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In Search of Oligo(2-thienyl)-Substituted Pyridine Derivatives: A Modular Approach to Di-, Tri- and Tetra(2-thienyl)pyridines

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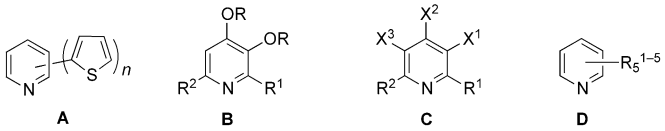
Dedicated to Professor Siegfried Hünig on the occasion of his 90th birthday

Abstract: Herein, we describe our attempts to systematically prepare a series of oligo(2-thienyl)-substituted pyridine derivatives. The crucial starting material, a β-alkoxy-β-ketoenamide, is easily available on a large scale by the reaction of lithiated methoxyallene with thiophene-2-carbonitrile and thiophene-2-carboxylic acid. This three-component reaction is followed by intramolecular cyclization to yield the suitably functionalized 2,6-di(2-thienyl)-substituted pyridine derivates. The two oxygen atoms allow the programmed activation of positions C-3, C-4, or C-5 of the pyridine ring to perform palladium-catalyzed coupling reactions with thiophene-2-boronic acid or 2-(tributylstannyl)thiophene, and alternatively, reductive removal of groups. With this concept, we were able to prepare five pyridine derivatives with 2-thienyl substituents in the 2,6-, 2,3,6-, 2,4,6-, 2,3,4,6-, and 2,3,5,6-positions. 2,3,4,5,6-Penta(2-thienyl)pyridine was not available with our methods. The UV/Vis and fluorescence spectra of all pyridines were recorded and showed a dependence on the substitution pattern and protonation state. For the protonated 2,3,5,6-tetra(2-thienyl)-substituted pyridine, a Stokes shift of about 180 nm with an emission at 515 nm was observed.

Keywords: allenes · fluorescence · nonaflates · palladium · pyridines · thiophenes

Introduction

Thiophenes[1] and pyridines[2] are among the most important five- and six-membered heterocycles. Whereas thiophene units are present in many compounds of interest in materials science,[3] in particular, as organic electronic materials,[4] the pyridine substructure is very common in biologically active and pharmaceutically relevant compounds,[5] as well as in building blocks used in supramolecular chemistry.[6] Surprisingly, no systematic combinations of these two important classes of heterocycles have been attempted,[7,8] for example, compounds with a pyridine core surrounded by a definite number of 2-thienyl substituents such as **A**. Compounds of this type should be of considerable interest with regard to their optical and electronic properties.[9,10] Our group has recently discovered an extremely flexible method to prepare highly functionalized pyridine derivatives of type **B**,[11] which allows the introduction of a broad range of substituents in all five positions of the heterocycle. The 3-, 4- and 5-positions of **B** can be modified to selectively generate compounds of type **C** containing functional groups that allow the introduction of a broad range of new substituents at the pyridine ring by palladium-catalyzed couplings leading to products with general structure **D**.[12] To demonstrate the robustness, scope, and limitation of our methods, we tackled the problem of preparing all types of oligo(2-thienyl)-substituted pyridine derivatives.[13] The absorption and emission behavior of the resulting compounds were also investigated.



Results and Discussion

Our reaction sequence starts with the addition of lithiated methoxyallene **2** (generated in situ from methoxyallene **1** by treatment with *n*-butyllithium)[14] to thiophene-2-carbonitrile (**3**) and subsequent treatment with an excess of thiophene-2-carboxylic acid (**4**) (Scheme 1). The desired β-alkoxy-β-ketoenamide **5** was isolated in 70% yield in multigram quantities.[15] The mechanism of this reaction has been described earlier in detail[11a] and is not presented here again. The intramolecular aldol-type condensation of the methyl ketone moiety of **5** with its amide carbonyl group is promoted by TMSOTf and triethylamine providing 71% of tetrasubstituted pyridine derivative **6**. This key compound was subsequently converted into nonaflate **7** by deprotonation with

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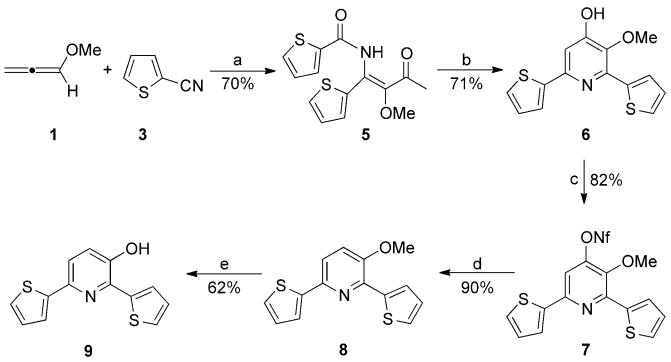
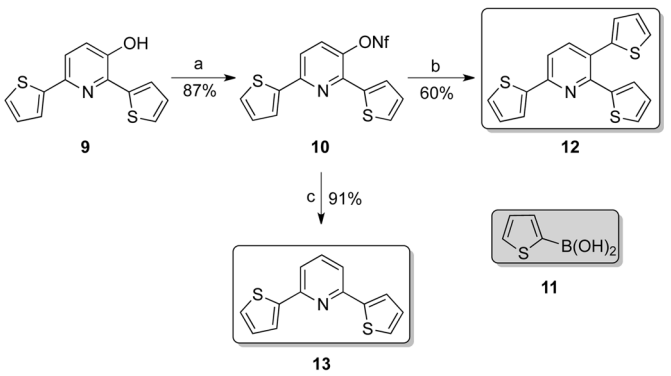


Scheme 1. Synthesis of β-alkoxy-β-ketoenamide **5** and subsequent transformations into pyridine derivatives **6**, **7**, **8**, and **9**. Reagents and conditions: a) *n*BuLi, Et_2O, −70 °C, 4 h; then thiophene-2-carboxylic acid (**4**), −70 °C to RT, 12 h; b) Et_3N, trimethylsilyl triflate (TMSOTf), 1,2-dichloroethane, sealed tube, 100 °C, 5 d; c) NaH, nonaflyl fluoride (NfF), THF, RT, 6 h; d) $Pd(OAc)_2$, 1,3-bis(diphenylphosphino)propane (DPPP), Et_3N, HCO_2H, DMF, sealed tube, 90 °C, 2 h; e) BBr_3 (1 M in CH_2Cl_2), CH_2Cl_2, 0 °C to RT, 12 h.

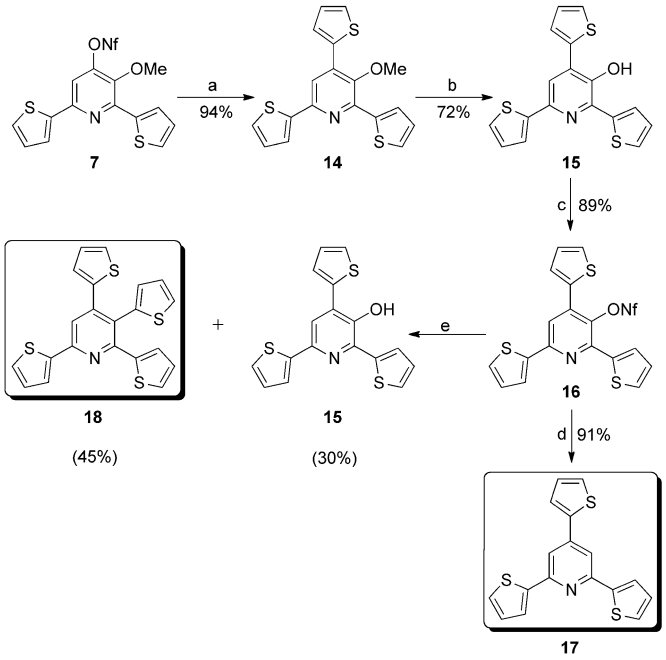
sodium hydride and the addition of NfF.[16] Subsequent reductive removal of the nonaflate unit[17] gave trisubstituted pyridine derivative **8**, which was transformed into 3-hydroxy-2,6-di(2-thienyl)pyridine (**9**) by treatment with boron tribromide in good overall yield. Compounds **6**, **7**, **8**, and **9** are crucial precursors in our efforts to prepare the desired oligo(2-thienyl)-substituted pyridine derivatives **A**.

Compound **9** was converted into the corresponding pyrid-3-yl nonaflate **10** under standard conditions in very good yield. This intermediate served as a precursor for the synthesis of 2,6-di(2-thienyl)pyridine (**13**) and of 2,3,6-tri(2-thienyl)pyridine (**12**) (Scheme 2). The trisubstituted compound **12** was formed in moderate yield by Suzuki coupling with **11**, whereas the disubstituted pyridine derivative **13** was obtained by reductive removal of the nonafloxy substituent under palladium catalysis. The first two compounds of our series have hence been prepared in fairly short sequences without any problems.



Scheme 2. Preparation and conversion of pyrid-3-yl nonaflate **10** into di- and trisubstituted pyridine derivatives **13** and **12**. Reagents and conditions: a) NaH, NfF, THF, RT, 6 h; b) thiophene-2-boronic acid (**11**), $Pd(OAc)_2$, K_2CO_3, PPh_3, DMF, 70 °C, 12 h; c) $Pd(OAc)_2$, DPPP, Et_3N, HCO_2H, DMF, sealed tube, 90 °C, 2 h.

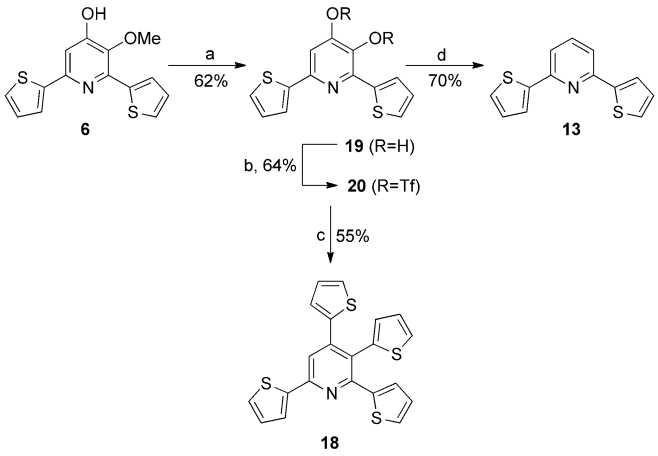
Next, we planned to synthesize a symmetrically substituted tri(2-thienyl)- and two tetra(2-thienyl)pyridine derivatives. The thiophene moiety was introduced into the 4-position of the pyridine core by performing a Suzuki coupling of nonaflate **7** with boronic acid **11** to give intermediate **14** in excellent yield (Scheme 3). Subsequent deprotection with



Scheme 3. Suzuki coupling of pyrid-4-yl nonaflate **7**, deprotection of **14** to **15**, and subsequent syntheses of tri- and tetrasubstituted pyridine derivatives **17** and **18**. Reagents and conditions: a) **11**, $[Pd(PPh_3)_4]$, K_2CO_3, DMF, 70 °C, 8 h; b) NaSEt, DMF, 90 °C, sealed tube, 2 h; c) NaH, NfF, THF, RT, 12 h; d) $Pd(OAc)_2$, DPPP, Et_3N, HCO_2H, DMF, sealed tube, 90 °C, 2 h; e) **11**, $[Pd(PPh_3)_4]$, K_2CO_3, DMF, 80 °C, 24 h.

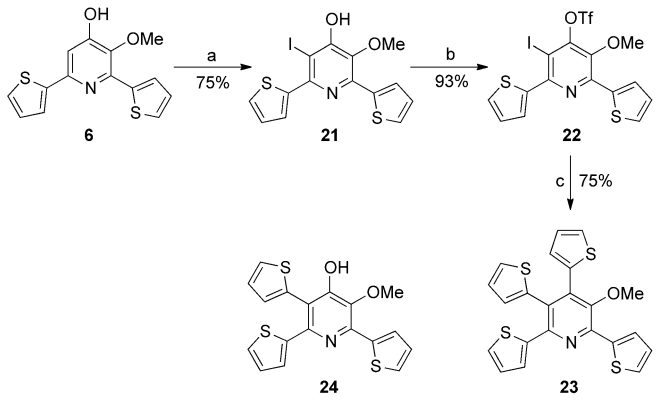
sodium ethanethiolate efficiently afforded 3-hydroxy-2,4,6-tri(2-thienyl)pyridine (**15**), which was converted into nonaflate **16** in excellent yield. This nonaflate was then reductively converted into the desired symmetrically substituted pyridine derivative **17** with 2-thienyl groups in the 2-, 4-, and 6-positions. Our first attempt to prepare tetrasubstituted compound **18** employed a Suzuki coupling of nonaflate **16** with boronic acid **11**. This resulted in a mixture of the desired product **18** (45%) together with the desulfonylated compound **15** (30%). It is known that aryl triflates and nonaflates can undergo this reaction under basic conditions,[18] and is very likely to be due to attack of a nucleophilic species present to the sulfur atom of the leaving group.

Alternatively, we prepared bis(triflate) **20** by deprotection of compound **6** and treatment of the resulting 3,4-dihydroxypyridine derivative **19** with Tf_2O and base (Scheme 4). Bis(triflate) **20** underwent a double Suzuki coupling with an excess of **11** to provide **18** in a slightly better yield (55%) than that obtained with the previous method. Bis(triflate) **20** was also subjected to reductive removal of the trifloxy groups, which again provided **13** (70% yield).



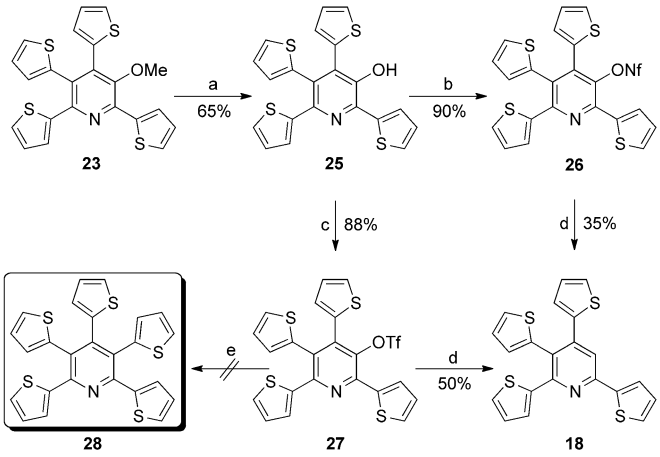
Scheme 4. Synthesis of bis(triflate) **20** as a precursor of di- and tetrasubstituted pyridine derivatives **13** and **18**. Reagents and conditions: a) 1 M ionic liquid consisting of $2AlCl_3/Me_3NHCl$ in CH_2Cl_2, RT, 2 h; b) trifluoromethylsulfonic acid anhydride (Tf_2O), Et_3N, 4-dimethylaminopyridine (DMAP), CH_2Cl_2, 0 °C to RT, 12 h; c) **11**, $Pd(OAc)_2$, K_2CO_3, PPh_3, DMF, 80 °C, 24 h; d) $Pd(OAc)_2$, DPPP, Et_3N, HCO_2H, DMF, sealed tube, 90 °C, 2 h.

Finally, we tried to prepare the penta(2-thienyl)-substituted pyridine derivative **28**. To make our intermediates ready for this target, an additional activating group had to be installed, allowing coupling reactions in the as yet unsubstituted 5-position of the pyridine core. Compound **6** was again an ideal precursor for this plan because iodination under basic conditions[11c] converted this pyridinol derivative into pentasubstituted product **21** offering three potential activating groups in good yield (Scheme 5). Transformation of the free hydroxyl group into a triflate gave compound **22** under standard conditions in excellent yield. The twofold Stille coupling of this intermediate with 2-(tributylstannyl)thiophene smoothly gave the desired tetra(2-thienyl)-substituted pyridine derivative **23** in 75% yield, whereas the Suzuki coupling of **22** with **11** gave a mixture of **23** (45%) together with the desulfonylated compound **24**. This experiment indicates that the Suzuki coupling of **22** probably proceeds faster at the 5-iodo than at the 4-triflate position.



Scheme 5. Synthesis of 5-iodo-substituted pyridinol derivative **21** and subsequent functionalization leading to pyridine derivatives **22**, **23**, and **24**. Reagents and conditions: a) I_2, Na_2CO_3, THF/H_2O (1:1), RT, 24 h; b) Tf_2O, pyridine (Py), DMAP, CH_2Cl_2, RT, 4 h; c) 2-(tributylstannyl)-thiophene, $[Pd(PPh_3)_4]$, DMF, 120 °C, 2 h.

With the aim of synthesizing **28**, we tried to achieve the missing transformations with **23**. Deprotection to **25** followed by nonaflation to **26** or by triflation to **27**, respectively, proceeded without any particular problems and in good to excellent yields (Scheme 6). The two activated compounds **26** and **27** were ready for subsequent coupling reactions, however, the attempted Suzuki reactions with **11** failed to generate the desired product **28**. In both cases, instead of **28** only the unsymmetrical tetrasubstituted pyridine derivative **18** was isolated in moderate yields as a result of reductive removal of the trifloxy or nonafloxy group. Similar events during attempted Suzuki couplings have been reported in the literature, for example, for calix[4]arene triflates, halopyrimidine, and halopyrrole derivatives.[19] The reducing agent in this side reaction is most likely to be DMF.[19b] As an alternative, we also tried to perform Stille couplings with **26** and **27**, but these attempts also failed and gave unidentifiable mixtures of products. These negative results indicate the limitations of our modular approach to highly substituted pyridine derivatives.

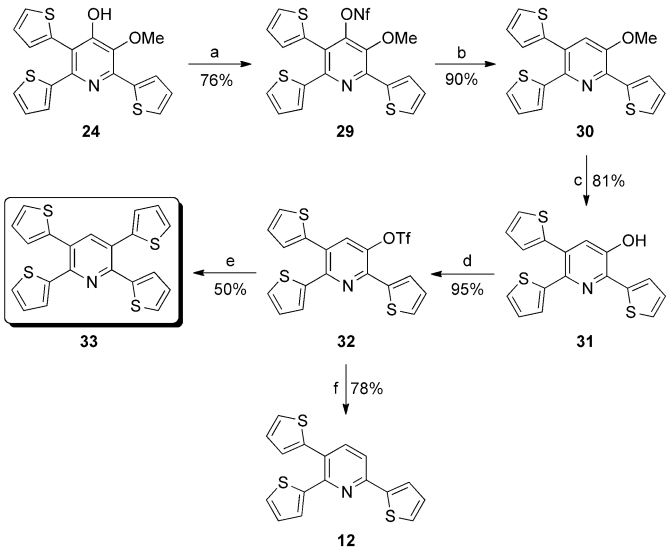


Scheme 6. Preparation of nonaflate **26** and triflate **27** and attempted coupling reactions to synthesize pentasubstituted pyridine derivative **28**. Reagents and conditions: a) NaSEt, DMF, sealed tube, 90 °C, 2 h; b) NaH, NfF, THF, RT, 12 h; c) Tf_2O, Et_3N, DMAP, CH_2Cl_2, 0 °C to RT, 8 h; d) **11**, $[Pd(PPh_3)_4]$, K_2CO_3, DMF, 70 °C, 24 h; e) 2-(tributylstannyl)thiophene, $[Pd(PPh_3)_4]$, DMF, 120 °C, 24 h.

The final palladium-catalyzed couplings of compounds such as **26** and **27** are apparently hampered by steric hindrance or by electronic deactivation. The oxidative addition of palladium(0) probably occurs (as indicated by the isolation of the reduction product **18**; Scheme 6), but subsequent transmetallation with the boron (or tin) species seems to be unfavorable in this case. We cannot rule out that the presence of two neighboring thiophene substituents displays an "electronic" effect on the intermediate palladium(II) species, possibly in a pincer-type position between two sulfur atoms. Additional studies should reveal whether less bulky

substituents are more suitable for coupling to the "small gap" offered in molecules such as **26** or **27** as opposed to 2-thienyl groups. It has to be mentioned here that a pyrid-3-yl nonaflate (with substituents different from 2-thienyl) was able to undergo a Suzuki coupling to a pentasubstituted pyridine derivative in low yield, with reductive removal of the nonafloxy group as a competing reaction.[11e]

Starting with semi-protected pentasubstituted pyridine derivative **24**, we could also prepare the symmetrical tetra(2-thienyl)-substituted pyridine **33** and the unsymmetrical tri(2-thienyl)-substituted pyridine **12** (Scheme 7). The required steps follow the methods described above and consist of nonaflation to intermediate **29**, reductive removal of the nonafloxy group to give **30**, and subsequent deprotection and triflation of **31** to give key compound **32**. All transformations proceeded in good to excellent yields. Finally, 2,3,5,6-tetra(2-thienyl)pyridine (**33**) was obtained in moderate yield by the standard Suzuki procedure employing **11** as a component, whereas trisubstituted compound **12** was obtained by this route through reduction of **32** in good yield.



Scheme 7. Synthesis of 3-trifloxy pyridine derivative **32** and subsequent transformations into tetra- and trisubstituted pyridines **33** and **12**. Reagents and conditions: a) NaH, NfF, THF, RT, 8 h; b) $Pd(OAc)_2$, DPPP, Et_3N, HCO_2H, DMF, sealed tube, 90 °C, 2 h; c) BBr_3 (1 M in CH_2Cl_2), 0 °C to RT, 12 h; d) Tf_2O, Et_3N, DMAP, CH_2Cl_2, 0 °C to RT, 4 h; e) **11**, [$Pd(PPh_3)_4$], K_2CO_3, DMF, 70 °C, 20 h; f) $Pd(OAc)_2$, DPPP, Et_3N, HCO_2H, DMF, sealed tube, 90 °C, 2 h.

Absorption and fluorescence spectra: With symmetrical and unsymmetrical oligo(2-thienyl)-substituted pyridine derivates in hand, we started to study their photophysical properties. The data of the absorption and emission in chloroform are collected in Table 1 and compared with the corresponding spectra of the protonated compounds obtained by using a solution in chloroform containing 1% of trifluoroacetic acid (TFA). The neutral pyridine derivatives generally show the strongest absorption at 290 to 305 nm with little influence of the substitution pattern, whereas with increasing number of 2-thienyl substituents the shoulder of these absorptions are systematically redshifted from about 330 to 355 nm. The 3-methoxy group as present in compounds **8** and **23** displays a stronger effect, shifting this shoulder to about 355 nm.

The emission is more dependent on the substitution pattern, resulting in smaller Stokes shifts for compounds with 2-thienyl substituents in 2,6- or 2,4,6-positions (ca. 90 nm for compounds **13** and **17**). Pyridine derivatives with 2-thienyl groups in the 2,3-positions (**12** and **18**) show higher Stokes shifts of about 105 nm, whereas the emission of the symmetrical tetrasubstituted pyridine **33** results in the strongest Stokes shift of 172 nm. Methoxy groups cause emissions at longer wavelengths than those of the pyridine derivatives without these substituents (compare **8** with **13** and **23** with **18**, Table 1). The UV/Vis and fluorescence spectra of **33** are depicted in Figure 1.

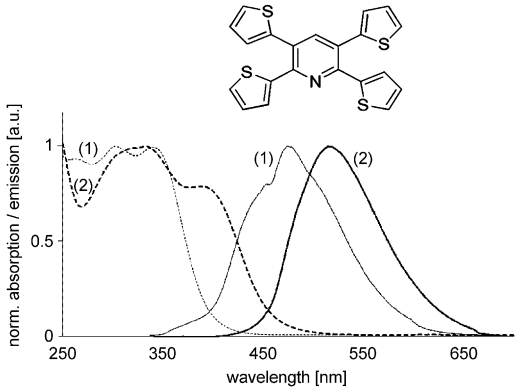


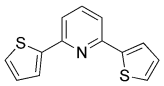
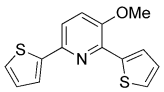
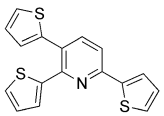
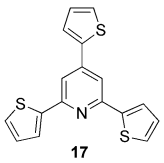
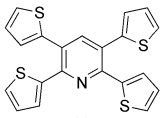
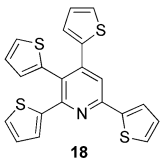
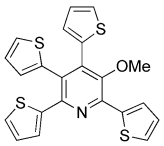
Figure 1. UV (dashed lines) and fluorescence spectra (solid lines) of **33** in $CHCl_3$ (lines 1) and in $CHCl_3$ with 1% TFA (lines 2).

A mixture of chloroform/TFA (99:1) should be sufficient to fully protonate the pyridine derivatives dissolved. The absorption and emission data of the resulting pyridinium salts are also included in Table 1, but are not discussed in detail. All absorptions are shifted to longer wavelengths, but there seems to be no general pattern if just the λ_{max} values are considered. The fluorescence of the protonated species leads to emissions in the range of 445 to 515 nm. Tetrasubstituted compound **33** shows the highest Stokes shift of 182 nm in the protonated form. The fluorescence spectrum of protonated **33** is also integrated into Figure 1.

Conclusion

Our building block system allowed the modular synthesis of a series of 2-thienyl-substituted pyridine derivatives. Starting from **1**, **3**, and **4**, a suitably functionalized 2,6-di(2-thienyl)-substituted pyridine derivative was obtained. Compound **11**, as additional thiophene component, and standard operations led to the simple preparation of di-, tri- and tetra-substituted

Table 1. Absorption and emission data of 2-thienyl-substituted pyridine derivatives.

2-Thienylpyridine	In $CHCl_3$			In $CHCl_3$/TFA (99:1)		
	absorption[a] λ_{max} [nm], (log ε)	emission[b,c] λ_{max} [nm]	Stokes shift [nm]	absorption[a] λ_{max} [nm], (log ε)	emission[b,c] λ_{max} [nm]	Stokes shift [nm]
 **13**	290 (4.27), 329 (sh) (4.12)	377	87	383 (4.34), 279 (sh) (4.14)	445	62
 **8**	294 (4.29), 352 (sh) (4.18)	402	108	403 (4.35), 299 (sh) (4.17)	476	73
 **12**	300 (4.29), 332 (sh) (4.25)	402, 422 (sh)	102	392 (4.23), 329 (sh) (4.16)	486	94
 **17**	299 (4.60), 348 (sh) (3.97)	392	93	362 (4.51), 283 (sh) (4.26)	452	100
 **33**	303 (4.28), 340 (sh) (4.28)	475, 451 (sh)	172	333 (4.28), 389 (sh) (4.17)	515	182
 **18**	301 (4.51), 343 (sh) (4.11)	408	107	378 (4.26), 292 (sh) (4.10)	474	96
 **23**	300 (4.35), 355 (sh) (4.04)	418	118	326 (4.09), 404 (sh) (4.08)	506	180

[a] Recorded at $c = 10^{-5}$ mol L^{-1} in 1 cm cuvettes. [b] Excitation at maximum absorption wavelength. [c] Recorded at $c = 10^{-5}$–10^{-6} mol L^{-1} in 1 cm cuvettes.

pyridine derivatives. The desired compound **28** was not available due to severe steric hindrance (or specific electronic effects) in the attempted final coupling step, hence showing the limitation of our approach to this class of compounds. The resulting oligo-2-thienyl-substituted pyridine derivatives show interesting photophysical properties, as demonstrated by their absorption and qualitatively studied fluorescence. Absorption and emission are strongly influenced by the number and position of 2-thienyl substituents. Symmetrically substituted **33** not only showed the strongest Stokes shift in the neutral form, but also as a protonated species with an emission at 515 nm. These results demonstrate that oligo(2-thienyl)-substituted pyridines are interesting compounds, the properties of which should be studied in more detail. The redox properties of these heterocycles and related compounds, including pyridine derivatives with 2,2′-di-5-thienyl substituents, will be reported in due course.

Experimental Section

The Experimental Section can be found in the Supporting Information and includes full compound characterization.

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