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Synthesis of α,α'-linked penta- and septaheterocycles by tandem Suzuki coupling

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ABSTRACT: The controlled synthesis of oligoaromatics can provide materials of wide utility. Here, we describe the preparation of higher order oligoheterocycles *via* a tandem Suzuki cross-coupling protocol. This method has allowed for the iterative construction of fluorescent α,α'-linked penta- and septaheterocyclic systems with modification of the terminal moiety allowing for fine-tuning of the emission features.

KEYWORDS: Suzuki coupling, oligoheterocycle, fluorescence.

INTRODUCTION

Multiple aromatic heterocyclic systems bridged *via* biaryl linkages represent important building blocks across a broad range of the chemical and material sciences [1, 2]. Within this arena, α,α'-linked heteroaromatics have emerged as important building blocks in functional π-conjugated materials [3–15] as well as key structural motifs in supramolecular [16–18] and coordination chemistry [18–23]. Due to their broad utility, extensive efforts have been focused on developing improved preparations of homogeneous and heterogeneous forms of so-called mixed oligoheterocycles [7–13, 24–30]. Typically, two generalized approaches have been pursued involving, (1) the synthesis of appropriate building blocks followed by oligomerization or (2) the preparation of smaller subunits that are then elaborated in an iterative approach through functionalization to produce higher order oligomers. Nevertheless and in spite of the progress made to date, there is still a need for generalizable procedures that permit the preparation of α,α'-linked heteroaromatics in an economically efficient and scalable manner.

Currently, a number of routes leading to bi- and tetraheteroaromatic species are known [9, 25–29]. However, methodologies allowing for the controlled synthesis of odd numbered ter-, penta-, and septaheterocyclic, especially non-thiophene, oligoaromatic systems remain limited [31–37]. We have, therefore, devoted efforts towards the preparation of higher order heterogeneous oligoheterocycles using α,α'-dibromo terheterocycles as precursors for the expedient synthesis of such systems. Here, we present the use of dibromo dipyrrolyl furan (**1**) as a model building block in a tandem Suzuki cross-coupling protocol to yield a series of mixed penta- and septaheterocycles from easily prepared starting material and commercially available coupling partners (Fig. 1). The iterative approach described here allows for the expedient synthesis of larger oligoheterocyclic constructs whose structural diversity provides control over key optical properties, including the UV-vis absorption spectra and fluorescence emission features. The net result are color and fluorescence differences that are easy to differentiate by the naked eye.

RESULTS AND DISCUSSION

Initial synthetic efforts were devoted to optimizing conditions that would allow the tandem Suzuki coupling between dibromo dipyrrolyl furan (**1**) [38] with

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[◊] SPP Full member in good standing.

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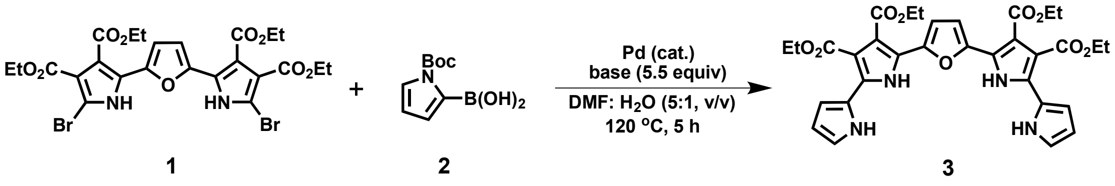
N-boc-2-pyrroleboronic acid (**2**). Toward this end, various Pd-salts (entries 1–4), bases (entries 4–6), concentrations of the aryl boronic acid (entry 7), and the palladium catalyst (entry 8) were tested (Table 1)[§]. Gratifyingly, optimized conditions were obtained upon heating **1** in *N*,*N*-dimethylformamide-H_2O (5:1, v/v) with $Pd(PPh_3)Cl_2$ (20 mol%), K_2CO_3 (5.5 equiv), and *N*-boc-pyrrole-2-boronic acid (4 equiv) at reflux. This gave 2,5-di-bipyrrolyl furan (**3**) in 98% yield.

Using this protocol we then examined the construction of various mixed oligo-heteroaromatics derived from the dipyrrolyl furan scaffold and various heteroaromatic pinacol boranes (Scheme 1).[†] Under these conditions good-to-excellent yields were obtained for a series of penta- (**4–7**) and septaheterocycles (**8**). For instance, commercially available indole-, furan, and thiophene-2-boronic acid pinacol esters were readily coupled to give the corresponding pentaheterocycles **4**, **5**, and **6** in 93%, 85%, and 86% yield, respectively[▯]. Although mixed oligoheterocyclic species analogous to **4**, **5**, and **6** have previously been reported, these prior protocols typically required greater step counts and proceeded in lower overall yields [39]. 2,2′-Bithiophene-5-boronic acid pinacol ester, a common precursor in oligothiophene synthesis [40], was coupled to give **7** in 92% yield. This method was also amenable to pyridine-based substrates, as demonstrated by the reaction between **2** and pyridine-4-boronic acid pinacol ester to give **8** in 95% yield.

To demonstrate the influence of the terminal heterocycle on the absorbance and fluorescence properties, the UV-vis and emission profile of compounds **3–8** were measured (Fig. 1). Torsion angles of synthesized compounds as well as the shorter terpyrrole and mixed tetrafuran-thiophene (**TFFT** & **FTTF**) are shown in Table 2. UV-vis spectral studies carried out in acetonitrile revealed molar absorptivities that varied as well as changes in the maximum absorption (λ_{max}). Specifically, for compound **3**λ_{max} = 349 nm (24,500 $M^{-1} \cdot cm^{-1}$) and λ_2 = 303 nm (20,700 $M^{-1}cm^{-1}$); for **4** the corresponding values were λ_{max} = 298 nm (17,600 $M^{-1} \cdot cm^{-1}$), λ_2 = 334 nm (16,250 $M^{-1} \cdot cm^{-1}$); in the case of **5** λ_{max} = 389 nm (15,400 $M^{-1} \cdot cm^{-1}$), whereas λ_{max} = 393 nm (13,500 $M^{-1} \cdot cm^{-1}$) for **6**; finally, the corresponding λ_{max} values for **7** and **8** were 368 nm (36,150 $M^{-1} \cdot cm^{-1}$) and 366 nm (24,900 $M^{-1} \cdot cm^{-1}$), respectively. The observed spectra lead us to suggest that a complex interplay between conjugation and electron density of the pendant heterocycle determines the predominant electronic transition [40] (Fig. 1).

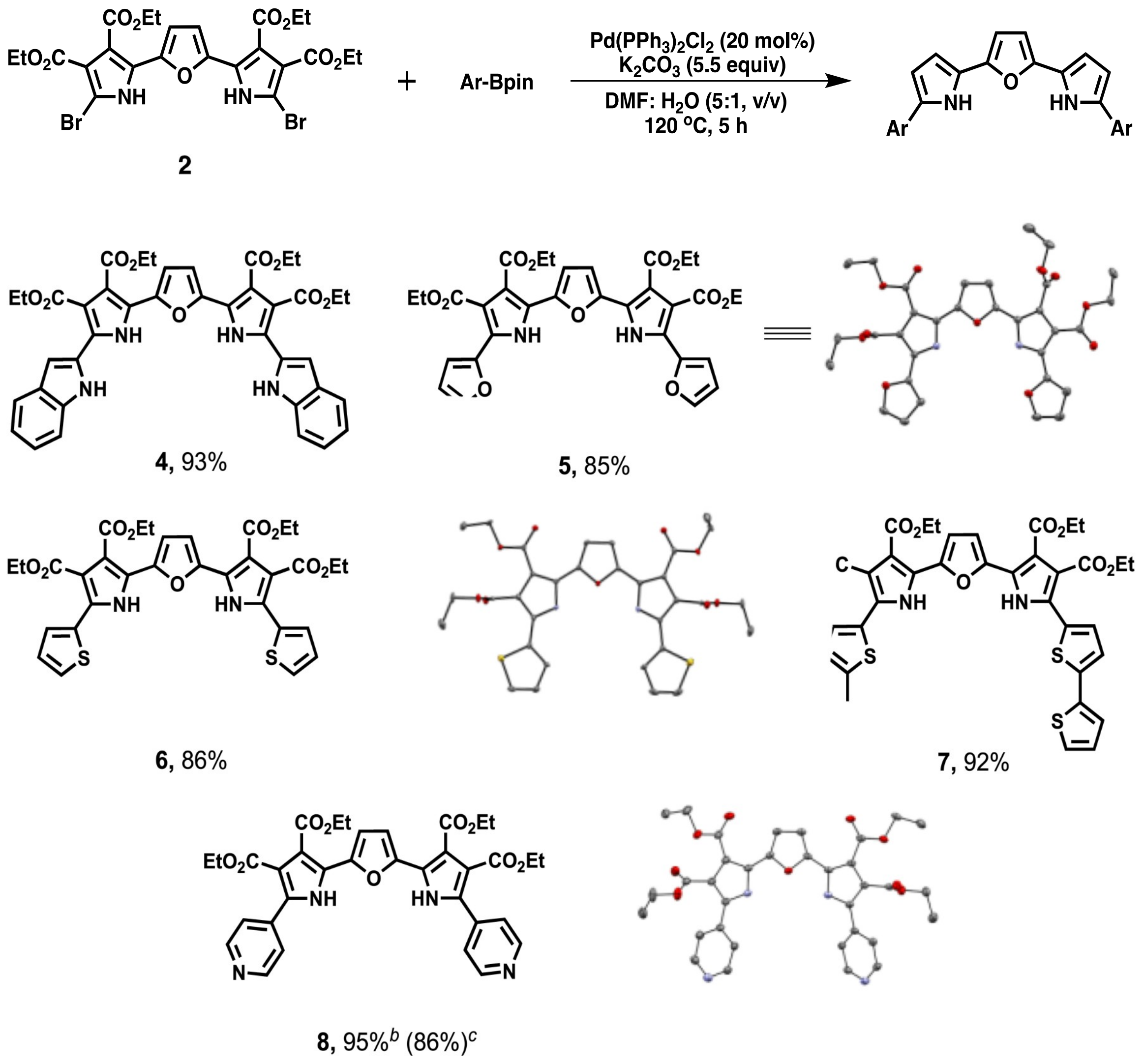
The emission spectra of pentaheterocycles **3**, **4**, **5**, **6**, and **8** recorded in acetonitrile were found to scale in accord with the electron density of the terminal heterocycle [41], with **3** giving an emission maximum (Em_{max}) at 490 nm, **4** at 498 nm, **5** at 481 nm, **6** at 485 nm, and **8** at 460 nm (Fig. 1). A bathochromic shift in the emission profile was also observed upon extending the conjugation, as demonstrated by bithiophene-capped septaheterocycle **7** that yielded an Em_{max} at 511 nm. These spectral differences are readily apparent to the naked eye when acetonitrile solutions of compounds **3–8** were illuminated with a hand held UV-vis lamp, as can be seen from inspection of Fig. 2. Absorption and

Table 1. Reaction development

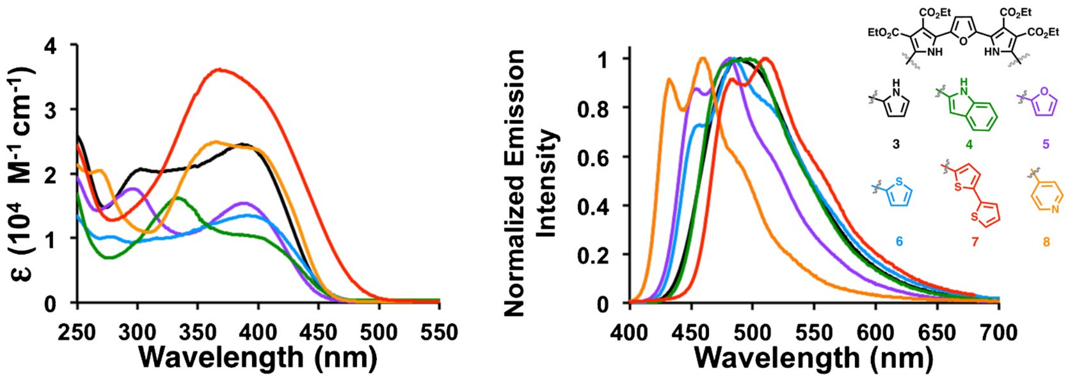


Entry	Pd cat.	Base	Yield (%)[b]
1	$Pd(OAc)_2$, Ph_3[c]	K_2CO_3	74
2	$Pd(dppf)Cl_2$	K_2CO_3	63
3	$Pd(dba)_2$	K_2CO_3	45
4	$Pd(PPh_3)_2Cl_2$	K_2CO_3	84
5	$Pd(PPh_3)_2Cl_2$	KO*t*Bu	62
6	$Pd(PPh_3)_2Cl_2$	K_3PO_4	43
7	$Pd(PPh_3)_2Cl_2$[d]	K_2CO_3	99 (98)[f]
8	$Pd(PPh_3)_2Cl_2$[e]	K_2CO_3	60

[a] Reactions performed on 0.05 mmol scale with standard conditions consisting of Pd-catalyst (20 mol%), base (5.5 equiv), and aryl boronic acid (2.4 equiv) in 2 mL of DMF: H_2O (5:1, v/v). [b] Yield determined by ^1H NMR spectral analysis in $CDCl_3$ using an internal standard (1,2-dichloroethane). [c] 40 mol% of PPh_3 was used. [d] 4 Equivalents of *N*-boc-pyrrole-2-boronic acid were used. [e] 10 mol% of the Pd-catalyst was used. [f] Isolated yield for a reaction run on a 0.1 mmol scale.



Scheme 1. Synthesis of penta- and septa-oligoheterocycles. [a] Reactions performed on 0.1 mmol scale. [b] Reaction performed on 0.2 mmol scale. [c] 2.4 equiv of pyridine-2-boronic acid pinacol ester was used. Crystal structures are shown as ORTEP plots with thermal ellipsoids set at the 50% probability. Hydrogen atoms are removed for clarity



(a) (b)

Fig. 1. (a) UV-vis and (b) emission spectra of penta- and septaheterocycles **3**–**8** in acetonitrile ([c]= 15 μM)

Table 2. Terminal heterocycle torsion angles based upon x-ray crystallography

Compound	Terminal heterocycle torsion angles
3	$N_1 - N_2$, 178.86°; $N_3 - N_4$, 179.78°
5	$O_1 - N_1$, 177.60°; $N_2 - O_3$, 4.96°
6	$T_1 - N_1$, 170.66°; $N_2 - T_2$, 173.27°
terpyrrole [42]	$N_1 - N_2$, 164.75°; $N_2 - N_3$, 154.83°
TFFT [28b]	$S_1 - O_1$, -2.89°; $O_1 - O_2$, -180°; $O_2 - S_2$, 2.89°
FTTF [28b]	$O_1 - T_1$, 175.08°; $T_1 - T_2$, 180°; $T_2 - O_2$, -175.08°

Table 3. Absorbance maxima, emission maxima, and Stokes shifts of synthesized and related compounds

Compound	Abs_{max} (nm)	Em_{max} (nm)	Stokes shift (cm^{-1})
3	386	490	9.61E5
4	307	481	5.75E4
5	393	485	1.09E5
6	334	498	6.10E4
7	366	460	1.06E5
8	368	511	6.99E4
terpyrrole [42]	327	433	9.43E4
4F [28b]	364	413	2.04E5
TFFT [28b]	378	440	1.61E5
FTTF [28b]	393	467	1.35E5
4T [28b]	392	479	1.15E5

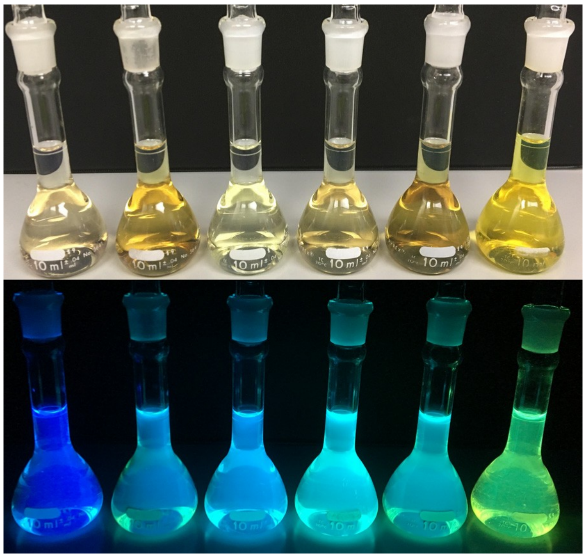


Fig. 2. Visual (top) and fluorescence (bottom) profiles of penta- and septaheterocycles **3**–**8** in acetonitrile ([c] = 15 μM).

emission maxima as well as Stokes shift of synthesized compounds, terpyrrole, tetrafuran (4F), mixed tetrafuran-thiophene (**TFFT** & **FTTF**), and tetrathiophene (4T) are compared in Table 3.

CONCLUSION

In conclusion, we have developed a facile synthesis of higher order α,α′-linked heterocycles using a tandem Suzuki cross coupling. This method utilizes easily prepared starting material as well as commercially available coupling partners to yield penta- and septaheterocycles in good to excellent yield while simultaneously allowing for fine-tuning of the photophysical properties. New routes towards the controlled synthesis of homo- and heterogeneous α,α′-linked aromatics in an iterative fashion, such as the one described, are expected to allow for the divergent preparation of previously unexplored constructs with potentially interesting and useful properties.

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Supporting information

Synthesis and characterization data, 1H and 13C NMR Spectra and X-ray Crystallographic data are given in the supplementary material. This material is available free of charge *via* the Internet at http://www.worldscinet.com/jpp/jpp.shtml. Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre (CCDC) under numbers **3** (F1P4): 1868976; **5** (F1P1F2): 1868977; **6** (F1P2T2): 1868979 and **8** (F1P2Py2): 1868980. Copies can be obtained on request, free of charge, *via* http://www.ccdc.cam.ac.uk/data_request/cif or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (fax:+44 1223-336-033 or email: deposit@ccdc.cam.ac.uk).

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[§] These conditions facilitated the *in situ* deprotection of the *N*-boc-pyrrole furnishing **3** without need for additional synthetic manipulation.

[†] Attempts to use 2-thienyl- and 2-furanylboronic acid derivatives under these conditions resulted in lower yields (*i.e*. less than 50% yield as determined

by ^{1}H NMR spectral analysis carried out in CD$_2$Cl$_2$ using an internal standard (1,2-dichloroethane). CCDC numbers: **3** (F1P4), 1868976; **5** (F1P1F2), 1868977; **6** (F1P2T2), 1868979; **8** (F1P2Py2), 1868980.

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