UNIVERSIDAD DE INVESTIGACION DE TECNOLOGÍA EXPERIMENTAL YACHAY TECH

Escuela de Ciencias Químicas e Ingeniería

TÍTULO: Synthesis of N-alkoxy phthalimides and their electrochemical behavior

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

Químico

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A mis padres.

Erick Steven Patiño Alonzo

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I would like to thank to:

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Erick Steven Patiño Alonzo

Resumen

En este trabajo se reporta la síntesis de cuatro N-alcoxi ftalimidas y su comportamiento electroquímico. Difenil metanol, geraniol, alcohol bencílico y 2-fenoxietanol fueron usados para sintetizar los productos de interés en condiciones de Mitsunobu. Adicionalmente, se siguió una estrategia de tosilación y desplazamiento nucleofílico con alcohol bencílico y 2-fenoxietanol para el mismo fin. Los potenciales de reducción de estas especies fueron determinados mediante experimentos de voltametria cíclica en ACN y DMF 0.1M TBAP. Experimentos de electrólisis mostraron la formación de tributilamina en conjunto con otras especies que aquí se proponen mas no han sido confirmadas.

Palabras Clave:

N-alcoxi ftalimidas, electrolisis, voltametria cíclica, Mitsunobu, reducción de 1 electrón.

Abstract

In this work, the synthesis of four N-alkoxy phthalimides and their electrochemical behavior is reported. Diphenyl methanol, geraniol, benzyl alcohol and 2-phenoxyethanol were used to synthesize the desired products under Mitsunobu conditions. Additionally, a protocol of tosylation-nucleophilic displacement was applied to benzyl alcohol and 2-phenoxyethanol for the same purpose. Cyclic voltammetry experiments in ACN and DMF 0.1M TBAP were suitable media to determine the reduction potential of such species. A few bulk electrolysis experiments showed the formation of tributylamine and several other products that appear in this works as proposed structures rather than confirmed.

Keywords:

N-alkoxy phthalimide, bulk electrolysis, cyclic voltammetry, Mitsunobu ,1-electron reduction.

ABREVIATIONS AND ACRONYMS

TBAP: Tetrabutylammonium Perchlorate

DMF: N,N-dimethylformamide

ACN: Acetonitrile

DCM: Dichloromethane

THF: Tetrahydrofuran

CV: Cyclic Voltammetry

AcOEt : Ethyl Acetate

R.E: Reference Electrode

W.E: Working Electrode

C.E Counter Electrode

PHTP: 2-(2-phenoxyethoxy)isoindoline-1,3-dione

PHTB: 2-(benzyloxy)isoindoline-1,3-dione

PHTD: 2-(benzyhydryloxy)isoindoline-1,3-dione

PHTG: (E)-2-((3,7-dimethylocta-2,6-dien-1-yl)oxy)isoindoline-1,3-dione

NHPI: N-hydroxy phthalimide

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CHAPTER I: General Introduction

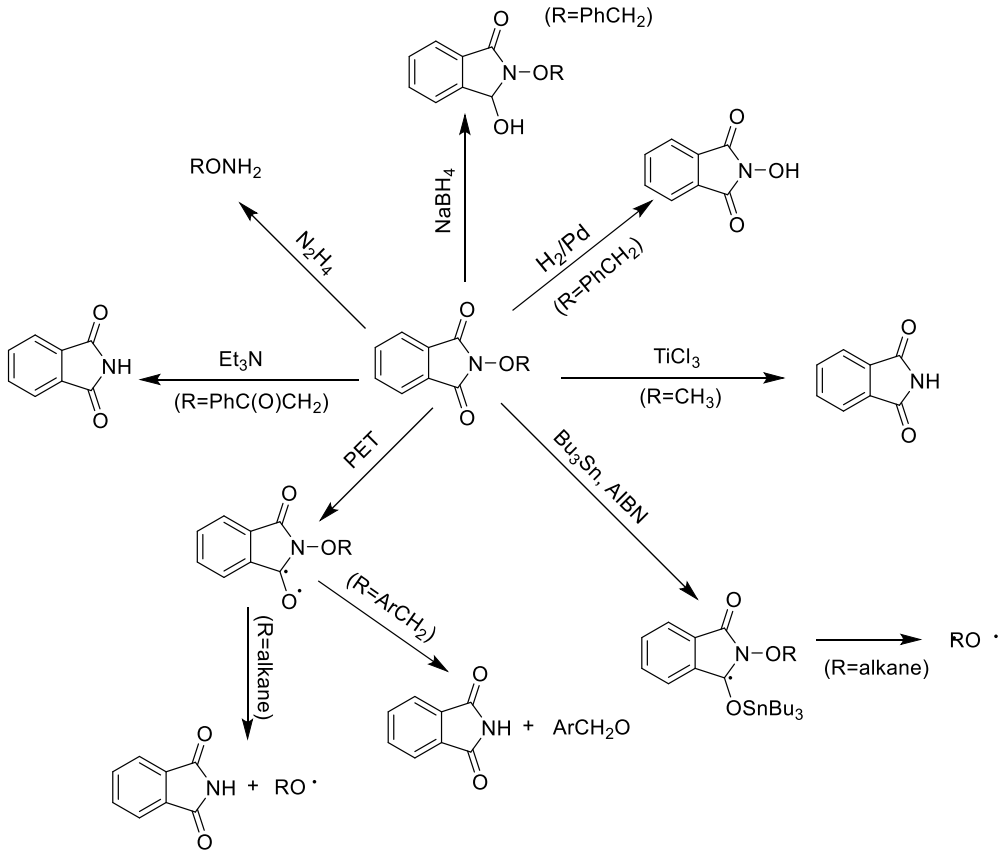
1.1.Introduction

N-hydroxy phthalimides **(NHPIs)** and its O-substituted derivatives have been of significant importance in many well-known synthetic steps to date such as hydroxylamine derivatives and others. NHPIs are of wide interest because of its organocatalyst nature in oxidation reactions of many organic substrates (alkanes, alkylaromatics, alcohols, etc.) and oxidative cross-coupling.[1] Its use comprehend a huge range of possibilities from industrial processes such as the conversion of cyclohexane into adipic acid to more fine chemicals with C-C and C-N bond formation. A few examples have been shown to have industrial scalability to a certain extent[2], but prior to that limitations must be faced. In fact, PINO (**P**hthal**i**mide **N**-**O**xyl radical) is the oxygen centered radical of NHPI which is usually obtained by interacting the NHPI with oxygen/peroxide. It has a catalytic effect when formed because it can promote free radical processes via hydrogen atom transfer (HAT). This catalyst has encountered many important problems that have kept it out of the possibility of big scale processes, associated mostly with its solubility. As another approach, the phthalimidic couple NHPI/PINO are already used as mediators in electrochemical oxidation reactions either for the consecution of oxygenated and non-oxygenated products.[3] In particular, N-alkoxy phthalimides and NHPI are insoluble in either aqueous or non-aqueous apolar media. Interestingly, new solutions have risen recently to improve their solubility: in organic solvents by introducing hydrophobic alkylic chain[2] or in aqueous media by using surfactants to work in a micellar environment[4].

N-alkoxy phthalimides can be synthesized by different approaches. In the past, simple N-alkoxy phthalimide were able to be prepared by dissolving N-hydroxy phthalimide in aqueous sodium bicarbonate and further addition of a convenient dialkyl sulphate to be stirred for several hours.[5] However, the toxicity and environmental risks of dialkyl sulphate leaded to alternative protocols for the preparation of such species. Currently, there are

three methods that are used to prepare N-alkoxy phthalimides.[6,7] First, the reaction of N-hydroxyphthalimide with an alkyl halide in presence of triethylamine or potassium carbonate, which has the advantage to be very general but presents variable yields and relatively long reaction times. Luckily, Wang, Li, X. and Li, J. showed that the time of reaction for this approach can be nicely decreased to less than 3h for some alkyl halides by using ultrasound irradiation under mild conditions in DMSO.[6] Similarly, Pawar et all showed that the yield of the reaction using potassium carbonate can be successfully improved with microwave radiation.[8] As a second alternative, the reaction of N-hydroxy phthalimide with alkyl halides in presence of DBU 1,8-diazabicyclo[5,4,0]-undec-7-ene in DMF which presents high yields at the expense of the high price of DBU and increased reaction time. And the last, the coupling of NHPI and secondary/primary alcohols under Mitsunobu conditions[9], which offers the possibility to work with alcohols instead of alkyl halides, that results in variable yields [10] and requires a tedious further purification. Castro J. and Matassa V. have reported a Mitsunobu-like process using a novel triphenylphosphine-cyclic sulfamide betaine[11] . However, despite this novel betaine works nicely in some cases, traditional Mitsunobu conditions in THF seems to be more effective for the coupling of alcohols and NHPI.[12]

N-alkoxy phthalimides are useful in many organic synthesis steps involving reducing agents such as O-alkoxyamine derivatives synthesis with hydrazine and more (Scheme 1). Lately, alkoxyl radicals (N-O bond cleavage product of N-alkoxy phthalimide) have shown to possess interesting applications. In fact, alkoxyl radicals has been shown to allow the functionalization of $C(sp^3)$-H, when alkoxy phthalimides are activated both by photo-redox catalysis under mild conditions or traditional reductive conditions (AIBN, Bu_3SnH)[10,13]. In particular, the N-alkoxy phthalimide precursor for the synthesis of a very complex polyketide showed to attain the final desired spiroketalic structure when the alkoxyl radical is formed in presence of AIBN and Ph_3SnH.[14] Thus, the radical activation using cleaner techniques of this species shows seems a promising field of study.



Scheme 1. Diverse chemical reactivity of N-alkoxy phthalimides in presence of different reducing agents.

In this work, the synthesis of four N-alkoxy phthalimides is reported. These products were synthesized from their corresponding alcohols starting materials by either using: a two-step synthesis comprehending tosylation and further nucleophilic displacement by N- hydroxy phthalimide, or a one-step coupling of alcohols to N-hydroxy phthalimide under Mitsunobu conditions and ultrasound irradiation. Typical characterization techniques (^{1}H-NMR, ^{13}-NMR, IR, and melting point) confirmed the authenticity of N-alkoxy phthalimides derived from 2-phenoxyethanol, benzyl alcohol, diphenyl methanol and geraniol (E isomer). Electrochemical studies were conducted on all 4 substrates. First, the reduction potentials by cyclic voltammetry in two electrolytic mediums (0.1M TBAP in DMF and 0.1M TBAP in ACN) were determined. Additionally, bulk electrolysis in ACN was conducted using an H-divided cell and yielded an array of products after 1-electron reduction. The electrolytic

solution clearly showed to be non-inert, taking part in the reactivity of the experiment and further formation of the electrolysis products. As expected, the amount of material isolated is overestimated, and the major product of it is tributylamine, derived from tetrabutylammonium perchlorate (TBAP).

1.2.Problem Statement

Radical activation using heavy metal (Sn, Pb, Zn, Cu, etc.) based reagents such as Ph_3SnH is not very recommended for all synthetic purposes as long as Sn traces might remain after purification. Indeed, pharmaceutical products have been restricted to use such reagents on the late stages of synthesis. Fortunately, electrochemistry appears as a very clean method for the activation of organic substrates upon reduction or oxidation. The so called organic electrosynthesis, has arisen along the last decades as a facile and promising tool, showing outstanding advantages in terms of yield, scalability, efficiency, reduced environmental pollution and versatility[15,16]. In fact, a good number of industry commercial processes that work based on this approach have been described trough the literature.[17] Hopefully, the organic chemistry community will adapt to this new methodology in the near future and probably will find an invaluable tool.

Currently, the electrochemical behavior and reactivity of N-alkoxy phthalimides has been scarcely studied with minor detail in a few works. Okada et al. published two works about the photo-sensitized decarboxylation of N-acyloxy phthalimides to yield chloroalkanes and alkanes with very interesting yields but reporting only the peak potentials of the synthesized species in ACN, TMAP 0.1M against SCE reference.[18,19] Additionally, Syroeshkin et al. reported a more electrochemistry-based work in which they also verify the well-known weakness of the N-O bond after the 1- electron reduction and subsequent formation of the RAs in a good number of N-alkoxy phthalimides derivatives[20]. However, the subsequent transformations after the first one-electron reduction remain elusive to be elucidated, which leaves this topic open for new research.

1.3.Objectives

1.3.1 General Objective

To synthesize four N-alkoxy phthalimides derivatives starting from their corresponding alcohols and to study their chemical behavior after 1-electron reduction

1.3.2 Specific Objectives

• To synthesize 2-(2-phenoxyethoxy)isoindoline-1,3-dione (PHTP) starting from 2-phenoxyethanol, determine its first reduction potential, perform its bulk electrolysis under selected conditions, and purify the electrolysis products by means of chromatography and determine their identity via spectroscopic characterization.

• To synthesize 2-(benzyloxy)isoindoline-1,3-dione (PHTB) starting from benzyl alcohol, determine its first reduction potential, perform its bulk electrolysis under selected conditions, and purify the electrolysis products by means of chromatography and determine their identity via spectroscopic characterization.

• To synthesize 2-(benzhydryloxy)isoindoline-1,3-dione (PHTD) starting from diphenyl methanol, determine its first reduction potential, perform its bulk electrolysis under selected conditions, and purify the electrolysis products by means of chromatography and determine their identity via spectroscopic characterization.

• To synthesize (E)-2-((3,7-dimethylocta-2,6-dien-1-yl)oxy)isoindoline-1,3-dione (PHTG) starting from geraniol, determine its first reduction potential, perform its bulk electrolysis

under selected conditions, and purify the electrolysis products by means of chromatography and determine their identity via spectroscopic characterization.

Chapter II: Methodology

1.4.Reagents

All reagents and chemicals were purchased from commercial suppliers unless otherwise stated **:** Benzyl Alcohol ≥ 99.5% was acquired from **J.T. Baker ;** Triphenylphosphine 97% was acquired from **Spectrum ;** 2-phenoxyethanol ≥ 99%, Geraniol 98%, Diphenyl Methanol 99% , p-Toluenesulfonyl Chloride (Tosyl Chloride) ≥ 98, N-hydroxy phthalimide 97% , Triethylamine 99% , Diisopropylamine 99%, Diethyl azodicarboxylate DEAD solution (40% wt. in Toluene), Postassium Hydroxide 85% , Chloroform-d (99.8% atom D) were acquired from **Sigma Aldrich**. Note: All reagents were used as purchased without prior purification.

DMF was dried by letting 50mL of the solvent stored with activated molecular sieve (4 Å) for two days. Then high-vacuum distillation was performed and tail, body and head were collected on different receiver flasks. DCM was pre-dried by distillation with $CaCl_2$ and further distillation with CaH_2. Anhydrous THF obtained from a MBRAUN (SPS 5 Solvent Purifier System). Anhydrous DMF (99.8%) was purchased from Sigma Aldrich to be used in cyclic voltammetry. Anhydrous ACN obtained from a MBRAUN (SPS 5 Solvent Purifier System) to be used for cyclic voltammetry and bulk electrolysis.

1.5.Equipment

Cyclic Voltammetry was conducted using a Metrohm (AUTOLAB PGSTAT30 Potentiostat). Electrolysis was conducted using the following equipment: Scribner Associates (279A Digital Coulometer) and VIMAR (Potentiostat/Galvanostat PG-3EV). Characterization by ^{1}H and ^{13}C-NMR was performed with the following equipment: Varian (500MHz, NMRSystem) and Bruker (300MHz, Avance). Finally, IR spectra was taken by

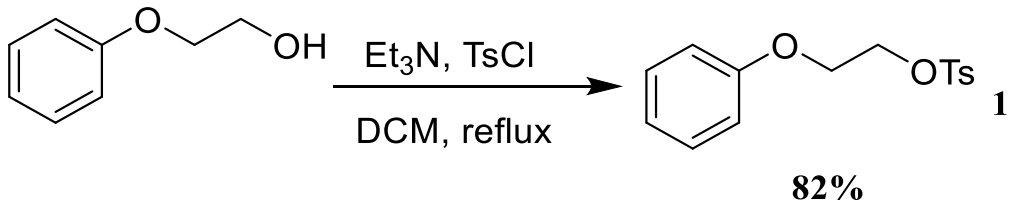
Bruker (Tensor 27, Platinum ATR). The samples were run and in some cases prepared by the technicians of Centro Conjunto de Investigación en Química Sustentable UAEM-UNAM, Toluca, Mexico.

1.6.Synthetic routes

Note on codification: The first three letters "PHT" are used since we are talking about N-substituted **pht**halimides and the last letter varying according to the starting alcohol: **P** for 2-phenoxy ethanol, **B** for benzyl alcohol, **D** for diphenyl methanol and **G** for geraniol (E isomer). In several cases we might be referring to our synthesized substrates as PHTX.

1.6.1 Synthesis of 2-phenoxyethyl 4-methylbenzenesulfonate 1 from 2-phenoxyethanol

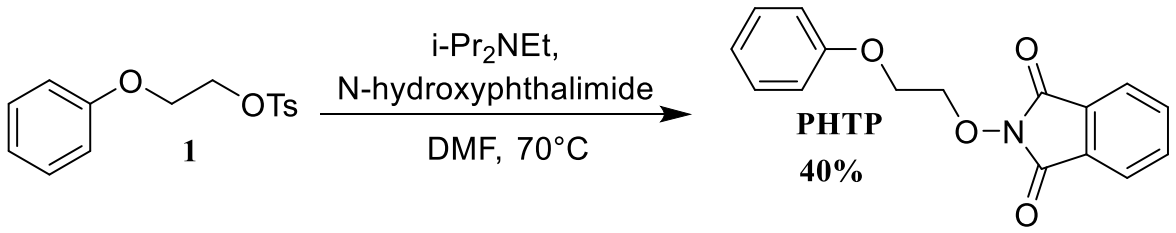
TsCl (12mmol, 2.30g) was added progressively to a solution of 2-phenoxyethanol (10mmol, 1.26mL), triethylamine Et_3N (16mmol, 1.35mL) in anhydrous dichloromethane 30mL over 10minutes at 0°C. The reaction mixture was then allowed to warm to ambient temperature and taken to reflux under stirring. Completion was achieved after 4 hours, and the reaction mixture was washed with brine (3x20mL). The resulting organic layer was dried over $MgSO_4$ and concentrated with vacuum and rotary evaporation, dry loaded in silica gel and purified by silica gel column chromatography (70-230 mesh) with gradient increasing the polarity from only n-hexane up to 80:20 n-hexane/ethyl acetate to afford 2-phenoxyethyl 4-methylbenzenesulfonate **1** in 82% yield (Scheme 2).



Scheme 2. Synthesis of 2-phenoxyethyl 4-methylbenzenesulfonate 1 from 2-phenoxyethanol.

1.6.2 Synthesis of (2-(2-phenoxyethoxy)isoindoline-1,3-dione) PHTP from 2-phenoxyethyl 4-methylbenzenesulfonate 1

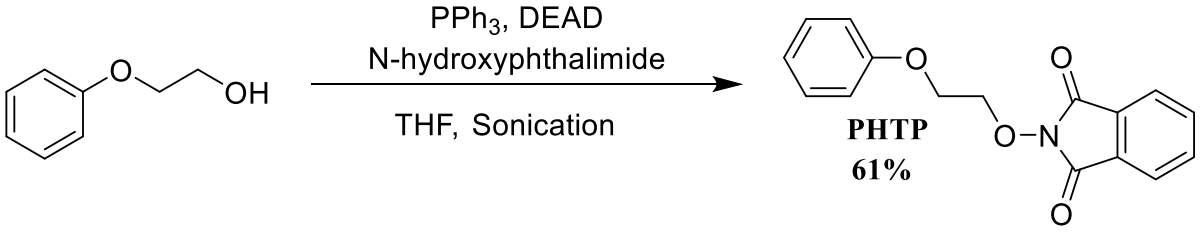
Next, the purified 2-phenoxyethyl 4-methylbenzenesulfonate **1** (1.71mmol, 0.500g) was dissolved in DMF together with NHPI (2.56mmol, 0.431g) and diisopropylethylamine (DIPEA) (3.42mmol, 0.59mL). The resulting mixture was heated at 70°C for one hour and then allowed to cool down to room temperature. The mixture was taken up in diethyl ether, washed with sodium bicarbonate (3x10mL) and brine (2x20mL). The organic layer was dried over $MgSO_4$, concentrated with vacuum and rotary evaporation and dry loaded in silica gel. Purification was carried out by silica gel column chromatography (70-230 mesh) with gradient increasing the polarity from n-hexane up to 80:20 hexane/ethyl acetate to afford (2-(2-phenoxyethoxy)isoindoline-1,3-dione) PHTP as a white powder in 40% yield (Scheme 3). The product obtained here was proven to be the same as obtained in section 2.3.3 by melting point determination.



Scheme 3. Synthesis of (2-(2-phenoxyethoxy)isoindoline-1,3-dione) PHTP from 2-phenoxyethyl 4-methylbenzenesulfonate 1.

1.6.3 Synthesis of (2-(2-phenoxyethoxy)isoindoline-1,3-dione) PHTP from 2-phenoxyethanol

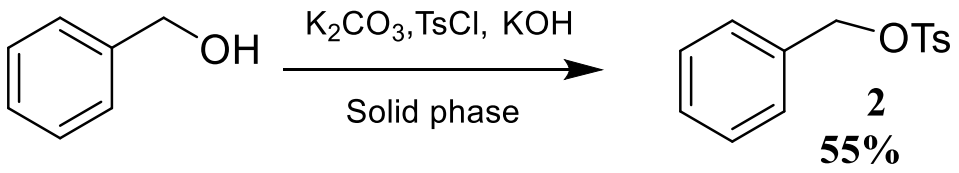
In a one-way round bottomed flask left in the oven overnight at 130°C, PPh_3 (2.2mmol, 0.577g), NHPI (2mmol, 0.336g) and 2-phenoxyethanol (2mmol, 0.25mL) were placed. The flask was purged with N_2 glove and syringe several times. Then, 1.2mL of dry THF were transferred into the reaction flask via cannula and the reaction mixture was placed in a sonicator as 40% DEAD dissolved in toluene (2.2mmol, 1mL) was added with a syringe drop-wise over 10 minutes. The reaction mixture was then allowed to react under sonication at 30-40 °C until completion after 4 hours (followed by TLC using dichloromethane/ethyl acetate/n-hexane eluent in 2:2:3 ratio or dichloromethane/n-hexane 1:1 ratio). The final product was concentrated in vacuum, dry loaded and purified by silica gel column chromatography (70-230 mesh) using only n-hexane at first and gradually increasing the polarity up until 80:20 hexane/ethyl acetate to afford the corresponding N-alkoxy phthalimide PHTP as a white powder in 61% yield (Scheme 4) . **Chemical Shifts: ^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.73ppm (q, 2H, Ar-H), 7.66ppm (q, 2H, Ar-H), 7.15ppm (t, 2H, Ar-H), 6.85ppm (t, 1H, Ar-H), 6.73ppm (d, 2H, Ar-H), 4.48ppm (t, 2H, OCH_2CH_2), 4.26ppm (t, 2H, OCH_2CH_2), **^{13}C-NMR** (300 MHz, $CDCl_3$) δ 163.47ppm (C=O), 158.32ppm (Ar-O), 134.59ppm (Ar), 129.57ppm (Ar), 129.52ppm (Ar), 128.96ppm (Ar), 123.64ppm (Ar), 121.32ppm (Ar), 114.71ppm (Ar), 76.15ppm (OCH_2CH_2O), 66.21ppm (OCH_2CH_2O) **M.p:** 132-134°C.



Scheme 4. Synthesis of (2-(2-phenoxyethoxy)isoindoline-1,3-dione) PHTP from 2-phenoxyethanol.

1.6.4 Synthesis of benzyl 4-methylbenzenesulfonate 2 from benzyl alcohol

Benzyl alcohol (10mmol, 1mL) and TsCl (15mmol, 2.92g) were placed in a mortar loaded with K_2CO_3 (35.8mmol, 5g) dried overnight at 110°C. The solid mixture was grinded vigorously for about 1 hour and the reaction was followed by TLC and presumably ended after that time (Note: the end of the reaction cannot be guaranteed as the mixture is not homogenous. In the TLC experiment, we spotted three times from different locations of the solid mixture). Remaining tosyl chloride was removed using KOH (42mmol, 2.80g) and grinding vigorously for several minutes. The product was taken up with diethyl ether and filtered through filter paper. The product was purified by crystallization in n-hexane and allowed to rest overnight to afford benzyl 4-methylbenzenesulfonate **2** in 55% yield (Scheme 5).

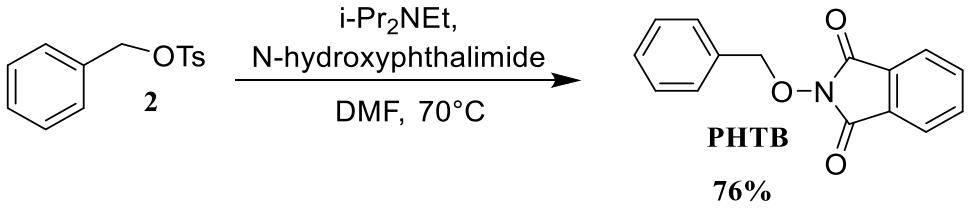


Scheme 5. Synthesis of benzyl 4-methylbenzenesulfonate 2 from benzyl alcohol.

1.6.5 Synthesis of 2-(benzyloxy)isoindoline-1,3-dione PHTB from benzyl 4-methylbenzenesulfonate 2

Next, benzyl 4-methylbenzenesulfonate (1.14mmol, 0.300g) was dissolved in 15mL of DMF together with NHPI (1.72mmol, 0.289 g) and DIPEA (2.3mmol, 0.4mL). The resulting mixture was heated at 70°C for 7 hours and then allowed to cool down to room temperature. The mixture was taken up in diethyl ether, washed with $NaHCO_3$ (3x10mL) and brine (2x20mL). The organic layer was dried over $MgSO_4$, concentrated with vacuum and rotary evaporation and dry loaded in silica gel. Purification was carried out by silica gel column chromatography (70-230 mesh) with gradient increasing the polarity from only n-hexane up to 80:20 n-hexane/ethyl acetate to afford PHTB 2-(benzyloxy)isoindoline-1,3-dione as a white powder in 76% yield in this step (Scheme 6), and 42%

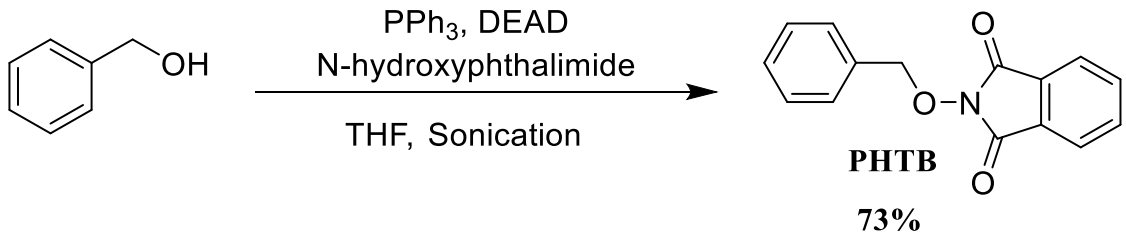
as the global yield. The product obtained here was proven to be the same as obtained in section 2.3.6 by melting point determination.



Scheme 6. Synthesis of 2-(benzyloxy)isoindoline-1,3-dione PHTB from benzyl 4-methylbenzenesulfonate 2.

1.6.6 Synthesis of 2-(benzyloxy)isoindoline-1,3-dione PHTB from benzyl alcohol

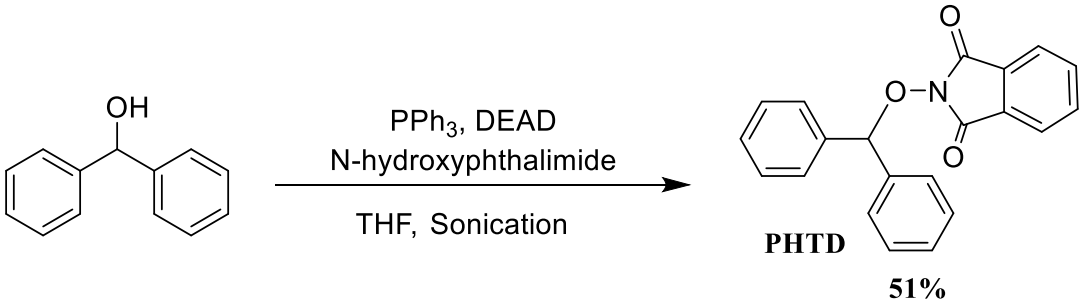
In a one-way round bottomed flask left in the oven overnight at 130°C, PPh_3 (2.2mmol, 0.577g), NHPI (2mmol, 0.336g) and benzyl alcohol (2mmol, 0.20mL) were placed. The flask was purged with N_2 glove and syringe several times. Then, 1.2mL of dry THF were transferred into the reaction flask via cannula and the reaction mixture was placed in a sonicator as 40% DEAD dissolved in toluene (2.2mmol, 1mL) was added with a syringe drop-wise over 10 minutes. The reaction mixture was then allowed to react under sonication at 30-40°C until completion after 4 hours (followed by TLC using dichloromethane/ethyl acetate/n-hexane eluent in 2:2:3 ratio or dichloromethane/n-hexane 1:1 ratio). The final product was concentrated in vacuum, dry loaded and purified by silica gel column chromatography (70-230 mesh) using only n-hexane at first and gradually increasing the polarity up until 80:20 n-hexane/ethyl acetate to afford the corresponding N-alkoxy phthalimide PHTB as a white powder in 73.4% yield (Scheme 7) .**Chemical Shifts: ^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.71ppm (q, 2H, Ar-H), 7.63ppm (q, 2H, Ar-H), 7.45ppm (q, 2H, Ar-H), 7.28ppm (m, 3H, Ar-H), 5.12ppm (s, 2H, OC**H**$_2$-Ar). **^{13}C-NMR** (300 MHz, $CDCl_3$) δ 163.97ppm (C=O), 134.93ppm (**Ar**-C-O), 134.21ppm (Ar), 130.37ppm (Ar), 129.83ppm (Ar), 129.36ppm (Ar), 129.04ppm (Ar), 123.97ppm (Ar), 80.36ppm (Ar-**C**-O). **M.p:** 140-142°C.



Scheme 7. Synthesis of 2-(benzyloxy)isoindoline-1,3-dione PHTB from benzyl alcohol.

1.6.7 Synthesis of 2-(benzhydryloxy)isoindoline-1,3-dione PHTD from diphenyl methanol

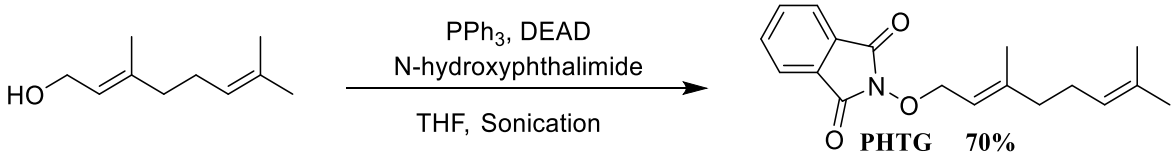
In a one-way round bottomed flask left in the oven overnight at 130°C, PPh_3 (2.2mmol, 0.577g), NHPI (2mmol, 0.336g) and diphenyl methanol (2mmol, 0.375g) were placed. The flask was purged with N_2 glove and syringe several times. Then, 1.2mL of dry THF were transferred into the reaction flask via cannula and the reaction mixture was placed in a sonicator as 40% DEAD dissolved in toluene (2.2mmol, 1mL) was added with a syringe drop-wise over 10 minutes. The reaction mixture was then allowed to react under sonication at 30-40°C until completion after 4 hours (followed by TLC using dichloromethane/ethyl acetate/n-hexane eluent in 2:2:3 or dichloromethane/n-hexane 1:1 ratio). The final product was concentrated in vacuum, dry loaded and purified by silica gel column chromatography (70-230 mesh) using only n-hexane at first and gradually increasing the polarity up until 80:20 n-hexane/ethyl acetate to afford the corresponding N-alkoxy phthalimide PHTD as a white powder in 51% yield (Scheme 8). **Chemical Shifts: ^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.63ppm (q, 1H, Ar-H), 7.56ppm (q, 1H, Ar-H), 7.46ppm (d, 2H, Ar-H), 7.25ppm (m, 8H, Ar-H), 7.17ppm (d, 2H, Ar-H), 6.44ppm (s, 1H, Ar-CHO-Ar). **^{13}C-NMR** (300 MHz, $CDCl_3$) δ 164.23ppm (C=O), 144.39ppm (Ar), 138.36ppm (Ar), 134.84ppm (Ar), 129.25ppm (Ar), 129.02ppm (Ar), 128.87ppm (Ar), 128.08ppm (Ar), 127.08ppm (Ar), 123.91ppm (Ar), 90.17ppm (Ar-C-O). **M.p:** 152-154°C



Scheme 8. Synthesis of 2-(benzhydryloxy)isoindoline-1,3-dione PHTD from diphenyl methanol.

1.6.8 Synthesis of (E)-2-((3,7-dimethylocta-2,6-dien-1-yl)oxy)isoindoline-1,3-dione PHTG from geraniol

In a one-way round bottomed flask left in the oven overnight at 130°C, PPh_3 (2.2mmol, 0.577g), NHPI (2mmol, 0.336g) and geraniol (2mmol, 0.36mL) were placed. The flask was purged with N_2 glove and syringe several times. Then, 1.2mL of dry THF were transferred into the reaction flask via cannula and the reaction mixture was placed in a sonicator as 40% DEAD dissolved in toluene (2.2mmol, 1mL) was added with a syringe drop-wise over 10 minutes. The reaction mixture was then allowed to react under sonication at 30-40°C until completion after 4 hours (followed by TLC using dichloromethane/ethyl Acetate/n-hexane eluent in 2:2:3 or dichloromethane/n-hexane 1:1 ratio). The final product was concentrated in vacuum, dry loaded and purified by silica gel column chromatography (70-230 mesh) using only n-hexane at first and gradually increasing the polarity until 80:20 n-hexane/ethyl acetate to afford the corresponding N-alkoxy phthalimide PHTG as a white powder in 70% yield (Scheme 9). **Chemical Shifts: ^{1}H-NMR** (500 MHz, CDCl3) δ 7.81ppm (q, 2H, Ar-H), 7.72ppm (q, 2H, Ar-H), 5.52ppm (t, 1H, O(CH_2)C**H**=C), 5.03ppm (s, 1H, $(CH2)_2$C**H**=C(CH_3)$_2$), 4.73ppm (d, 2H,OC**H**$_2$), 2.03ppm (s, 4H, (C**H$_2$**)$_2$), 1.71ppm (s,3H, CH_3), 1.63ppm (s,3H, CH_3), 1.56ppm (s,3H, CH_3). **^{13}C-NMR** (300 MHz, $CDCl_3$) δ 163.51ppm (C=O), 146.68ppm (CH=**C**(CH_3)(CH_2)), 134.06ppm (Ar), 131.60ppm (CH=**C**(CH_3)$_2$), 128.65ppm (Ar), 123.29ppm (CH_2**C**H=), 123.08ppm (Ar), 116.44ppm (O-CH_2**C**H=), 73.65ppm (O-**C**H_2), 39.34ppm (=(CH_3)C**C**H_2CH_2), 25.94ppm (CH_2**C**H_2CH=), 25.31ppm (CH_3),17.33ppm (CH_3),16.24ppm (CH_3)**.**
M.p: 80-82°C



Scheme 9. Synthesis of (E)-2-((3,7-dimethylocta-2,6-dien-1-yl)oxy)isoindoline-1,3-dione PHTG from geraniol.

1.7.Electrochemical Experiments

1.7.1 Cyclic Voltammetry electrodes cleaning

Ag/Ag^+ reference electrode **(Fig. 1)** in DCM was washed with Acetonitrile/DMF and dried carefully with paper towel before every measurement. After the experiment it was washed with deionized water, methanol and acetone and carefully dried with paper towel before stored. Stainless Steel strip counter electrode was washed with Acetone and dried with a hair dryer prior to every measurement. After the experiment it was washed with Deionized water and Acetone before stored. Glassy Carbon working electrode was polished prior to every measurement with polish cloth, drops of water and alumina polishing powder 0.5μm and 0.05 μm successively. After the experiment it was washed with deionized water and acetone.

Figure 1. Ag/Ag^+ reference electrode used for cyclic voltammetry and electrolysis experiments.

1.7.2 General procedure for determination of electrochemical window measurement

In a thermostated heart-shaped electrochemical cell 10mL of a 0.1M TBAP in ACN (DMF) solution was added (Fig. 2). Three electrodes were dipped in solution and properly accommodated: Glassy Carbon (W.E.), Stainless Steel (C.E.) and Ag/Ag^+ (R.E.). The temperature was kept at 20°C and purged with N_2 for 10 minutes. Cyclic Voltammetry experiment was carried out at 100mV/s using a potentiostat. Upper and lower vertex were progressively increased until showing currents (i) in the range of 0.01-0.1mA.

1.8. General procedure for determination of the reduction potentials

In a thermostated heart-shaped electrochemical cell 10mL of a 0.1M TBAP and 5mM of the corresponding analyte in ACN (DMF) solution was added (Fig. 2). Three electrodes were dipped in solution and properly accommodated: Glassy Carbon (W.E.), Stainless Steel (C.E.) and Ag/Ag^+ (R.E.). The temperature was kept at 20°C and purged with N_2 for 10 minutes. Cyclic Voltammetry experiment was carried out at 100mV/s along the entire electrochemical window previously determined in the two mediums, using a potentiostat.

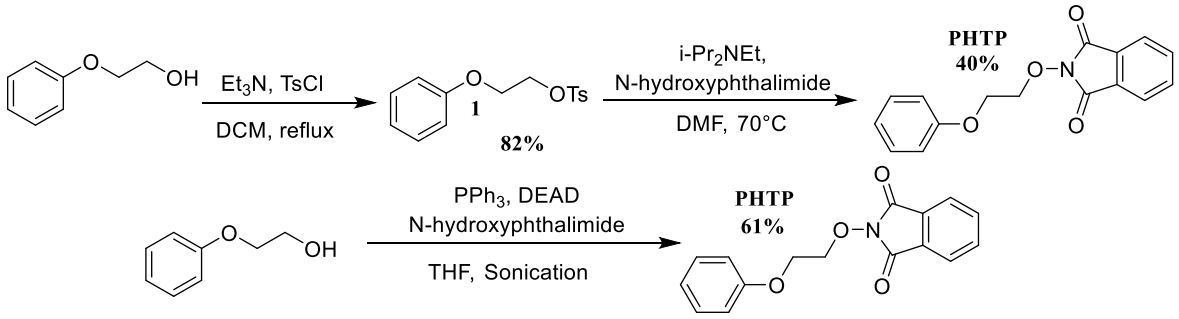
Figure 2. 15mL thermostated heart-shaped electrochemical cell used for Cyclic Voltammetry.

CHAPTER III: Results and Discussion

1.9.Organic synthesis

1.9.1 Synthesis of PHTP 2-(2-phenoxyethoxy)isoindoline-1,3-dione

The synthesis of PHTP over two steps afforded the N-alkoxy phthalimides in an overall yield of 33% (82% and 40%, in two steps). However, initial attempts of the tosylation of alcohol at room temperature afforded the tosylate at significantly lower yields (~60%, not reported in this work). Mitsunobu reaction under sonication, in the other hand, afforded the N-alkoxy phthalimide in 61% yield in straightforward manner after 4h (Scheme 10). The authenticity of the product is confirmed by ^{1}H-NMR, ^{13}C-NMR and IR spectroscopies.



Scheme 10. Synthetic routes followed for the obtention of PHTP.

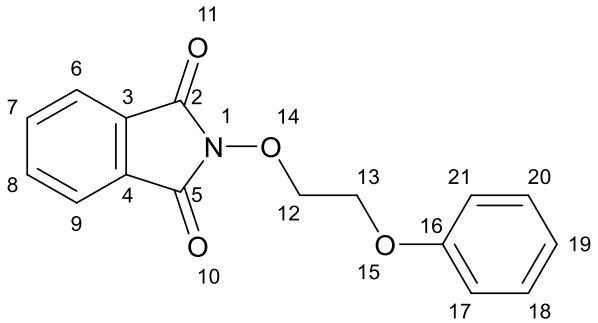


Figure 3 shows the ^{1}H-NMR spectra of PHTF. Herein, the phthalimide portion of the molecule is confirmed as two sets of quadruplets integrating for two protons each shows up with the highest chemical shifts. Next, the protons of the other aromatic portion arise as three signals in the order meta-, para-, and ortho- , splitting accordingly to the expected count of neighbor protons and integrating nicely. The spectrum is completed with four methylene protons belonging to carbons 12 and 13.

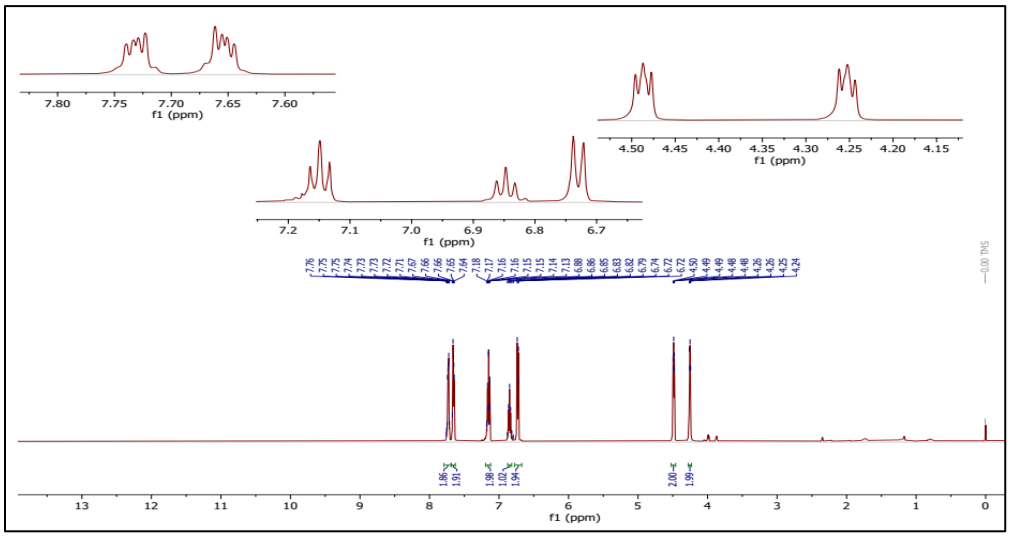


Figure 3. ^{1}H-NMR spectra of PHTP (500 MHz, $CDCl_3$)

In the ^{13}C-NMR spectrum (Fig. 4), carbonyl carbons 2 and 5 are assigned the highest chemical shift of this spectra at 163.47ppm, followed by phenolic carbon 16 located at 158.32ppm. Next, aromatic signals are present in the 135-114ppm range, and finally two signals can be seen at 76.15ppm (not to be confused with chloroform peaks) and 66.21ppm, which are assigned to Carbon 12 and 13, respectively.

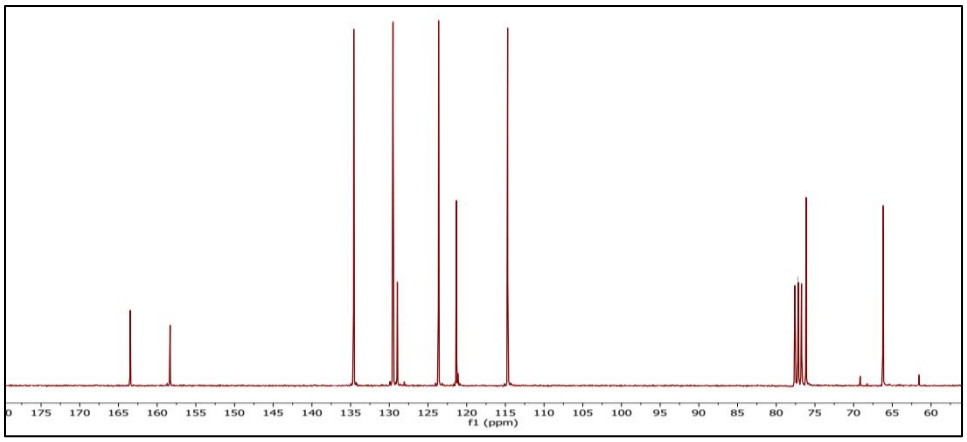


Figure 4. ^{13}C-NMR spectra of PHTP (300 MHz, $CDCl_3$).

In the IR spectrum presented in Figure 5, the following signals can be seen. C=O functional group is present as a strong sharp signal at 1718cm^{-1}. C-N bond of aromatic amine (stretching) present at 1381cm^{-1}in the phthalimide section. The aromaticity of the structure is confirmed by typical signals such as: Stretching sp^2 C-H signals from aromatic rings at 3067cm^{-1} and 3044cm^{-1}, and C=C bond stretching appears as strong peaks at 1600cm^{-1} and 1494cm^{-1}. Additional, other signals tell about the substitution of the aromatic rings : sp^2 C-H ring bending are assigned as strong sharp signals at 692cm^{-1} for disubstituted pattern from the phthalimide ring, and at 755cm^{-1} for monosubstituted pattern from the other ring (a second peak is missing for this feature and might be obscured by that of sp^2 C-H disubst.) An overtone peak can be seen at 1791cm^{-1}, but other peaks obscured by carbonyl peak. sp^3 C-H appear at 2962cm^{-1}, 2927cm^{-1} and 2874cm^{-1}(stretching) and 1469cm^{-1} (methylene scissoring bending).

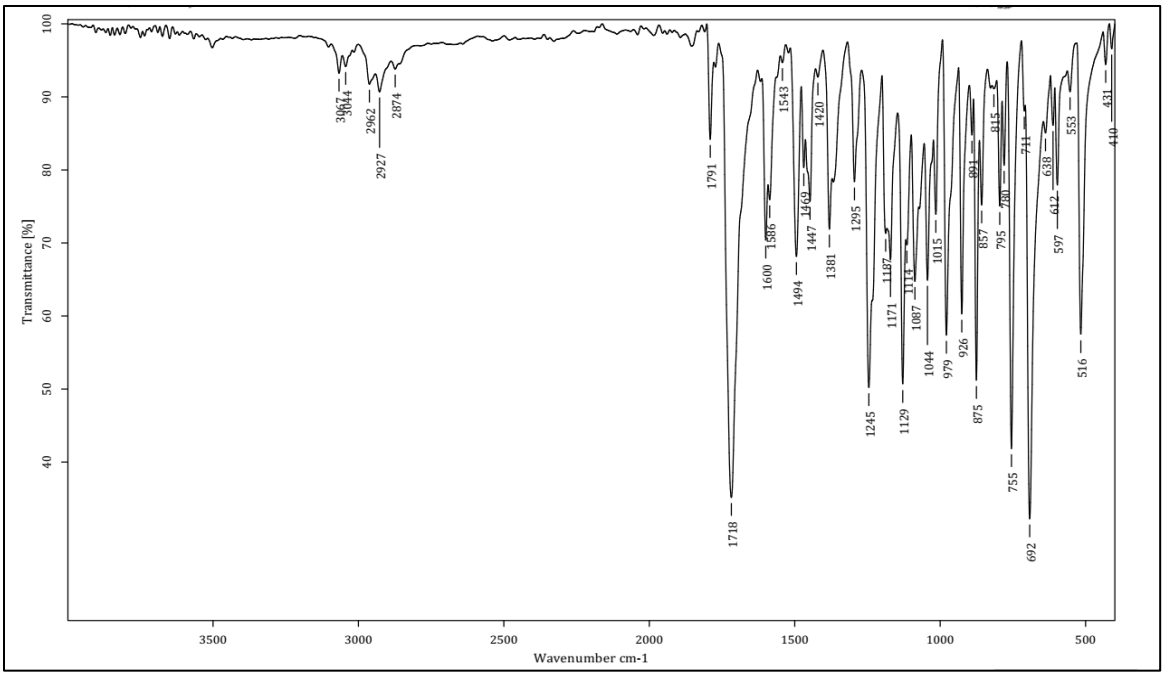
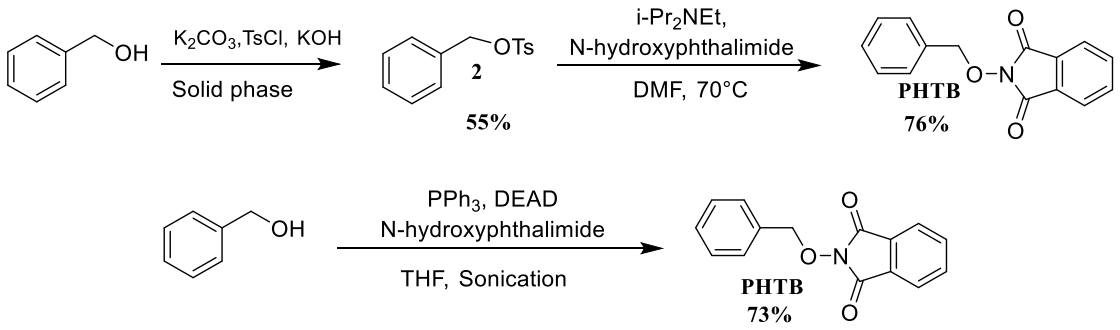


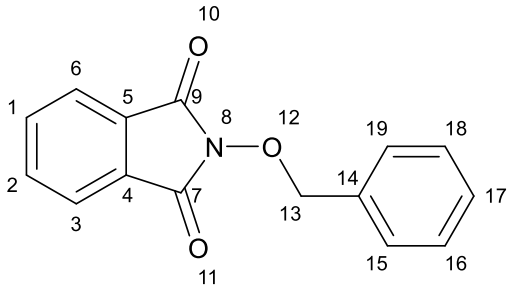
Figure 5. FT-IR spectra of PHTP.

1.9.2 Synthesis of PHTB 2-(benzyloxy)isoindoline-1,3-dione

Synthesis of PHTB via tosylation in DCM was unsuccessful. Subsequently, solid phase synthesis of the tosylate was considered and worked better as it afforded the corresponding tosylate in 55% yield after crystallization. .The removal of the tosyl group via nucleophilic displacement with N-hydroxyphthalimide in DMF resulted in 76% yield (and finally 42%, overall). Alternatively, Mitsunobu reaction afforded the product with 73% yield after 4.5 hours of reaction (Scheme 11). The authenticity of the product is confirmed by ^{1}H-NMR, ^{13}C-NMR and IR spectroscopies.



Scheme 11. Synthetic routes followed for the obtention of PHTB.



In this ^{1}H-NMR spectrum (Fig. 6), the phthalimide portion is confirmed again as two sets of quadruplets integrating for two protons each shows up with the highest chemical shifts. Next, the protons of the other aromatic ring appear. First, two protons in the *meta*- position at 7.45ppm and then two overlapped signals that integrates for three protons (those in *para*- and *ortho*- position,). The methylene protons on carbon 13 appear as the strongest signal at 5.12ppm with integral consistent to the expected proton count.

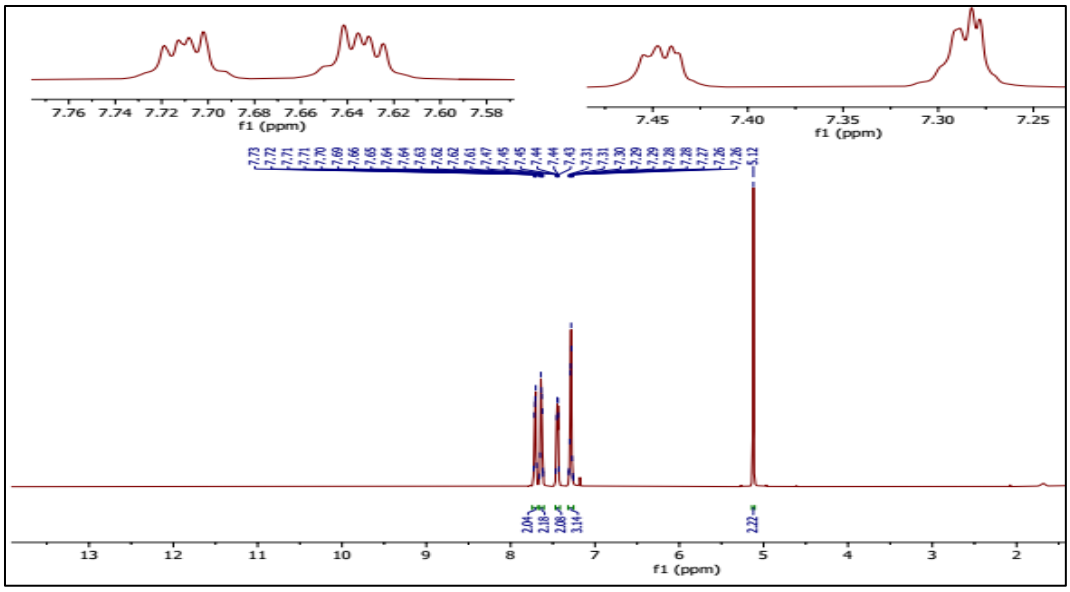


Figure 6. ^{1}H-NMR spectra of PHTB (500 MHz, $CDCl_3$).

PHTB structure is also confirmed by ^{13}C-NMR spectra (Fig. 7), where carbonyl carbons 7 and 9 are assigned to 163.97ppm. Next, a region of aromatic signals shows ups leaded by carbon 14 at 134.93ppm and extending up to 123ppm. Carbon 13 shows up at 80.36ppm sufficiently far from chloroform peaks.

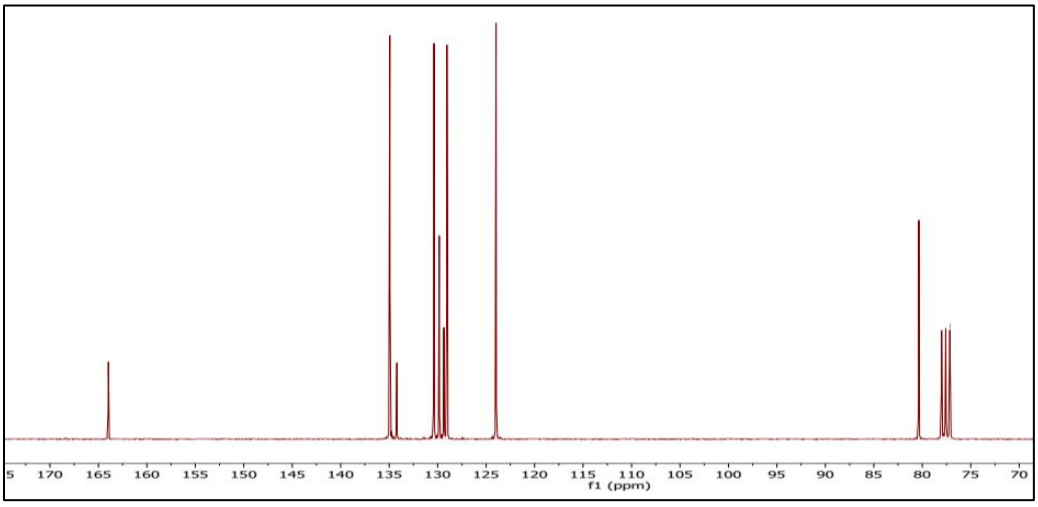


Figure 7. ^{13}C-NMR spectra of PHTB (300 MHz, $CDCl_3$).

In the IR spectrum presented in Figure 8, the following signals can be seen. Carbonyl C=O is present as a strong sharp signal at 1725cm^{-1}. C-N bond of aromatic amine (stretching) present at 1378cm^{-1}in the phthalimide section. Aromatic features such as: sp^2 stretching C-H signals from aromatic rings at 3076cm^{-1} and 3037cm^{-1} and C=C bond stretching yields a pair of peaks at 1605cm^{-1} (w) and 1461cm^{-1} (m). Additional, other signals tell about the substitution of the aromatic rings: sp^2 C-H ring bending appears as strong sharp signals at 696cm^{-1} for the disubstituted pattern and at 761cm^{-1} for a monosubstituted pattern (a second peak missing for this feature and might be obscured by that of sp^2 C-H disubst.) An overtone peak can be seen at 1787cm^{-1}, but C=O seems to obscure the missing overtones. sp^3 C-H appear at 2957cm^{-1} and 2887cm^{-1} (stretching) and 1461cm^{-1} (methylene scissoring bending).

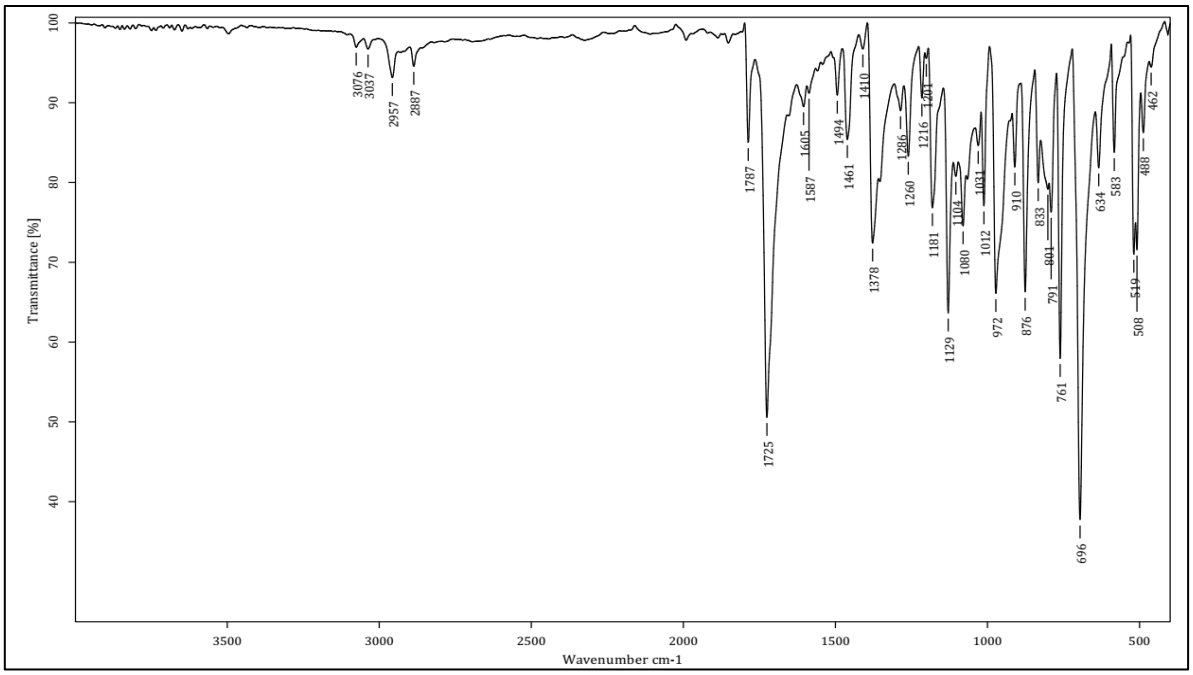
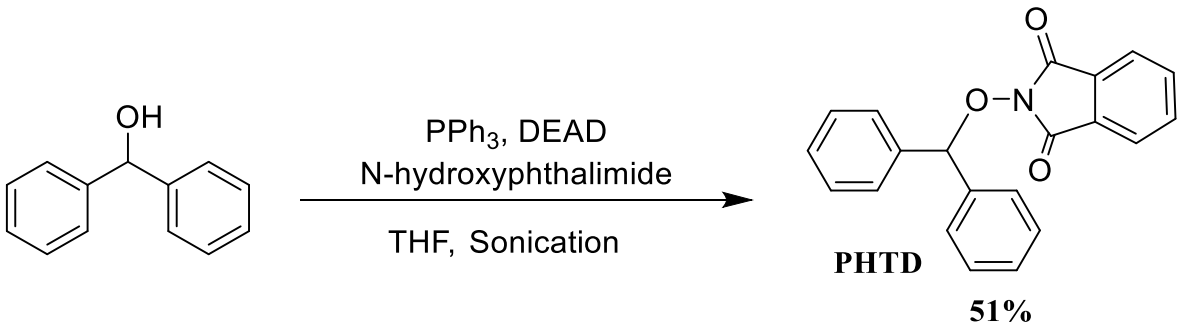


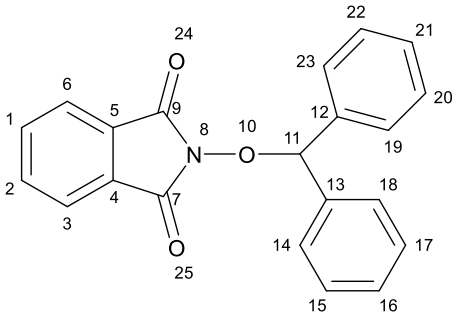
Figure 8. FT-IR spectra of PHTB.

1.9.3 Synthesis of PHTD 2-(benzhydryloxy)isoindoline-1,3-dione

PHTD was obtained in straightforward manner using Mitsunobu conditions for a final yield of 51% after column chromatography (Scheme 12). The authenticity of the product is confirmed by ^{1}H-NMR, ^{13}C-NMR and IR spectroscopies as shown below.



Scheme 12. Synthetic route followed for the obtention of PHTD.



In Figure 9, the ^{1}H-NMR spectra of PHTD is presented. Here, the phthalimide portion of the molecule seems to split signals differently as PHTF and PHTB. Here two protons appear as two quadruplets and are assigned to be bound to carbon 1 and 2. Next, a doublet that integrates for two protons are assigned as being connected to carbon 3 and 6, since they only might be observing one proton each: proton of carbon 1 (2) observing that proton of carbon 6 (3), respectively. Next, a multiplet integrating for eight protons are assigned to

those aromatic protons located on *ortho*- and *meta*- positions of the two aromatic rings of the diphenyl methoxy substituent. The aromatic region is completed with those atoms on *para*- position. Finally, the proton located on the methine carbon 11 shows up at 6.44ppm.

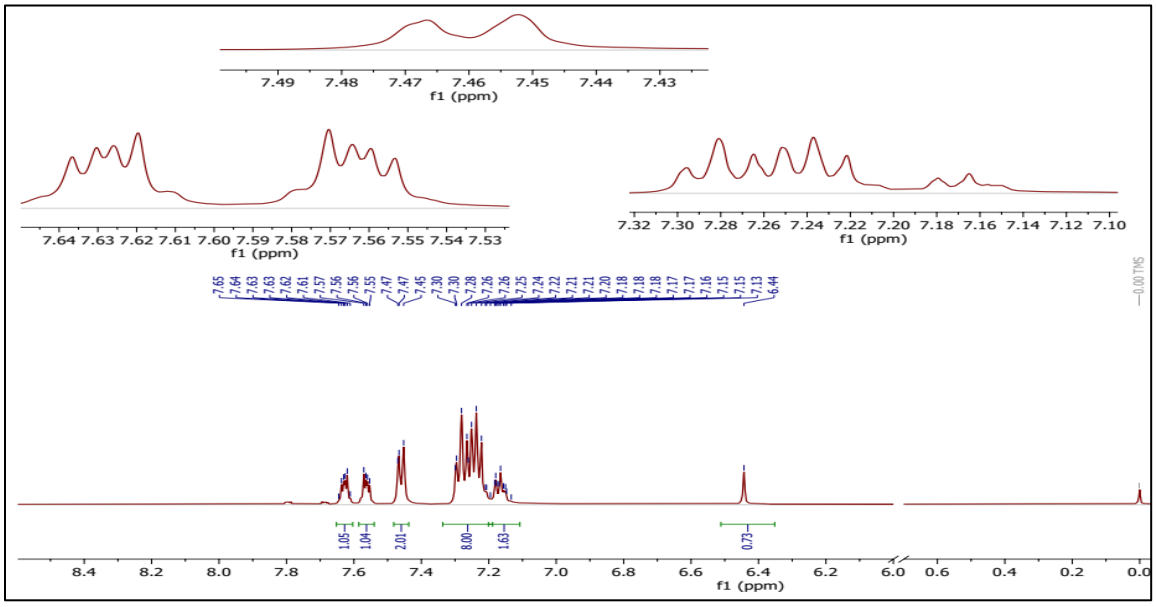


Figure 9. ^{1}H-NMR spectra of PHTD (500 MHz, $CDCl_3$).

In the ^{13}C-NMR (Fig 10), carbonyl signal shows up at 164.23ppm accounting from carbon 7 and 9. At 144ppm the aromatic section starts leaded by those of the phenolic carbons 12 and 13, and extends up to 123ppm. Finally, carbon 11 appears fairly far at 90.17ppm.

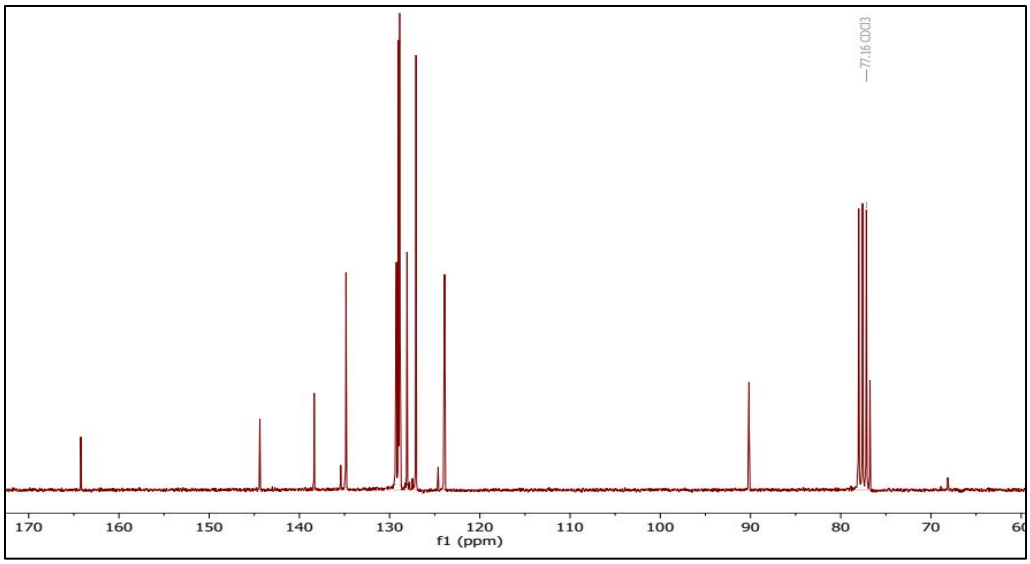


Figure 10. ^{13}C-NMR spectra of PHTD (300 MHz, $CDCl_3$).

In the IR spectrum presented in Figure 11, the following signals can be seen. C=O functional group is present as a strong sharp signal at 1722cm^{-1}. C-N bond of aromatic amine (stretching) present at 1370cm^{-1}in the phthalimide section. Aromaticity is confirmed by: peaks at 3086cm^{-1}, 3062cm^{-1} and 3029cm^{-1} coming from sp^2 C-H aromatic stretching, and C=C bond stretching gives a pair of peaks at 1604cm^{-1} and 1494cm^{-1}. The substitution features can be observed in: sp^2 C-H ring bending appears as strong sharp signals at 694cm^{-1} for the disubstituted pattern and a pair of peaks at 749cm^{-1} and 761cm^{-1} (out-of-plane) for monosubstituted pattern. C-H overtones located at 1789cm^{-1}, 1811cm^{-1}. It is noteworthy that unlike PHTF, PHTB and PHTG, this structure only possesses one methine C-H alkyl bond, thus alkyl C-H stretch are not visible at wavenumbers slightly smaller than 3000cm^{-1} and cannot be assigned here.

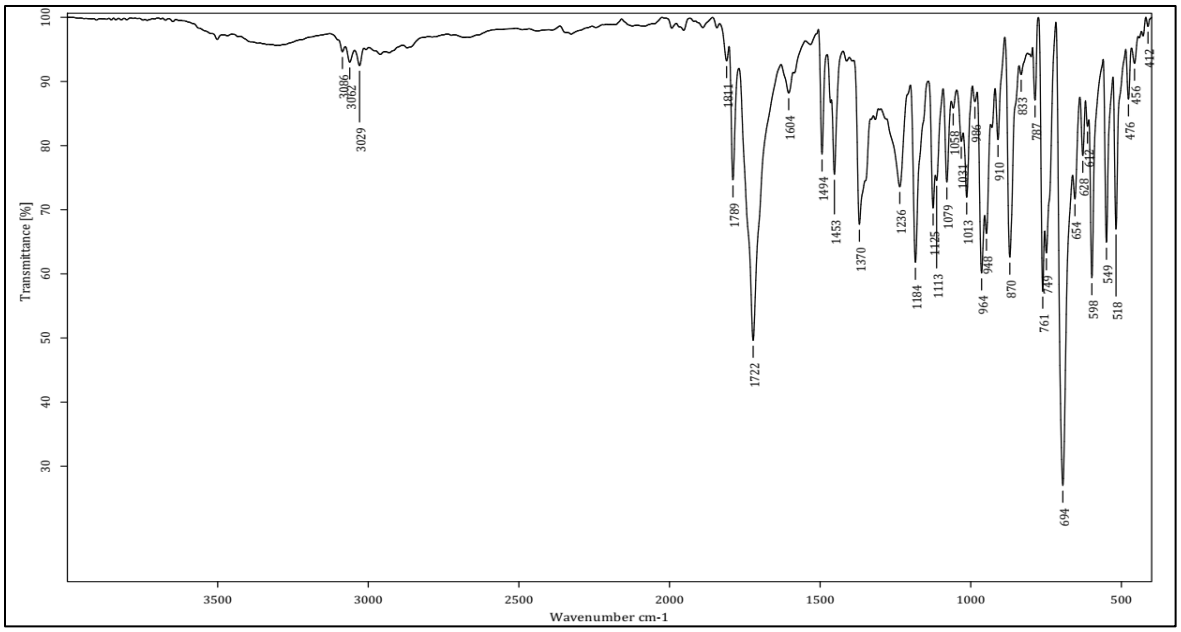
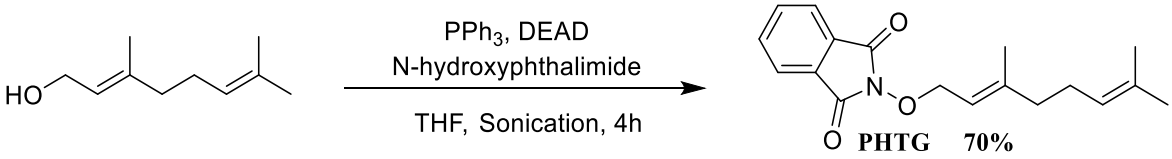


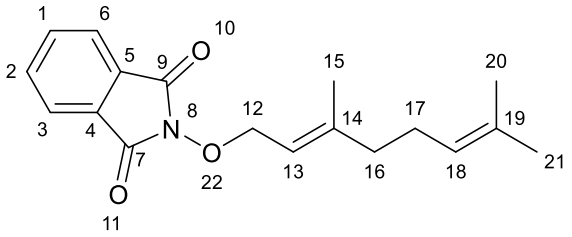
Figure 11. FT-IR spectra of PHTD.

1.9.4 Synthesis of PHTG (E)-2-((3,7-dimethylocta-2,6-dien-1-yl)oxy)isoindoline-1,3-dione

The tosylation of geraniol was attempted in conditions identical to those used for 2-phenoxyethanol and benzyl alcohol. However the reaction did not proceed. The solid phase approach was carried out identically as described for PHTB, however ^{1}H-NMR showed only trace signals of the expected structure showing that this route was unpractical. Finally, the synthesis was achieved under Mitsunobu conditions, which yielded the desired N-alkoxy phthalimide in 70% yield (Scheme 13). As a comment, Mitsunobu conditions on a 70/23 (E/Z) isomeric mixture of geraniol/nerol (**non-commercial**) as starting material yielded 64% of the N-alkoxy phthalimides (spectroscopic information is not reported in this work).



Scheme 13. Synthetic route followed for the obtention of PHTG



In the ^{1}H-NMR spectrum of PHTG (Fig. 12), the phthalimide section splits as two quadruplets with the highest chemical shift and are assigned to be bound to carbon 1, 2, 3 and 6. Next, two C-sp^{2} (H) appear: first, a multiplet located on carbon 18 (5.03ppm) and last a triplet located on carbon 13 (5.52ppm), observing those two protons of carbon 12. In the other hand, the two protons of the methylene carbon 12 (4.73ppm) split as a doublet since they observe that one proton on carbon 13. The four protons of the methylene carbons 16 and 17 are integrated as a single signal. However, if that one signal is zoomed in, it can be seen that it consists of two overlapped signals. Finally, three singlets integrating for three protons each appear in the C(sp^{3}) region, and are assigned to these protons expected on carbons 21, 20 and 15.

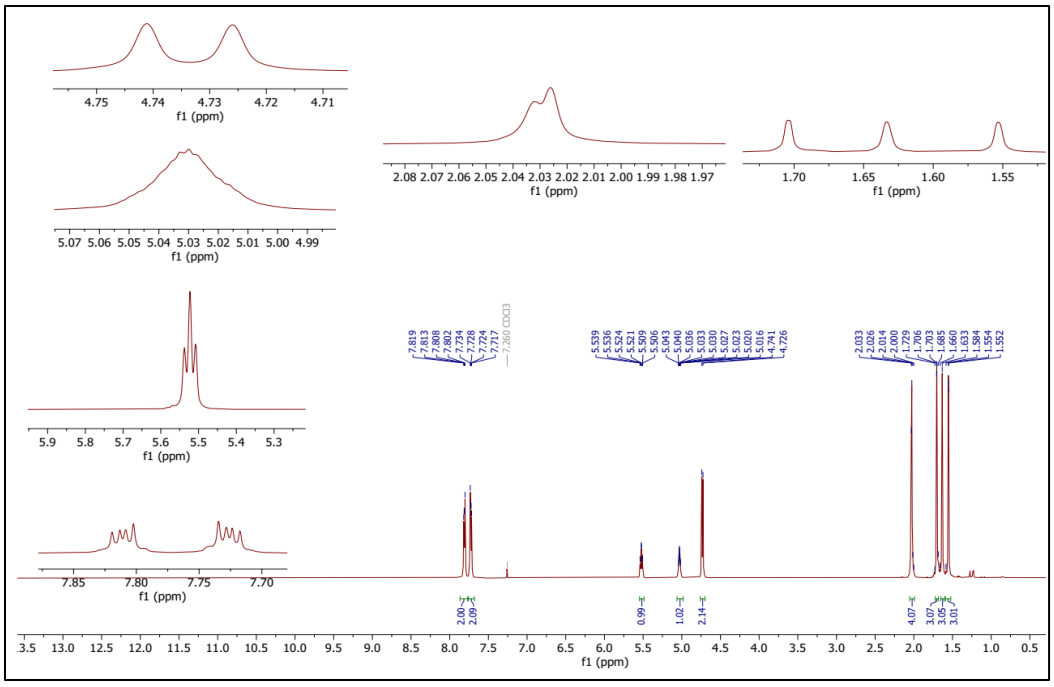


Figure 12 . ^{1}H-NMR spectra of PHTG (500 MHz, $CDCl_3$).

In the ^{13}C-NMR experiment (Fig. 13), carbonyl signals arise at 163.51ppm from carbon 9 and 7. Next, C-sp^2 signals can be seen arising from the aromatic ring of the phthalimide and the double bonded carbons from the terpenoid alkylic chain in the 147-116ppm range. Carbon 21 signal arises next to chloroform peaks at 73.64ppm, followed by five C-sp^3 methylene (two, from carbon 16 and 17) and methyl (three, from carbon 21, 20 and 15) signals in the 40-16ppm range.

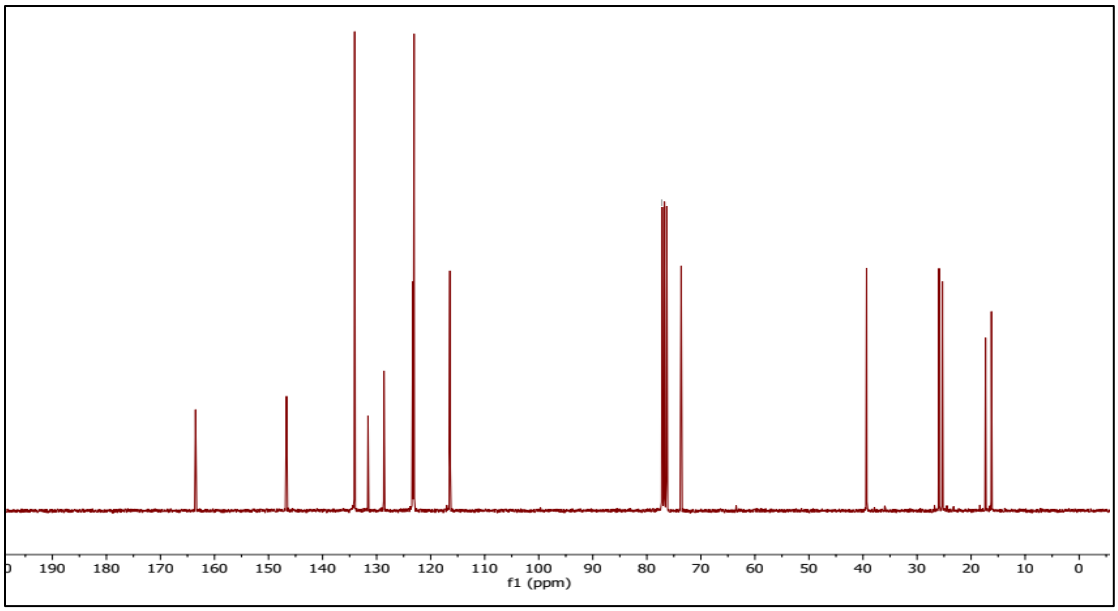


Figure 13. ^{13}C-NMR spectra of PHTG (300 MHz, $CDCl_3$).

In the IR spectrum presented in Figure 14, the following signals can be seen. Carbonyl C=O is present as a strong sharp signal at 1716cm^{-1}. C-N bond of aromatic amine (stretching) present at 1357cm^{-1}in the phthalimide section. Aromaticity is confirmed with: sp^2 stretching C-H signals from aromatic rings at 3095cm^{-1}, 3032cm^{-1} and 3029cm^{-1}. Aromatic C=C bond stretching signals at 1609cm^{-1} and 1470cm^{-1}. Substitution : sp^2 C-H bending for a disubstituted ring (from the phthalimide aromatic ring) appears as a strong sharp signal at 699cm^{-1} and overtone for the ortho substitution pattern at 1784cm^{-1} and 1843cm^{-1}. The existence of several C-H bonds is confirmed with four peaks at 2973cm^{-1}, 2911cm^{-1}, 2881cm^{-1}, and 2854cm^{-1} in the zone of alkyl stretching immediately under 3000cm^{-1}. Methyl C-H bending sym. (germ-dimethyl) splits into two bands at 1370cm^{-1} and 1395cm^{-1}, and asymmetric methyl C-H bending at 1447cm^{-1}. Methylene sp^3 C-H bending 1462cm^{-1}. CH_2 bending rocking 713cm^{-1} (long-chain band). C=C stretching for 1,1-disubstituted alkene at1661cm^{-1}. At 835cm^{-1} C-H out-of-plane bending alkene trisubstituted.

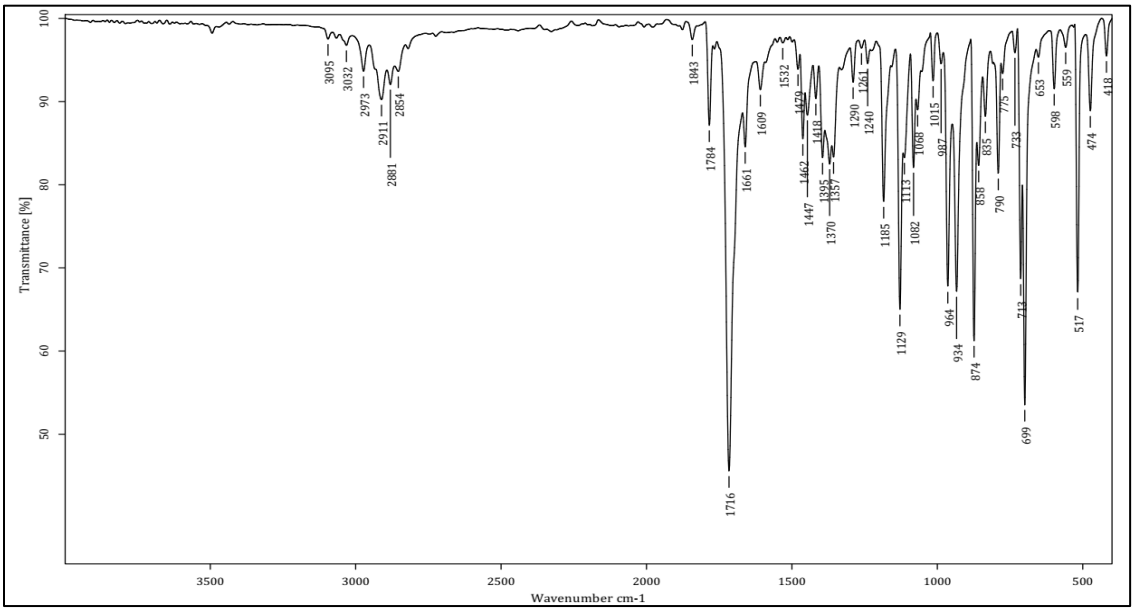


Figure 14. FT-IR spectra of PHTG.

Despite the times of reaction under Mitsunobu conditions are not very short in our results; they are neither longer (~4 hours or less). However, the use of sonication certainly has been shown to maintain the time of reaction in the range of a few hours in this work, and even up to minute scale through the literature.[21,22] Furthermore, considering that we have worked with alcohols (pKa > 13.5 in our substrates) as starting materials it must be noted that their pKa is not low enough (should be less than 12) to enhance the protonation of the PPh_3-DEAD adduct and promote the reaction towards the coupled product (see appendix 1). Indeed, the coupling of a few more acidic carbohydrates (pKa ~11) to NHPI under Mitsunobu conditions was reported to yield from moderate to excellent yields (54-97%) in one hour using a significant excess of reagents in regards to the substrate (1:4).[23]

When comparing our results to those reported by Zhang et al.[10] it can be seen that the yields are disperse (30-94%) when coupling NHPI to primary or secondary alcohols, so that, the main factor determining success must be pKa and not the number of substituents itself,

unless substituents influence positively pKa. Our results show that diphenyl methanol coupling to NHPI yielded the less (51%) against the other three couplings despite this one is the most acidic (pKa 13.5) of the set. The bulkiness of the phenyl groups might then be playing a role in the kinetics, hindering the alcohol from undergoing bimolecular nucleophilic substitution with ease (see appendix 1). In the other hand, the primary alcohols geraniol (70%), benzyl alcohol (73%) and 2-phenoxyethanol (61%) did it better despite having greater pKa in comparison to diphenyl methanol (pKa 16.3, 15.4 and 15.1 respectively, against 13.5). It could be argued that beyond the pKa ~12 threshold, the pKa is no longer a determining factor but steric hindrance could be. More data must be collected to clarify these trends.

1.10. Electrochemical experiments

1.10.1 Electrochemical Windows in ACN 0.1M TBAP and DMF 0.1M TBAP

Electrochemical windows were measured in two mediums: ACN and DMF, keeping the other variables constant (temperature at 20°C, 100mV/s, 0.1M TBAP). In particular, ACN medium yields a wide and quite symmetrical ~4 volts electrochemical window (~-2V to ~+2V) at a cut-off of 0.01mA (Fig. 15 left). In the other hand, DMF medium yields a slightly less (~3.8V) non-symmetrical but still wide electrochemical window (~-2.5V to ~+1.3V) (Fig. 15 right)

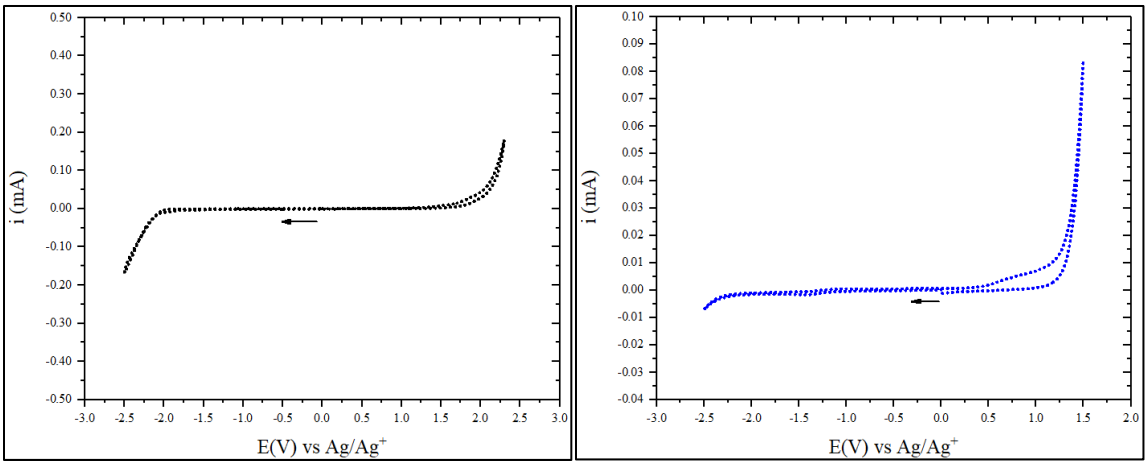


Figure 15. Electrochemical windows of ACN 0.1M TBAP at 20°C and 100mV/s (black dotted curve on the left) and DMF 0.1M TBAP at 20°C and 100mV/s (blue dotted curve on the right).

1.10.2 Cyclic Voltammetry of PHTP

PHTP N-alkoxy phthalimide cyclic voltammograms shows only one reduction peak corresponding to such substrate in both experiments (**I-RA** at -1748.66mV and **I-RD** at -1766.97mV). However, in the experiment carried out in ACN medium a complementary peak appears (**I-OA** at +1500mV) which might be either informing about the reversible oxidation of the electro-generated species produced in the reduction sweep (Fig. 16 left). However, the height of the oxidation peak (**I-OA**) accounts for a relatively high concentration, thus being more likely to assume it is just the starting material being oxidized for the first time. In the DMF medium this cannot be seen since the electrochemical window ends at similar potentials and might be obscured (Fig. 16 right). It is worth mentioning that electrolysis in ACN must be performed in a divided cell but not necessarily if performed in DMF. The first Reduction peak potentials do not differ significantly in these medium.

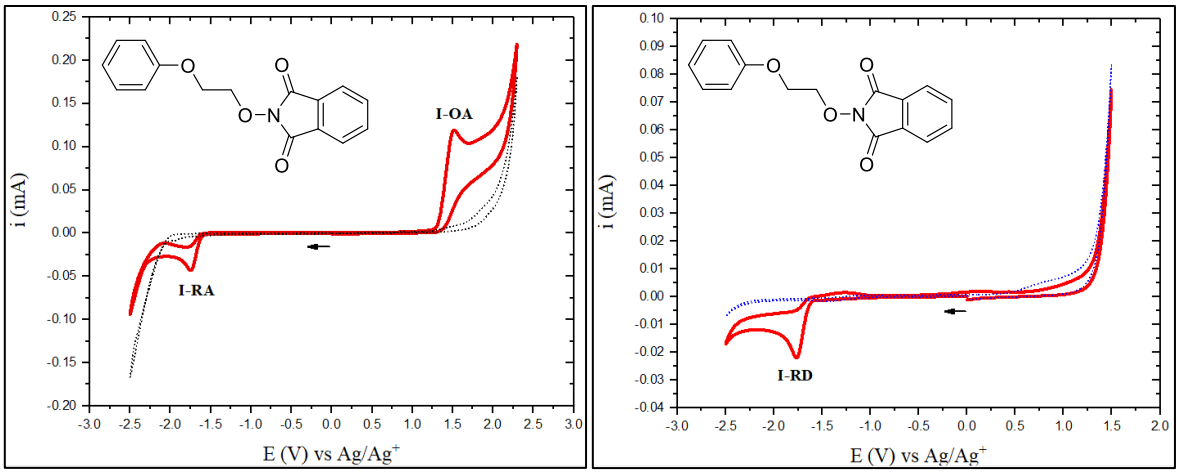


Figure 16. PHT**P** (2-(2-phenoxyethoxy)isoindoline-1,3-dione) in ACN (left) and DMF (right) 0.1M TBAP at 20°C and 100mV/s. Peaks of reduction at -1748.66mV and -1766.97mV, respectively.

1.10.3 Cyclic voltammetry of PHTB

PHTB N-alkoxy phthalimide cyclic voltammogram in ACN yields a single reduction peak **(I-RA)** in the whole experiment and no clue of any complementary oxidation along the voltammetry range (Fig. 17 left). However, in DMF the scenario is more complex since the benzylic derivative yields three reduction peaks (**I-III-RD**, at -1730mV, -1900mV, and -2290mV, respectively) before reaching the end of the electrochemical window at about -2.5V. In the other hand, two weak signals (**I-OD** and **II-OD** at -1280mV and +70mV) can be seen in the oxidation sweep (Fig. 17 right). The first reduction peak potentials do not differ significantly in these medium.

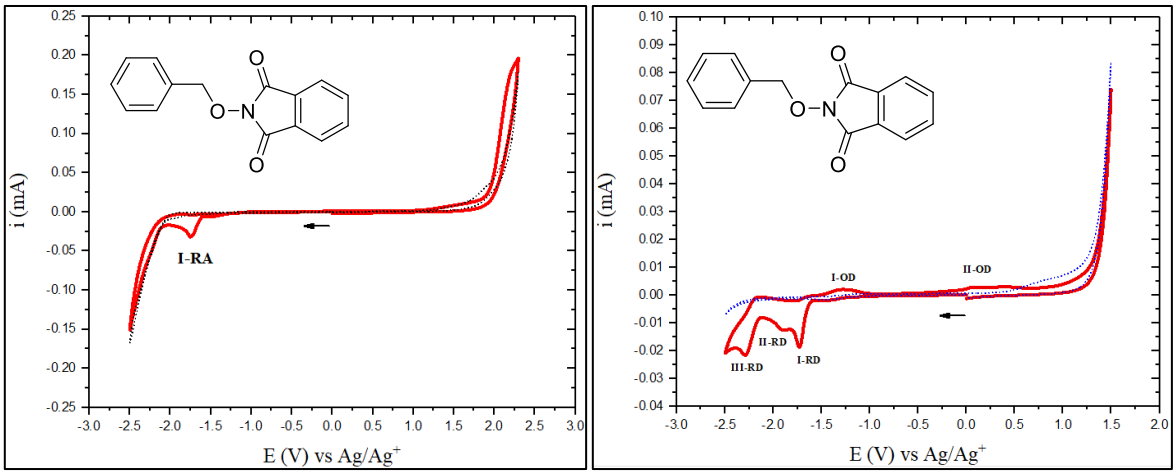


Figure 17. PHT**B** (2-(benzyloxy)isoindoline-1,3-dione) in ACN (left) and DMF (right) 0.1M TBAP at 20°C and 100mV/s. Peaks of reduction at -1751.10mV and -1730.96mV, respectively.

1.10.4 Cyclic voltammetry of PHTD

PHTD cyclic voltammogram in ACN shows a reduction peak (**I-RA** at -1678.16mV) and a shoulder (**II-RA** at -2090mV) on the cathodic sweep and one shoulder (**I-OA** at +1820mV) on the anodic one, as well (Fig. 18 left). In the other hand, the experiment carried out in DMF yields a more complex scenario along the reduction sweep (Fig. 18 right). Three reduction peaks (**I-III-RD** at -1701mV, -1900mV and -2180mV, respectively) and one oxidation peak (**I-OD** at -2100mV), complementary to the third reduction, are noted here. The reduction peak potentials do not differ significantly. Additionally it should be noted that electrolysis in ACN must be performed in a divided cell but not necessarily if performed in DMF.

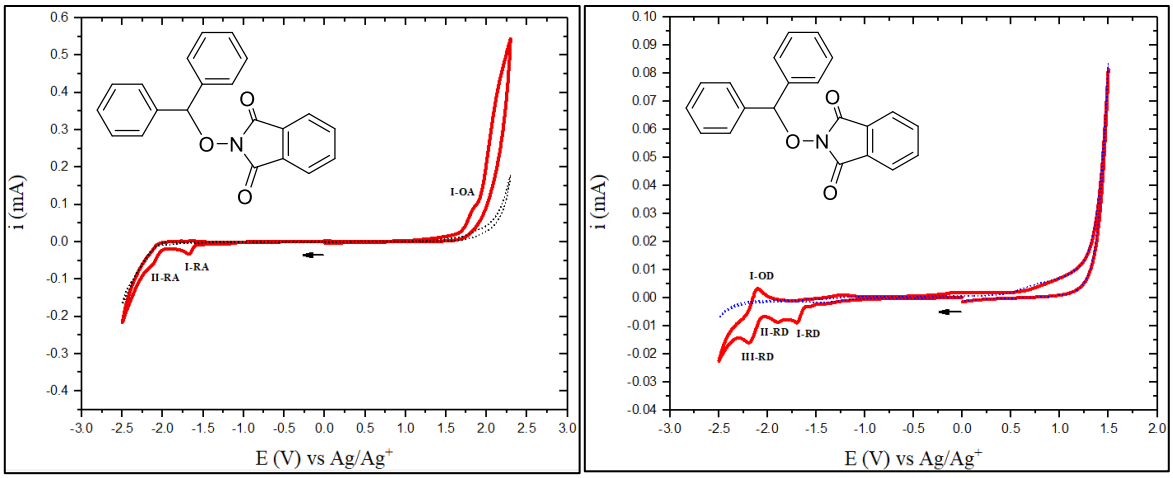


Figure 18. PHT**D** (2-(benzhydryloxy)isoindoline-1,3-dione) in ACN (left) and DMF (right) 0.1M TBAP at 20°C and 100mV/s. Peaks of reduction at -1678.16mV and -1701.97mV, respectively.

1.10.5 Cyclic voltammetry and bulk electrolysis of PHTG

PHTG N-alkoxy phthalimide derivative yields the following voltammograms. In the experiment run in ACN it can be seen a single peak **I-RA** along the reduction sweep at -1776mV, and a clearly visible oxidation peak **I-OA** at starting at about +1650mV and immediately a shoulder that is not well resolved due to the end of the electrochemical window (Fig. 19 left). In the other hand, the DMF experiment yields a prominent first reduction peak (**I-RD**) at -1784.67mV which turns into a region of constant current around 0.01mA after that reduction (Fig. 19 right). In the anodic sweep a little signal (**I-OD**) can be seen at potentials around -1670mV. Again, electrolysis in ACN must be performed in a divided cell but not necessarily if performed in DMF.

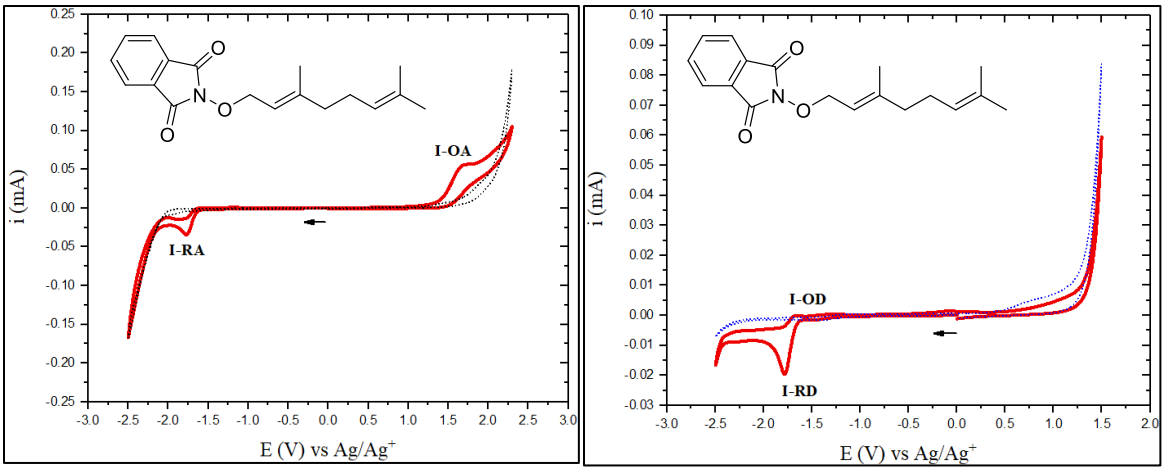


Figure 19. PHT**G** ((E)-2-((3,7-dimethylocta-2,6-dien-1-yl)oxy)isoindoline-1,3-dione) in ACN (left) and DMF (right) 0.1M TBAP at 20°C and 100mV/s. Peaks of reduction at -1776.12mV and -1784.67mV, respectively.

Remarkably, if compared to the obtained cathodic section in DMF, the outcome of the cathodic section of all substrates looks similar (in the case of PHTP and PHTG) or even simpler (PHTB and PHTD) when measured in ACN. Recall that, some oxidation peaks might be obscured in DMF conditions by the premature end of the electrochemical window. At first glance, the electrochemical behavior of PHTB and PHTD in DMF show a visual similitude to what has been reported by Syroeshkin et al.[20] These authors use the same Benzyl N-alkoxy phthalimide PHTB and inform about four reduction peaks in the cathodic sweep, proposing that these peaks account for the reduction of N-alkoxy phthalimide, NHPI, benzaldehyde, and the second reduction of NHPI. However, our measurements were taken under similar but not identical conditions (solution volume 5mL greater, temperature 5°C cooler, stainless steel C.E instead of Pt wire and Ag/Ag^+ R.E instead of SCE). Their voltammetry shows four height increasing sharp signals that are contained in a nearly one-volt range. Our experiment, in the other hand, shows three sharp signals up to the end of the electrochemical window. Such range, from the first reduction potential to the end of the electrochemical window resembles less than 1 volt long, being that presumably we are missing one last peak at the expense of the end of the electrochemical window in such conditions, or it is overlapped with other peak. PHTD, likewise, shows three peaks but no comparison can be made since it has not been reported earlier to the date. Indeed, to the

best of our knowledge, this is the first time that the reduction potential of PHTD, PHTP and PHTD are reported.

Conclusions and Recommendations

1.11. Conclusions

- 2-(2-phenoxyethoxy)isoindoline-1,3-dione (PHTP) was successfully synthesized by two synthetic routes and its structure completely confirmed by spectroscopic techniques. Its first reduction potential was measured in ACN and DMF at 0.1M TBAP. The bulk electrolysis products were isolated but the majority did not weight enough for characterization. The spectroscopic information of those that weighted enough has not been obtained until the date of this work.

- (2-(benzyloxy)isoindoline-1,3-dione) (PHTB) was successfully synthesized by two synthetic routes and its structure completely confirmed by spectroscopic techniques. Its first reduction potential was measured in ACN and DMF at 0.1M TBAP. Four products were characterized after bulk electrolysis

- (2-(benzhydryloxy)isoindoline-1,3-dione) (PHTD) was successfully synthesized by one synthetic route and its structure completely confirmed by spectroscopic techniques. Its first reduction potential was measured in ACN and DMF at 0.1M TBAP. Two products were characterized after bulk electrolysis

- ((E)-2-((3,7-dimethylocta-2,6-dien-1-yl)oxy)isoindoline-1,3-dione) (PHTG) was successfully synthesized by one synthetic route and its structure completely confirmed by spectroscopic techniques. Its first reduction potential was measured in ACN and DMF at 0.1M TBAP. Two products were characterized after bulk electrolysis.

1.12. Outlook

Bulk electrolysis was conducted on each of the synthesized substrate. Despite these few results are presented here, it is important to remark that the experiments well carried out only one time thus are presented as an outlook but not as decisive results. Hopefully, this information will be enriched in the future for further reports.

1.12.1 Electrolysis electrodes cleaning

Ag/Ag^{+} reference electrode **(Fig. 1, see on CHAPTER II)** in DCM was washed with a few milliliters of ACN HPLC and pipette, and then dried carefully with paper towel before dip in solution. After the experiment it was again washed in ACN HPLC, dried carefully with paper towel before its storage. Platinum gauze counter electrode (Fig. 20) was dipped in deionized water several for several minutes and washed with acetone before its storage. Glassy carbon plate (Fig. 21) was washed with deionized water and acetone several times before its storage.

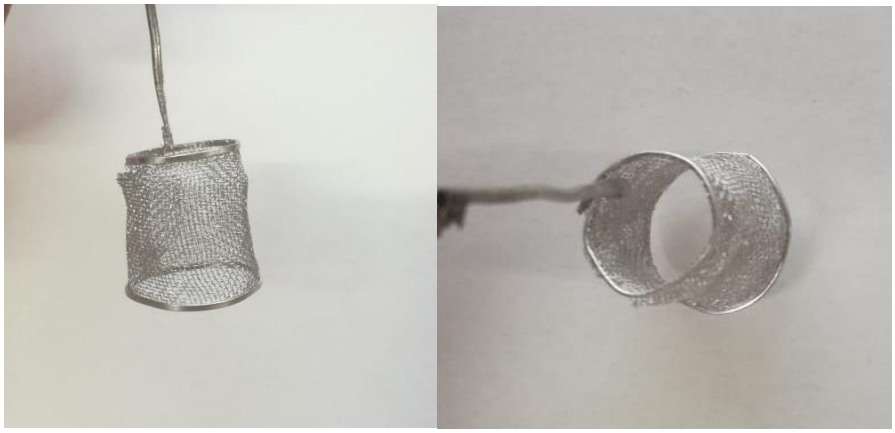


Figure 20. Pt gauze counter electrode used for electrolysis experiments

Figure 21. Glassy carbon plate electrode used for electrolysis experiments

1.12.2 General procedure for electrolysis

In a H-type cell divided with a porous membrane, 25mL solutions of 0.1M TBAP in acetonitrile were poured in each compartment (Fig. 22 and Fig. 23). Three electrodes were used: glassy carbon plate (W.E.), platinum gauze electrode (C.E) and Ag/Ag^{+} (R.E.). W.E and R.E were placed together in one compartment and C.E in the other one. Solutions of both compartments were purged with N_2 for 8-10 minutes each and immediately the system was put under N_2 atmosphere. Pre-electrolysis was carried out for 3 minutes at the chosen reduction potential for the electrolysis. Next, the analyte was added in the compartment containing W.E. and R.E. and allowed to achieve full solubility. Additional, 10mL extra of supporting electrolyte were prepared in case of analyte sticking to the walls of the cell. In such case a Pasteur pipette and a few mL of that solution was used to wash the walls and help the solids get to the electrolysis solution. Electrolysis was carried out at room temperature at the chosen reduction potential (About 100mV more reducing than the peak potential of reduction). The reaction was followed by TLC, coulombimetry and stopped after completion.

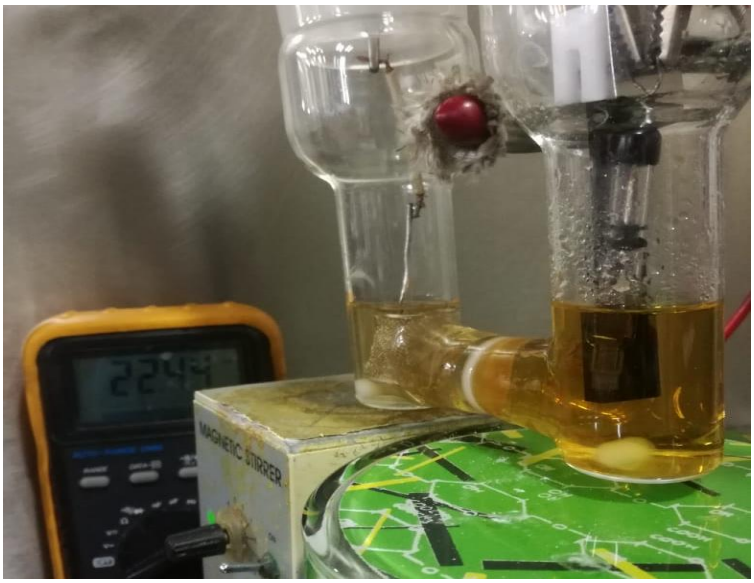


Figure 22. Close-up of the H-type divided cell during electrolysis. On the **closer** compartment the analyte being reduced and W.E and R.E dip in solution while adopting a deep yellow color. On the **farther** compartment the complementary oxidation reaction taking place on the dip C.E. and staining yellowish-clear the supporting electrolyte. Stirring was set at a moderate rate.

Figure 23. Setup used for electrolysis. **Equipment:** Power Supplier, Coulombimeter, Potentiostat/Galvanostat, Multimeter, H-type cell and stirring devices.

Note on electrodes placement: W.E. was placed as horizontal and straight as possible so that the effective surface area can be calculated by noting the solvent line in the electrode once the electrolysis is over. R.E was placed as close to the working electrode as possible. C.E and working electrode were placed accordingly to be facing each other.

Table 1 describes the experimental features of the four bulk electrolysis experiments performed in this work.

Table 1. Experimental variables used for bulk electrolysis of four N-alkoxy phthalimides in ACN 0.1M TBAP.

Entry	T (°C)	Mass (mg)	Electrolysis potential (mV vs Ag/Ag^+)	Charge computed (C)	Charge used (C)	W.E surface area (cm^2)	Time (min)
PHTP	19	200	1860	68.1	78.01	5.98	45
PHTB	19	200	1900	84.0	100.0	5.98	50
PHTD	19	200	1800	58.6	60.0	5.2	105
PHTG	18	150	1900	48.3	48.4	5.2	165

The electrolysis experiments of all substrates yielded overall weights that exceeded the expected according to the initial amount of starting material (Table 2), indicating that side-reaction with solvent and supporting electrolyte did occur at the potential of electrolysis which will be shown next.

Table 2. Excess weight reported for each electrolysis experiment.

Starting Material	Input (mg)	Output (mg)	% recovered
PHTP	200	847.1	423%
PHTB	200	609.8	305%
PHTG	160	711.1	444%
PHTD	200	918.0	459%

1.12.3 Treatment of the reaction mixture after electrolysis

The solution containing the analyte was transferred from the cell to a round-bottomed flask using a pipette. 30mL of distilled water was added to the flask and the new mixture evaporated with rotary evaporation to take out most of the organic solvent. The organic compounds were extracted using three fractions of ethyl acetate (20, 15, 15mL) and dried over dry $MgSO_4$. The resulting reaction mixture was dry-loaded in celite and purified by column chromatography in silica gel (pore size 60 Å, 70-230 mesh) using n-hexane at first and gradually increasing the polarity up to 70% n-Hexane : 30% ethyl acetate. The last products on the column were taken out using 100% ethyl acetate,100% acetone, 100% ethanol, 100%water in that order.

Each purified fraction was collected in round-bottomed flasks, which were previously weighted in analytical balance at room temperature, to then evaporate the mobile phase. The remaining solvent traces were taken out under vacuum for 3 hours at least. The flasks were weighted again at room temperature and the weight variation was determined. If weighted ≥10mg. The electrolysis products were removed from the flasks pouring 0.3,0.2,0.2mL of Chloroform-d ($CDCl_3$) and taken out each time with a glass Pasteur pipette to recover most of the material to be sent to ^{1}H-NMR analysis (If weighted near to 50 mg the sample was also sent to ^{13}C-NMR). If weighted in the order of hundreds of

milligrams, 50mg of product were used to prepare the sample and sent to ^{1}H-NMR and ^{13}C-NMR.

1.12.4 Code assignation

The codification of the isolated electrolysis products was made using the following system: “Letter representing the N-alkoxy phthalimide reduced upon electrolysis” + “Number of experiment for that compound” + “-” + “Letter representing the chronological elution out of the chromatographic experiment of the isolated species assigned alphabetically” + “EP”

Given that, an example might be assigning the code to the fourth (fourth letter of the alphabet: D) compound eluting out of the column for the first electrolysis (experiment 1 for that substrate) of the compound PHTB (letter B to depict this is the N-alkoxy phthalimide of the benzyl alcohol), yielding the following codification: B1-DEP.

1.12.5 Bulk electrolysis of PHTP

In the electrolysis experiments, twelve fractions were collected with codes F1-AEP to F1-LEP (Table 3). However, only the last two fractions yielded enough to be sent to ^{1}H-NMR and ^{13}C-NMR analysis.

Table 3. Informative data on the collected fractions after of electrolysis of PHTP.

Code	Weight	Characterization
F1-AEP	2.7mg	N/A
F1-BEP	1.4mg	N/A
F1-CEP	1.1mg	N/A
F1-DEP	2.7mg	N/A
F1-EEP	2.8mg	N/A
F1-FEP	Thrown away	N/A
F1-GEP	Still not weighted	N/A
F1-HEP	8.8mg	N/A
F1-IEP	8.2mg	N/A
F1-JEP	5.5mg	N/A
F1-KEP	737.9mg	^{1}H-NMR & ^{13}C-NMR
F1-LEP	76mg	^{1}H-NMR & ^{13}C-NMR

The bulk electrolysis products were isolated but the majority did not weight enough for characterization. The spectroscopic information of those that weighted enough has not been obtained until the date of this work.

1.12.6 Bulk electrolysis of PHTB

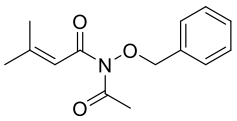
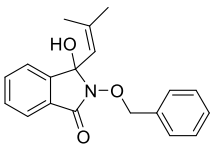
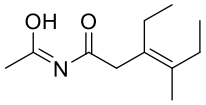
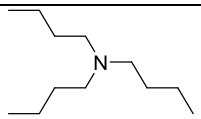
In the bulk electrolysis experiment, eight fractions were collected after column chromatography with codes B1-AEP to B1-HEP (Table 4) from which five of them weighted the necessary for ^{1}H-NMR and three of these were suitable samples for ^{13}C-NMR.

Table 4. Informative data on the collected fractions after electrolysis of PHTB.

Code	Weight	Characterization
B1-AEP	11.1mg	^{1}H-NMR
B1-BEP	1.9mg	N/A
B1-CEP	14.4mg	^{1}H-NMR
B1-DEP	5mg	N/A
B1-EEP	14.8mg	^{1}H-NMR
B1-FEP	2.7mg	N/A
B1-GEP	443mg	^{1}H-NMR & ^{13}C-NMR
B1-HEP	116.mg	^{1}H-NMR & ^{13}C-NMR

Fractions B1-AEP, B1-CEP, B1-EEP, B1-GEP and B1-HEP yielded enough material to run ^{1}H-NMR (^{13}C-NMR spectra are not available at the date of this draft was written) According to only ^{1}H-NMR fractions B1-AEP, B1-CEP, B1-EEP and B1-HEP yielded the structures presented in Table 7

Table 7. Structures determined for the products of electrolysis of PHTB.

 *N*-acetyl-*N*-(benzyloxy)-3-methylbut-2-enamide Chemical Formula: $C_{14}H_{17}NO_3$ Molecular Weight: 247.29 **B1-AEP (**11.1mg**)**	 2-(benzyloxy)-3-hydroxy-3-(2-methylprop-1-en-1-yl)isoindolin-1-one Chemical Formula: $C_{19}H_{19}NO_3$ Molecular Weight: 309.37 **B1-CEP (**14.4mg**)**
 (*Z*)-*N*-((*E*)-3-ethyl-4-methylhex-3-enoyl)acetimidic acid Chemical Formula: $C_{11}H_{19}NO_2$ Molecular Weight: 197.28 **B1-EEP (**14.8mg**)**	 tributylamine Chemical Formula: $C_{12}H_{27}N$ Molecular Weight: 185.36 **B1-GEP** (443mg)

B1-GEP is clearly originated by a side-reaction of the supporting electrolyte (TBAP) and directly related to the formation of B1-CEP, as a four carbon alkyl chain could be stated to attack nucleophilically on a carbonyl of the starting material PHTB and further elimination-protonation. The high amount of tributylamine B1-GEP (443mg or ~2.4mmol) indicates that a fraction of the butyl chain follows this path but the remaining must react differently. Moreover, both the amount of tributylamine and the fact of PHTB being reacted with it reveal that the side reaction of reduction of TBAP does not happen at the end of electrolysis but starts at any point along the experiment in which PHTB is still available to form 14.4mg of B1-CEP. Product B1-AEP (11.1mg) reassembles most of the structure of the starting material. This structure is presumably formed upon a fragmentation of the radical anion of PHTB. Apparently, three carbons might be loss from the aromatic ring of the isoindole-1,3-dione from PHTB since ^{1}H-NMR experiment shows that the aromatic signals have disappeared and new methyl and alkene signals arise. A methyl shift could also be part of this process.

Traces of hexane appear in the NMR spectra, inferring that more time in vacuum was needed. The proposed structure of B1-EEP apparently comes mainly from the phthalimidic section of the starting material. However, a three carbon excess can be noted. In case of the nitrogen truly having such bonding, it could be proposed that the N-O bond of the starting material is broken and the negative charge remains on the phthalimide as reported previously by Syroeshkin et al.[20], leading to an arrangement that ends in the formation of the hydroxyl group by further protonation. B1-HEP is a mixture of Bu_3N tributylamine + some other species still not characterized.

1.12.7 Bulk electrolysis of PHTD

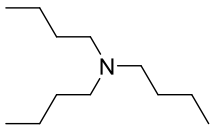
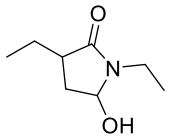
In the bulk electrolysis experiment, five fractions were collected (D1-AEP to D1-EEP) (Table 5) from which all of them yielded enough material to run ^{1}H-NMR and three of these ^{13}C-NMR.

Table 5. Informative data on the collected fractions after electrolysis of PHTD

Code	Weight	Characterization
D1-AEP	35mg	^{1}H-NMR
D1-BEP	73.9mg	^{1}H-NMR & ^{13}C-NMR
D1-CEP	18.8mg	^{1}H-NMR
D1-DEP	636.3mg	^{1}H-NMR & ^{13}C-NMR
D1-EEP	154mg	^{1}H-NMR & ^{13}C-NMR

Fractions from D1-AEP to D1-EEP all have ^{1}H-NMR available. (^{13}C-NMR spectra are not available to the date this work was written) According to ^{1}H-NMR these fractions yielded the following structures presented in Table 8 (To the date of this work was written, fractions D1-AEP to D1-CEP are still under revision).

Table 8. Structures determined for the products of electrolysis of PHTD.

 tributylamine Chemical Formula: $C_{12}H_{27}N$ Molecular Weight: 185.36 **D1-DEP** (636.3mg)	 1,3-diethyl-5-hydroxypyrrolidin-2-one Chemical Formula: $C_8H_{15}NO_2$ Molecular Weight: 157.21 **D1-EEP** (154mg)

Here, tributylamine (D1-DEP) has been formed in an exaggerated amount. TBAP must have lost one of the butyl chain as a cation, that we expect to be part of the other substrates that could have been formed in the experiment. In the other hand, our proposal for the product isolated from D1-EEP fraction mostly resembles the phthalimide section, but having the aromaticity loss, a new ethyl chain on nitrogen and a hydroxyl group replacing one of the starting carbonyls. These three major changes arise at first glance, but certainly D1-EEP might be a proof of N-O bond rupture.

1.12.8 Bulk electrolysis of PHTG

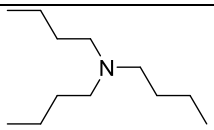
In the bulk electrolysis experiments, eight fractions were collected (G1-AEP to G1-HEP) (Table 6) from which three of them yielded enough material to run ^{1}H-NMR but only two of these ^{13}C-NMR.

Table 6. Informational data about the collected fractions of electrolysis of PHTG.

Code	Weight	Characterization
G1-AEP	10.7mg	^{1}H-NMR
G1-BEP	8.7mg	N/A
G1-CEP	4.6mg	N/A
G1-DEP	7.8mg	N/A
G1-EEP	7.3mg	N/A
G1-FEP	1.1mg	N/A
G1-GEP	0.1118g	^{1}H-NMR & ^{13}C-NMR
G1-HEP	0.5591g	^{1}H-NMR & ^{13}C-NMR

Fractions G1-AEP, G1-GEP and G1-GEP yielded ^{1}H-NMR, from which G1-AEP is still under revision and the other two are proposed to be the following (Table 9). (^{13}C-NMR spectra are not available at the date of this draft was written)

Table 9. Structures determined for the products of electrolysis of PHTG.

 aziridine Chemical Formula: C_2H_5N Molecular Weight: 43.07 **G1-GEP (**0.1118g)	 tributylamine Chemical Formula: $C_{12}H_{27}N$ Molecular Weight: 185.36 **G1-HEP (**0.5591g)

Here, fraction G1-HEP reveals Tributylamine again. The formation of a very strained aziridine is what we propose for G1-GEP. Fragmentation of the starting material to lead to the bonding of Nitrogen in this structure seems quite unlikely, as both carbonyls and aromatic ring must be lost by N-O bond rupture.

1.13. Recommendations

The tosylation of benzyl alcohol to obtain from benzyl 4-methylbenzenesulfonate 2, might be enhanced by: using any grinding equipment in order to ensure more homogeneity in the reaction mixture (and decrease human error as well), using KOH to remove remaining TsCl and further crystallization but purify the desired tosylate through column chromatography. Avoiding KOH is less risky but using column chromatography might mean a more expensive synthesis. The convenience of both alternatives should be assessed if working with cheap alcohols in bigger scale.

As another approach, the electrolysis experiments were carried out at nearly the same conditions of the cyclic voltammetry. ACN medium was preferred over DMF since it possesses a higher vapor pressure, thus facilitating the purification of electrolysis products. Also, from cyclic voltammetry experiments it was noted that solubility seemed to proceed easier on ACN solvent. Additionally, since tributylamine originated from TBAP appears in great excess causes an overestimation of the isolated products. In the future, it should worth to try using a different salt that yields a wider electrochemical window as a solution to this fact. Another solution must be to try the electrolysis at reduction potentials only slightly greater than the measured on cyclic voltammetry at the expense of needing more time under reaction, not to say to try new solvents.

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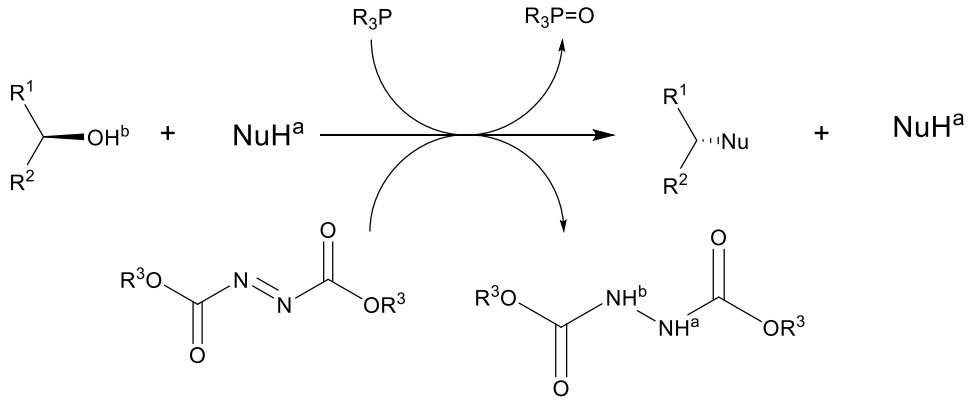
APPENDICES

1.14. APPENDIX 1

Mitsunobu Reaction

Mitsunobu reaction is the dehydrative coupling of a primary or secondary alcohol (occasionally tertiary alcohols) to a pronucleophile (NuH) which is mediated by the reaction between a dialkyl azodicarboxylate (DEAD, R^3: Et; DIAD, R: iPr) and a trialkyl or triarylphosphine (frequently PPh_3) (Scheme 13) to afford a final product with clean inversion of the initial stereochemistry, if secondary alcohols are used. This reaction was first reported by its discoverer Oyo Mitsunobu in 1967.

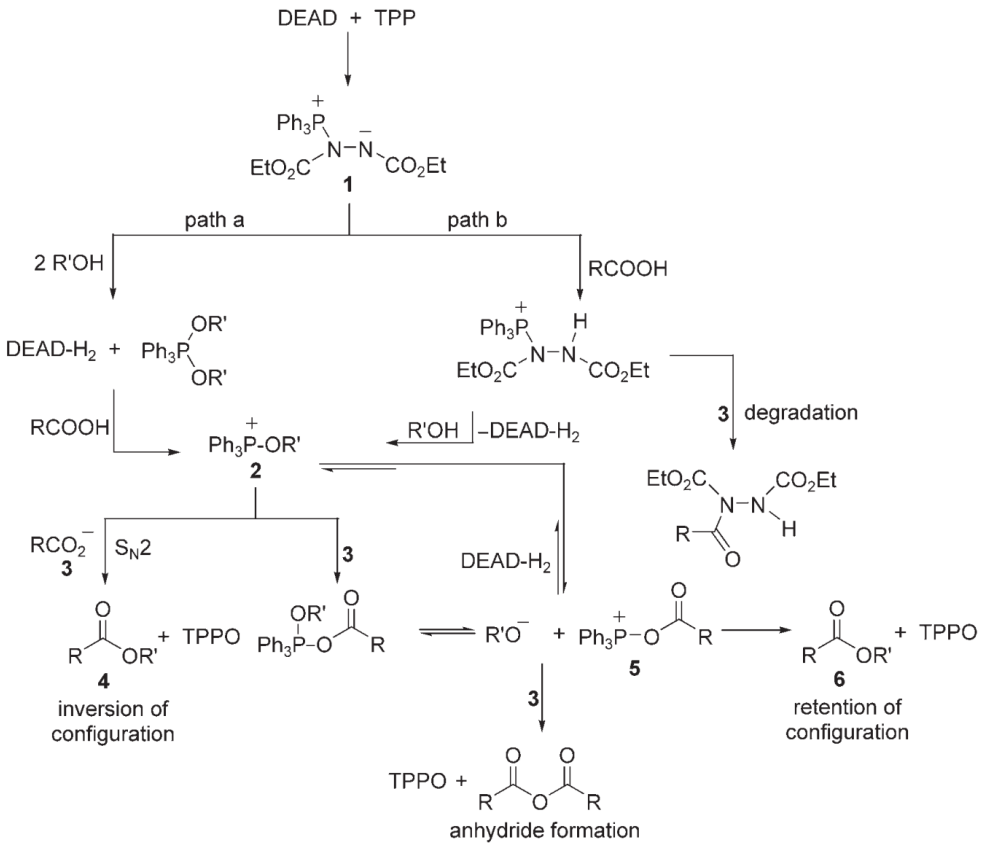


Scheme 13. General Scheme of Mitsunobu Reaction

The Mitsunobu reaction occurs under mild-neutral conditions and typically at temperatures from 0°C up to room temperature, or slightly more, in relatively low polar solvents such as THF, diethyl ether, DCM and toluene.[24]

Mechanism:

The first step in the Mitsunobu reaction is the nucleophilic addition of PPh_3 (TPP) to DEAD to form the Morrison-Brunn-Huisgen betaine **1** (Scheme 14).This molecule can then either undergo two reaction paths. In **path a**, the betaine reacts with two molecules of the alcohol R'OH to produce eventually DEAD-H_2, alkoxyphosphonium **2**, and carboxylate/nucleophile **3**. Alternatively, it can deprotonate the acid/pronuclophile (RCOOH) to form eventually, again, DEAD-H_2, **2** and **3**, in **path b**. Nucleophilic displacement of (Ph_3P=O) TPPO from **2** by **3** completes the reaction to form the coupled product **4** with inverted stereochemistry respect to the alcohol starting material. **2** is also in equilibrium with the acyloxyphosphonium **5**, and in some cases results the coupled product **6** which retains the original configuration. It is usually agreed that the pKa of the pronucleophile must be around 12 or below, since the betaine **1** has a pKa ~12 and removes the acidic proton of the pronucleophile, otherwise the alkylation of DEAD proceeds and forms an additional side-product. Furthermore, it has been reported that, in some cases, **5** can be formed first and then transformed into **2**, which may explain the formation of **6** when very sterically hindered secondary alcohols are used, as conversion of **5** into **2** can be sensitive to steric constraints.[25]



Scheme 14. Current understanding of the mechanism of the Mitsunobu reaction.