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Synthesis of π-conjugated systems bearing thiophene and pyrrole heterocycles through palladium catalyzed cross-coupling reactions

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ABSTRACT

A series of thienylpyrroles and bithienylpyrroles together with their formyl derivatives **5a–d** were synthesized using commercially or readily available coupling components, through three different palladium catalyzed cross-coupling reactions (Suzuki-Miyaura, Stille and decarboxylative coupling). The synthesis of compounds **5** via the Suzuki-Miyaura reaction produced the title compounds in better yields than the other coupling reactions, while, decarboxylative coupling resulted in the lower yields. UV–visible and ^{1}H NMR studies confirm the existence of significant intramolecular charge transfer (ICT) from the donor pyrrole heterocycle to the acceptor group and a high polarizability of the whole π-conjugated systems. Together these characteristics indicate their strong potential as versatile precursors for the preparation of push-pull heterocyclic compounds for optical applications.

1. Introduction

Conjugated systems bearing thiophene and pyrrole rings play important roles in the chemistry of natural products, agriculture, materials science and supramolecular and medicinal chemistry. In materials science they have found applications as nonlinear optical chromophores, conducting polymers, and anion binding agents, while in medicinal chemistry, they are important building blocks for the synthesis of antitumor agents displaying also antiviral, antibacterial, antifungal, insecticidal and herbicidal activities.[1,2]

This wide array of interesting properties has inspired the development of a variety of procedures for the preparation of differently substituted pyrroles. Methods of synthesis include the classical Knorr, Paal-Knorr and Hanstzch strategies, transition-metal-catalyzed couplings, 1,3-dipolar cycloadditions procedures and multicomponent protocols.[1d,3] On the other hand, methods for the construction of 2-(2′-thienyl)pyrroles remain limited.[4]

The chemistry of 2-(2′-thienyl)pyrroles is a very recent field in the chemistry of heterocyclic compounds. In the last few years, synthetic 2-(2′-thienyl)pyrrole derivatives have come in focus. Although over 60 years have passed since the synthesis of the first 2-(2′-thienyl) pyrrole: *bis*-2-[5-(2-thienyl)pyrrole]azametine dihydrochloride) was reported by Edward Knott[5] at Kodak, Ltd., the synthesis of functionalized 2-(2′-thienyl)pyrroles remains challenging. Conventional methods for the synthesis of pyrroles such as Knorr, Hantzsch, Barton-Zard (except the Paal-Knorr synthesis) typically produce low yields and modest regioselectivity and have not found wide use for the preparation of pyrroles bound to thiophene. Therefore, the development of new methods for the synthesis of these heterocyclic systems is an important and challenging objective.

Until recently, no sufficiently efficient and general method of preparation had been discovered. As a consequence, although these compounds remained attractive they were difficult to obtain and were consequently not extensively studied. The development of this field began in the 1970s, when new methods for pyrrole synthesis (e.g., coupling reactions, condensation of heteroarylacetylenes with trimethylsilyl cyanide as well as those with the use of isocyanides, other cyano compounds, azides, etc.) appeared or the existing procedures were modified to produce five-membered aromatic heterocycles. In particular, 2-(2′-thienyl)pyrroles and their *N*-methyl and *N*-vinyl derivatives have been prepared in a variety of ways. Among the previously reported routes to 2-aryl- and 2-heteroarylpyrroles, the Trofimov reaction of ketoximes with acetylene (or their precursors) is one of the most important. The synthesis of 2-(2′-thienyl)-1-vinylpyrroles by this method was first reported in 1977 by Trofimov et al. with a yield of 50%.[6a] This procedure allows the synthesis not only of 2-(2′-thienyl)pyrroles unsubstituted on the nitrogen atom but also their 1-vinyl derivatives.[6]

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More recent reports on the synthesis of 2-(2′-thienyl)pyrroles includes the preparation of those heterocycles through 1,3-dipolar cycloaddition of azomethine ylides with *bis*-sulfonyl ethylenes,[7] TMSOTf-mediated reaction of donor-acceptor cyclopropanes with 2-cyanothiophene reactions,[8] a novel version of the Trofimov reaction,[9] metal-catalyzed cross-coupling reactions, direct arylation reactions and palladium-catalyzed direct desulfitative C–H bond heteroarylation.[10]

Nevertheless only four examples concerning the synthesis of 1-methyl-2-(2′-thienyl)pyrrole have been reported either by modification of the Trofimov reaction,[9] through Negishi cross-coupling,[10a] through metal catalyzed direct arylation,[10b] or using palladium-catalyzed direct desulfitative C–H bond heteroarylation.[10n] However no studies have been published concerning the comparative study for the synthesis of 2-(2′-thienyl)pyrroles and bithienylpyrroles and the corresponding formyl-derivatives using several palladium catalyzed cross-coupling reaction such as Suzuki, Stille and decarboxylative coupling.

In 2005 our research group reported the synthesis of a large variety of 1-alkyl(aryl)-2-(2′-thienyl)pyrrole derivatives, through the combination of the Friedel–Crafts and Lawesson reactions.[11a–b] Our systematic study reveals that the reaction of secondary aryl-(2′-thienyl)-4-oxobutanamides with Lawesson's reagent (LR) can yield 2-(2′-thienyl)pyrroles (3–58%) and/or 2,2′-bithiophenes (7–55%) in different yields/ratios depending on the substituent(s) of the precursor arylamines. In the case of the secondary *N*-propyl-4-(2′-thienyl)-4-oxobutanamide treatment with an equimolar amount of LR only resulted in the corresponding 1-propyl-2-(2′-thienyl)pyrrole with a 47% yield.

This method is interesting because it employs mild reaction conditions and simple work-up procedures and allows the preparation of a large variety of 2-(2′-thienyl)pyrroles functionalized in position 1 with alkyl and aryl groups. Nevertheless, in some cases, the yields are low and a mixture of 2-(2′-thienyl)pyrroles and 2,2′-bithiophenes can be obtained.

On the other hand, these novel 1-alkyl(aryl)-2-(2′-thienyl)pyrroles are a versatile type of heterocyclic systems which were used as precursors in several types of reactions, allowing the preparation of a variety of new donor-acceptor 2-(2′-thienyl)pyrroles selectively functionalized on the thiophene or pyrrole rings with formyl-, dicyanovinyl-, tricyanovinyl-, benzothiazole, benzimidazole and aromatic or heterocyclic azo groups. The characterization of the optical (linear and nonlinear), photochromic, thermal properties in solution, in PMMA matrixes and in liquid crystals revealed that the novel π-conjugated heterocyclic systems can be used as solvatochromic probes and as efficient and thermally stable OLEDs, nonlinear optical and photochromic materials.[12]

Based on our earlier work[12,13] as well as the results published by other groups[10] we were motivated to investigate the synthesis of (bi)thienylpyrrole heterocyclic systems and their formyl-derivatives by Suzuki-Miyaura, Stille and decarboxylative couplings in order to choose the most efficient method for the synthesis of appropriate building blocks that can facilitate the construction of π-conjugated systems for optical applications.

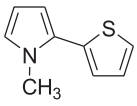
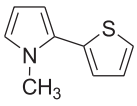
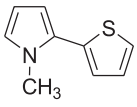
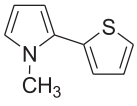
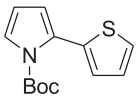
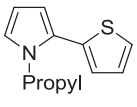
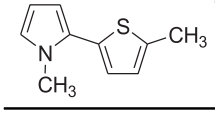
2. Results and discussion

2.1. Synthesis of compounds 5 through Suzuki, Stille and decarboxylative cross-couplings

From all compounds **5a**–**d** only the synthesis of **5a** has been previously reported by other groups. **5a** has been prepared through Negishi coupling of (*N*-methylpyrrolyl)-zinc chloride and 2-bromothiophene in the presence of the palladium(II)chloride-1,1′-*bis*(diphenylphosphino)ferrocene catalyst with 70% yield,[10a] by direct palladium catalyzed arylation of *N*-methylpyrrole with 2-bromothiophene with a 61% yield using KOAc as base, DMA as solvent and $PdCl(C_3H_5)$(dppb) catalyst.[10m] Modification of the Trofimov reaction gave also the same 2-(2′-thienyl)pyrrole in 46% yield,[9] and more recently, the synthesis of **5a** was also reported by a palladium-catalyzed direct desulfitative C–H bond heteroarylation with a 42% yield, in which thiophene-2-sulfonyl chloride was coupled with 1-methylpyrrole in the presence of lithium carbonate base, in dioxane at 140 °C and using $PdCl_2(CH_3CN)_2$ as catalyst.[10n]

Similar 2-(2′-thienyl)pyrrole derivatives have also been reported by other cross-coupling reactions: 1-Boc-2-(thiophen-2-yl)-1*H*-pyrrole[10j] through Suzuki coupling (35% yield), and 1-methyl-2-(5-methylthiophen-2-yl)-1*H*-pyrrole[10k] through decarboxylative coupling between 1-methyl-2-pyrrolecarboxylic acid and 2-bromo-5-methylthiophene, producing a 78% yield, using Pd[P(*t*-Bu)$_3$]$_2$ catalyst, Cs_2CO_3 base and DMF as solvent. The similar 1-propyl-2-(2′-thienyl)pyrrole derivative was also reported previously by us through the combination of Friedel–Crafts and Lawesson reactions in 47% yield.[11b] (Table 1).

Table 1
Yields for compound **5a** and for similar 2-(2′-thienyl)pyrrole derivatives through several methods of synthesis

Compound	η (%)	Method of synthesis	Reference; year
 **5a**	71	Negishi cross-coupling reaction	10a; 1998
 **5a**	46	Modification of Trofimov reaction	9; 2005
 **5a**	61	Direct arylation	10m; 2014
 **5a**	42	Direct desulfitative C–H bond heteroarylation	10n; 2015
	35	Suzuki cross-coupling reaction	10j; 1998
	47	Combination of the Friedel–Crafts and Lawesson reactions	11b; 2006
	78	Decarboxylative coupling	10k; 2006

Among a diverse number of synthetic transformations, transition-metal catalyzed reactions offer, at the present, one of the most efficient ways to prepare bi-heterocyclic systems. Therefore, we decide to study the synthesis of (bi)thienylpyrrole derivatives through Suzuki, Stille and decarboxylative cross-coupling reactions.[10]

Suzuki coupling is a versatile method of synthesis possessing a large number of advantages: it employs readily available reagents under the mild reaction conditions, it is largely unaffected by the presence of water, it tolerates a broad range of functional groups, it generally proceeds regio- and stereoselectively, while the inorganic by-products are non-toxic and easily removed from the reaction mixture.[10g,h] The Stille coupling is also extremely versatile, proceeding under neutral conditions and tolerating a wide range of substituents on both coupling partners.[10d] The decarboxylative coupling have several advantages when compared to traditional Suzuki and Stille cross-coupling reactions such as stability, lower cost and greater diversity, the ease of storing and handling the carboxylic acid couplers, and the simple experimental reactions conditions without the necessity of employing an inert atmosphere. Moreover in this synthetic methodology, the carboxylic acid function controls the regioselectivity of the reaction and only carbon dioxide is released as waste.[10f,10k,10l]

2.1.1. Suzuki coupling. (Bi)thienylpyrroles **5a**–**d** were synthesized through the Suzuki cross-coupling reaction of commercially available 1-methyl-2-pyrrole boronic acid pinacol ester with commercially available (bi)thienyl bromides **2a**–**c** and **2d**[13d] synthesized by us as previously reported. The Suzuki coupling reactions were performed in 1,2-dimethoxyethane (DME) and aqueous 2 M Na_2CO_3 (2 equiv) under an argon atmosphere and $Pd(PPh_3)_4$ (3 mol %) was used as palladium catalyst at 80 °C[13b,c] for 24 h (Scheme 1). Compounds **5** were obtained in fair to good yields 15–85% (Table 2). Better yields were obtained for the synthesis of compounds **5a** and **5c**[12i] (82 and 85%, respectively) when compared to the corresponding formyl derivatives (**5b**, 75%) and (**5d**, 15%). These results are probably the consequence of an increase in the polarity of the compounds with increasing extension of the π-spacer as well as the introduction of the formyl group on the thiophene ring, which hinders its purification using silica gel column chromatography.

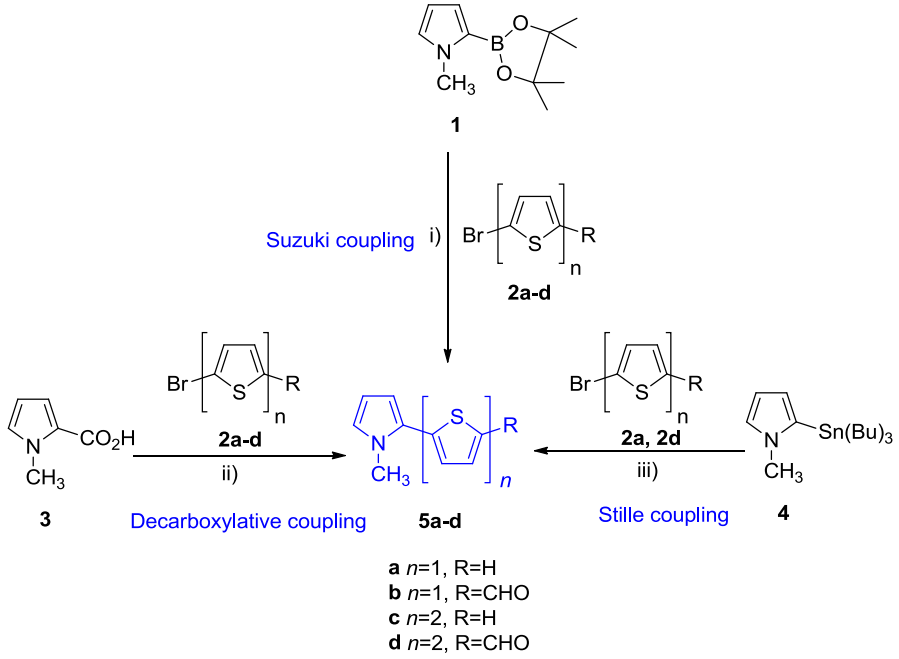
carboxylic acids and aryl halides.[10k,l] Having in mind their results, the synthesis of compounds **5a**–**d** through decarboxylative coupling was performed in DMF at 140 °C in an open air flask using as coupling components 1-methyl-2-pyrrolecarboxylic acid and heteroaryl bromides **2a**–**d**, *n*-$Bu_4NCl\cdot H_2O$ as additive, Cs_2CO_3 as base and Pd[P(*t*-Bu_3)]$_2$ (5 mol %) catalyst. *n*-$Bu_4NCl\cdot H_2O$ was used as additive in order to synthesize compounds **5a**–**d** in higher yields through clean reactions without the corresponding diarylated C–H coupling products, due to the regioselectivity of the transformation.[10k,l]

Compounds **5** were prepared in moderate to good yields (39–64%) (Table 2) after an easy purification of the reaction mixtures through silica gel column chromatography in which only compounds **5** were isolated. Better yields were obtained when more electron rich heteroaromatic bromides were used as coupling components. Compounds **5a** (64%) and **5c** (52%) were prepared in higher yields

Table 2
Yields for the synthesis of compounds **5a**–**d** through Suzuki, Stille and decarboxylative cross-coupling reactions

Comp.	R	n	Suzuki coupling[a] (yield %)	Stille coupling[b] (yield %)	Decarboxylative coupling[c] (yield %)
5a	H	1	82	—	64
5b	CHO	1	75	71	51
5c	H	2	85	—	52
5d	CHO	2	15	—[d]	39

[a] Reaction conditions: 1-methyl-2-pyrrole boronic acid pinacol ester (1.2 equiv), heteroaryl bromide (1 equiv), $Pd(PPh_3)_4$ (0.03 equiv), Na_2CO_3, inert atmosphere (N_2), DME; 80 °C; 24 h.
[b] Reaction conditions: 1-methyl-2-(tributylstannyl)-1*H*-pyrrole (1.1 equiv), heteroaryl bromide (1 equiv), $Pd(PPh_3)_4$ (0.01 equiv), inert atmosphere (N_2), toluene; 80 °C; 24 h.
[c] 1-methyl-2-pyrrolecarboxylic acid (2 equiv), heteroaryl bromide (1 equiv), Pd[P(*t*-Bu_3)]$_2$ (0.05 equiv), Cs_2CO_3 (1.5 equiv), *n*-$Bu_4NCl\cdot H_2O$ (1 equiv), DMF; 140 °C; 1–4 h.
[d] A complex reaction mixture was obtained. It was not possible to isolate/purify the resulting coupling compound.



Scheme 1. Synthesis of compounds **5a**–**d** through Suzuki (Method A), Stille (Method B), and decarboxylative (Method C) cross-coupling reactions.

2.1.2. Decarboxylative coupling. Earlier Forgione and Bilodeau reported systematic studies concerning the palladium-catalyzed decarboxylative cross-coupling reaction between (hetero)aromatic

compared, respectively to compounds **5b** (51%) and **5d** (39%).

Comparison between the three methods of synthesis showed that smaller yields were obtained for the preparation of compounds

5 through the decarboxylative coupling reaction. In order to improve the yields we decided to investigate several factors (solvent, temperature, catalyst, stoichiometry of the coupling components) that could potentially affect the reaction outcome for compounds **5** (Table 3). The results showed that higher reaction temperatures and more polar solvents improve the yield of the coupled product **5b** from 13% (DME) to 51% yield (Table 3, entries 1–3). A better yield of **5b** was also obtained when 2 equivalents of carboxylic acid was used (51%) instead of 1.2 equivalents (20%) (Table 3, entries 1 and 4). The yield of compound **5c** was also improved from 52 to 66% when Pd[$P(PPh_3)_3]_4$ catalyst was used instead of Pd[$P(t\text{-}Bu_3)]_2$ (Table 3, entries 5 and 6). This result might possibly be due to the higher air sensitivity of the Pd[$P(t\text{-}Bu)_3]_2$compared to Pd[$P(PPh_3)_3]_4$ which will diminish its catalytic activity.

Table 3
Palladium-catalyzed heteroarylation of 1-methyl-2-pyrrolecarboxylic acid with (bi) thienyl bromides **2a**–**d** using different reaction conditions

Entry	Comp.	Solvent	Temperature (°C)	Equiv. 3:2	Catalyst	Yield (%)
1	**5b**	DMF	140	2:1	Pd[$P(t\text{-}Bu)_3]_2$	51
2	**5b**	DME	80	2:1	Pd[$P(t\text{-}Bu)_3]_2$	13
3	**5b**	THF	66	2:1	Pd[$P(t\text{-}Bu)_3]_2$	25
4	**5b**	DMF	140	1.2:1	Pd[$P(t\text{-}Bu)_3]_2$	20
5	**5c**	DMF	140	2:1	Pd[$P(t\text{-}Bu)_3]_2$	52
6	**5c**	DMF	140	2:1	Pd[$P(PPh_3)_3]_4$	66

2.1.3. Stille coupling. The synthesis of (bi)thienylpyrroles **5b** and **5d** through Stille coupling[13a] was performed in toluene at 80 °C for 24 h with commercially available 1-methyl-2-(tributylstannyl)-1*H*-pyrrole and heteroaromatic bromides **2b** and **2d**, using $Pd(PPh_3)_4$ catalyst (Scheme 1). Compound **5b** was prepared in a similar yield (71%) compared to the Suzuki coupling reaction (75%). Attempted synthesis of compound **5d** gave a complex reaction mixture from which it was not possible to isolate/purify the coupling compound.

At this stage, a comparison can also be made between the yields obtained for compound **5a** using other synthetic methods reported earlier and the Suzuki coupling described above. In fact compound **5a** was prepared in a higher yield (82%) by Suzuki coupling compared to their preparation through the modification of the Trofimov reaction[9] (46%), the Negishi coupling[10a] (71%), direct arylation reaction[10m] (61%) or direct desulfitative C–H bond heteroarylation[10n] (42%) (Table 1).

The structures of compounds **5** were clearly confirmed by their analytical and spectral data. All pyrroles **5**, exhibited three ^{1}H NMR signals as two doublets at about 6.02–6.12, and 6.21–6.57 ppm and a signal as an apparent triplet at 6.81–7.00 ppm. These signals were attributed respectively, to protons 4 and 3 and 5 in the pyrrole ring. In all of the ^{1}H NMR spectra of derivatives **5a**–**d** a singlet at about 3.68–3.84 ppm was also detected. This signal was attributed to the NCH_3 protons of the pyrrole heterocycle. Compounds **5b** and **5d** exhibit two doublets at about 7.38–7.50 and 7.97–7.98 ppm due to protons 4- and 3-H of the dissubstituted thiophene ring with coupling constants of 4.0 Hz. Additionally, for compounds **5b** and **5d**, another singlet was also observed at about 9.84–9.87 ppm due to the proton of the C*H*O group.

2.2. Electronic structure analysis

A previously analysis of the structures and charge transfer transitions of π-conjugated systems **5a**–**d** was made by ^{1}H NMR spectroscopy (Fig. 1). The ^{1}H NMR chemical shifts reflect a charge separation in the ground state. The analysis of these data in push-pull systems such as compounds **5b** and **5d** bearing formyl

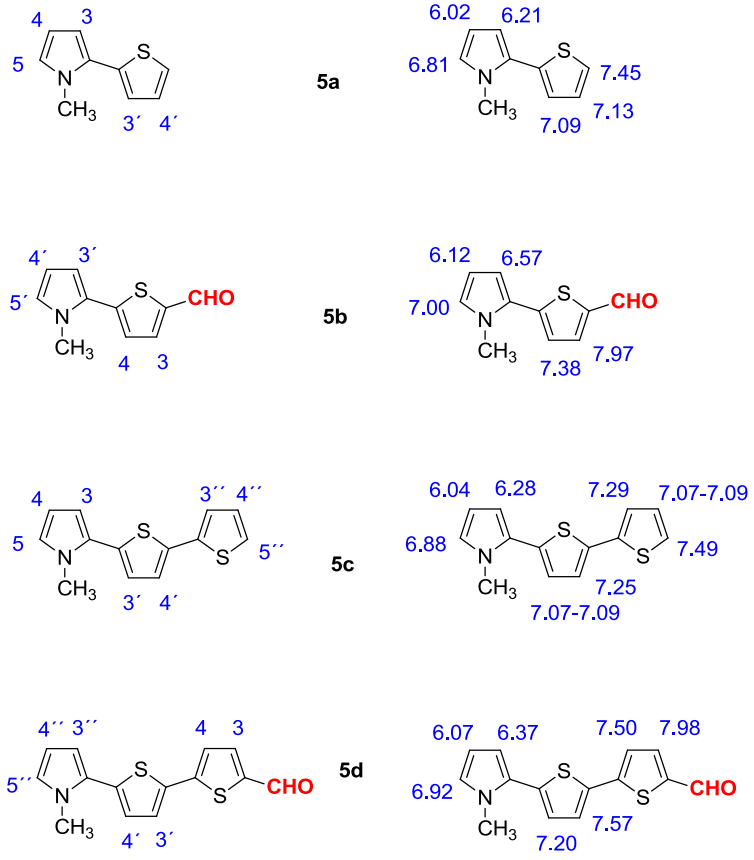


Fig. 1. Structure of compounds **5a**–**d** with the assignment of the ^{1}H NMR chemical shifts in DMSO-d_6.

acceptor groups also confirms their push-pull character with a significant intramolecular charge transfer (ICT) from the donor pyrrole heterocycle to the acceptor group and a high polarizability of the whole donor-acceptor π-conjugated systems. This analysis is supported by the observation that the chemical shifts of the protons in compounds bearing acceptor groups linked to position 5 of the thiophene ring on the pyrrolyl-(bi)thiophene spacer exhibit signals that are downfield shifted relative to the unsubstituted derivatives **5a** and **5c** indicating CT from the donor to the acceptor groups and demonstrating the ease of electron communication within the whole heterocyclic systems.

Due to their electronic properties compounds **5a**–**d** are versatile precursors for the synthesis of several push-pull systems either through direct aromatic electrophilic reactions or by conversion of the formyl group in more electron-withdrawing moieties.[12]

2.3. UV–visible studies

The electronic spectra of compounds **5**, recorded in dioxane solutions (10^{-4} M) showed an intense lowest energy charge-transfer absorption band in the UV–visible region (Table 4, Fig. 2). The position of this band depended on the electronic nature of the substituent (H or CHO) at position 5 of the thiophene heterocycle as well as the length of the π-conjugated system. The reason for the substantial red shift in compounds **5b** (λ_{max}=381 nm) and **5d** (λ_{max}=407 nm), functionalized with the acceptor formyl group, relative to that of unsubstituted (bi)thienylpyrroles **5a** and **5c** (λ_{max}=298 and 352 nm, respectively) was the strong withdrawing inductive and conjugative effect of the CHO substituent at the 2 position of the thiophene ring (Table 3, entries 2 and 4, respectively).

Table 4
UV–visible absorptions and IR data for compounds **5**

Entry	Compound	λ_{max}[a] (nm)	log ε	ν[b] (cm^{-1})
1	**5a**	298	4.19	—
2	**5b**	381	4.31	1658 (C=O)
3	**5c**	352	4.25	—
4	**5d**	407	4.42	1649 (C=O)

[a] The UV–visible spectra were obtained in dioxane.
[b] The IR spectra were obtained in liquid film ($CHCl_3$).

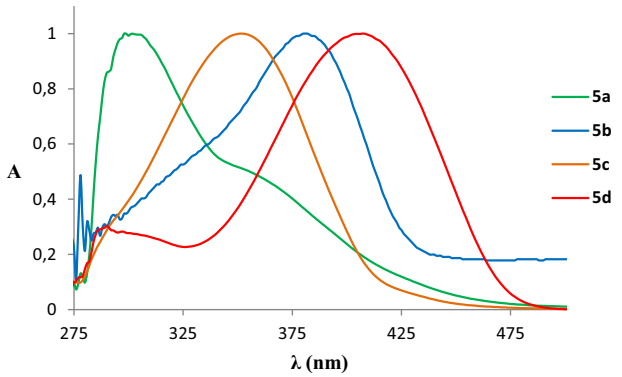


Fig. 2. UV–visible absorption spectra of compounds **5a**–**d** in dioxane solutions (10^{-4} M) at room temperature.

It was also observed that the wavelength of maximum absorption for compounds **5** was shifted to longer wavelengths (26–54 nm) as the number of thiophene units increased, as expected from the increase in conjugation. In the case of compounds **5a** and **5c** a bathochromic shift of 54 nm was observed when a second thiophene ring was introduced on the π-spacer. As expected the same trend was also observed with bithienylpyrrole **5d** (λ_{max}=407 nm) when compared to **5b** (λ_{max}=381 nm). This observation clearly indicates that the incorporation of thiophene units in push-pull compounds enhances their charge-transfer properties. The optical data obtained are not unexpected and can be largely explained by the bathochromic effect of sulfur and also the increase of the π-overlap between the thiophene units.[13a–b] The shifts of the absorption maxima are proportional to the intramolecular charge-transfer (ICT) between the electron-releasing and electron-withdrawing groups. In general, the stronger the donor and/or acceptor group, the lower the energy difference between ground and excited states, and the longer the wavelength of absorption.[14]

3. Conclusions

In summary, we have achieved the synthesis of a series of 2′-thienylpyrroles and 2,2′-bithienylpyrroles as well as their formyl derivatives **5a**–**d** using three different palladium catalyzed cross-coupling reactions (Suzuki-Miyaura, Stille and decarboxylative coupling). Better yields for compounds **5** were obtained through the Suzuki coupling reaction.

Previously we have reported the synthesis of 2′-thienylpyrrole derivatives through the combination of the Friedel–Crafts and Lawesson reactions. In order to obtain their corresponding formyl derivatives, 2′-thienylpyrroles were submitted to Vilsmeier formylation or litiation followed by reaction with DMF.[11] Using Suzuki-Miyaura, Stille and decarboxylative couplings it was possible to prepare (bi)thienylpyrroles as well their formyl-derivatives in a one-step reaction using readily available reagents and simple and convenient procedures.

The (bi)thienylpyrroles **5** studied exhibit an absorption band in the UV–visible range influenced by the functionalization of the conjugated system by the formyl group as well by the length of the π-conjugated bridge. Structural analysis of the compounds by ^{1}H NMR confirms their push-pull character with a significant intramolecular charge transfer (ICT) from the donor pyrrole heterocycle to the acceptor group and a high polarizability of the whole donor-acceptor π-conjugated systems.

In agreement with previous findings[12] the new compounds should enable the construction of new push-pull systems for several optical applications. In particular we plan to use compounds **5** as precursors in the preparation of new derivatives for photochromic and NLO applications.

4. Experimental

4.1. Materials

1-Methyl-2-pyrrole boronic acid pinacol ester **1**, 2-bromothiophene **2a**, 2-formyl-5-bromo-thiophene **2b**, 5-bromo-2,2′-bithiophene **2c**, 1-methyl-1*H*-pyrrole-2-carboxylic acid **3** and 1-methyl-2-(tributylstannyl)pyrrole **4** were purchased from Aldrich and Maybridge and used as received. TLC analyses were carried out on 0.25 mm thick precoated silica plates (Merck Fertigplatten Kieselgel 60F254) and spots were visualized under UV light. Chromatography on silica gel was carried out on Merck Kieselgel (230–240 mesh).

4.2. Synthesis

The synthesis of the formyl-bithienyl bromide precursor **2d** has been described elsewhere.[13d]

4.2.1. Method A: Suzuki coupling. General procedure for the synthesis of pyrroles **5** through Suzuki cross coupling reaction:

Bromo-thiophene derivatives **2a**–**d** (1 equiv) were coupled to 1-methyl-1*H*-pyrrole-2-boronic acid (1.2 equiv) in a mixture of DME (10 ml), aqueous 2 M Na_2CO_3 (1 ml) and $Pd(PPh_3)_4$ (3 mol %) at 80 °C under nitrogen. The reaction was monitored by TLC, which determined the reaction time (24 h). After cooling, the mixture was extracted with dichloromethane (3×20 ml) and a saturated solution of NaCl was added (20 ml) and the phases were separated. The organic phase was washed with water (3×10 ml) and with a solution of NaOH (10%) (1×10 ml). The organic phase obtained was dried with $MgSO_4$, filtered, and the solvent removed to give a crude mixture. The crude products were purified through a silica gel chromatography column using petroleum ether (40–60 °C) and mixtures of petroleum ether (40–60 °C) and dichloromethane. The elution began with petroleum ether (40–60 °C) and continue with mixtures of petroleum ether (40–60 °C)-dichloromethane of increasing polarity until (50:50) to yield the pure coupled products **5a**–**d**.

4.2.2. Method B: Stille coupling. To a degassed solution of heteroaromatic halides **2b** and **2d** (1 equiv), and stananne **4** (1.1 equiv), in toluene (5 ml) was added $Pd(PPh_3)_4$ (0.01 equiv). The mixtures were heated at 80 °C under argon. After 24 h the reaction mixtures were cooled to room temperature and then filtered and washed with cold toluene. The filtrates obtained were then washed with a saturated solution of KF (3×30 ml), water (3×30 ml) and a saturated solution of NaCl (50 ml). The resulting organic layers were dried with $MgSO_4$, and the solvent was removed in vacuum to give the crude products as oils which were purified through a silica gel chromatography column using petroleum ether (40–60 °C) and mixtures of petroleum ether (40–60 °C) and dichloromethane. The elution began with petroleum ether (40–60 °C) and continued with mixtures of petroleum ether (40–60 °C)-dichloromethane of increasing polarity until (50:50).

4.2.3. Method C: decarboxylative coupling. General procedure for the synthesis of pyrroles **5a**–**d** through decarboxylative cross-coupling reaction:

The following reagents were added to an open flask: heteroaromatic halides **2a**–**d** (1 equiv), 1-methyl-2-pyrrolecarboxylic acid **3** (2 equiv), *n*-$Bu_4NCl\cdot H_2O$ (1 equiv), Cs_2CO_3 (1.5 equiv) and catalyst $Pd[P(t\text{-}Bu)_3]_2$ (0.05 equiv). Anhydrous DMF (4 ml) was then added and the mixture was stirred for 1–4 h in an oil bath at 140 °C. The reaction mixture was then diluted with ethyl acetate (50 ml), and the organic layer was washed with saturated $KHSO_4$ solution (2×10 ml) and with brine (1×20 ml). The organic layer was dried over $MgSO_4$ and filtered, and the solvent removed to give the crude mixtures. The crude products were purified through a silica gel chromatography column using petroleum ether (40–60 °C) and mixtures of petroleum ether (40–60 °C) and dichloromethane. The elution began with petroleum ether (40–60 °C) and continue with mixtures of petroleum ether (40–60 °C)-dichloromethane of increasing polarity until (50:50) to yield the pure coupled products **5a**–**d**.

In all chromatography purifications the fractions containing the pure compounds **5a** and **5c** were eluted using a mixture of petroleum ether (40–60 °C)-dichloromethane (70:30). On the other hand, more polar derivatives **5b** and **5d** were eluted using a mixture of petroleum ether (40–60 °C)-dichloromethane (50:50).

1-Methyl-2-(thiophen-2-yl)-1H-pyrrole **5a**.[10m] Brown oil (method A: 82%; method C: 64%). ^{1}H NMR (DMSO-d_6) δ 3.68 (s, 3H, CH_3), 6.02 (dd, 1H, J=3.2 and J=2.4 Hz, 4-H), 6.21 (dd, 1H, J=3.6 and J=2.4 Hz, 3-H), 6.83 (tap, 1H, J=2.0 Hz, 5-H), 7.09 (dd, 1H, J=5.2 and J=3.6 Hz, 4′-H), 7.13 (dd, 1H, J=3.6 and J=2.4 Hz, 3′-H), 7.45 (dd, 1H, J=5.2 and J=1.2 Hz, 5′-H). ^{13}C NMR (DMSO-d_6) δ 35.0, 107.5, 109.3, 124.3, 124.5, 124.6, 126.3, 127.8, 134.6. λ_{max} (Dioxane)/nm 298 (ε/dm^3 mol^{-1} cm^{-1} 19,840). IR ($CHCl_3$): υ 3102, 2923, 1695, 1506, 1470, 1445, 1414, 1348, 1300, 1231, 1201, 1089, 1056, cm^{-1}. MS (EI) m/z (%)=163 ([M]$^+$, 100), 162 (49), 148 (18), 122 (11), 121 (17). HMRS: m/z (EI) for C_9H_9NS; calcd 163.0456; found: 163.0459.

5-(1-Methyl-1H-pyrrol-2-yl)thiophene-2-carbaldehyde **5b**. Brown solid. Mp 180–181 °C (method A: 75%; method B: 71%; method C: 51%). ^{1}H NMR (DMSO-d_6) δ 3.81 (s, 3H, CH_3), 6.10 (dd, 1H, J=3.6 and J=2.2 Hz, 4′-H), 6.57 (dd, 1H, J=4.0 and J=2.2 Hz, 3′-H), 7.00 (tap, 1H, J=2.0 Hz, 5′-H), 7.38 (d, 1H, J=4.0 Hz, 4-H),7.97 (d, 1H, J=4.0 Hz, 3-H), 9.84 (s, 1H, CHO). ^{13}C NMR (DMSO-d_6) δ 36.0, 107.8, 110.2, 124.9, 124.9, 125.1, 125.6, 128.2, 136.9, 185.5. λ_{max} (Dioxane)/nm 381 (ε/dm^3 mol^{-1} cm^{-1} 20,417). IR ($CHCl_3$): υ 3107, 3011, 2945, 2737, 1894, 1658, 1555, 1512, 1475, 1445, 1380, 1328, 1288, 1230, 1164, 1093, 1054 cm^{-1}. MS (EI) m/z (%)=191 ([M]$^+$, 100), 190(47), 163 (63), 162 (37), 148 (24). HMRS: m/z (EI) for $C_{10}H_9NOS$; calcd 191.0405; found: 191.0403.

1-Methyl-2-(5-(thiophen-2-yl)thiophen-2-yl)-1H-pyrrole **5c**.[12i] Dark green oil (method A: 85%; method C: 52%) ^{1}H NMR (DMSO-d_6) δ 3.73 (s, 3H, CH_3), 6.04 (dd, 1H, J=3.6 and J=2.8 Hz, 4-H), 6.28 (dd, 1H, J=3.6 and J=1.6 Hz 3-H), 6.88 (tap, 1H, J=2.2 Hz, 5-H), 7.07–7.09 (m, 2H, 4′- and 4″H), 7.25 (d, 1H, J=4.0 Hz, 3′-H), 7.29 (dd, 1H, J=3.6 and J=1.2 Hz, 3″-H), 7.49 (dd, 1H, J=5.2 and J=1.2 Hz, 5″-H). ^{13}C NMR (DMSO-d_6) δ 35.2, 107.9, 109.9, 123.3, 123.9, 124.1, 124.3, 124.9, 126.7, 127.7, 133.9, 135.9, 137.2. λ_{max} (Dioxane)/nm 352 (ε/dm^3 mol^{-1} cm^{-1} 17,880). IR ($CHCl_3$): υ 3102, 3071, 2945, 1692, 1503, 1453, 1416, 1318, 1294, 1237, 1200, 1090, 1055 cm^{-1}.

5-(5-(1-Methyl-1H-pyrrol-2-yl)thiophen-2-yl)thiophene-2-carbaldehyde **5d**. Dark yellow solid (method A: 15%; method B: complex mixture/not isolated, method C: 39%). Mp 138–140 °C. ^{1}H NMR (DMSO-d_6) δ 3.76 (s, 3H, CH_3), 6.07 (dd, 1H, J=4.0 and J=2.8 Hz, 4″-H), 6.37 (dd, 1H, J=3.6 and J=2.0 Hz, 3″-H), 6.92 (tap, 1H, J=2.0 Hz, 5″-H), 7.20 (d, 1H, J=4.0 Hz, 4′-H), 7.50 (d, 1H, J=4.0 Hz, 4-H), 7.57 (d, 1H, J=4.0 Hz, 3′-H) 7.98 (d, 1H, J=4.0 Hz, 3-H), 9.87 (s, 1H, CHO). ^{13}C NMR (DMSO-d_6) δ 35.3, 108.0, 110.3, 124.7, 125.0, 125.5, 125.9, 127.8, 132.6, 136.7, 139.3, 140.8, 145.5, 183.7. λ_{max} (Dioxane)/nm 407 (ε/dm^3 mol^{-1} cm^{-1} 26,360). IR ($CHCl_3$): υ 3422, 1649, 1563, 1482, 1452, 1415, 1315, 1281, 12224, 1206, 1078, 1048, cm^{-1}. MS (EI) m/z (%)=273 ([M]$^+$, 100), 272 (24), 258 (11). HMRS: m/z (EI) for $C_{14}H_{11}NOS_2$; calcd 273.0282; found: 273.0284.

4.3. Instruments

NMR spectra were obtained on a Varian Unity Plus Spectrometer at an operating frequency of 300 MHz for 1H NMR and 75.4 MHz for ^{13}C NMR or a Bruker Avance III 400 at an operating frequency of 400 MHz for ^{1}H NMR and 100.6 MHz for ^{13}C NMR using the solvent peak as internal reference at 25 °C. All chemical shifts are given in parts per million using σH Me_4Si=0 ppm as reference and J values are given in hertz. Assignments were made by comparison of chemical shifts, peak multiplicities, and J values and were supported by spin decoupling-double resonance and bidimensional heteronuclear HMBC and HMQC correlation techniques. IR spectra were determined on a BOMEM MB 104 spectrophotometer using liquid film ($CHCl_3$). UV–vis absorption spectra (200–800 nm) were obtained using a Shimadzu UV/2501PC spectrophotometer. Mass spectrometry analyses were performed at the 'C.A.C.T.I.dUnidad de Espectrometria de Masas' at the University of Vigo, Spain. All melting points were measured on a Gallenkamp melting point apparatus and are uncorrected.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2016.02.054.

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