b) Diring, S.; Retailleaub, P.; Ziessel, R. *Tetrahedron Lett.* **2007**, *48*, 8069.

(5) Seela, F.; Steker, H. *Liebigs Ann. Chem.* **1984**, 1719.

(6) Berry, D. A.; Jung, K.-Y.; Wise, D. S.; Sercel, A. D.; Pearson, W. H.; Mackie, H.; Randolph, J. B.; Somers, R. L. *Tetrahedron Lett.* **2004**, *45*, 2457.

(7) Tumkevicius, S.; Dodonova, J.; Kazlauskas, K.; Masevicius, V.; Skardziute, L.; Jursenas, S. *Tetrahedron Lett.* **2010**, *51*, 3902.

(8) (a) Mohamed, M. S.; El-Domany, R. A.; El-Hameed, R. H. A. *Acta Pharm.* **2009**, *59*, 145. (b) Wiesner, J. B.; Ugarkar, B. G.; Castellino, A. J.; Barankiewicz, J.; Dumas, D. P.; Gruber, H. E.; Foster, A. C.; Erion, M. D. *J. Pharm. Exp. Ther.* **1999**, *289*, 1669. (c) Calderwood, C. J.; Johnston, D. N.; Munschauer, R.; Rafferty, P. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1683. (d) Altmann, E.; Missbach, M.; Green, J.; Susa, M.; Wagenknecht, H.; Widler, L. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 853. (e) Widler, L.; Green, J.; Missbach, M.; Susa, M.; Altmann, E. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 849. (f) Gibson, C. L.; Huggan, J. K.; Kennedy, A.; Kiefer, L.; Lee, J. K.; Suckling, C. J.; Clements, C.; Harvey, A. L.; Hunter, W. N.; Tulloch, L. B. *Org. Biomol. Chem.* **2009**, *7*, 1829. (g) Hess, S.; Muller, C. E.; Frobenius, W.; Reith, U.; Klotz, K.-N.; Eger, K. *J. Med. Chem.* **2000**, *43*, 4636. (h) Naus, P.; Pohl, R.; Votruba, I.; Dzubak, P.; Haiduch, M.; Ameral, R.; Birkus, G.; Wang, T.; Ray, A. S.; Mackman, R.; Cihlar, T.; Hocek, M. *J. Med. Chem.* **2010**, *53*, 460.

(9) **Representative Procedure for the Preparation of 4-Aryl-7-(*tert*-butoxycarbonyl)-2-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidines 2 – Compound 2a**
To a solution of compound **1a**[7] (0.42 g, 1.83 mmol) in anhyd CH_2Cl_2 (5 mL) DIPEA (0.48 mL, 2.75 mmol), DMAP (0.07 g, 0.57 mmol), and di(*tert*-butyl)dicarbonate (0.6 g, 2.75 mmol) were added. The reaction mixture was refluxed for 80 min, CH_2Cl_2 was evaporated under reduced pressure, and the residue was purified by column chromatography (eluent: $CHCl_3$) to give compound **2a** (0.37g, 61%); mp 76–77 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.74 (s, 9 H, CMe_3), 6.89 (d, *J* = 4.2 Hz, 1 H, 5-H), 7.58–7.61 [m, 3 H, 3′,4′,5′-H (Ph)], 7.74 (d, *J* = 4.2 Hz, 1 H, 6-H), 8.06–8.09 [m, 2 H, 2′,6′-H (Ph)]. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.3, 86.0, 104.1, 116.9, 128.0, 129.2, 129.3, 131.2, 136.6, 147.3, 154.4, 156.2, 160.6. HRMS: *m/z* calcd for $C_{17}H_{16}ClN_3O_2$ $[M + H]^+$: 330.1004; found: 330.1000.

(10) **Representative Procedure for the Preparation of 2,4-Diaryl-7-(*tert*-butoxycarbonyl)-7*H*-pyrrolo[2,3-*d*]-pyrimidines 3a–c – Compound 3a**
A solution of compound **2a** (0.07 g, 0.21 mmol) in anhyd 1,4-dioxane (5 mL) was degassed with argon, and $Pd(OAc)_2$ (2.0 mol%) and dicyclohexyl(2-biphenyl)phoshine (4.0 mol%) were added with stirring under argon. The mixture was stirred for 10 min, then 4-ethoxyphenylboronic acid (0.042 g, 0.25 mmol) and anhyd K_3PO_4 (0.11 g, 0.52 mmol) were added. The reaction mixture was refluxed for 4 h. Then the solvent was evaporated under reduced pressure, and H_2O (5 mL) was added to dissolve inorganic salts. The obtained solution was extracted with $CHCl_3$ (3 × 25 mL), the combined organic layers were dried with Na_2SO_4, filtered, and evaporated under reduced pressure to dryness. The resulting solid was purified by column chromatography (eluent: $CHCl_3$) to give compound **3a** (0.07 g, 79%); mp 141–141.9 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.49 (t, *J* = 6.9 Hz, 3 H, Me), 1.81 (s, 9 H, CMe_3), 4.16 (q, *J* = 6.9 Hz, 2 H, OCH_2), 6.88 (d, *J* = 4.2 Hz, 1 H, 5-H), 7.05 [dm, *J* = 9.0 Hz, 2 H, 3′,5′-H ($EtOC_6H_4$)], 7.58–7.61 [m, 3 H, 3′,4′,5′-H (Ph)], 7.75 (d, *J* = 4.2 Hz, 1 H, 6-H), 8.20 [dm, *J* = 7.9 Hz, 2 H, 2′,6′-H (Ph)], 8.68 [dm, *J* = 9.0 Hz, 2 H, 2′,6′-H ($EtOC_6H_4$)]. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.1, 28.5, 63.7, 84.9, 104.4, 114.5, 115.9, 127.1, 129.0, 129.3, 130.1, 130.4, 131.4, 138.4, 148.6, 154.3, 158.2, 159.9, 161.1. HRMS: *m/z* calcd for $C_{25}H_{25}N_3O_3$ $[M + H]^+$: 416.1969; found: 416.1962.

(11) **Representative Procedure for the Preparation of 2,4-Diaryl-7*H*-pyrrolo[2,3-*d*]pyrimidines 4a–c – Compound 4a**
To a solution of compound **3a** (0.1 g, 0.24 mmol) in a mixture of acetone (9 mL) and H_2O (2 mL) concd HCl (0.06 mL, 1.94 mmol) was added. The reaction mixture was refluxed with stirring for 7 d, then cooled to r.t., the precipitate was filtered off to give compound **4a** (0.06g, 80%); mp 275–276 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.39 (t, *J* = 6.9 Hz, 3 H, Me), 4.13 (q, *J* = 6.9 Hz, 2 H, OCH_2), 6.90 (dd, J^3 = 3.5 Hz, J^4 = 1.8 Hz, 1 H, 5-H), 7.08 [dm, *J* = 9.0 Hz, 2 H, 3′,5′-H ($EtOC_6H_4$)], 7.59–7.65 [m, 4 H, 6-H, 3′,4′,5′-H (Ph)], 8.31 [dm, *J* = 7.9 Hz, 2 H, 2′,6′-H (Ph)], 8.49 [dm, *J* = 9.0 Hz, 2 H, 2′,6′-H ($EtOC_6H_4$)], 12.21 (s, 1 H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 15.4, 63.9, 100.9, 113.4, 114.9, 128.4, 129.3, 129.6, 129.7, 130.8, 131.7, 138.9, 154.5, 156.1, 157.0, 160.6. HRMS: *m/z* calcd for $C_{20}H_{17}N_3O$ $[M + H]^+$: 316.1444; found: 316.1446.

(12) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727.

(13) **Representative Procedure for the Preparation of 2,4,7-triaryl-7*H*-pirolo[2,3-*d*]pirimidines(5) – Compound 5a**
A solution of compound **4a** (0.06 g, 0.19 mmol) in anhyd 1,4-dioxane (3 mL) was degassed with argon, and CuI (1 mol%) and anhyd K_3PO_4 (0.07 g, 0.33 mmol) were added.

The mixture was stirred for 10 min, then 4-iodobenzonitrile (0.04 g, 0.17 mmol) and *trans*-1,2-diaminocyclohexane (10 mol%) were added. The reaction mixture was refluxed with stirring and after 1 h and 2 h, respectively, an additional amount of 1 mol% CuI was added. The total amount of CuI used in the reaction was 3 mol%, and total reflux time was 6 h. Then EtOAc (5 mL) was added to the reaction mixture, and the solution was filtered through a layer of silica gel. The solvents were removed under reduced pressure and the residue purified by column chromatography (eluent: hexane–EtOAc = 27:1) to give compound **5a** (0.071g, 90%; mp 206.3–206.8 °C (from 2-PrOH–EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.51 (t, *J* = 6.9 Hz, 3 H, Me), 4.17 (q, *J* = 6.9 Hz, 2 H, OCH_2), 7.04–7.09 [m, 3 H, 5-H, 3′,5′-H (4-EtOPh)], 7.61–7.62 [m, 4 H, 6-H, 3′,4′,5′-H (Ph)], 7.93 [dm, *J* = 9.0 Hz, 2 H, 3′,5′-H (N_7-Ph)], 8.21 [dm, *J* = 9.0 Hz, 2 H, 2′,6′-H (N_7-Ph)], 8.30 [m, *J* = 7.9 Hz, 2 H, 2′,6′-H (Ph)], 8.10 [dm, *J* = 9.0 Hz, 2 H, 2′,6′-H (4-EtOPh)]. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.1, 63.8, 104.2, 109.7, 114.6, 114.9, 118.8, 123.6, 126.9, 129.1, 129.3, 129.9, 130.5, 131.1, 133.7, 138.5, 141.8, 153.3, 158.5, 159.1, 161.1. HRMS: *m/z* calcd for $C_{27}H_{20}N_4O$ $[M + H]^+$: 417.1710; found: 417.1710.