

Short Note

4,4''-Dichloro-4'-(2-thienyl)-2,2':6',2''-terpyridine

Jérôme Husson *  and Laurent Guyard

Institut UTINAM UMR CNRS 6213, Université de Bourgogne-Franche-Comté, 16 route de Gray, 25030 Besançon CEDEX, France

* Correspondence: jerome.husson@univ-fcomte.fr; Tel.: +33-3-81666291

Received: 25 June 2019; Accepted: 4 July 2019; Published: 9 July 2019



Abstract: A new thiophene-substituted terpyridine derivative has been prepared and characterized. This ligand features a thiophene heterocycle (as an electrochemically polymerizable unit) as well as two chlorine atoms for further functionalization.

Keywords: ligand; pyridine derivatives; thiophene derivatives

1. Introduction

Terpyridine (terpy) derivatives (especially 2,2':6',2''-terpyridines) and their complexes have been widely studied [1]. In fact, an important number of terpyridine-based compounds can be prepared by varying the substitution pattern onto the terpyridine scaffold and/or the nature of the complexed metal. Terpyridines and their complexes have found a vast range of applications such as sensitizers in solar cells [2], catalysts [3], materials for water treatment [4], electrochromic materials [5], or as chromophores [6], just to name a few. Terpyridine complexes that are substituted with a thiophene ring are interesting compounds because they also find many possible applications in material science [7] or medicinal chemistry and biology [8,9], for example. Especially, the thiophene heterocycle allows for the formation of polymeric materials through electrochemical polymerization. The so obtained terpyridine-containing materials have shown potential uses as sensors [10] or as electrochromic materials [11], for example. Therefore, the synthesis of new terpy derivatives that bear a pendant thiophene ring is still of interest. This article follows our previous work on furan-containing terpy [12] and describes the synthesis and characterization of 4,4''-dichloro-4'-(2-thienyl)-2,2':6',2''-terpyridine (1) (Figure 1). This ligand not only features a thiophene ring but also possesses two chlorine atoms on the outer pyridine rings, which allow for future functionalization of this terpyridine.

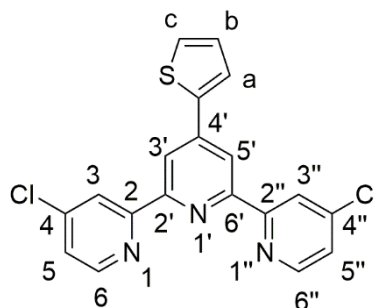


Figure 1. Structure and atom numbering of 4,4''-dichloro-4'-(2-thienyl)-2,2':6',2''-terpyridine (1).

2. Results and Discussion

Amongst all methods available for the preparation of terpyridine derivatives [13–15], the one from Wang and Hanan [16] was selected, although sometimes this method fails in producing

terpyridine derivatives [17]. Thus **1** was simply prepared by mixing 4-chloro-2-acetylpyridine [18], thiophene-2-carboxaldehyde, and potassium hydroxide in ethanol and aqueous ammonia (Figure 2).

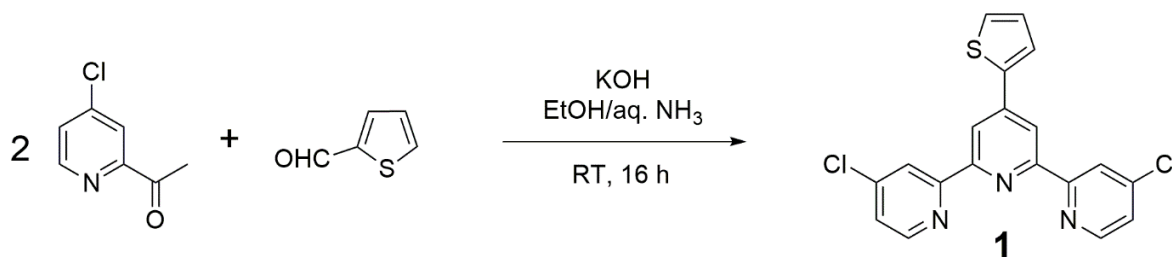


Figure 2. Preparation of terpyridine (Compound **1**).

Crude **1** precipitated from the reaction mixture and was isolated by simple filtration. At this point, the material collected was sufficiently pure (>98% by quantitative NMR [19]) to be used for further experiments (e.g., preparation of metal complexes) without purification.

The identity of compound **1** was confirmed by different analytical techniques. Firstly, NMR spectra (¹H and ¹³C) agreed with the chemical structure. Especially, the singlet for proton 3' and 5' was clearly seen at $\delta = 8.72$ ppm. Furthermore, signals for protons 3, 3'', 6, and 6'' were merged into a multiplet while protons 5 and 5'' appeared as a doublet of doublet (Figure 3). Such an ¹H NMR pattern has been already observed for 4,4''-dichloro-2,2':6',2''-terpyridine [20].

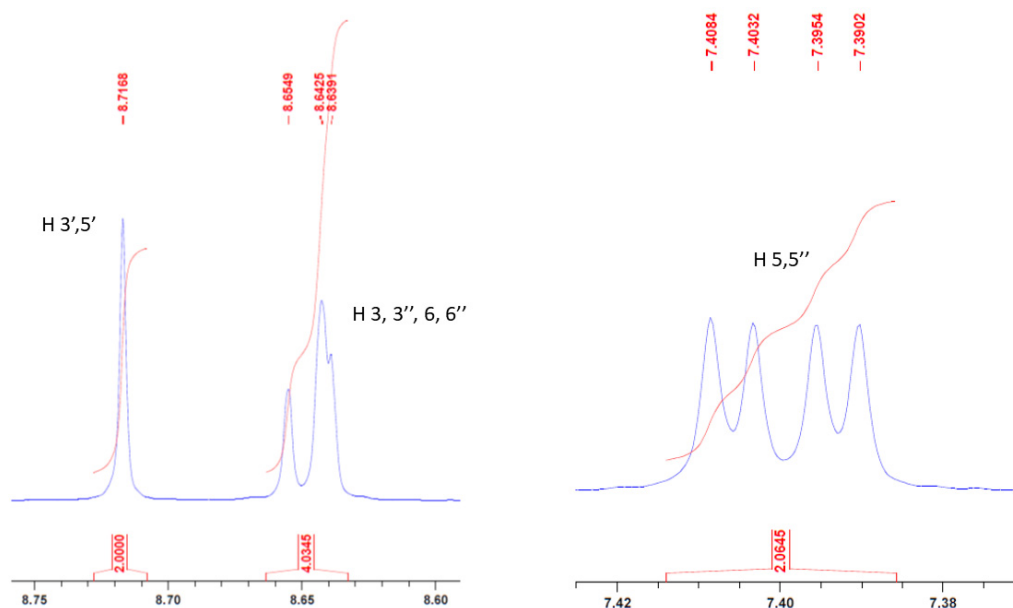


Figure 3. Part of NMR spectrum showing signals for protons (3',5'), (3,3'',6',6''), and (5,5'').

Additionally, the formation of the title compound was confirmed by HR-MS (Figure S3) since the $[M + H]^+$ ion peak, as well as the isotopic distribution, corresponded to molecular formula (C₁₉H₁₂Cl₂N₃S⁺). In fact, the experimental recorded spectrum was in good agreement with the simulated one (Figure 4).

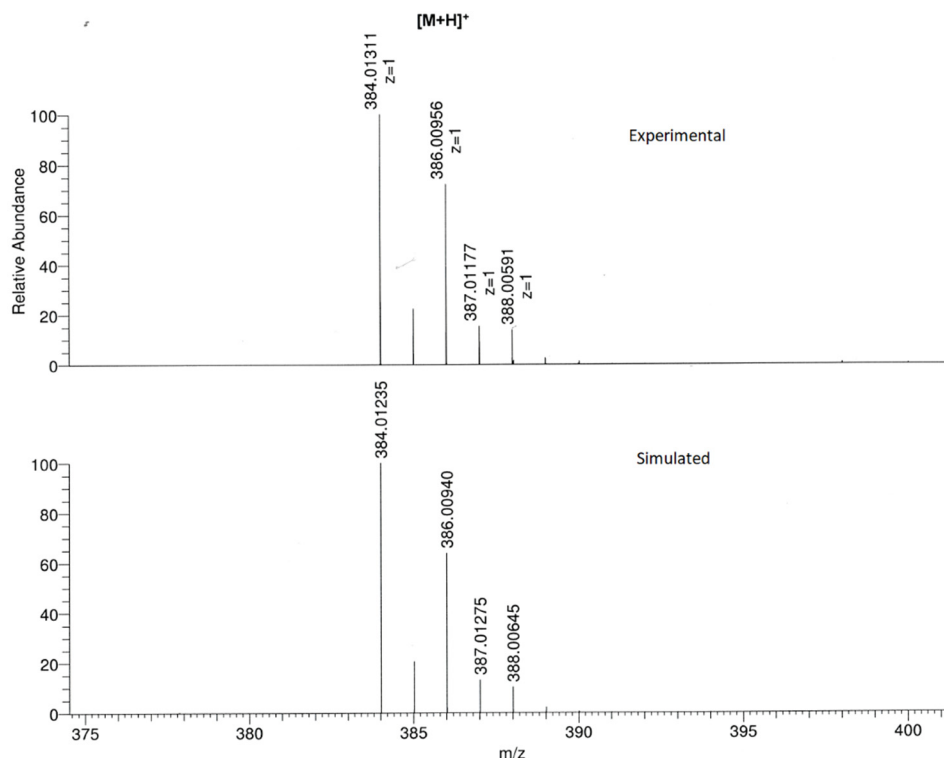


Figure 4. Experimental (top) and simulated (bottom) mass spectra for $[M + H]^+$ ion.

3. Materials and Methods

The 4-chloropicolinonitrile was purchased from ABCR GmbH (Karlsruhe, Germany) and used as received. Methylmagnesium chloride (20% solution in THF) was purchased from Merck Schuchardt (Hohenbrunn, Germany). This Grignard solution was titrated prior to use with salicylaldehyde phenylhydrazone according to literature [21] and the measured concentration was 2.9 M. All other chemicals were purchased from ACROS organics (Geel, Belgium). Anhydrous THF was obtained from a solvent purification system (Innovative Technology, Amesbury, MA, USA). The 4-chloro-2-acetylpyridine was prepared according to the literature [18]. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 400 (Bruker, Wissembourg, France) at 400 and 100 MHz, respectively, using CDCl_3 as a solvent. Melting point was recorded with a Stuart SMP 10 melting point apparatus (Bibby Sterilin, Stone, UK) and was uncorrected. Elemental analysis was performed at Service d'Analyses Elementaires, UMR 7565 CNRS, Vandoeuvre-les-Nancy, France. HR-MS was recorded at Sayence SATT, Dijon, France.

3.1. Preparation of 4-Chloro-2-acetylpyridine

To a solution of methylmagnesium chloride (50 mL; 0.145 mol, excess) at 0°C under argon was added dropwise a solution of 4-chloropicolinonitrile (5.00 g; 0.036 mol) in anhydrous THF (120 mL). The reaction mixture was stirred at room temperature for 6 h. The solution was then poured cautiously onto a saturated ammonium chloride aqueous solution (120 mL) at 0°C , and the pH of the solution was adjusted to 1 with concentrated hydrochloric acid. The resulting solution was stirred at room temperature overnight and then neutralized with 25% aqueous ammonia. The aqueous solution was extracted with ethyl acetate (6×50 mL). Organic layers were combined, washed with brine (2×100 mL), dried over sodium sulphate, and concentrated. The crude product was purified by flash chromatography with cyclohexane/ethylacetate as eluent (100:0 to 95:5). Pure product was obtained as a pale-yellow oil (2.58 g; 50%). Spectroscopic data agreed with those reported in the literature [18].

3.2. Preparation of 4,4''-Dichloro-4'-(2-thienyl)-2,2':6',2''-terpyridine

To a solution of 4-chloro-2-acetylpyridine (3.11 g; 20 mmol) in ethanol (50 mL) was added thiophene-2-carboxaldehyde (1.12 g; 10 mmol), 85% potassium hydroxide pellets (1.54 g; 24 mmol), and 25% aqueous ammonia (30 mL). The reaction mixture was stirred at room temperature for 16 h. The solid was then filtered on a glass sintered funnel and washed with ice-cold 50% ethanol until washings were colorless. The product was dried under vacuum over phosphorus pentoxide. Compound **1** was obtained as a beige solid (2.20 g; 57%). Mp = 216–219 °C (dec.). ¹H NMR (CDCl₃, 400 MHz), δ (ppm): 8.72 (s, 2H, H3', 5'), 8.64–8.65 (m, 4H, H3, 3'', 6, 6''), 7.78 (dd, 1H, Ha, J = 4.0 Hz, J = 1.0 Hz), 7.49 (dd, 1H, Hc, J = 5.0 Hz, J = 1.0 Hz), 7.40 (dd, 2H, H5, 5'', J = 5.2 Hz, J = 2.1 Hz), 7.20 (dd, 1H, Hb, J = 5.0 Hz, J = 4.0 Hz). ¹³C NMR (CDCl₃, 100 MHz), δ (ppm): 157.3, 155.0, 150.0, 145.2, 143.7, 141.4, 128.4, 127.5, 126.1, 124.2, 121.6, 118.0. Elemental analysis for C₁₉H₁₁Cl₂N₃S: C, 59.38; H, 2.89; N, 10.93; S, 8.34. Found C, 58.89; H, 2.94; N, 10.59; S, 8.30. HR-MS: calc. for (C₁₉H₁₁Cl₂N₃S + H)⁺ 384.01235, found 384.01311.

4. Conclusions

A new thiophene-substituted terpyridine was prepared and characterized. Future work will focus on further functionalizing this ligand owing to the presence of two chlorine atoms onto the outer rings. For instance, these chlorines could be substituted by different nucleophiles as already reported for 4'-chloro-2,2':6',2''-terpyridine [22–24] or 4,4''-dichloro-2,2':6',2''-terpyridine [20,25,26]. Experiments are currently in progress in our laboratory to prepare new terpyridine derivatives by this method.

Supplementary Materials: The following are available online: Figure S1: ¹H NMR of **1**, Figure S2: ¹³C NMR of **1**, Figure S3: HR-MS of **1**, Figure S4: detailed molecular ion peak.

Author Contributions: J.H. conceived and carried out the experiments, analyzed data, and prepared the manuscript. L.G. analyzed data and contributed to manuscript preparation.

Funding: This research was funded by Université de Franche-Comté (CHRYSLIDE Project).

Conflicts of Interest: The authors declare no conflict of interest.

References

- Schubert, U.S.; Hofmeier, H.; Newkome, G.R. *Modern Terpyridine Chemistry*; Wiley-VCH: Weinheim, Germany, 2006.
- Saccone, D.; Magistris, C.; Barbero, N.; Quagliotto, P.; Barolo, C.; Viscardi, G. Terpyridine and Quaterpyridine Complexes as sensitizers for Photovoltaic Applications. *Materials* **2016**, *9*, 137. [[CrossRef](#)] [[PubMed](#)]
- Winter, A.; Newkome, G.R.; Schubert, U.S. Catalytic Applications of Terpyridines and their Transition Metal Complexes. *ChemCatChem* **2011**, *3*, 1384–1406. [[CrossRef](#)]
- Oyetade, O.A.; Nyamori, V.O.; Jonnalagadda, S.B.; Martincigh, B.S. Removal of Cd²⁺ and Hg²⁺ from aqueous solutions by adsorption onto nitrogen-functionalized carbon nanotubes. *Desalin. Water Treat.* **2018**, *108*, 253–267. [[CrossRef](#)]
- Allan, J.T.S.; Quaranta, S.; Ebralidze, I.I.; Egan, J.G.; Poisson, J.; Laschuk, N.O.; Gaspari, F.; Easton, E.B.; Zenkina, O.V. Terpyridine-Based Monolayer Electrochromic Materials. *ACS Appl. Mater. Interfaces* **2017**, *9*, 40438–40445. [[CrossRef](#)] [[PubMed](#)]
- Fernandes, S.S.M.; Besley, M.; Ciarrocchi, C.; Licchelli, M.; Raposo, M.M.M. Terpyridine derivatives functionalized with (hetero)aromatic groups and the corresponding Ru complexes: Synthesis and characterization as SHG chromophores. *Dyes Pigment.* **2018**, *150*, 49–58. [[CrossRef](#)]
- Husson, J.; Knorr, M. 2,2':6',2''-Terpyridines Functionalized with Thienyl Substituents: Synthesis and Applications. *J. Heterocyclic Chem.* **2012**, *49*, 453–478. [[CrossRef](#)]
- Qin, Q.-P.; Wang, Z.-F.; Wang, S.-L.; Luo, D.-M.; Zou, B.-Q.; Yao, P.-F.; Tan, M.-X.; Liang, H. In vitro and in vivo antitumor activities of three novel binuclear platinum(II) complexes with 4'-substituted-2,2':6',2''-terpyridine ligands. *Eur. J. Med. Chem.* **2019**, *170*, 195–202. [[CrossRef](#)] [[PubMed](#)]

9. Shen, Y.; Shao, T.; Fang, B.; Du, W.; Zhang, M.; Liu, J.; Liu, T.; Tian, X.; Zhang, Q.; Wang, A.; et al. Visualization of mitochondrial DNA in living cells with super-resolution microscopy using thiophene-based terpyridine Zn(II) complexes. *Chem. Commun.* **2018**, *54*, 11288–11291. [[CrossRef](#)] [[PubMed](#)]
10. Savan, E.K.; Koytepe, S.; Pasahan, A.; Erdogdu, G.; Seckin, T. Amperometric Simultaneous Measurement of Copper and Cobalt Ions with Polythiophene Incorporating Pendant Terpyridine Groups. *Polym.-Plast. Technol. Eng.* **2014**, *53*, 1817–1824. [[CrossRef](#)]
11. Liang, Y.W.; Strohecker, D.; Lynch, V.; Holliday, B.J.; Jones, R.A. A Thiophene-Containing Conductive Metallopolymer Using an Fe(II) Bis(terpyridine) Core for Electrochromic Materials. *ACS Appl. Mater. Interfaces* **2016**, *8*, 34568–34580. [[CrossRef](#)]
12. Husson, J.; Guyard, L. 4'-(5-Methylfuran-2-yl)-2,2':6',2''-terpyridine: A new ligand obtained from a biomass-derived aldehyde with potential application in metal-catalyzed reactions. *Molbank* **2018**, *2018*, M1032. [[CrossRef](#)]
13. Heller, M.; Schubert, U.S. Syntheses of functionalized 2,2':6',2''-terpyridines. *Eur. J. Org. Chem.* **2003**, *6*, 947–961. [[CrossRef](#)]
14. Fallahpour, R.A. Synthesis of 4'-substituted-2,2':6',2''-terpyridines. *Synthesis* **2003**, *2*, 155–184. [[CrossRef](#)]
15. Thompson, A.M.W.C. The synthesis of 2,2':6',2''-terpyridine ligands- versatile building blocks for supramolecular chemistry. *Coord. Chem. Rev.* **1997**, *160*, 1–52. [[CrossRef](#)]
16. Wang, J.; Hanan, G.S. A Facile Route to Sterically Hindered and Non-Hindered 4'-Aryl-2,2':6',2''-Terpyridines. *Synlett* **2005**, *8*, 1251–1254. [[CrossRef](#)]
17. Rocco, D.; Housecroft, C.E.; Constable, E.C. Synthesis of Terpyridines: Simple Reactions-What Could Possibly Go Wrong? *Molecules* **2019**, *24*, 1799. [[CrossRef](#)] [[PubMed](#)]
18. Busto, E.; Gotor-Fernandez, V.; Gotor, V. Biocatalytic preparation of optically active 4-(*N,N*-dimethylamino)pyridines for application in chemical asymmetric catalysis. *Tetrahedron-Asymmetry* **2006**, *17*, 1007–1016. [[CrossRef](#)]
19. Bharti, S.K.; Roy, R. Quantitative ¹H NMR spectroscopy. *Trac-Trends Anal. Chem.* **2012**, *35*, 5–26. [[CrossRef](#)]
20. Harzmann, G.D.; Neuburger, M.; Mayor, M. 4,4''-Disubstituted Terpyridines and Their Homoleptic Fe^{II} Complexes. *Eur. J. Inorg. Chem.* **2013**, *19*, 3334–3347. [[CrossRef](#)]
21. Love, B.E.; Jones, E.G. The Use of Salicylaldehyde Phenylhydrazone as an Indicator for the Titration of Organometallic Reagents. *J. Org. Chem.* **1999**, *64*, 3755–3756. [[CrossRef](#)]
22. Lowe, G.; Droz, A.S.; Vilaivan, T.; Weaver, G.W.; Tweedale, L.; Pratt, J.M.; Rock, P.; Yardley, V.; Croft, S.L. Cytotoxicity of (2,2':6',2''-Terpyridine)platinum(II) Complexes to *Leishmania donovani*, *Trypanosoma cruzi*, and *Trypanosoma brucei*. *J. Med. Chem.* **1999**, *42*, 999–1006. [[CrossRef](#)] [[PubMed](#)]
23. Bode, S.; Enke, M.; Bose, R.K.; Schacher, F.H.; Garcia, S.J.; van der Zwaag, S.; Hager, M.D.; Schubert, U.S. Correlation between scratch healing and rheological behaviour for terpyridine complex based metallopolymers. *J. Mater. Chem. A* **2015**, *3*, 22145–22153. [[CrossRef](#)]
24. Mutai, T.; Cheon, J.-D.; Arita, S.; Araki, K. Phenyl-substituted 2,2':6',2''-terpyridine as a new series of fluorescent compounds-their photophysical properties and fluorescence tuning. *J. Chem. Soc. Perkin Trans. 2* **2001**, 1045–1050. [[CrossRef](#)]
25. Brandl, T.; Hoffmann, V.; Pannwitz, A.; Haussinger, D.; Neuburger, M.; Fuhr, O.; Bernhard, S.; Wenger, O.S.; Mayor, M. Chiral macrocyclic terpyridine complexes. *Chem. Sci.* **2018**, *9*, 3837–3843. [[CrossRef](#)] [[PubMed](#)]
26. Moore, C.M.; Bark, B.; Szymczak, N.K. Simple Ligand Modifications with Pendent OH Groups Dramatically Impact the Activity and Selectivity of Ruthenium Catalysts for Transfer Hydrogenation: The Importance of Alkali Metals. *ACS Catal.* **2016**, *6*, 1981–1990. [[CrossRef](#)]

