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A New Method for Synthesis of Nolatrexed Dihydrochloride

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Abstract:

A new synthetic method for nolatrexed dihydrochloride (thymitaq) has been developed. The synthesis was accomplished in three steps featuring the direct conversion of the starting 4-bromo-5-methylisatin into the methyl anthranilate by potassium peroxydisulfate/sodium methoxide. In the final Ullmann reaction potassium carbonate was employed in place of sodium hydride, and the amount of copper catalysts was significantly reduced. Moreover, sodium sulfide solution was utilized to efficiently remove copper under approximately neutral conditions instead of hydrogen sulfide/methanol under strongly acidic conditions. By means of these modifications, nolatrexed dihydrochloride was ensured to be prepared in good yield and high purity.

Introduction

2-Amino-6-methyl-5-(4-pyridylthio)-3*H*-quinazolin-4-one dihydrochloride (nolatrexed dihydrochloride, **1**), which is also known as thymitaq, is being developed for the treatment of unresectable hepatocellular carcinoma (HCC).[1] As a folate analogue, thymitaq works as an inhibitor of thymidylate synthase (TS) that directly binds the TS folate site, resulting in the inhibition of DNA replication, DNA damage, S-phase cell cycle arrest, and caspase-dependent apoptosis.[2−4] Its phase II clinical studies suggest that thymitaq has survival benefits in patients with HCC.[5,6] Currently thymitaq is under phase III clinical trials.[7]

The first synthesis of nolatrexed (**1**, free base) was reported by Webber at the early stage of drug discovery process (Scheme 1, the route **A**: **2**→**3**→**4**→**5**→**7**·**HCl**→ the free base **1** and the partially different route **B**: **2**→**3**→**6**→**5**).[8] The starting material 4-bromo-5-methylisatin (**2**) was prepared from 2-bromo-4-nitrotoluene via the Sandmeyer reaction in the Webber method, and now it is commercially available on the Chinese market on 100 kilograms of scale. However, the reported preparation of the free base **1** in the lab for drug screening did not provide information about quality control, such as the identifications of related substances, and the solutions to manufacturing problems. Lately Chen and Wan presented three synthetic routes **C**, **D**, and **E** on 10 grams scale (Scheme 1, the route **C**: **2**→**6**→**7**→ the free base **1**→**1**; the divergent route **D**: **2**→**3**→**8**→**7**; the route **E**: **2**→**3**→**8** (→**7**, one pot) → the free base **1**), of which the route **E** with one-pot synthesis from **8** to free base **1** was believed the best.[9] Unfortunately, there was not enough detailed quality control information required for a product of pharmaceutical quality in this paper either.

Recently Wennerberg and his co-workers reported a large-scale synthetic process for **1** with a quality that meets the specifications as pharmaceuticals (the route **F**: (**2**→)**3**→**7**→ the free base **1** →**1**).[10] They explored a couple of reagents which could be used to form quinazolinone **7** from the anthranilic acid (**3**) and found 1-amidino-1,2,4-triazole hydrochloride was the most convenient among the tested reagents. They also optimized the Ullmann reaction by replacing NaH, which was assumed to result in the formation of two impurities, with solid NaOH, and employing excessive 2,4,6-trimercapto-2-triazine trisodium salt (TMT-15) instead of H_2S/methanol solution to get rid of trace copper. Regardless of its many advantages, this elegant approach suffered tedious isolation and purification procedures. Herein we describe a concise synthetic method for **1** featuring a direct conversion of 4-bromo-5-methylisatin into its methyl anthranilate by potassium peroxydisulfate/sodium methoxide in methanol. The anthranilate was then converted into quinazolinone **7** on kilogram scale through a well-established method (Scheme 1, route A: **5**→**7**). To ensure that nolatrexed was obtained in high yield and purity, the amounts of copper catalysts were minimized, and H_2S was replaced with Na_2S solution as a copper scavenger for the final Ullmann reaction.

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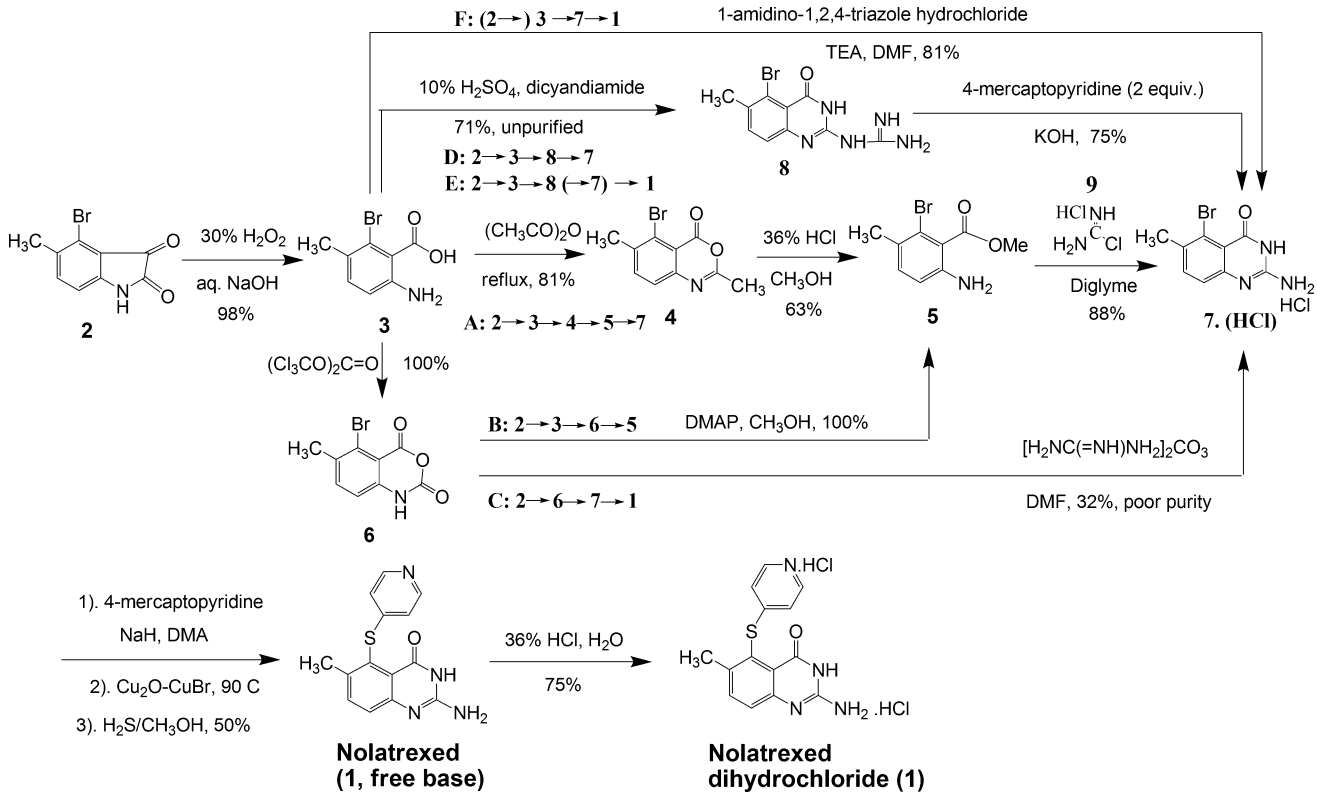
Scheme 1. **Synthetic routes A−F from 4-bromo-5-methylisatin (2) to nolatrexed dihydrochloride (1)**



Results and Discussion

By analyzing the structural characteristics of nolatrexed (**1**), one can find that there usually are two critical steps to synthesize **1**: (1) Ullmann reaction between the quinazolinone and 4-mercaptopyridine; (2) the formation of the quinazolinone via the cyclization of an appropriate intermediate, such as **3**, **5**, or **6** which may be derived from 4-bromo-5-methylisatin (**2**).

At first we took the formation of 2-aminoquinazolinones into serious consideration. 2-Aminoquinazolinones can be synthesized from anthranilic acids, anthranilates, isatoic anhydrides, or anilines[11] by reacting them with a number of reagents such as cyanamide, haloformamidine and guanidine. Among the reported methods, Chen's synthetic route **E** and the Wennerberg approach (the route **F**) were believed best, but they suffered either complicated separation procedures, tedious purification, special reagents applied, or low yields in the formation of the 2-aminoquinazolinones (**7** or **8**) as discussed before. The routes **A** and **B** (Scheme 1), however, gave us a piece of very useful information that **7·HCl** was readily prepared in high yield from **5** and chloroformamidine hydrochloride (**9**), and the crude **7·HCl** could be easily isolated by filtration and directly used for the next step without further purification. Moreover, **9** could be prepared from very cheap $CaCN_2$.[12] Naturally, we wondered whether there was a simple method to transform **2** to **5** directly if the oxidation of **2** was carried out in methanol rather than water used in the conversation **2→3** in Scheme 1. Bearing this idea in mind, we made a literature search, and found a literature reference describing a simple direct conversion from isatins to their anthranilates.[13]

Next, we tried to employ this type of conversion into our synthesis of **1** and designed a new route (**G**) from **2**: **2→5→7·HCl→** the free base **1** →**1** (Scheme 2). At the beginning, the literature procedure from **2** to **5** was followed with 30% H_2O_2 as an oxidizing agent, but the yield was not satisfactory. Even if 98% H_2O_2 was employed, **5** was obtained still in a moderate yield (60−70%). We found that in this reaction the major side product was **3**, which was postulated to come from the hydrolysis of **5**, as one molecule of H_2O_2 gave off one molecule of water in the oxidation reaction. Therefore, a peroxide oxidizing agent which does not generate water under basic condition was desirable. It had been mentioned in the patent that some peroxide compounds might be applicable to this oxidation.[13a] $K_2S_2O_8$ was then tried, instead of highly explosive 98% H_2O_2, and a better yield (84.2%) and a good purity of **5** (96.0%) were achieved. The major impurity (2.5%) in **5** was identified as **6** by LC/MS in light of the integration to the oxidation mechanism.[13b]

Compound **5** was then converted into **7·HCl** according to the literature procedure.[8] Decomposition of **9**[14] was not observed in this case, and the yield did not decline when the reaction scaled up to 1.2 kg of **5**. The crude **7·HCl** with 96.1% purity

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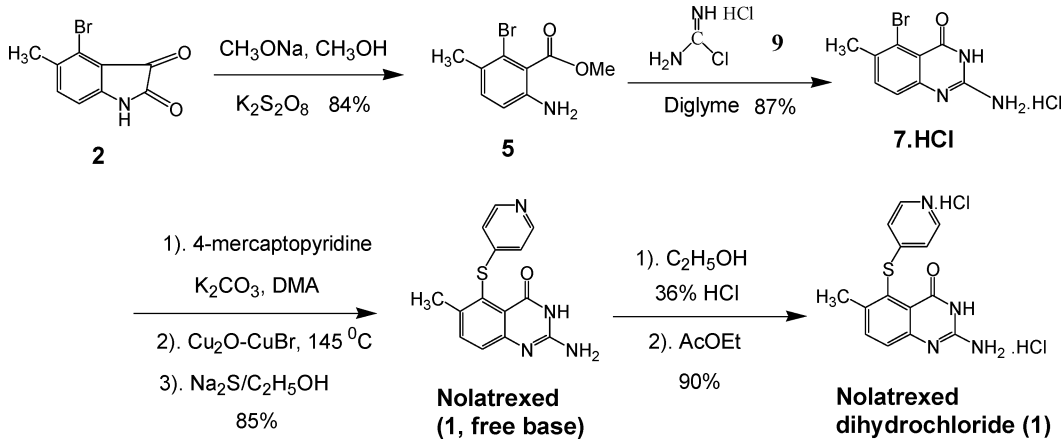
(14) 14. By following the reference,[12] chloroformamidine hydrochloride (**9**) was prepared in 84% yield; White crystals; Mp 134−138 °C dec; IR (KBr, cm^{-1}): 3463, 3033, 2248, 1692, 1612, 1413; $CH_4N_2Cl_2$ (114.963) calculated: C 10.45, H 3.51, N 24.37; found C 10.27, H 3.59, N 24.65.

Scheme 2. **Synthetic route G from 4-bromo-5-methylisatin (2) to nolatrexed dihydrochloride (1)**



could be collected by filtration and directly used for the next step without further purification.

From our primary results of the Ullmann reaction between **7·HCl** and 4-mercaptopyridine, we realized that a large amount of Cu_2O and CuBr might be mainly responsible for the complicated isolation as well as for the possible generation of more impurities. Intensive investigation on Ullmann reactions revealed that cuprous oxide or cuprous halides could be used in quantities as low as 1−10% equiv, and mild bases, e.g. K_2CO_3 and Cs_2CO_3, had been widely applied even when thiophenols were used as reactants.[15] What should be mentioned here was that 4-mercaptopyridine was so expensive that the preference was to utilize it as little as possible. Thus, we decreased the amount of both Cu_2O and CuBr to 2.5% equiv, and 4-mercaptopyridine to 1.3 equiv. To avoid the hydrolysis of the quinazolinone ring by caustic alkali, anhydrous K_2CO_3 was employed instead of hazardous NaH. The reaction was performed in DMA at 145 °C for 4 h. After the evaporation of the reaction mixture, the resulted dark residue was dispersed in 95% ethanol and adjusted to pH 4 with aqueous 36% HCl.

The removal of copper compounds from the Ullmann reaction was usually carried out under strongly acidic conditions when basic aqueous Na_2S was employed as a copper scavenger because **1** would precipitate as its free base under basic conditions. However, we believed that there would be a slight difference between the pH values for copper (I, II) sulfide and **1** free base to precipitate from Na_2S solution. So we carefully adjusted the pH value of the reaction mixture to 6−7 with saturated aqueous Na_2S and found dark copper (I, II) sulfide indeed precipitated, whereas no white solid, i.e. nolatrexed, precipitated. The dark mixture was filtered to give a slightly yellow solution, which was further basified to pH 9 with aqueous 28% NH_3 solution to provide the free base of **1** (nolatrexed) in 85% yield and 96.6% purity. The content of the major impurity was 3.0%, which was isolated from a couple of grams of the sample by flash chromatography and primarily identified as 4,4′-dithiodipyridine.[16] The content of heavy metals including copper was less than 20 ppm. If the appearance of nolatrexed looked gray or tan, or the content of heavy metals was larger than 20 ppm, the above purification sequence would be repeated. The main difference of this method from others is the removal of copper under approximately neutral conditions rather than strongly acidic conditions. Under neutral conditions copper could be scavenged by S^{2-} more completely than under strongly acidic conditions.

With the free base form in our hands, nolatrexed was easily converted into its dihydrochloride form. To a mixture of nolatrexed and ethanol was added an excess of aqueous 36% HCl (2.5 equiv). The formed mixture was then warmed to 50−60 °C to give a clear solution. Due to the susceptibility of nolatrexed to acids, the solution was filtered immediately and cooled down to room temperature. Ethyl acetate was added to force more **1** to precipitate. The mixture was kept at 0 °C overnight, filtered to afford **1** in 90% yield with 99.7% purity. The content of the only major impurity, which was unidentified, was 0.3%, and the copper content was less than 10 ppm. Fortunately, the major impurity detected in free base **1** had completely disappeared from **1** dihydrochloride.

Conclusion

We have developed a three-step synthetic method for nolatrexed dihydrochloride (thymitaq) starting from 4-bromo-5-methylisatin, with the formation of the methyl anthranilate directly from 4-bromo-5-methylisatin by potassium peroxydisulfate as the key step. In the Ullmann reaction mild base anhydrous potassium carbonate was employed instead of NaH, the amounts of cupric oxide and cupric bromide were both reduced drastically, and the copper compounds were removed more efficiently by aqueous Na_2S solution under approximately neutral condi-

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tions. Nolatrexed dihydrochloride of high purity and high yield could be prepared via this concise synthetic method.

Experimental Section

Melting points were determined with a Büchi 540 melting point apparatus and are uncorrected. TLC was performed on glass plates (GF_{254}, 50 mm × 100 mm). IR spectra were run on FI-IR spectrometer (Perkin-Elmer) with oily samples as film and with solid samples as pellets (KBr). ^{1}H NMR spectra were recorded on Bruker AV-400. LC/MS analysis for methyl 2-amino-6-bromo-5-methylbenzoate (**5**) was performed on LC/MS Agilent 1100 series charged with 4.6 mm × 250 mm (5 μ) and precolumn 4.6 mm × 25 mm. HPLC analyses for the 2-aminoquinazolinone hydrochloride (**7·HCl**), nolatrexed (**1**, free base), and nolatrexed dihydrochloride (**1**) were executed on Shimadzu CLASS-VP charged with Nucleosil C_{18} (4.6 mm × 250 mm, 7 μ) at 254 mn of detection wavelength and at 1 mL of flow rate. The gradient elution for nolatrexed dihydrochloride (**1**) was employed, ramping from 88/12 [phosphate buffer (pH 4.94, 100 mg of Na_2HPO_4 and 117.5 g of NaH_2PO_4 in 1000 mL of water)/acetonitrile] to 72/28 during 35 min. Each injection volume was 10 μL at 1 mg/mL of concentration. Silica GF_{254} for TLC was purchased from Qingdao Marine Chemical Company, China.

4-Bromo-5-methylisatin was purchased from Medicalchem Co. Ltd. (Yencheng, China). *N*,*N*-Dimethyl acetamide (DMA) and diglyme were dried over 4 Å molecular sieves for more than 10 days. All reactions were carried out under nitrogen protection.

Methyl 2-Amino-6-bromo-5-methylbenzoate (5). To a mixture of **2** (1.60 kg, 6.67 mol) and anhydrous methanol (6.70 L) was added sodium methoxide (22.6%, 4.80 kg, 20.1 mol) to give a violet solution, to which $K_2S_2O_8$ (1.90 kg, 7.03 mol) was added in parts below 10 °C with an ice−water bath. After addition the reactant mixture turned yellow, and stirring was continued for 1 h at r.t. The reaction mixture was then adjusted to pH 8−9 with aqueous 36% HCl (1.24 L) below 15 °C and the excessive $K_2S_2O_8$ was destroyed by aqueous 5% $Na_2S_2O_4$ solution (450 mL). After rotary evaporation under a reduced pressure at 55 °C, a brown liquid was left, and it was mixed with CH_2Cl_2 (6 L) and H_2O (4 L). The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (4 L). The combined organic phases were dried over Na_2SO_4 and concentrated with a rotavapor. The resulted brown liquid was further distilled under high vacuum to give 1.37 kg of **5** as a colorless liquid (165−175 °C/6−8 mmHg); Yield: 84.2%; Purity: 96.0% (R_t = 4.21 min); MS (ESI$^+$) *m*/*z*: 246.0, 244.0 [M + 1]$^+$; IR (KBr cm^{-1}): $\tilde{\nu}$ 3472, 3382, 2953, 2924, 1716, 1622, 1480, 1277, 816; ^{1}H NMR ($CDCl_3$): δ 2.28 (s, 3 H, Ar−CH_3), 3.91 (s, 3 H, -OCH_3), 4.26 (br s, 2 H, NH_2), 6.54 (d, J = 8.2 Hz, 1 H, Ar−H), 7.00 (d, J = 8.2 Hz, 1 H, Ar−H). One major impurity: 2.48% (R_t = 5.24 min); MS (ESI$^+$) *m*/*z*: 260, 258 [M + 1]$^+$.

2-Amino-5-bromo-6-methyl-3H-quinazolin-4-one Hydrochloride (7·HCl). To a solution of **5** (1.20 kg, 4.92 mol) in diglyme (10 L) was added **9** (566 g, 4.92 mol) at r.t. with vigorous stirring. The mixture was heated at reflux (160−165 °C) for 1 h and then cooled to 0 °C. The precipitate was collected by filtration, washed with ether (∼2 L), and finally dried in vacuum (35−40 mmHg) at 70 °C for 24 h to afford 1.24 kg of **7·HCl** as an off-white powder; Yield: 86.7%; Purity: 96.1% (eluents: CH_3CN-H_2O = 10−90, pH 4.94; R_t = 37.9 min); R_f = 0.59 [ethyl acetate/(0.63 M NH_3 in ethanol) = 6/4]; Mp > 300 °C (lit.[8a] Mp > 390 °C and yield: 88%); IR (KBr cm^{-1}): $\tilde{\nu}$ 3170, 1716, 1658, 1470, 812; ^{1}H NMR (DMSO-d_6): δ 2.40 (s, 3 H, −CH_3), 7.06 (s, 1 H, N−H), 7.33 (d, J = 8.6 Hz, 1 H, Ar−H), 7.69 (d, J = 8.6 Hz, 1 H, Ar−H), 8.00 (br s, 2 H, NH_2), 12.0 (br s, 1 H); ^{1}HNMR (DMSO-d_6 −D_2O): δ 2.34 (s, 3 H, −CH_3), 7.18 (d, J = 8.4 Hz, 1 H, Ar−H), 7.61 (d, J = 8.4 Hz, 1 H, Ar−H); MS (ESI$^+$) *m*/*z*: 256.0, 254.0 [M − Cl]$^+$; (ESI$^-$) *m*/*z*: 253.9, 251.9 [M − Cl − 2]$^+$; The content of one unknown major impurity was 3.2%.

2-Amino-6-methyl-5-(4-pyridylthio)-3H-quinazolin-4-one (Nolatrexed; the Free Base 1). To a mixture of 4-mercaptopyridine (396 g, 3.56 mol), Cu_2O (0.99 g, 6.9 mmol), and CuBr (0.98 g, 6.9 mol) in anhydrous DMA (8 L) were added anhydrous K_2CO_3 (1.14 kg, 8.25 mol) and **7·HCl** (800 g, 2.75 mol). The mixture was heated at 140−145 °C for 4 h, and most of the solvent was then removed by distillation under reduced pressure. A brown residue was dispersed with 95% ethanol (4 L) and H_2O (4 L) while warm, and acidified with aqueous 36% HCl solution (∼2 L) to pH 4 when cooled below 20 °C. To the acidic mixture was added dropwise aqueous saturated Na_2S solution (680 mL) to reach pH 6−7 to remove copper compounds until a white precipitate (nolatrexed) emerged. Charcoal (40 g) was added, and stirring was continued for 15 min. A slightly yellow solution was obtained by filtration and basified to pH 9 with aqueous 28% NH_3 solution (1.60 L). The precipitate was collected by filtration, washed with water, and dried under vacuum (35−40 mmHg) at 100−110 °C for 24 h to yield 665 g of nolatrexed (**1**, free base) as a white powder; Yield: 85.0%; Purity: 96.6% (eluents: CH_3CN-H_2O = 10−90, pH 4.94; R_t = 11.8 min); R_f = 0.31 [ethyl acetate/(0.63 M NH_3 in ethanol) = 6/4]; Mp 300−302 °C (lit.:[8a] a tan solid; Mp 301−302 °C); MS (ESI$^+$) *m*/*z*: 285.1 [M + 1]$^+$; the major impurity: 3.0% (R_t = 13.0 min); Mp 73−77 °C; ^{1}H NMR (DMSO-d_6): δ 7.95 (d, J = 6.4 Hz, 4 H), 8.81 (d, J = 6.4 Hz, 4 H); MS (ESI$^+$) *m*/*z*: 219.2 [M − 1]$^+$; The ^{1}H NMR data were identical to those for 4,4′-dithiodipyridine in the database,[17] and this impurity was determined to be 4,4′-dithiodipyridine on the basis of its mp, MS, and ^{1}H NMR data.

2-Amino-6-methyl-5-(4-pyridylthio)-3H-quinazolin-4-one Dihydrochloride (1, Nolatrexed Dihydrochloride). To a mixture of nolatrexed (500 g, 1.76 mol) in ethanol (6 L) was added 36% HCl (378 mL, 4.40 mol). The mixture was warmed to a clear solution to 50−60 °C and then

filtered immediately when warm. The mixture was cooled down to r.t., and ethyl acetate (6 L) was added. The mixture was kept at 0 °C overnight. The precipitate was collected by filtration, washed with cooled anhydrous ethanol, and finally dried under vacuum (35−40 mmHg) at 60 °C for 12 h to provide 567 g of **1** as white crystals; Yield: 90.2%; Purity: 99.7% (R_t = 8.72 min); IR (KBr cm^{-1}): $\tilde{\nu}$ 3401, 3058, 2929, 1701, 1621, 1471, 799; ^1H NMR (DMSO-d_6): δ 2.43 (s, 3H, $-CH_3$), 7.53 (d, J = 6.9 Hz, 2H, Pyr-H), 7.67 (d, J = 8.5 Hz, 1H, Ar−H), 7.92 (d, J = 8.5 Hz, 1 Hz, Ar−H), 8.30 (br s, 3H, NH_3), 8.52 (d, J = 6.9 Hz, 2H, Pyr-H); MS (ESI^+) m/z: 285 [M − 1−2Cl]$^+$; (ESI^+) m/z: 283 [M − 1− 2HCl]$^+$. See Supporting Information for its TGA and DSC. The content of one unknown major impurity was 0.30% (R_t = 17.0 min).

Acknowledgment

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Supporting Information Available

Spectroscopic data for compounds **1**, **5**, **7**, and **9** and for impurity 4,4′-dithiodipyridine. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Spectrum ID: WHSP48928 in Integration Spectral Database System of Organic Compounds. Data were obtained from the National Institute of Advanced Industrial Science and Technology.