Bioorganic & Medicinal Chemistry Letters 28 (2018) 3099–3104

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

The design, synthesis, and evaluation of organic dithienopyrrole-based D-π-A dyes for use as sensitizers in photodynamic therapy

Shinichiro Fuse[a,*], Keisuke Matsumura[a], Miori Takizawa[a,b], Shinichi Sato[a], Hiroyuki Nakamura[a,*]

[a] Laboratory for Chemistry and Life Science, Institute of Innovative Research, Tokyo Institute of Technology, 4259 Nagatsuta-cho, Midori-ku, Yokohama 226-8503, Japan
[b] School of Life Science and Technology, Tokyo Institute of Technology, 4259 Nagatsuta-cho, Midori-ku, Yokohama 226-8503, Japan

ARTICLE INFO

InChIKey:
CSZHBPSGFIRARQ-LFIBNONCSA-N*Keywords:*
Photodynamic therapy
Suzuki-Miyaura coupling
One-pot synthesis
Dithienopyrrole

ABSTRACT

Dithienopyrrole-based organic dyes that combine an electron-donating moiety (D), a π-conjugated bridge moiety (π), and an electron-accepting moiety (A) were designed and synthesized in short steps by previously developed one-pot Suzuki-Miyaura coupling approach. Absorption wavelengths of the dyes were readily tuned by altering the D and A moieties. The use of a strongly electron-withdrawing cyanopyridone acceptor enabled NIR absorption. A synthesized sensitizer, **2j**, exerted potent phototoxicity mainly via a Type I mechanism in cells. A nitrogen atom in the dithienopyrrole ring serves as a connecting point for the introduction of functional building blocks that can improve the properties of sensitizers, which makes this D-π-A sensitizer a valuable template for the further development of sensitizers.

Photodynamic therapy (PDT) has garnered much attention as a non-invasive, selective, and cost-effective cancer therapy.[1] In PDT, a sensitizer is administered to cancer patients and damages cancer cells under photo irradiation via Type I (hydrogen/electron transfer) and/or Type II (singlet oxygen generation) pathways, which leads to cell death. Several sensitizers have been approved and clinically used for PDT.[2] Many porphyrin-based sensitizers have been developed in ongoing efforts to improve PDT.[3] Although tremendous effort has been extended to develop new sensitizers, the number of available sensitizers remains somewhat limited due to the many requirements: proper absorption wavelength (NIR absorption is desirable), high absorptivity, high stability under photo irradiation and physiological conditions, low levels of dark toxicity, high levels of tumor accumulation, and rapid excretion from the body following PDT.[3a] In addition, sensitizers that damage cancer cells involving Type I mechanisms are considered advantageous under hypoxic conditions in cancers.[4] A sensitizer that could fulfill all requirements awaits development.

We have developed an efficient synthetic approach to thiophene-based, organic dyes that combines an electron-donating moiety (D), a π-conjugated bridge moiety (π), and an electron-accepting moiety (A).[5] We recently reported that the D-π-A sensitizer **1** exerted potent phototoxicity via both Type I and Type II mechanisms (Fig. 1).[6] However, this did not demonstrate absorption in the NIR region. Herein, we report the design and synthesis of dithienopyrrole-based D-π-A sensitizer **2**. Use of strongly electron-withdrawing cyanopyridone acceptor enabled NIR absorption. Evaluation revealed that one of the synthesized sensitizers, **2j**, exerted potent phototoxicity mainly via a Type I mechanism.

We designed the dithienopyrrole-based D-π-A sensitizer **2** for four reasons: 1) dithienopyrrole consists of a fused ring system with extended π-conjugation that enables a red shift of absorption; 2) dithienopyrrole consists of 5-membered heteroaromatic rings (pyrrole and thiophene), and when linked to a benzene ring, both dithienopyrrole and benzene rings reside on a common plane that allows an extension of the π-conjugated system, which results in a red-shift of absorption;[7] 3) a nitrogen atom in the dithienopyrrole ring serves as a connecting point for the introduction of a functional group; and, 4) dithienopyrrole is readily available.

Initially, we prepared dithienopyrrole-based 12 D-π-A sensitizers, **2a–2l** from a combination of 3 donors and 4 acceptors with different levels of electron-donating and -withdrawing abilities (Scheme 1). In order to improve the solubility of the sensitizers, a *tert*-butyl group was attached to the dithienopyrrole ring via the nitrogen atom. A one-pot Suzuki-Miyaura coupling[8] of dibromo dithienopyrrole **3**[9] with 3 donors, **4a–4c**, and thiophene boronic acid **5** was based on our previously reported procedure,[5f] and afforded the desired compounds **2a**, **2e**, and **2i** in moderate yields. A subsequent Knoevenagel condensation of three aldehydes with 3 acceptors, **6a–6c**, afforded the desired D-π-A sensitizers **2b–2d**, **2f–2h**, and **2j–2l** in moderate to excellent yields. Knoevenagel condensations of **2e** with **6a** did not afford the desired product **2f**

* Corresponding authors.
E-mail addresses: sfuse@res.titech.ac.jp (S. Fuse), hiro@res.titech.ac.jp (H. Nakamura).

https://doi.org/10.1016/j.bmcl.2018.07.025
Received 11 June 2018; Received in revised form 13 July 2018; Accepted 14 July 2018
Available online 17 July 2018
0960-894X/

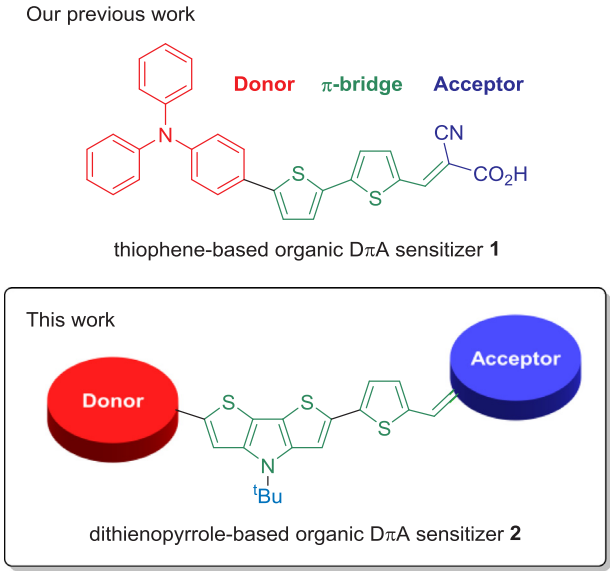
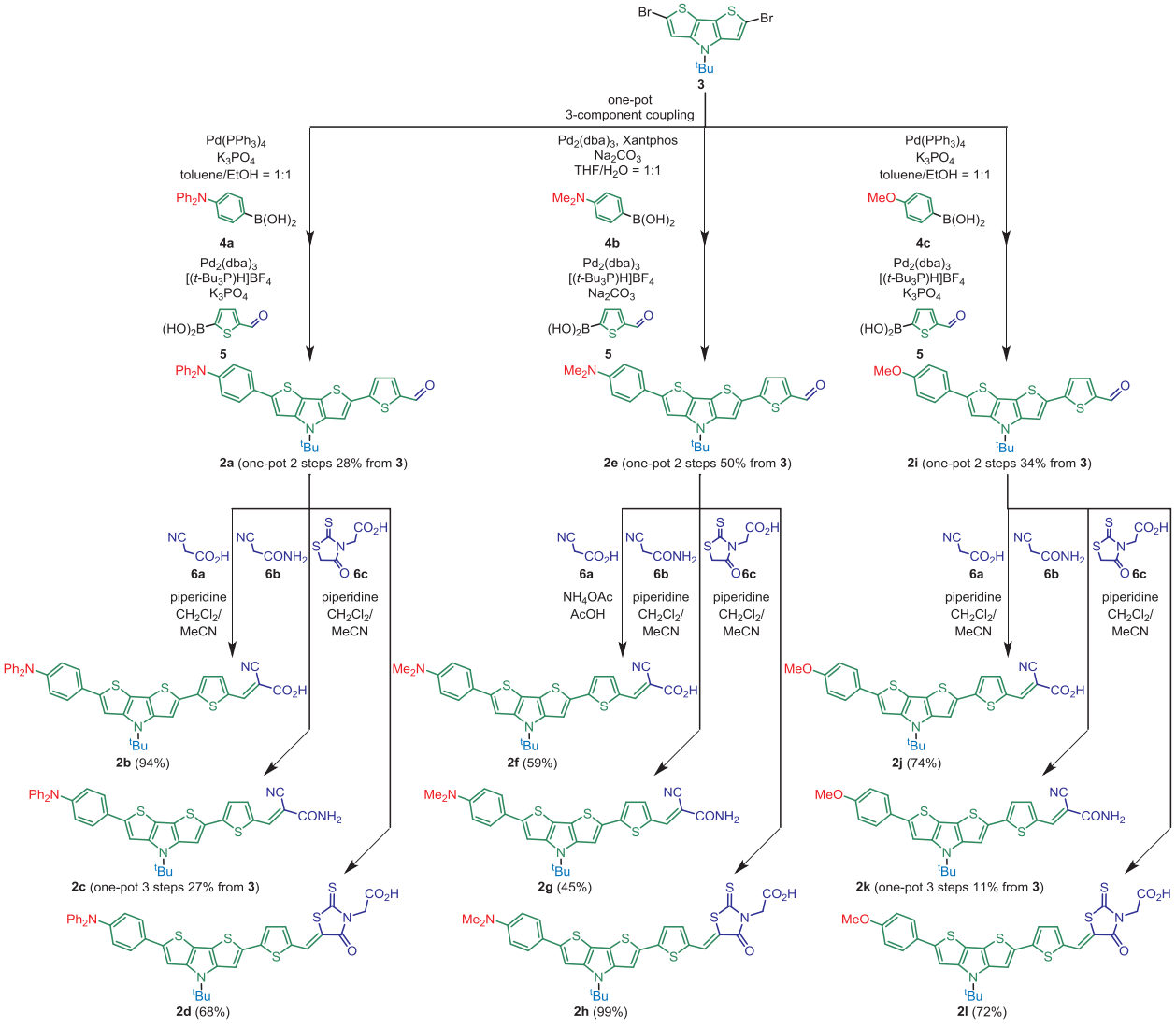


Fig. 1. Chemical structures of our previously reported thiophene-based organic D-π-A sensitizer **1**, and of the new dithienopyrrole-based organic D-π-A sensitizer **2**.

under basic conditions, and, therefore, acidic conditions were used for the synthesis of **2f**. In the cases of the syntheses of **2c** and **2k**, Knoevenagel condensation was performed in a one-pot fashion.[5f]

The photo absorption spectra of **2a–2l** in DMSO were measured (Fig. 2 and Table 1). The D-π-A sensitizers exerted good absorption intensity (ε = 20,000–53,000 L mol^{-1} cm^{-1}) as shown in Table 1. As expected, the introduction of a dithienopyrrole moiety to sensitizer **1** resulted in a *ca* 40 nm red shift (Table 1, entry 1 vs. 2). When a sensitizer had a more electron-donating donor (Me_2N- > Ph_2N- > MeO-), it tended to have longer wavelength absorption (**2e** with Me_2N-: λ_{max} = 488 nm, **2a** with Ph_2N-: λ_{max} = 477 nm, **2i** with MeO-: λ_{max} = 469 nm), as shown in entries 2, 7, and 11. On the other hand, the electron-withdrawing ability of the acceptors (rhodanine > cyanoacrylic acid > cyanoacrylic amide > aldehyde) was not consistent with absorption wavelength. In detail, the sensitizer **2b** with more electron-withdrawing cyanoacrylic acid acceptor had similar or shorter wavelength absorption comparing with those of the sensitizers **2c** and **2a** with less electron-withdrawing cyanoacrylic amide and aldehyde acceptors, respectively (**2d** with rhodanine: λ_{max} = 557 nm, **2b** with cyanoacrylic acid: λ_{max} = 477 nm, **2c** with cyanoacrylic amide: λ_{max} = 526 nm, **2a** with aldehyde: λ_{max} = 477 nm), as shown in entries 2, 3, 5, and 6. We speculated that the deprotonation of cyanoacrylic acid generated less electron-withdrawing cyanoacrylate, which shortened the absorption wavelength. In order to confirm this speculation, a



Scheme 1. Preparation of dithienopyrrole-based 12 D-π-A sensitizers, **2a–2l**.