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New synthetic route to pyrimido[4,5-*g*]quinazoline-4,9-diones

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ABSTRACT

A facile and moderate to high yielding protocol is reported for the synthesis of 2,7-bis(5-bromothiophen-2-yl)-3,8-bis(2-decyltetradecyl)-3,8-dihydropyrimido[4,5-*g*]quinazoline-4,9-dione, which can be potentially used to synthesize other pyrimido[4,5-*g*]quinazoline-4,9-diones. Moreover, new pyrimido[4,5-*g*]quinazoline-4,9-diones synthesized by this route can potentially be used as organic semiconductors.

Organic field effect transistors (OFETs) consisting of π-conjugated organic semiconductors can be potentially used as low-cost chemo- and bio-sensors utilizing the electrical responses of organic semiconductors to chemical or biological analytes.[1–4]

Quinazolinones occur in approximately 150 natural alkaloids.[5] Quinazolinones have been actively studied as they represent an important class of compounds due to their wide range of intrinsic biological activities.[6] For example, they have demonstrated anti-microbial, anti-tumor, anti-inflammatory, anti-convulsant, anti-hypertensive, and anti-malarial activities.[7,8] Due to the importance of quinazolinones for biological activity and pharmaceutical relevance, research in the synthesis of various quinazolinones have been conducted.[5–17]

A pyrimido[4,5-*g*]quinazoline-4,9-dione compound has two quinazolinone moieties fused to a central benzene ring, which allows delocalization of π-electrons between 2 and 7 positions. Its 2,7-(hetero)aryl disubstituted derivatives (Fig. 1) are potential small molecule semiconductors and may be used as building blocks for polymer semiconductors if polymerizable functionalities are attached to the Ar groups. Use of such pyrimido[4,5-*g*]quinazoline derivatives and their polymers as channel semiconductors may potentially furnish biosensing capability to OFETs.

Pyrimido[4,5-*g*]quinazoline-4,9-diones were prepared in the early 1900s.[18] However, in comparison with quinazolinones, there have been much fewer reports on the synthesis of pyrimido[4,5-*g*]quinazoline-4,9-diones, because most of the usual methods to prepare quinazolines were unsuccessful.[19] The majority of

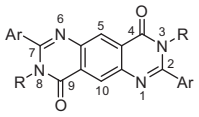

Figure 1. A general structure of 2,7-di(hetero)arylpyrimido[4,5-*g*]quinazoline-4,9-dione, where Ar is a (hetero)aryl such as phyl and 2-thienyl, and R is a suitable substituent such as an alkyl group.

pyrimido[4,5-*g*]quinazoline-4,9-diones reported to date have no substituents or have alkyl substituents at the 2,7-positions.[17–21] For 2,7-di(hetero)aryl substituted pyrimido[4,5-*g*]quinazoline-4,9-diones, only the synthesis of 2,7-diphenylpyrimido[4,5-*g*]quinazoline-4,9-dione was reported.[22] They used 2,5-diaminoterephthalic acid as a starting material to prepare 2,7-diphenylpyrimido[4,5-*g*]-quinazoline-4,9-dione with several routes. Unfortunately, synthetic details were limited. From our understanding stoichiometric amounts of Lewis-acid (i.e., $AlCl_3$ or P_2O_5) were used in majority of reactions with secondary aldimines. However, exact yields for 2,7-diphenylpyrimido[4,5-*g*]quinazoline-4,9-dione were not revealed.

In this Letter we describe for the first time the synthesis of di(thiophen-2-yl)pyrimido[4,5-*g*]quinazoline-4,9-dione (**6**), and its derivatives based on a newly established route (Scheme 1).

Synthesis of the key compound 2,5-diamino-1,4-benzene-dicarboxylic acid 1,4-dimethyl ester (**2**) was initially attempted by refluxing dimethyl 2,5-dihydroxycyclohexa-1,4-diene-1,4-dicarboxylate and excess ammonium acetate in the presence of a catalytic amount of glacial acetic acid in toluene and air following a literature procedure.[23] However, only **1** was produced in high yield (95%). To oxidize **1**, sulfur was added portion wise to a

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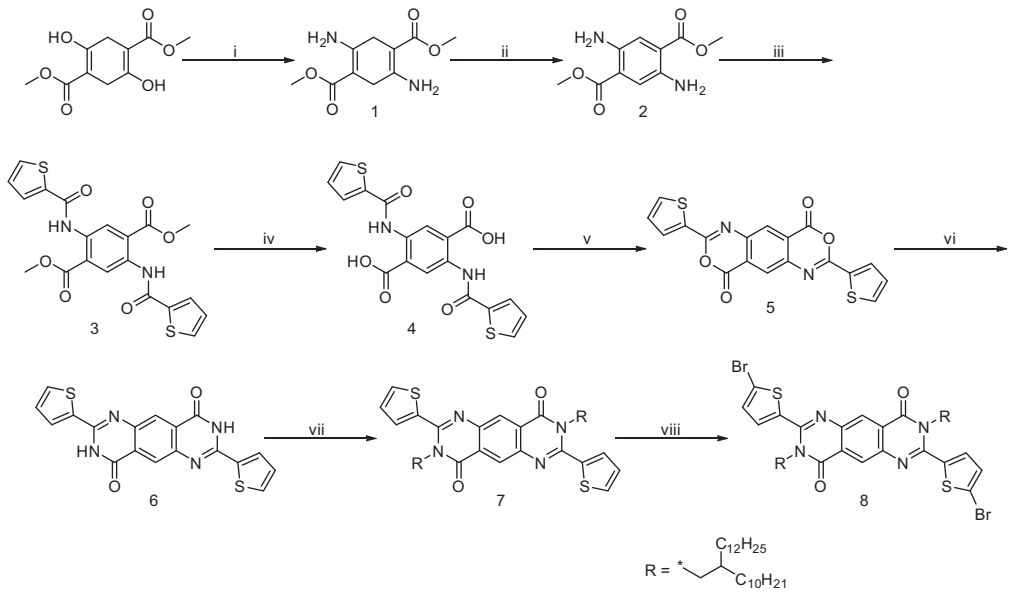

Scheme 1. Reagents and conditions: (i) toluene, ammonium acetate, catalytic amount of acetic acid, 16 h (95%); (ii) *n*-butanol, sulfur, gentle reflux, 18 h (90%); (iii) DCM, 2-thiophenecarbonyl chloride, pyridine, 0 °C, 30 min, rt, 18 h (79%); (iv) ethanol, lithium hydroxide, 60 °C, 3 h (86%); (v) acetic anhydride, reflux, 3 h (78%); (vi) ammonium acetate, 170 °C, 1 h, 30% sodium hydroxide, ethanol, reflux, 1 h (95%); (vii) DMF, K_2CO_3, 130 °C, 16 h (73%); (viii) NBS, chloroform, 0 °C, rt, overnight (75%).

solution of **1** in *n*-butanol and the mixture was heated to gentle reflux for 18 h, forming **2** in high yield (90%). Attempts to convert **2** directly to **6** by reacting with 2-thiophenecarbonitrile using 4 M hydrochloric acid in 1,4-dioxane in a sealed reaction vessel at 100 °C for several days[24] were unsuccessful.

Therefore, N-acetylation of **2** followed routine acetylation procedures[25] was conducted to afford **3** in moderate yield (79%). A direct synthesis of **6** from **3** was also attempted using a pressure reactor in aqueous ammonium hydroxide at 120 °C for several days.[25] However, ring closure did not occur due probably to the limited solubility of **3** in the reaction medium. Subsequently the diacid **4**, which was prepared in 86% yield by hydrolyzation of **3** with lithium hydroxide, was reacted with formamide at 150 °C[26] in order to produce **6**, but the target compound was not formed.

Finally compound **6** was successfully synthesized (95% yield) through the oxidative ring closure[27] of **4** in refluxing acetic anhydride to form compound **5** (78% yield) and the subsequent amination[28] of **5** by heating in ammonium acetate at 170 °C and successively with 30% sodium hydroxide.

Due to the extremely low solubility of **6** in all solvents tested, N-alkylation was performed to solubilize **6**. Compound **6**, K_2CO_3, and 11-(bromo-methyl)tricosane in DMF were heated to 130 °C and left for 16 h to afford **7** in 73% yield. To demonstrate potential functionalization of this pyrimido[4,5-*g*]quinazoline-4,9-diones derivative, the thiophene moieties were then brominated at the 5 positions with NBS. A catalytic amount of bromine was added to accelerate the bromination to afford **8** in 75% yield.

In summary, a facile method for the synthesis of 2,7-di(thiophen-2-yl)pyrimido[4,5-*g*]quinazoline-4,9-diones has been disclosed. In the next step we will use compounds **7** and **8** as channel semiconductors in OFETs to investigate their field effect performance and their response to select biological analyte molecules. Compound **8** having two polymerizable bromo groups is also potentially a monomer for the synthesis of more mechanically robust bio-sensitive π-conjugated polymers for OFETs. With modest to high yields obtained in all steps, we believe that this synthetic route will renew interest toward the synthesis of pyrimido[4,5-*g*]quinazoline-4,9-diones.

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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.tetlet.2015.03.085.

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