UNIVERSIDAD DE INVESTIGACIÓN DE TECNOLOGÍA EXPERIMENTAL YACHAY

Escuela de Ciencias Químicas e Ingeniería

TÍTULO: Synthesis of 3,4-dimethoxythiophene from 2,2'-thiodiglycolic acid diethyl ester

Trabajo de integración curricular presentado como requisito para la obtención del título de
Química

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A mi hermana y mejor amiga, Melanie Hidalgo y a mis padres por el amor incondicional y la motivación para superar cada obstáculo.

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Resumen

Los tiofenos 3,4-dialcoxisustituidos y sus derivados son usados como precursores de monómeros en el área de polímeros conductores para diversas aplicaciones que van desde celdas solares, OLEDs, hasta dispositivos biotecnológicos. El 3,4-dimetoxitiofeno se puede transformar fácilmente a otros monómeros mediante transeterificación. En el presente trabajo se obtuvo 3,4-dimetoxitiofeno a partir del ácido tiodiglicólico dietil éster con un rendimiento global de 12% después de 4 pasos siguiendo los métodos reportados en la literatura basados en el método general de Fager. Las siguientes modificaciones se hicieron: metilación directa a partir de la sal disódica para ahorrar un paso en la síntesis total y el uso de radiación de microondas en una reacción de *O*-metilación libre de disolvente. Cuatro métodos para la *O*-metilación se intentaron y fueron evaluados cuantitativamente utilizando criterios de la Química Verde, tales como: economía atómica, reducción de disolvente y eficiencia energética. Se demostró que el mejor método no fue necesariamente aquel con el rendimiento más alto sino con la mayor eficiencia.

Palabras Clave:

3,4-dimetoxitiofeno, libre de disolvente, economía atómica, eficiencia energética

Abstract

3,4-dialkoxysubstituted thiophenes and their derivatives are used as precursors of monomers in the field of conducting polymers for diverse applications ranging from solar cells or OLEDs to biothecnological devices. 3,4-dimethoxythiophene can easily be transformed to other monomers by transetherification. In this work, 3,4-dimethoxythiophene was obtained from 2,2'-thiodiglycolic acid diethyl ester with a global yield of 12% after 4 steps following literature methods based on general Fager's method. The following modifications were done: methylation direct from the disodium salt to save one step in the total synthesis and the use of a solvent free- microwave assisted *O*-methylation reaction. Four methods for the *O*-methylation step were tested and quantitatively evaluated through Green Chemistry criteria: atom economy, reduction of solvent and energy efficiency. It was shown that the best method was not the one with highest reaction yield but highest method efficiency.

Key Words:

3,4-dimethoxythiophene, solvent-free, atom economy, energy efficiency

ABREVIATIONS AND ACRONYMS

DMF	N,N'-Dimethylformamide
DMS	Dimethylsulfate
EDOT	3,4-ethylenedioxythiophene
MeCN	Acetonitrile
MeOH	Methanol
OLEDs	Organic Light Emitting Diodes
OPVs	Organic Photovoltaics
PEDOT	Poly(3,4-ethylenedioxythiophene)
PXDOT	Poly(3,4-ortho-xylenedioxythiophene)
$TMABF_4$	Tetramethylammonium tetrafluoroborate
TMAC	Tetramethylammonium chloride

INDEX

CHAPTER 1. INTRODUCTION – JUSTIFICATION

1.1 General Introduction

3,4-dimethoxythiophene is a molecule of industrial as well as research interest as a precursor of 3,4-dialkoxysubstituted thiophenes and derivatives used for fabricating conducting polymers[1]. Kieseritzky[2] proved a simple one-step conversion of 3,4-dimethoxythiophene to 3,4-ethylenedioxythiophene EDOT, the most used monomer in the conducting polymers field. The resulting polymer PEDOT has a big scope of applications in organic photovoltaic devices such as solar cells and OLED's[1]. PEDOT belongs to the polyaromatics family of the organic conducting polymers. It shows high conductivity of about 300 S/cm, high stability in the oxidized state and it is almost transparent in thin films, which are the reasons why it is highly used for solar cells applications[3,4]. In addition to EDOT, 3,4-dimethoxythiophene allows to synthetize modified EDOT monomers which lead to polymers with good electrochromic[5], thermal, optical and photoluminescence properties[6]. Wang[7] used 3,4-dimethoxythiophene to synthetize a propylenedioxythiophene-based copolymer with potential application in solar cells.

Other modified EDOT monomers synthetized from 3,4-dimethoxythiophene have been used to generate polymers with excellent conductivity for bioelectronics' applications, which include: an electrode capable of quantitatively detect human serum albumin in synthetic urine as a bioindicator for kidney failure[8] and polymers with antimicrobial[9] and antifouling[10] properties. Besides being a precursor for poly(3,4-dialkoxythiophene)s , 3,4-dimethoxythiophene can generate a polymer itself through electropolymerization as demonstrated by Fall[11] in acetonitrile and micellar media and by Hagiwara[12] in polycarbonate.

Given their desirable properties and their applications in the materials, bioelectronics and other fields, attention has been paid to the synthesis of 3,4-dialkoxythiophenes and their derivatives. In this context, the reported synthesis methods for 3,4-dimethoxythiophene are hereby shortly reviewed. Modifications to the existing methods have been proposed in the present work to follow as much as possible the

principles of green chemistry as leading evaluation criteria instead of pursuing the solely objective of increasing the reaction yield.

1.2 Synthesis of 3,4-dialkoxythiophenes

Traditionally, 3,4-dialkoxythiophenes have been prepared following the general Fager's method[13] (**Figure 1**) with a total of 5 steps. The first step in the synthesis of 3,4-dimethoxythiophene consists of a Hinsberg condensation with diethyl 2,2'-thiodiacetate and diethyl oxalate in ethanol with sodium methoxide as the base. A disodium salt is obtained from the condensation, which after acidification gives 3,4-dihydroxythiophene-2,5-dicarboylate. This is the starting material for other 3,4-disubstituted thiophenes. *O*-methylation of the starting material is accomplished with dimethyl sulfate. Further saponification and decarboxylation with copper chromium oxide are performed to give 3,4-dimethoxythiophene as a colorless liquid. Some modifications to Fager's method have been done throughout in order to increase the reaction yields at each step. Merz[14] made two improvements: addition of a [18]crown-6 as catalyst for the *O*-methylation reaction; and decarboxylation by distillation without a copper catalyst. Overberger[15] used diazomethane as the methylating agent to obtain 2,5-dicarbethoxy-3,4-dimethoxythiophene in 95.4% yield. Nevertheless, diazomethane must be generated *in situ* by reported methods[16]. The precursor of diazomethane, namely, N-methyl-p-nitrosulfonamide is commercially available under the name of Diazald. Zhao[17] improved the yield of decarboxylation of the diacid to 95% by using metal phthalocyanines as catalysts. The reaction was performed with short time and in aqueous media, resulting in a facile separation of the product by steam distillation. Cisneros[18] proved a microwave mediated decarboxylation of 3,4-dialkoxythiophene-2,5-dicarboxylic acids. The use of Ag_2CO_3 and microwave irradiation allowed to have good yields and shorter reaction times.

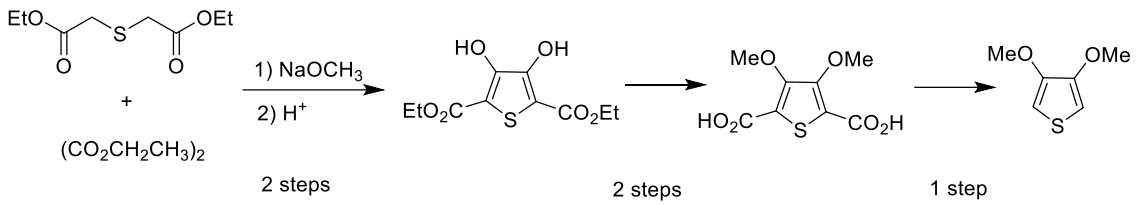


Figure 1. General scheme of Fager's method

Nowadays, the development of new materials suitable for different technological and energetic applications require the most efficient, yet least expensive and most environmentally friendly syntheses. In the case of 3,4-dimethoxythiophene, research must be directed towards developing new synthetic routes or modifications to the existing ones that follow most of the principles of green chemistry with the available reagents. Green chemistry is to be understood as the design of processes to obtain profitable substances while avoiding the use or generation of hazardous materials[19]. The 12 principles are summarized as follows[19]:

1) Prevention of waste
2) Atom economy by incorporation of most atoms in raw materials into the final product.
3) Less use and generation of hazardous materials.
4) Design for safer chemicals.
5) Less use of solvents or auxiliary substances.
6) Design for energy efficiency and minimization of economic and environmental impacts.
7) Use of renewable raw materials.
8) Reduction of derivatives or additional reagents that could generate waste.
9) Preference of catalytic reagents.
10) Design for innocuous degradation products.
11) Real-time analysis for pollution prevention.
12) Safer chemistry for accident prevention, minimization of risk.

Although desirable, it is impossible to accomplish all 12 principles throughout one synthetic route while keeping high yields and low costs of reagents/reactants. Some successful and well-proven green chemistry reactions include cycloadditions, Diels Alder, diazocoupling, and C-C coupling with organometallic catalyzers. For instance, Kieseritzky[2] performed a single step synthesis of 3,4-dimethoxythiophene with a good yield of 60% by ring closure between 2,3-dimethoxy-1,3-butadiene and sulfur chloride. Nevertheless, the yield drops to 5% when the buffer material is not added to the reaction mixture.

In recent work, Cisneros[20] et al. used 3,4-dimetoxythiophene as a precursor of a 18-membered ring ether-crown. The aforementioned 18-membered ring with potential application as a conducting polymer in OPVs is obtained by transetherification of 3,4-dimetoxythiophene and 1,3-benzenedimethanol. Other monomers such as PEDOT or PXDOT are prepared by Williamson and Mitsunobu reactions with 2,5-dicarbethoxy-3,4-dihydroxythiophene generated in the second step of the synthesis of 3,4-dialkoxythiophenes. Given its wide range of derivatives with potential applications in the conducting polymers field, and the availability of 2,2'-thiodiglycolic acid diethyl ester in the laboratory in large scale, the synthetic route by Cisneros[20] was chosen in the present work to generate the target molecule instead of the one-step synthesis proposed by Kieseritzky[2]. One challenge however to improve this synthetic route is to find the best conditions for the *O*-methyaltion reaction.

1.4 *O*-methylation of 3,4-dihydroxysubstituted thiophenes

Besides the *O*-methylation of 2,5-dicarbethoxy-3,4-dihydroxythiophene with dimethyl sulfate in Fager's method and with diazomethane by Cisneros[20], other methylating agents an conditions such as heating mode, time and solvent can be explored. Methods for *O*-methylation of phenols such as 1,2-dihydroxyphenol should apply to the target molecule diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate and its corresponding disodium salt as they have closely related values of pKa at the hydroxyl groups 9.5±0.1 and 8.40±0.20, respectively. (Calculated using Advanced Chemistry Development (ACD/Labs) Software V11.02 (© 1994-2019 ACD/Labs)).

Banikhaled[21] obtained 1,2-bis(methoxy) benzene in 81% yield from 1,2-dihydroxybenzene by allowing it to react with methyl iodide (4 eq) at 80°C during 12 h in dimethylformamide. Karunakaran[22] obtained 85% yield of the same product by switching the solvent to acetonitrile and remaining the same conditions.

Heravi[23] proved *S*-methylation on thiols and *O*-methylation on naphthols and phenols using microwave irradiation. Their protocol consisted of grinding the corresponding phenol together with sodium hydroxide, dimethyl sulfate and basic alumina and placing it on a beaker under microwave irradiation. This procedure allowed to reduce reaction times for this kind of *O*-methylation from hours to minutes and to avoid the use of solvent as compared to conventional solution phase methylations.

Because of the toxicity of dimethyl sulfate[24] and methyl iodide[25], and the risk of detonation of diazomethane[16], other methylating agents such as dimethyl carbonate have been the focus of research for *O*-methylation of aromatic compounds. However, dimethyl carbonate is a poor methylating agent[26], so that a catalyst is needed for the reaction to proceed with good yields. Lee[26] uses dimethyl carbonate together with a catalytic amount of base for the *O*-methylation of some phenols, such as 1-naphthol. The reaction times are significantly long ranging from 4 hours to 7 days depending on the base and temperature used. Rajabi[27] proved *O*-methylation of 1-naphthol by using dimethyl carbonate, a catalytic amount of $BF_3 \cdot OEt_2$ and microwave irradiation, which allowed to remarkably reduce the reaction time to 3 minutes.

Furthermore, Zhang[28] and coworkers were able to synthetize anisole from phenol using an electrochemical method. This *O*-methylation consisted of a galvanostatic electrolysis in a two platinum electrode cell containing a solution of phenol and tetramethylammonium chloride, TMAC, which also acted as the methylating agent. Anisole was obtained in 75.2% yield when the reaction was performed with 1:1 mol ratio of phenol and TMAC and 71.2% yield when sodium phenate was used instead of phenol. The best yield (81.8%) was obtained for a molar ratio of 1:2 of sodium phenate: TMAC, which suggest a better performance of the disodium salt for the *O*-methylation reaction as compared to the corresponding phenol.

1.5 Problem Statement

Environmental management requires switching as far as possible energy obtained from fossil fuels to renewable energies. Nevertheless, the development of new technologies, energy harvesting and energy storage devices highly depends on the development of advanced materials with some desired properties, e.g., transparent conducting polymers for solar cells. In addition to research issues, Ecuador and other countries in Latinamerica face other major challenges such as unavailability and high cost of some reagents, both as consequence of the lack of fine chemical industry and added costs to transport by importation. Furthermore, 3,4-dimethoxythiophene presents some transportation issues (very low temperature and good sealing) because when isolated, it was found to be unstable towards oxygen[13,15], so that it is advisable to either store it at low temperatures, under inert atmosphere or use it immediately[15]. Therefore, it is necessary to develop methods to synthetize raw materials, which make both: generate a wide range of products with potential profit and mitigate manufacturers' and environmental impact.

1.6 General and specific objectives

- ***General objective***

To synthetize 3,4-dimethoxythiophene starting from 2,2'-thiodiglycolic acid diethyl ester.

- ***Specific objectives***

  - To synthetize disodium salt of 2,5-dicarbethoxy-3,4-dihydroxythiophene.
  - To synthetize 2,5-dicarbethoxy-3,4-dihydroxythiophene.
  - To synthetize 2,5-dicarbethoxy-3,4-dimethoxythiophene by 4 different methods of *O*-methylation.
  - To evaluate each method with Green Chemistry principles as criteria to find the best conditions for *O*-methylation reaction.
  - To synthetize 3,4-dimethoxythiophene-2,5-dicarboxylic acid.
  - To synthetize 3,4-dimethoxythiophene by decarboxylation.

CHAPTER 2. METHODOLOGY

2.1 Reagents

Commercial products and distilled water were used as received without further purification. Organic solvents were distilled following stablished protocols of the laboratory. Diethyl oxalate was distilled under high vacuum (4mmHg) at 48°C. 2,2'-Thiodiglycolic acid diethyl ester was previously synthetized by the research group of Dr. Frontana and available in sufficient quantity for this work. The ^{1}H-NMR spectrum to verify its purity is shown in the Annex section (**Figure A 1).** Dimethyl sulfate (99,8%), methyl iodide (99%), sodium ethoxide (95%), *N*-*N*-Dimethylformamide (99.8%), potassium hydroxide (85%), pyridine (99%) and copper chromite (RA) were purchased from Sigma-Aldrich (Toluca, Mexico). Chlorhidric acid (36.7%) was purchased from Fermont (Mexico City, Mexico). Absolute ethanol (RA) and sodium hydroxide (97%) were purchased from Tecsiquim (Toluca, Mexico). Methanol (99.9%) was purchased from JT Baker (Mexico City, Mexico). Tetramethylammonium tetrafluoroborate (98%) was purchased from Fluka (Mexico City, Mexico).

2.2 Equipment

Discover® SP from CEM (Matthews, NC, USA) was used for the solid state microwave assisted *O*-methylation of the disodium salt of 2,5-dicarbethoxy-3,4-dihydroxythiophene.

Characterization by ^{1}H-NMR was performed with the following equipment: Varian (500 MHz, NMR System, 11.74 T plated magnets) and Bruker (300 MHz, Avance, 7.04 T plated magnets). Mass spectra were obtained from Shimadazu (GCMS-QP2010 Plus). Finally, IR spectra was taken by Bruker (Tensor 27, Platinum ATR). The samples were run and in some cases prepared by the technicians of *Centro Conjunto de Investigación en Química Sustentable UAEMéx-UNAM*, Toluca, Mexico.

2.3 Synthetic pathway to 3,4-dimethoxythiophene

Figure 2 shows the synthetic route to get 3,4-dimethoxythiophene from 2,2'-thidoglycolic acid diethyl ester based on previous work by Cisneros[20]. Two major improvements were proposed in this work, namely: 1) direct *O*-methylation from the

disodium salt **1** to avoid an additional step to get diol **2** and, 2) the use of a less hazardous methylating agent and less solvent in the methylation reaction to obtain compound **3**.

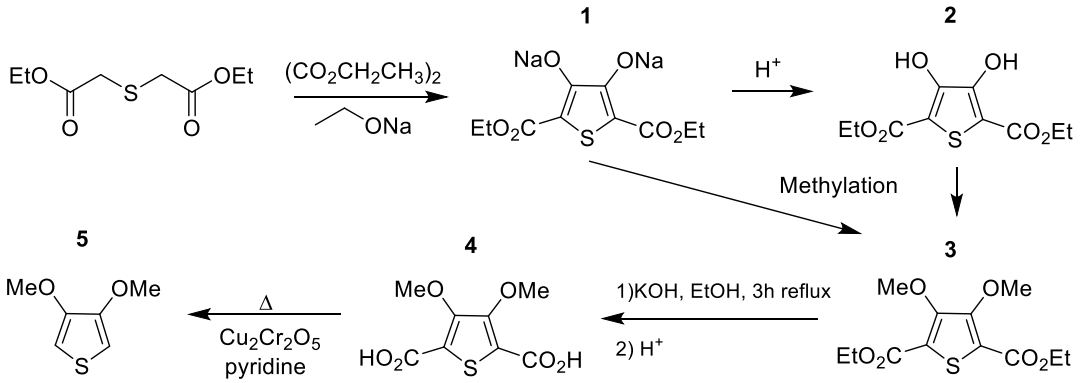


Figure 2. Overall scheme of synthetic route for 3,4-dimethoxythiophene

2.3.1 Synthesis of disodium salt of 2,5-dicarbethoxy-3,4-dihydroxythiophene **(1)** [20]

A 500 mL 3-necked flask dried overnight was saturated with $N_{2(g)}$ for 10 min. 100 mL of absolute ethanol and 40 mL of distilled diethyl oxalate (294 mmol) were poured into the flask on an ice bath with mechanical stirring. 33.1570 g of sodium ethoxide (487 mmol) were slowly added changing the color of the solution from yellow to red. The remaining solid was washed with 10 mL of absolute ethanol. The reaction mixture was left for 20 min with mechanical stirring. 35 mL of 2,2'-thiodiglycolic acid diethyl ester (194 mmol) were diluted and thoroughly mixed with 10 mL of absolute ethanol in an addition funnel. The diluted ester was added to the reaction mixture dropwise and then left with magnetic stirring for 1 hour rendering a color change to orange. The flask was left to room temperature for 15 min. The reaction was left to reflux using a heating mantle for 3 hours. Heating was turned off and the reaction was left with magnetic stirring for 17 hours. The precipitate was washed and filtered twice with about 700 mL of absolute ethanol and left to dry overnight. The resulting disodium salt gave 47.6802 g of a yellow solid (80.77%). ^{1}H-NMR (D_2O, 300MHz) δ (ppm): 4.36-4.32 (q, 4H) -OC<u>H</u>$_2$CH$_3$, 1.42-1.38 (t, 6H) -OCH$_2$C<u>H</u>$_3$.

2.3.2 Synthesis of 2,5-dicarbethoxy-3,4-dihydroxythiophene **(2)** [20]

19.84 g of the disodium salt (65 mmol) were dissolved in hot water (60°C to 70°C). HCl 2M was added dropwise until pH<2. The precipitate was filtered and left to dryness overnight. The dry solid was grinded and dissolved in 100 mL of hot ethyl acetate. The

mixture was heated until 50 mL of ethyl acetate evaporated and then 50 mL of ethanol were added. Crystallization and filtration with cold ethanol were performed 3 times to obtain 11.24 g of compound **2** (56.27%). ^{1}H-NMR ($CDCl_3$, 300MHz) δ (ppm): 9.35 (s, 2H) -OH, 4.36-4.29 (q, 4H) -OC$\underline{H}_2CH_3$, 1.35-1.28 (t, 6H) –$OCH_2C\underline{H}_3$.

2.3.3 Synthesis of 2,5-dicarbethoxy-3,4-dimetoxytiophene **(3)**

Method A [14]

492.1 mg of compound **1** (1.6 mmol) were dissolved in 1 mL of dimethyl sulfate (DMS) (10.5 mmol) and heated for 2 hours at 100°C under N_2 atmosphere. The excess of DMS was evaporated under high vacuum for 2 hours and the remaining was neutralized with about 3 mL of NaOH 6N up to pH=12. The white solid was filtered with cold water to give 0.4662 g of compound **2** (38.56%). The reaction was repeated by changing the reaction time to 1 h and 4 h and adding solvent to a 1:4 ratio (g of disodium salt: mL of acetonitrile). Yields for each trial are shown in **Table 1** in the Results section. ^{1}H-NMR ($CDCl_3$, 300MHz) δ (ppm): 4.41-4.33 (q, 4H) –OC$\underline{H}_2CH_3$, 4.01 (s, 6H) –OCH_3, 1.42-1.37 (t, 6H) –$OCH_2C\underline{H}_3$. MS (EI, 75 eV): m/z 288 (M^+, 73%), 259 (19), 243 (68), 241 (100), 231 (8), 215 (46), 213 (96), 185 (32), 169 (53), 156 (19), 83 (15).

Method B [23]

0.3042 g of compound **1** (1 mmol), 0.2 mL of DMS (2 mmol) and 1.09 g of basic alumina were thoroughly mixed in a 10 mL tube. The mixture was heated at 100°C by a microwave reactor for 7 min at an initial power of 100 W. After heating, the product was extracted with acetone. The liquid phase was passed through celite and activated carcoal to remove impurities. The product was further purified by column chromatography with a mobile phase of hexane: ethyl acetate of increasing polarity up to 80:20 to give 0.0753 g of compound **3** (26.15%). The reaction was repeated by subtracting microwave irradiation and by doubling the disodium salt: DMS ratio. Yields for each trial are shown in **Table 1** in the Results section.

Method C [22]

0.5222 g of compound **1** (1.7 mmol) were dissolved under magnetic stirring with 2 mL of dry acetonitrile for 20 minutes. 2 mL of iodomethane (32.1 mmol) were added dropwise over an ice bath. Then the reaction temperature was increased to 80°C and left overnight at that temperature with magnetic stirring. The reaction mixture was poured into ice cold water and then extracted using ethyl acetate. The organic layer was dried with anhydrous $MgSO_4$ and then evaporated. The final product was purified by column chromatography using 90:10 hexane: ethyl acetate as mobile phase to give 0.4947 g of compound **3** (33.60%).

Method D [28]

40 mg of compound **1** (0.13 mmol) were dissolved in 25 mL of a solution of $TMABF_4$ 0.02M in methanol: DMF (5:1). The final molar ratio was disodium salt:$TMABF_4$ (1:4). The solution was placed into the electrolysis cell consisting in two parallel platinum electrodes as the cathode and anode. The cell was placed on a water bath to maintain a temperature of 40°C to enhance solubility of the disodium salt in the medium. Galvanostatic electrolysis was performed by providing a constant current density of 1.00 A/dm^2 during 2 h. The current needed was calculated by means of the current density and the electrode area. The time needed to complete the reaction was calculated by means of Faraday's law considering 1.5 eq of charge. The reaction mixture was supported in celite by evaporating the solvent and then extracted by column chromatography. The reaction was repeated by using compound **2** as starting material, with a current density of 2.5 A/dm^2 for 3 h at 19°C. The results for each trial are summarized in **Table 2** in the Results section.

*2.3.4 Synthesis of 3,4-dimethoxythiophene-2,5-dicarboxylic acid (***4***)* [18]

0.61 g of compound **3** (2.1 mmol)**,** 0.6 g of KOH (10.6 mmol) and 25 mL of ethanol were heated to reflux for 3 h. A white precipitate is observed. 45 mL of water were added to the reaction mixture and heated at 80°C for 1 h with magnetic stirring. HCl 2M was added dropwise until pH≤2 to form a precipitate. The white solid was filtered with cold water and then dried overnight to high vacuum to give 0.40 g of 3,4-dimethoxythiophene-2,5-

dicarboxylic acid (81.61%). ^{1}H-NMR (DMSO-d_6, 300MHz) δ (ppm): 14.5-12.5 (br, 2H) -OH, 3.92 (s, 6H) –OCH_3.

2.3.5 Decarboxylation of 3,4-dimethoxythiophene-2,5-dicarboxylic acid 4 to obtain 3,4-dimethoxythiophene ***(5)*** [11]

0.19 g of compound **4** (0.8 mmol) were dissolved in 3 mL of pyridine. 0.27 g of $Cu_2Cr_2O_5$ were added. The reaction mixture was left to reflux at 160°C with magnetic stirring under $N_{2(g)}$ atmosphere during 7 h. It was left to cool at room temperature and then treated with cold water and HCl 10% to remove the excess of pyridine. The excess of copper chromite was filtered and washed with ethyl acetate. The raw product was further extracted from the aqueous phase with ethyl acetate. The organic fractions were joint, washed with brine and water and dried over anhydrous $MgSO_4$. The solvent was then evaporated. The remaining oil was purified by column chromatography with a mobile phase of hexane: ethyl acetate of increasing polarity up to 70:30 to give 31.2 mg of compound **5** (33.22%). ^{1}H-NMR ($CDCl_3$, 300MHz) δ (ppm): 6.20 (s, 2H), 3.86 (s, 6H) –OCH_3.

CHAPTER 3. RESULTS AND DISCUSSION

Figure 3 shows the synthetic route followed in this work to obtain 3,4-dimethoxythiophene with a global yield of 12% after 4 steps together with a summary of the best yields obtained for the different conditions tested in each step.

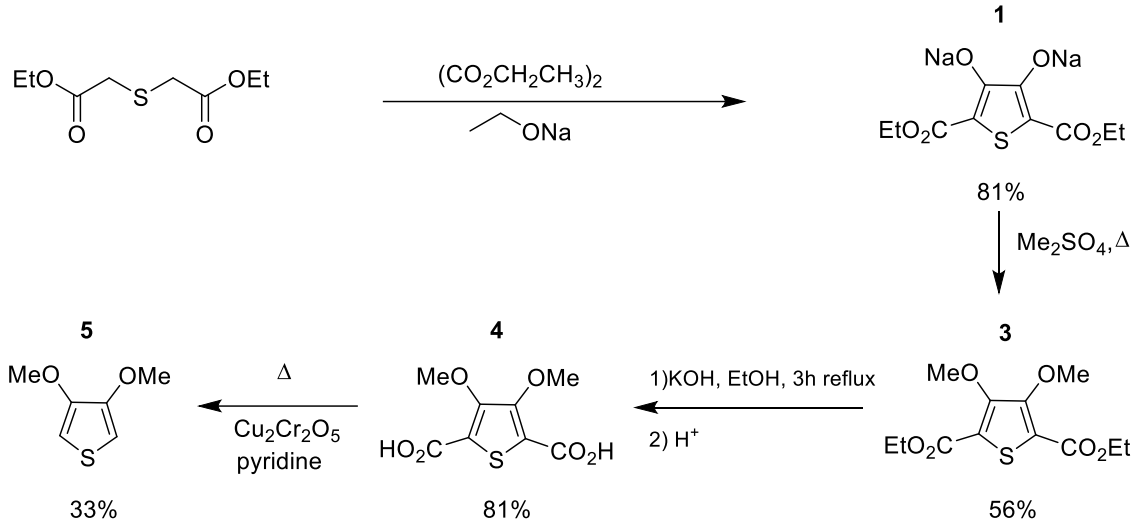


Figure 3. Synthetic route for the preparation of 3,4-dimethoxythiophene

3.1 Synthesis of disodium salt of 2,5-dicarbethoxy-3,4-dihydroxythiophene **(1)**

Disodium salt **1** was obtained by a Hinsberg condensation of 2,2-thiodiglycolic acid diethyl ester with diethyl oxalate and sodium ethoxide as the base. The yield for this reaction was near 81% after two filtrations from cold absolute ethanol. The product is a yellow odorous solid as reported in the literature[20].

Figure 4 shows the ^{1}H-NMR spectrum of compound **1**. This salt was found to be highly hygroscopic, so that even after drying it in the oven overnight, some moisture remained and hence a very tall solvent residual peak appears at 4.65 ppm corresponding to H_2O in D_2O[29]. The quartet at 4.36-4.32 ppm and triplet at 1.42-1.38 ppm confirm the presence of the ethyl groups.

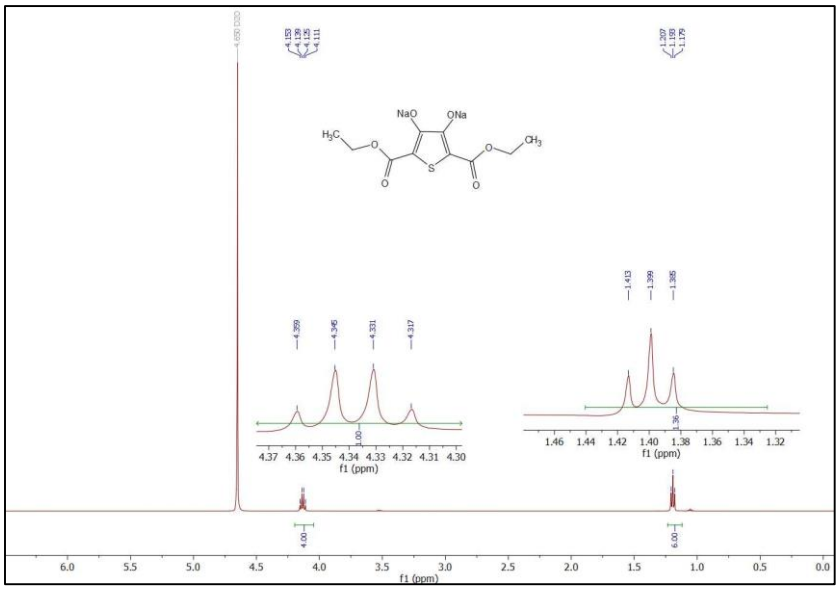


Figure 4. [1]H-NMR Spectrum of disodium salt of 2,5-dicarbethoxy-3,4-dihydroxythiophene, D_2O, 300MHz

3.2 Synthesis of 2,5-dicarbethoxy-3,4-dihydroxythiophene **(2)**

2,5-dicarbethoxy-3,4-dihydroxythiophene was obtained as a white solid by acidification of the corresponding disodium salt **1** with a yield of 56%. The measured melting point of 132°C is very close to the reported in the literature (134°C) [30]. **Figure 5** shows the ^{1}H-NMR spectrum of compound **2**. The singlet at 9.35 ppm integrating for 2H verifies the presence of the hydroxyl groups, as result of the acidification. The triplet and quartet corresponding to the ethyl groups appear at 4.36-4.29 ppm and 1.35-1.28 ppm, respectively.

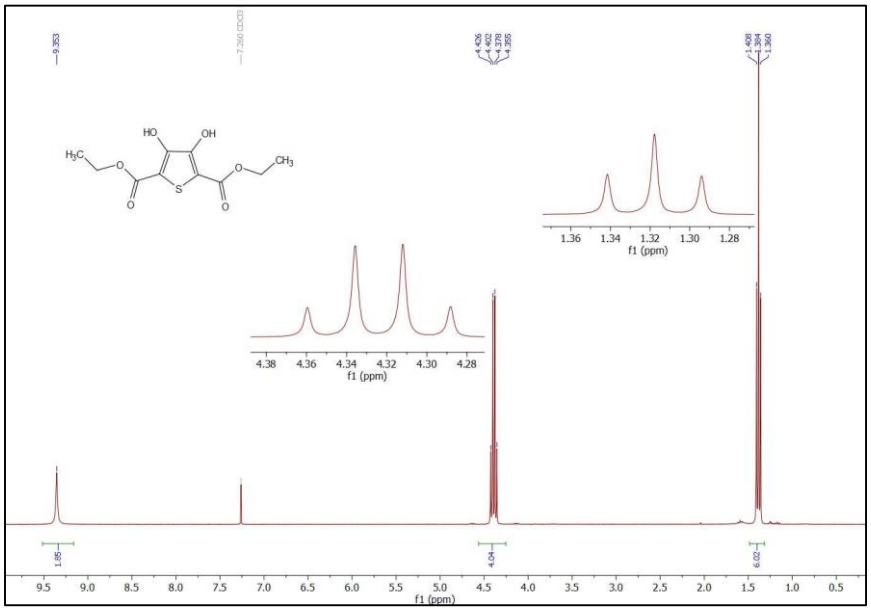


Figure 5. [1]H-NMR Spectrum of 2,5-dicarbethoxy-3,4-dihydroxythiophene, $CDCl_3$, 300MHz

3.3 Synthesis of 2,5-dicarbethoxy-3,4-dimetoxytiophene **(3)**

2,5-dicarbethoxy-3,4-dimethoxythiophene was obtained as a white solid by *O*-methylation of compound **1**. Characterization by ^{1}H-NMR, IR and MS was performed with the product isolated from trial 2 of Method B. This product was kept as and standard and the products of the other trials were compared to it by TLC (50:50 hexane, diethyl acetate, Rf=0.78) and melting point (mp=48°C). **Figure 6** shows the ^{1}H-NMR spectrum of compound **3**. The singlets at 4.01 ppm integrating for 6H confirm the presence of methoxy groups as the result of the O-methylation in both positions, 3 and 4. The quartet and triplet peaks corresponding to the ethyl groups appear at 4.41-4.33 ppm and 1.42-1.37 ppm, respectively.

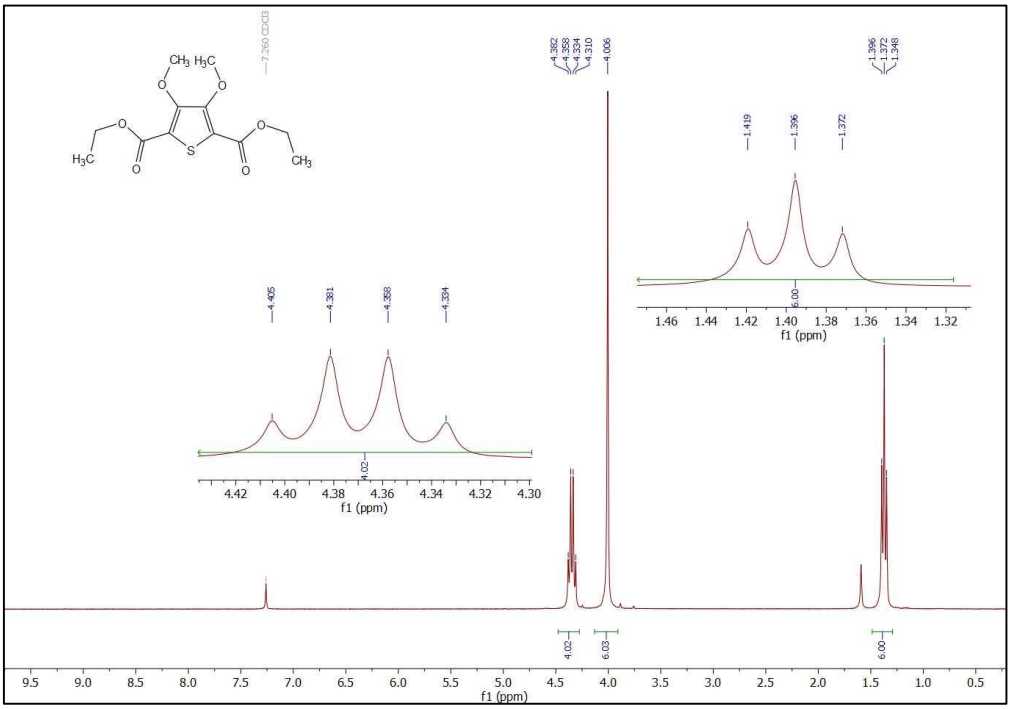


Figure 6. ^{1}H-NMR Spectrum of 2,5-dicarbethoxy-3,4-dimethoxythiophene, $CDCl_3$, 300MHz

Figure 7 shows the IR spectrum of compound **3**. Characteristic peaks appear in 1704cm^{-1} for the stretching of carbonyl groups of the diester moieties and sharp peaks around 1500 cm^{-1} for stretching of C-C in aromatics. A strong peak at 1263 cm^{-1} indicates C-O stretching for alkyl aryl ether corresponding to the methoxy groups.

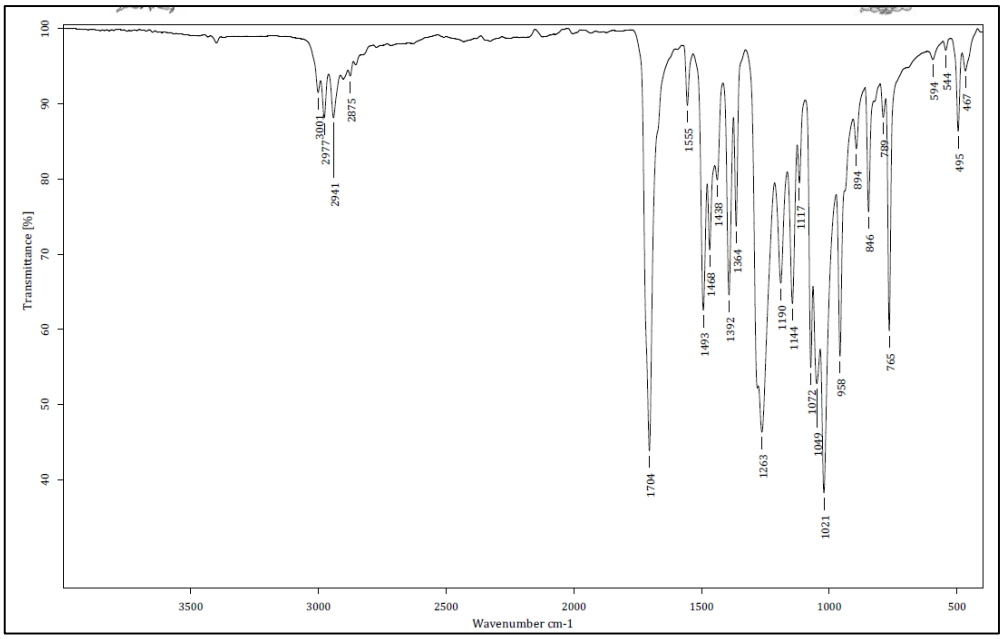


Figure 7. IR Spectrum of 2,5-dicarbethoxy-3,4-dimethoxythiophene

Figure 8 shows the mass spectrum of compound **3**. The identity of compound **3** is verified by the appearance of the molecular ion (m/z=288) and a peak at m/z=259, which results from the loss of a formyl radical coming from one of the methoxy groups, as suggested by Fisichella[31] (**Scheme 1**). First, a hydrogen rearrangement occurs from the methoxy group to the oxygen of the carbonyl of the ester. Then, a formyl radical is lost to give an ion of m/z= 259. Hence, it is verified that *O*-methylation occurs in both positions.

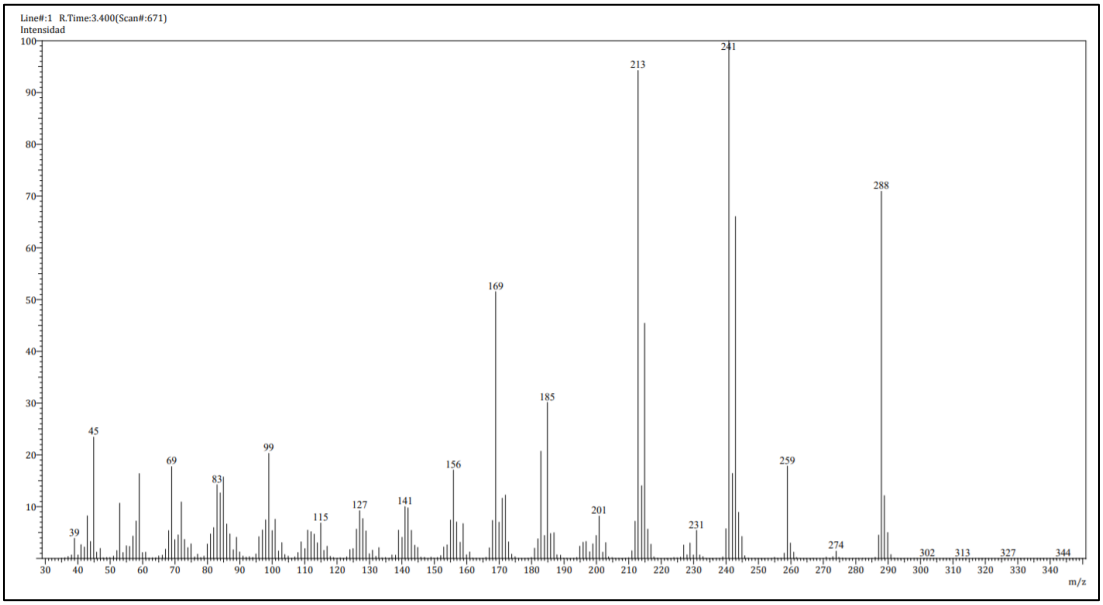
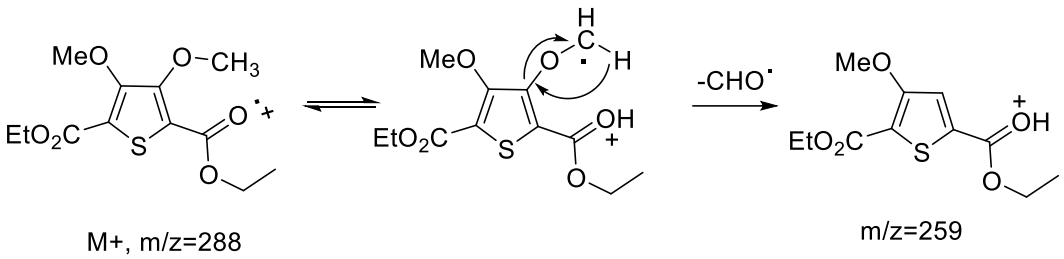


Figure 8. Mass spectrum of 2,5-dicarbethoxy-3,4-dimethoxythiophene. Ionization mode: EI



*Scheme 1. Fragmentation of molecular ion of compound **3***

Four methods were tested for this reaction, which differ by the methylating agent, the substrate:solvent ratio, the time of reaction, temperature and the heating mode. **Table 1** summarizes the reaction conditions and yields obtained for each trial for methods A, B and C. In method A, it can be noticed that increasing the time of reaction by double between the first two trials by keeping all other conditions unchanged, does not significantly increase the yield of reaction. On the other hand, the yield can increase up to 56% when doubling the time of reaction but also adding some solvent in a 1:4 ratio (g of substrate:mL of solvent). The initial choice of a 1:7 mol:mol ratio between the disodium salt and DMS is given by two factors: 1) the already reported poor ability of DMS as a methylating agent in this reaction[13] and, 2) DMS readily dissolves the disodium salt **1**, so that using a sufficient high amount (about 1 mL for 500 mg of substrate) allows to have it in double function as methylating agent and solvent. However, it was found that the addition of extra solvent is favorable as it allows to significantly reduce the amount of dimethyl sulfate, i.e. the methylating agent to a 1:3 ratio (mol of **1**: mol DMS). This outcome is due to the reaction mechanism, namely a nucleophilic substitution SN_2, which is enhanced by the use of non-protic polar solvents, such as in this case acetonitrile.

Table 1. Results for methylation of compound 1 through method A to C

#	Method A				
	Disodium salt: DMS	Disodium salt: MeCN (g:mL)	Time (min)	Temperature (°C)	Yield (%)
1	1:7	0	60	100	34.58
2	1:7	0	120	100	38.56
3	**1:3**	**1:4**	**240**	**100**	**56.38**
	Method B				
	Disodium salt: DMS	Disodium salt: MeCN (g:mL)	Time (min)	Temperature (°C)	Yield (%)
4	1:2 (+alumina)	0	20	100	4.70
5	1:2 (+alumina)	0	7	100 (mw)	26.15
6	1:4 (+alumina)	0	7	100 (mw)	31.94
	Method C				
	Disodium salt: MeI	Disodium salt: MeCN (g:mL)	Time (h)	Temperature (°C)	Yield (%)
7	1:19	1:4	14	80	33.60

In method B, for the first trial heating was performed on an oil bath. In comparison to method A, the low substrate:DMS ratio was achieved herein by using a solid support, namely, basic alumina as proposed by Heravi[23] for *O*-methylation of phenols and *S*-methylation of thiols. As seen by the poor yield of 4.7%, the use of the solid support does not guarantee a successful methylation within a small period of time. Thereof, switching the heating mode to a controlled microwave irradiation allows not only to increase the yield to 26.15%, but also to reduce the time of reaction by almost 3 times less. In the third trial, the disodium salt: DMS ratio was increased to 1:4 and the time of reaction was left unchanged. This trial rendered near 32% of yield, which is comparable to the yield of the first trial with method A, where the reaction was performed with about twice as much of methylating agent and 8 times as much of reaction time. Therefore, the use of a solid support coupled with microwave irradiation presents three main advantages: reducing the amount of methylating agent, reducing the time of reaction and the possibility of performing a solvent-free reaction.

In method C, the methylating agent was methyl iodide opposed as in methods A and B. The substrate:MeI ratio as well as the amount of solvent and temperature were used as suggested by the literature for the *O*-methylation of 1,2-dihydroxybenzene[21,22]. The

reaction yield is low despite the long reaction time (14 h) and the high amount of methylating agent, which are both significantly higher than those for methods A and B. Because of this poor conversion, no further trials changing reaction conditions were attempted with method C.

Table 2 summarizes the conditions used for the synthesis attempts of compound **3** by method D. This method consists of a galvanostatic electrolysis of the disodium salt **1** and the diol **2** with a tetramethyl ammonium salt working as the supporting electrolyte and simultaneously as the methylating agent in a polar non-aqueous medium. The electrolysis was successfully proved by Zhang[28] for *O*-methylation of phenol to obtain anisole on Pt electrode with TMAC as the aforementioned tetramethyl ammonium salt. The purpose of this method was to use a less hazardous methylating agent, less temperature and heterogeneous catalysis, as the reaction is given on the surface of the electrode. Nevertheless, both attempts with the disodium salt at 40°C and a current density of 1 A/dm^2 and with the diol **2** at 19°C and a current density of 2.5 A/dm^2 would not render the desired dimethylated product **3**. However, it is worth to mention that a major product of the electrolysis different than the starting disodium salt was isolated, yet not fully elucidated.

Table 2. Results for methylation of compound 1 and 2 through method D

Electrode area	106 mm^2	
Reactant	Compound **1**	Compound **2**
Reactant:$TMABF_4$	1:4	1:4
Current density (A/dm^2)	1.0	2.5
Temperature (°C)	40	19
Solvent	MeOH:DMF	DMF
Yield (%)	0	0

In order to evaluate the performance of these methods according to green chemistry principles, some parameters such as atom economy, solvent used and energy for heating were calculated for each trial, using the following equations:

$$Atom\ Economy = \frac{MW\ (desired\ product)}{\sum MW\ (reactants)} \quad (1)^{19}$$

$$Solvent\ used = \frac{Total\ solvent\ (mL) + 0.000001mL}{moles\ of\ reactant} \quad (2)$$

$$Energy\ for\ heating = Power\left(\frac{J}{s}\right) * time(\min) * 60 \quad (3)$$

This values are summarized in **Table 3**. For the case of atom economy, the reagents used for purification where not taken into consideration, so that only the molecular weight of the methylating agent and the disodium salt were used in the denominator of the fraction. The total amount of solvent used for purification was not considered because column chromatography was performed in most cases. A relatively negligible value of 0.000001mL is added to the equation to avoid a division to zero in the calculation of the method efficiency ME. Temperature and heat capacity were not considered for the calculation of energy for heating, since the time for heating was taken once the oil bath reached the desired temperature. The energy used per time was calculated as E = P*t, where P is the power in watts and t is time in seconds. Heating was performed in method A and C using an oil bath on a hot plate. It was assumed that the average hot plate consumes 180 Watts for a 500 mL liquid volume. The power for the microwave assisted heating increased from 8 W to 100 W and stood around 100 W for the rest of the reaction. Method D was not taken into account as no product could be obtained from it. Finally, the method efficiency ME according to green chemistry criteria is proposed as follows:

$$ME\ \left(\frac{mol}{kJ*mL}\right) = \frac{Atom\ economy * Yield}{Energy\ for\ heating * ratio\ of\ solvent\ used} \quad (4)$$

Equation 4 is proposed for the quantification of the method efficiency in agreement with Green Chemistry principles. Method efficiency increases as the atom economy and yield increase, while the energy for heating and amount of solvent decrease. ME is calculated

in **Table 3** for each trial. Including the reaction yield to the equation allows to consider waste generation, since unreacted salt and side products diminish the reaction yield, and hence the method efficiency.

Table 3. Evaluation criteria for methods A-C

#	Method A				
	Atom economy	Ratio of solvent used (mL/mol)	Energy for heating* (kJ)	Yield	ME
1	0.26	0.000304	648	0.3458	0.449
2	0.26	0.000304	1296	0.3856	0.251
3	0.45	1216	2592	0.5638	7.97E-8
	Method B				
	Atom economy	Ratio of solvent used (mL/mol)	Energy for heating (kJ)	Yield	ME
4	0.55	0.000304	216	0.0470	0.391
5	**0.55**	**0.000304**	**75.6**	**0.2615**	**6.218**
6	0.38	0.000304	75.6	0.3194	5.225
	Method C				
	Atom economy	Ratio of solvent used (mL/mol)	Energy for heating* (kJ)	Yield	ME
7	0.10	1216	9072	0.3360	3.09E-9

*This value only considers the energy to keep an average oil bath in a 500mL flask to the desired temperature. It only works for laboratory scale reactions. For industrial scale, other considerations should apply.

According to the reaction yield, trial 3 would be the best option for the *O*-methylation reaction of compound **2.** However, it is the second worst option as calculated by ME. The value of ME measures the amount of reactant that is methylated by energy and solvent spent. The higher it is, the more product by less energy and less solvent is obtained. In other words, the lower the inverse of ME is, the lower energy and solvent are needed for 1 mole of disodium salt to be methylated. The highest ME values are obtained by trials 5 and 6 of method B. In this case, the solvent-free reaction and the lower reaction time contribute most to this outcome, despite the lower yields. In this behalf, the method chosen as the best for O-methylation reaction is method B with the conditions set in trial 5. It is worth to mention that in case that Method D worked, it would have had a low ME because of the high energy demand as the time of heating the water bath surrounding the electrolysis cell is stechiometrically dependent of the

amount of substrate. This method also fails at solvent use, since $TMABF_4$ has very low solubility in acetonitrile, so that huge amounts of solvent are needed to accomplish the desired mol ratio of substrate and methylating agent. However, if further Green Chemistry principles are taken into account, such as hazardouseness of the methylating agent and catalysis, method D would have had good outcomes in ME because of the use of mild $TMABF_4$ compared to toxic DMS or MeI, and the use of heterogeneous catalysis (electrode surface).

3.4 Synthesis of 3,4-dimethoxythiophene-2,5-dicarboxylic acid **(4)**

3,4-dimethoxythiophene-2,5-dicarboxylic acid was obtained as a white solid by saponification of compound **3** with a yield of 81%. **Figure 9** shows the ^{1}H-NMR spectrum of compound **4**. The weak but broad band from 14.5 to 12.5 ppm which integrates for 2H confirms the presence of the carboxylic acids.

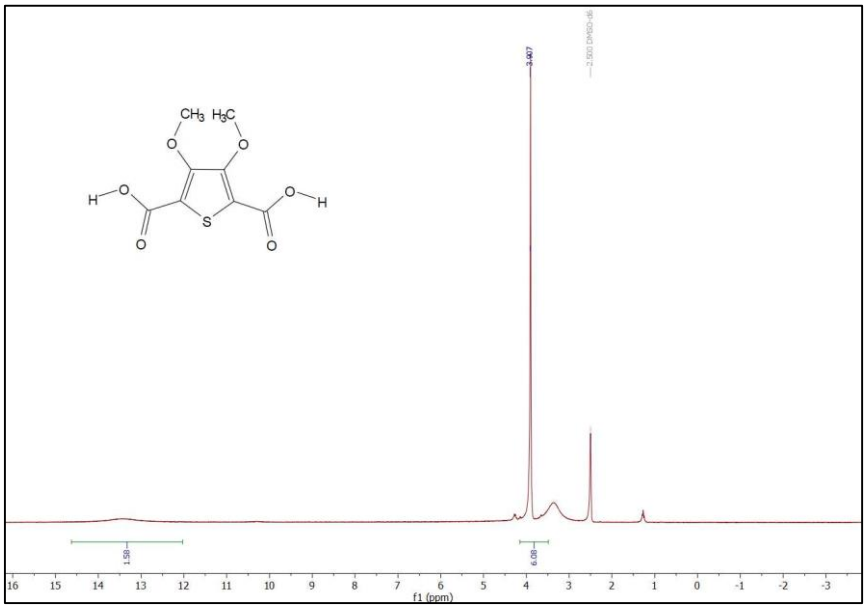


Figure 9. ^{1}H-NMR Spectrum of 3,4-dimethoxy-thiophene-2,5-dicarboxylic acid, DMSO-d_6, 300MHz

Figure 10 shows the IR spectrum of compound **4**. The peak for the stretching of the carbonyl group of the dicarboxylic acid is shifted to a lower wavenumber (1667 cm^{-1}) as compared to the diester of compound **3**, as expected. This is because the sample was tested in solid state, which favors the dimerization of carboxylic acids. The formation of hydrogen bonds weakens the C=O bond and causes a lower frequency. The appearance of a broad band around 2600-3000 cm^{-1} absent in the IR spectrum of the diester **3** confirms the presence of the hydroxyl groups of the dicarboxylic acid.

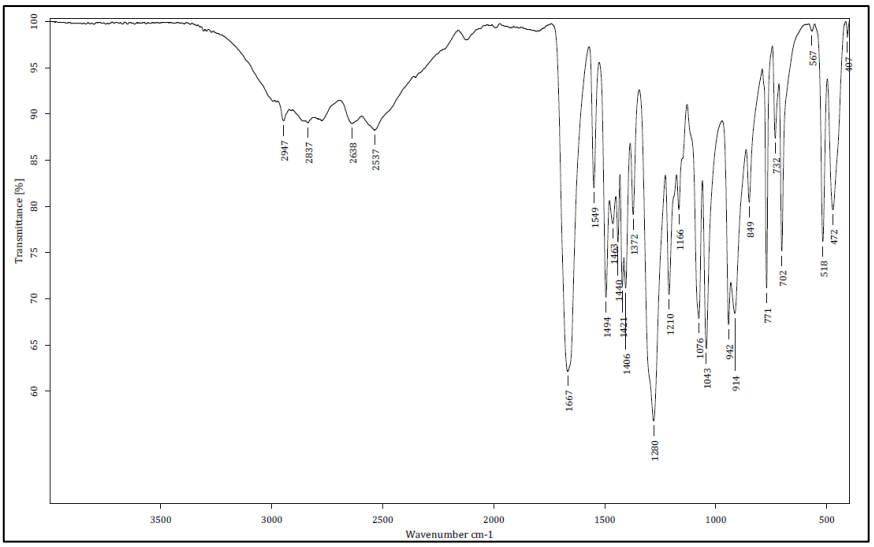


Figure 10. IR Spectrum of 3,4-dimethoxy-thiophene-2,5-dicarboxylic acid

*3.5 Decarboxylation of 3,4-dimethoxythiophene-2,5-dicarboxylic acid **(4)** to obtain 3,4-dimethoxythiophene* **(5)**

3,4-dimethoxythiophene was obtained as a colorless to pale yellow liquid by decarboxylation of compound **4** with a yield of 33%. **Figure 11** shows the ^{1}H-NMR spectrum of compound **5**. The singlet corresponding to the dimethoxy groups appear at lower chemical shift as compared to compound **4** because of the loss of electron withdrawing groups.

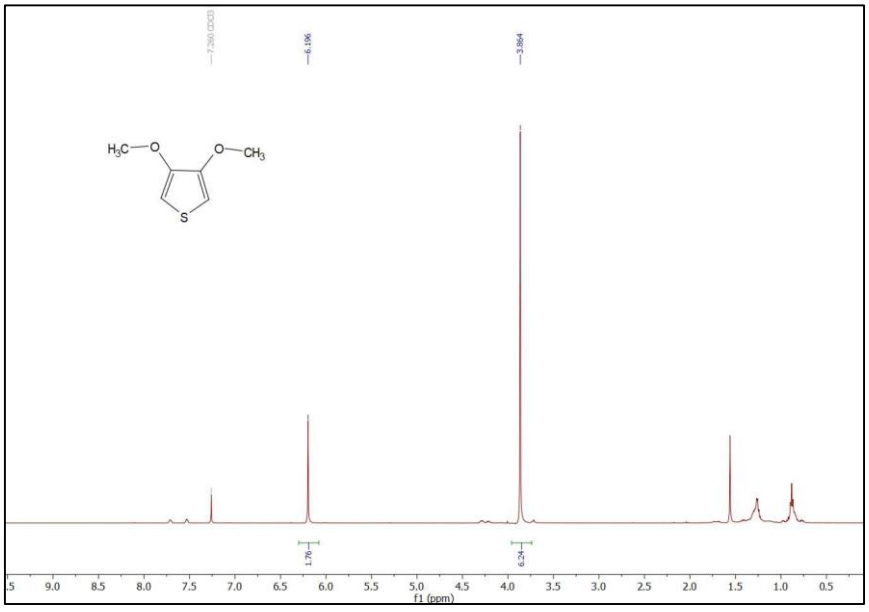


Figure 11. ^{1}H-NMR Spectrum of 3,4-dimethoxythiophene, $CDCl_3$, 500MHz

As reported in the literature, this compound was found to be unstable under oxygen at room temperature, as well as very volatile. Purification was difficult as it was very

miscible with the solvents used for column chromatography. Many solvent residual peaks appear at the beginning of the spectrum in **Figure 11**, namely, a multiplet and triplet of hexane at 1.26 and 0.88 ppm[29], respectively, and residual water from hexane at 1.56 ppm[29] as the solvent was not dried before evaporation. Finally, the lack of a broad band for the dicarboxylic groups and the singlet at 6.2 ppm integrating for 2H corresponding to the aromatic hydrogens confirm the identity of the target molecule.

Herein, the synthesis of 3,4-dimethoxythiophene was performed from 2,2'-thiodiglycolic acid diethyl ester by modifications to the reported methods in literature following general Fager´s method with a global yield of 12% after 4 steps. The *O*-methylation to convert compound **2** into the dimethylated product **3** was accomplished by 3 of the 4 proposed methods and where evaluated according to Green Chemistry criteria.

CONCLUSIONS AND RECOMMENDATIONS

Conclusions

3,4-dimethoxythiophene was obtained from 2,2'-thiodiglycolic acid diethyl ester with a global yield of 12% after 4 steps. The disodium salt of 2,5-dicarbethoxy-3,4-dihydroxythiophene was obtained with a yield of 81%. Acidification of the disodium salt allowed to obtain 2,5-dicarbethoxy-3,4-dihydroxythiophene with 56% yield. Methylation of the disodium salt allows to save one step in the synthesis of 3,4-dimetoxythiophene in contrast to using 2,5-diethoxycarbonyl-3,4-dihydroxythiophene and adding KOH. O-methylation was accomplished by 3 different methods by changing methylating agent, time of reaction, use of solvent and heating control with variable yields, being 56.38% the highest. Solvent-free microwave assisted heating allows to reduce the amount of DMS for the O-methylation reaction, as well as reducing the time of reaction, thus, the energy requirement to get comparable yields. The best method efficiency as main evaluation criteria using Green Chemistry principles was obtained by trial 5 of method B. 3,4-dimethoxythiophene-2,5-dicarboxylic acid was obtained with 81% yield and was then decarboxylated to get the target molecule with a 33% yield by reported methods.

Recommendations

- For further studies, purification parameter should be taken into account for the evaluation criteria. For instance, in method A treatment of the excess of DMS is needed given the high substrate:DMS ratio, which adds waste generation to the synthesis. In method B, an extraction with organic solvent is necessary to obtain the crude product from the basic alumina before performing column chromatography.

- Cost of reactants and reagents, as well as some quantitative way to analyze the hazardousness of the methylating agent should also be included.

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ANNEX 1

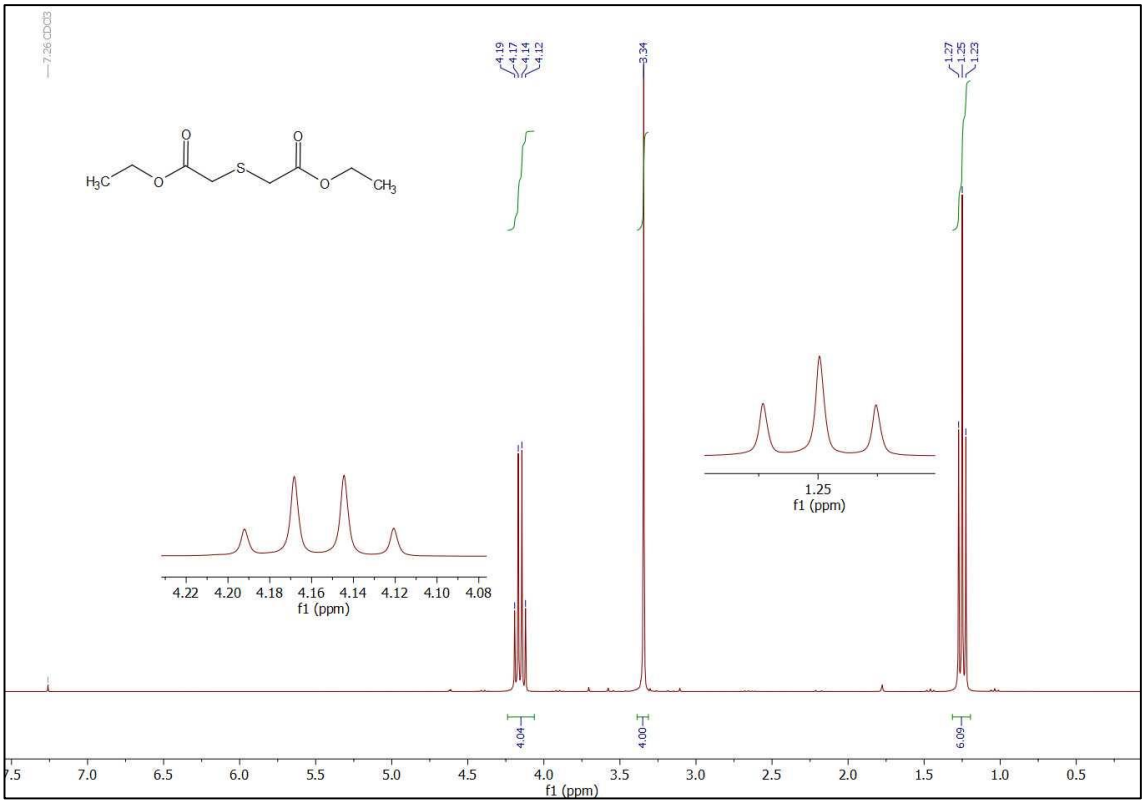

Figure A 1. ^{1}H-NMR Spectrum of 2,2'-thiodiglycolic acid diethyl ester, $CDCl_3$, 300MHz