

Push–Pull Aminobithiophenes — Highly Fluorescent Stable Fluorophores

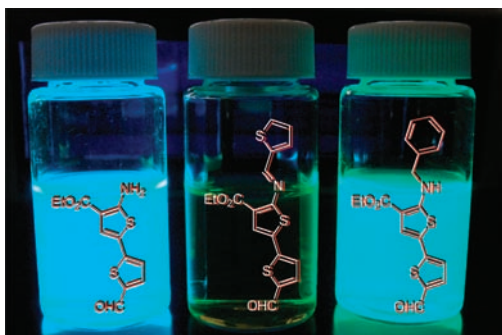
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ABSTRACT



Stable 2-aminobithiophenes were prepared using the Gewald reaction. The resulting *push–pull* bithiophenes exhibited both unprecedented high fluorescence yields and stability in addition to demonstrating fluorescence on–off properties.

Fluorophores play important roles in many applications including emitting devices,¹ nonlinear optics,² and lasers.³ They have also attracted much attention as sensors owing in part to their extreme sensitivity to subtle environmental modifications that are signaled by changes in either fluorescence intensity or emission color. These properties are ideal for obtaining structural information,⁴ fluorophore orientation,⁵ distances,⁶ and the location of active sites,⁷ especially in biological contexts.⁸

Ideal fluorophores for sensitive signaling applications at low concentrations must exhibit high fluorescence quantum yields (Φ_f).⁹ This is possible with multiple fused

aromatic systems such as pyrene,¹⁰ perylene,¹¹ fluorescein,¹² and BODIPY¹³ and FITC dyes,¹⁴ whose reduced degrees of freedom suppress nonradiative singlet excited state deactivation modes. Such systems however are susceptible to both challenging chemical modification and synthesis in addition to limited solubility in media of the desired study. While nonrigid conjugated systems such as bithiophene can be readily modified for addressing the shortcomings of their rigid counterparts, they are weakly fluorescent ($\Phi_f = 0.015$).¹⁵ The fluorescence yield of nonrigid conjugated biaryls can dramatically be increased by incorporating complementary electron-donating and -withdrawing groups.¹⁶ The electronic *push–pull* effect is typically achieved with an electron-donating amine.¹⁷ Primary amino fluorophores are interesting because the

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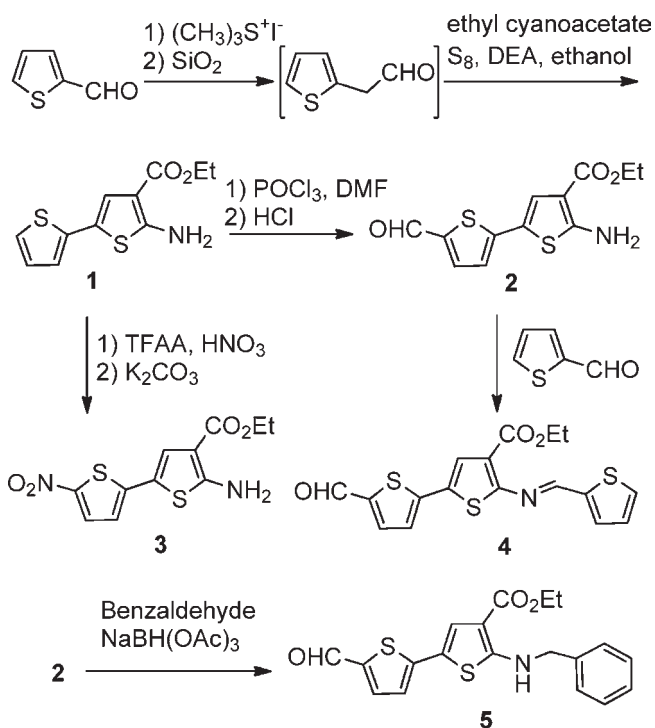
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emission properties can be tailored by reacting the amine. Also, by changing the electron density of the amine, dramatic fluorescence changes occur, making primary amino fluorophores interesting *in situ* reaction sensors. Unfortunately, primary aminothiophenes are highly unstable and few aminobithiophenes are known.¹⁸

Stable 2-aminothiophenes can be prepared, provided they contain an electron-withdrawing group in the 3-position, possible via the Gewald reaction.^{19,20} Despite the extensive use of this reaction for preparing pharmacologically relevant 2-aminothiophenes, 2-aminobithiophene derivatives have not been reported. We were therefore incited to prepare such derivatives, especially conjugated *push–pull* aminobithiophenes for achieving highly fluorescent and stable bithiophenes. The preparation of *de novo* conjugated aminobithiophenes **1–5** and their cursory spectroscopic characterization are herein presented.

Scheme 1. Synthesis of **1–5**



The preliminary step involved in the Gewald^{19,20} reaction is the Knoevenagel condensation of activated cyano methylenes such as ethyl cyanoacetate or malononitrile with α -methylene carbonyl compounds catalyzed by secondary and tertiary amines. This is followed by cyclization

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and oxidization with elemental sulfur. The advantage of the Gewald reaction is that the desired 2-aminothiophenes are prepared in one pot and can be isolated by standard purification methods. Moreover, the products are air stable and do not require inert atmospheres for handling. The unsaturated aldehyde precursor required for the Knoevenagel condensation was obtained in 61% yield by the rearrangement of thienyloxirane by adding trimethylsulfonium iodide to 2-thiophene carboxaldehyde.²¹ 2-Thienylacetaldehyde was immediately used without isolation and purification by combining it with ethyl cyanoacetate, elemental sulfur, and diethylamine (DEA) in ethanol and stirred at room temperature. The resulting **1** was isolated as a solid in 25% overall yield for the combined steps and was stable under ambient conditions. Although higher yields of the Gewald reaction are expected with malononitrile owing to the symmetric Knoevenagel intermediate formed, the advantage of ethyl cyanoacetate is that the ester of **1** can be readily modified. This provides a handle to both tailor the solubility and covalently link the prefluorophore to other substrates. Nonetheless, the yield of **1** is consistent for the Gewald reaction.²²

The nitro function is highly complementary to the 2-amino group of **1**, resulting in a strong electronic *push–pull* system. Addition of the nitro group was done by standard nitration in trifluoroacetic anhydride (TFAA) and nitric acid to afford **3**. An aldehyde was also selected as an alternate electron-withdrawing group for preparing the targeted highly fluorescent fluorophore, given that the nitro group is known to quench the fluorescence in certain fluorophores. The aldehyde group was introduced into **1** by Vilsmeier–Haack formylation. **2** was isolated in 41% yield after removal of the amine protecting *N,N*-dimethyl imine group by acidic hydrolysis. The protecting group is formed by condensation between the amine and DMF catalyzed by the acid generated by decomposition of the POCl₃ *in situ*. Although the terminal functional groups in **2** could potentially condense leading to Schiff base polymers, no such autocondensation products were observed. This is most likely owing to the collective electronic effects of the two groups that deactivate both the amine and aldehyde, preventing autocondensation. The preparation of both *push–pull* fluorophores is summarized in Scheme 1.

Product identification of **1–5** was done according to standard methods (see Supporting Information). Structural confirmation of **2** was additionally done by X-ray crystallography. Suitable X-ray quality crystals were grown by evaporation in acetone. The molecule crystallizes in a monoclinic *P2₁/c* space group with four molecules per lattice. The resolved crystal confirmed the correct structure for the compound, as seen in Figure 1. It is evident that the heteroatoms orient themselves in a *syn* arrangement, which is uncommon for bithiophenes.²³ Meanwhile, the

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heterocycles are coplanar. The average angle between the two thiophene mean planes was found to be twisted by $4.26(14)^\circ$. Also, the carbonyl group is in the same plane with a torsion angle of $0.1(2)^\circ$ from the adjacent thiophene ring. Similarly, the amino group is also in the thiophene plane with a torsion angle of $1.02(12)^\circ$ from its adjacent thiophene.

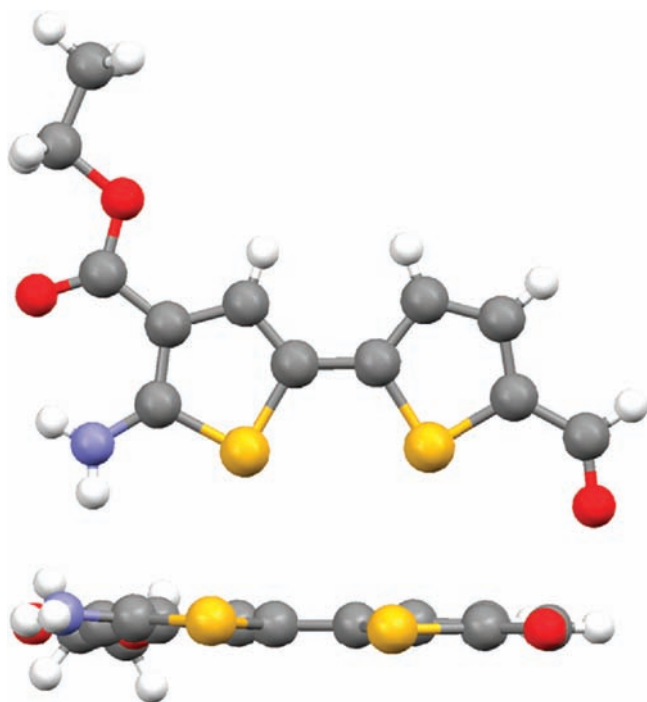


Figure 1. X-ray crystal structure of **2**. Top: face view. Bottom: edge view.

Intermolecular interactions between the molecules within the crystal lattice occur between the hydrogen on the terminal amine and carbonyl oxygen ($2.034(18)$ Å) of an adjacent molecule. Additional hydrogen bonding occurs between the hydrogen on the terminal amine and the ester oxygen of another molecule with a distance of $2.231(19)$ and $2.299(19)$ Å.

Absolute quantum yields of **1–5** were measured with an integrating sphere.^{24,25} The Φ_{fl} values derived from this method are precise and absolute because they do not rely on actinometric standards, which are excitation wavelength, emission yield, emission wavelength, and solvent dependent. The measured Φ_{fl} for **2** and **3** are 83 and 76%, respectively (Table 1). These are in contrast to **1** and bithiophene, whose $\Phi_{\text{fl}} < 0.01$. The near unity fluorescence yields of **2** and **3** confirm that bithiophenes can be rendered fluorescent courtesy of the *push–pull* effect from the complementary electron-donating/-accepting groups. It is noteworthy that the fluorophores do not photobleach or undergo photochemical reactions even at extended irradiation times (18 h at 320 nm) and that **2–5** are stable

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Table 1. Absorbance and Fluorescence Data for **1–5**^a

	λ_{abs} (nm) ^b	λ_{em} (nm) ^c	Φ_{fl} ^d
Bithiophene ^e	303	362	0.013
1	330	427	0.06
2	406	498	0.83
3	494	600	0.76
4	424	492	≈ 0
5	422	507	0.74

^a Measured in anhydrous deaerated dichloromethane. ^b Absorbance maximum. ^c Fluorescence maximum. ^d Absolute quantum fluorescence yield measured with an integrating sphere. ^e Measured in dioxane taken from literature.¹⁵

under ambient conditions. This was confirmed spectroscopically (abs. and flu.) and by NMR.

Not only can the fluorescence of bithiophene be dramatically enhanced by incorporating complementary electron-donating and withdrawing groups but also the emission color can also be tuned. For the aldehyde-amino pair (**2**), the emission is bathochromically shifted by 130 nm from the unsubstituted bithiophene while the emission of the stronger nitro-amino pair (**3**) is shifted by 240 nm (Figure 2). The emission wavelength can similarly be adjusted by converting **2** to a secondary amine as seen with **5**. Most importantly, the fluorescence can be completely quenched by changing the *push–pull* electronics into a *pull–pull* effect. This is possible by converting the amine into an imine electron-accepting group (**4**), as seen in the inset of Figure 2. The secondary amine **5** was further prepared to demonstrate that fluorescence quenching was due to electronic effects. As seen from the photographs in the inset of Figure 2 and Table 1, there is no effect of primary vs secondary amine on the fluorescence yield. The *push–pull* aminothiophene therefore has fluorescent *on/off* properties with extremely high fluorescence yields possible in the *on* state.

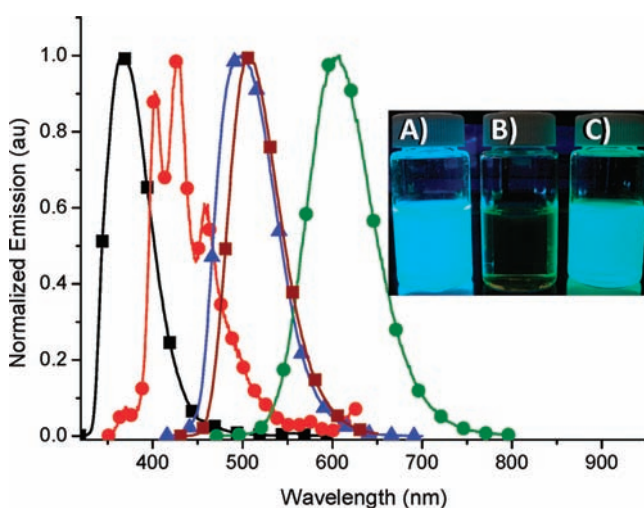


Figure 2. Fluorescence spectra of bithiophene (black ■), **1** (red ●), **2** (blue ▲), **3** (green ●), and **5** (brown ■) measured in deaerated dichloromethane. Inset: photographs of **2** (A), **4** (B), and **5** (C) in dichloromethane excited with a long wavelength UV-lamp.

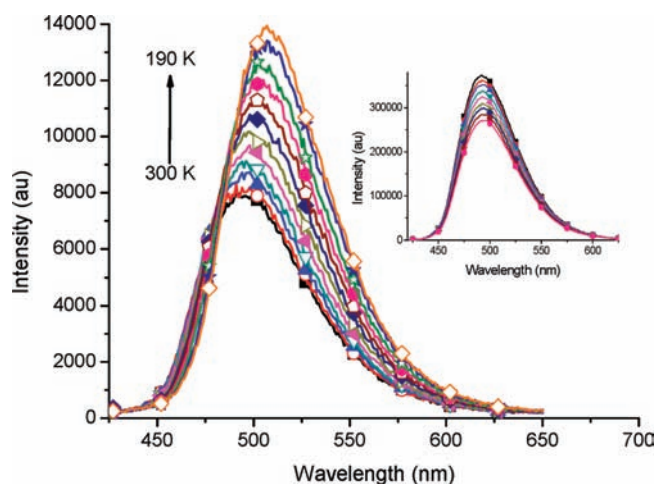


Figure 3. Temperature dependent fluorescence of **4** measured in deaerated dichloromethane between 190 and 300 K excited at 424 nm. Inset: fluorescence quenching of **2** with (*E*)-*N*-benzylidenedecan-1-amine excited at 404 nm.

The imine **4**, derived from the acid catalyzed condensation of **2** with 2-thiophenecarboxaldehyde, was additionally prepared for examining the electronics effect at the terminal positions on the fluorescence yield. As seen in Table 1, the fluorescence of **4** is completely quenched. To determine whether the fluorescence suppression was due to rotational deactivation, the fluorescence as a function of temperature was investigated. According to Figure 3, the fluorescence increased by only 57% upon lowering the temperature to a point where bond rotation deactivation processes are suppressed. The absence of dramatic fluorescence increase at low temperatures implies that **4** is quenched from intramolecular

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electronic effects. This was proven by examining the Stern–Volmer intermolecular quenching of **2** with an imine prepared from benzaldehyde and decylamine.^{26,27} The derived bimolecular rate constant was $8.5 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$, with the lifetime of **2** = 1.3 ns. The diffusion controlled rate constant implies fluorophore deactivation by photoinduced electron transfer from the fluorophore to the imine quencher.²⁸ This demonstrates the sensor-like properties of the 2-aminothiophene fluorophores whose fluorescence can be turned on or off by perturbing the terminal amine. Similarly, the fluorescence yield can be quenched by imine formation with the terminal aldehyde of **2**.

In summary, we have demonstrated the first examples of stable 2-aminobithiophenes. The conjugated biaryls could be made highly fluorescent by incorporating complementary electron-donating and -withdrawing groups in the terminal positions. In fact, the measured quantum yields of the electronic *push–pull* systems are comparable to currently used fluorophore probes. While 2-aminobithiophenes can be prepared by the Gewald reaction, the reaction can potentially be applied to any α -methylene carbonyl compound. This modular approach provides the means to prepare bithiophenes that could fluoresce at discrete wavelengths by using different precursors with various electronic groups such as EDOT or benzotriazole. New fluorophores with the desired emission wavelength can therefore be easily prepared. The robustness of the 2-aminothiophenes toward chemical modification taken together with its near unity fluorescence yield serves to illustrate the potential use of this new class of compounds as fluorophores and on/off sensors.

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Supporting Information Available. Experimental procedures, ¹H NMR and ¹³C NMR and spectroscopic data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.