Universidade de Lisboa
Faculdade de Farmácia

New photochemical cross coupling reactions to prepare carboxylic anhydrides from aldehydes and alcohols

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Mestrado Integrado em Ciências Farmacêuticas

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Co-orientador: Doutor Pedro M. P. Góis, Professor Associado

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This study was carried out in the Department of Chemistry and Pharmacy of the University of Sassari, under the supervision of Professor Lidia De Luca and with the collaboration of PhD student Silvia Gaspa.

Resumo

Os anidridos são compostos orgânicos, bastante utilizados pela sua maior reatividade, comparativamente à dos ácidos carboxílicos, estando presentes em vários tipos de reações, tais como condensação, esterificação, entre outras. No setor farmacêutico, estes compostos apresentam diversas aplicações, em múltiplos processos da produção de fármacos e síntese de péptidos. Uma área em que o seu interesse tem, também, crescido ultimamente é no desenvolvimento de novos sistemas de libertação de fármacos.

Tendo em conta a sua importância e aplicação, vários métodos de síntese destes compostos têm sido desenvolvidos ao longo dos anos, com o objetivo de chegar a uma alternativa eficiente e económica, que possa ser aplicada a um largo espetro de reagentes.

Os métodos clássicos para a síntese de anidridos envolvem o tratamento de ácidos carboxílicos com um agente acilante. Este último vai ativar o grupo carbonilo, permitindo o ataque por outros nucleófilos. É comum que se utilizem cloretos de acilo como reagentes primários desta reação. Uma alternativa a este processo é a combinação de ácidos carboxílicos com um forte agente desidratante. No entanto, os processos acima mencionados apresentam algumas desvantagens, tais como o emprego de reagentes tóxicos e/ou caros e a necessidade de decorrerem em condições extremas e utilizarem agentes catalisadores. Para além disso, os seus rendimentos são baixos e os produtos obtidos apresentam uma elevada instabilidade, sendo necessário um processamento dos produtos que pode ser extenso. Todas estas características limitam a sua aplicabilidade em processos de larga escala e têm levado à busca pelo desenvolvimento de novos métodos.

Como forma de ultrapassar as limitações referidas, têm surgido várias metodologias inovadoras, que incluem o uso de catalisadores metálicos ou de reações fotoredox com luz visível. Atualmente, uma alternativa que está a ganhar cada vez mais destaque prende-se com a substituição dos ácidos carboxílicos e derivados como reagentes primários por aldeídos e álcoois, pela sua maior disponibilidade. Vários métodos têm sido propostos nesta linha de procedimento, podendo ou não recorrer a metais catalisadores. No entanto apresentam algumas desvantagens, tais como o baixo número de produtos obtidos, uma vez que apenas um determinado espetro de aldeídos aromáticos é compatível com este processo de síntese. Os rendimentos obtidos não são, também, tão elevados quanto o desejável.

Neste trabalho, é proposto um novo procedimento para a síntese de anidridos a partir de aldeídos e álcoois, utilizando a radiação solar como catalisador. O método em questão foi baseado em estudos anteriores e está dividido em dois passos sequenciais, sendo iniciado pela oxidação do aldeído ou do álcool através do ácido tricloroisocianúrico, em diclorometano e à temperatura ambiente. Após a ativação pela luz solar, é possível obter um cloreto de acilo no final do primeiro passo. De seguida, procede-se à adição do ácido carboxílico correspondente e de trietilamina a 0 ºC, o que leva à síntese do anidrido simétrico com bom rendimento.

Apesar de nos estudos anteriores ainda não se ter estabelecido o mecanismo pelo qual se rege a reação, é feita uma proposta neste trabalho. Assim, sugere-se que o processo se inicie com a conversão do aldeído num cloreto de acilo, através da oxidação pelo TCCA, que segue um mecanismo radicalar catalisado pela luz solar. No segundo passo da reação, dá-se o ataque nucleofílico do cloreto de acilo pelo ácido carboxílico, previamente ativado pela trietilamina. No caso dos álcoois, supõe-se que o mecanismo seja o mesmo que o proposto para os aldeídos, sendo necessário a conversão prévia do álcool primário num aldeído, pela formação de um hipoclorito.

O estudo iniciou-se com a utilização de aldeídos como reagentes primários, aplicando as condições ótimas de reação, determinadas num estudo simultâneo. Foram utilizados vários tipos de aldeídos, tanto aromáticos como alifáticos, de forma a determinar-se o campo de aplicação do método. Relativamente à utilização de aldeídos aromáticos, estes permitiram a obtenção de anidridos simétricos com bons rendimentos, especialmente recorrendo a aldeídos com substituintes eletrodadores. No entanto, foram também obtidos bons resultados com substituintes eletrofílicos, à exceção do 4-nitrobenzaldeído e 4-cianobenzaldeído, devido à pouca reatividade destes compostos, e do 4-trifluorometillbenzaldeído. Os maus resultados deste último deveram-se a falhas no procedimento.

Quanto à utilização de álcoois como reagentes primários, o ponto de partida foi a determinação das condições ótimas da reação, de modo a estabelecer o tempo de reação e a quantidade de TCCA e solvente utilizados no primeiro passo, bem como a quantidade de trietilamina e a utilização de ácido carboxílico ou de água para a realização do segundo passo. Depois de determinadas as melhores condições, estas foram aplicadas à síntese de anidridos, tendo sido possível obter um produto, com bom rendimento. No entanto, o tempo do estudo foi limitado, pelo que se devem proceder a investigações futuras.

Tendo em conta os resultados, este estudo apresenta-se como uma boa alternativa aos atuais procedimentos de produção de anidridos, sendo um método bastante seletivo que evita a formação de produtos secundários. Para além disso, é também um método bastante económico, uma vez que utiliza uma razão estequiométrica ótima de reagentes, evitando o seu uso em excesso. Os reagentes utilizados foram escolhidos pelas suas características ecológicas e económicas, sendo compostos facilmente disponíveis e vantajosos a baixo custo.

Palavras-chave: Álcoois, aldeídos, anidridos, luz solar, oxidação, ácido tricloroisocianúrico.

Abstract

Anhydrides are important organic compounds, applied in pharmaceutical sciences to a number of processes during drug production and synthesis of peptides. Furthermore, these compounds have been displaying an increasing interest and applicability in the development of new drug delivery systems. Thus, it is important to find an effective method for the synthesis of anhydrides, that is both green and economic. In this work, a metal-free oxidative cross-coupling process for the synthesis of anhydrides from aldehydes or benzylic alcohols is presented. The aldehydes or alcohols were oxidized *in situ* into their corresponding acyl chlorides, using the sun light as an activator. The acyl chloride was then reacted with the corresponding carboxylic acid, in the presence of triethylamine to give the desired anhydride. All reagents applied in this method are green and readily available and are used in an optimal stoichiometric ratio. Using aldehydes, it was possible to obtain a number of aromatic and aliphatic symmetric anhydrides, in good yields. Regarding the use of alcohols, this study focused on determining the optimal reaction conditions and afterwards it was possible to obtain one product in good yield. The method has a general applicability, being a selective, economical and green alternative for the synthesis of anhydrides.

Keywords: Alcohols, aldehydes, anhydrides, oxidation, solar light, trichloroisocyanuric acid.

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Firstly, I have to thank to the University of Sassari, where this study was conducted, for the opportunity of doing my Erasmus internship there. My deep appreciation goes to Prof. Lídia and Silvia, for all their patience and willingness to help me throughout this whole process, but also for how they welcomed me into their lab, making me feel like I was home during those three months. Also to Prof. Pedro Góis, that took the time to help me make sense of things.

To my friends, I will always be grateful for keeping me motivated and for always making time for me and my existential crisis, even though their agenda was just as busy and stressful as mine.

Finally, to my family, a “thank you” will never be enough to express how much I appreciate all their efforts to make this possible. They were always there to comfort me in the most difficult moments and I couldn’t have made it without them.

Abbreviations

2,4-DNP – 2,4-dinitrophenylhydrazine;

Ar – Aromatic

CAM – Cerium ammonium molybdate;

d - Doublet

DCM - Dichloromethane

dd – Doublet of doublets

dt - Doublet of triplets

Et_3N – Triethylamine;

EtOAc – Etyl acetate;

Hex – Hexane;

m - Multiplet

mp – Melting point

NMR – Nuclear magnetic resonance spectroscopy;

t - Triplet

TBHP – *tert*-Butylhydroperoxide;

TCCA – Trichloroisocyanuric acid;

td - Triplet of duplets

TLC – Thin layer chromatography;

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1 Introduction

1.1 Structure and Chemistry

The carboxyl group is one of the most widely occurring functional groups in chemistry. There are several related compounds, called carboxylic acid derivatives, that contain a carbonyl group with an electronegative atom attached to the carbonyl carbon, leading to major changes in reactivity. Carboxylic acid derivatives include four major families of related compounds: halides, anhydrides, esters, and amides, and many of which have an important role in biology. Carboxylic anhydrides can be perceived as a carboxylic acid with an acyl group as a substituent attached to the oxygen (***Figure 1.1***). (1,2)

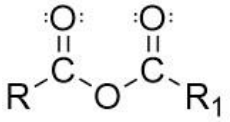


Figure 1.1 General structure of an anhydride

1.2 Anhydrides importance and major applications

In organic chemistry, carboxylic anhydrides are important acylating compounds, due to their high reactivity when compared with carboxylic acids, and are commonly used as functional reagents in many types of reactions, such as condensation reactions, esterification reactions, etc. (3) In pharmaceutical sciences, anhydrides can be applied in a number of processes during drug production and synthesis of peptides. (4,5) In addition to that, these compounds have been displaying an increasing interest and applicability in the development of new drug delivery systems. Due to predictable drug release profiles, anhydride-based polymers have been presenting a prominent role in controlled-release applications and, for the past few years, nanoparticles containing anhydrides have been developed for oral drug delivery systems, immunization and allergy treatment, with great results regarding their efficacy. (6,7) Furthermore, Jie Fu *et al* have produced a new family of ether-anhydride copolymers that allow efficient drug release following inhalation. (8) Also in biochemistry anhydrides seem to have an important role, serving as reagents for the synthesis of peptides and as labelling agents in quantitative proteomics. (9)

1.3 Methodologies for the synthesis of anhydrides

The classical pathway for the formation of anhydrides involves treating carboxylic acids with an acylating agent, such as acyl halides, activated esters or reactant anhydrides, that activates the carbonyl function to attack by other nucleophiles (***Figure 1.2***). (10) Acyl chlorides, as one of the most common acyl halides, are widely used as starting reagents for this reaction (11,12). Traditionally, these compounds are formed from the parent carboxylic acid, by reacting it with thionyl chloride ($SOCl_2$) or phosphorus tribromide (PBr_3) (***Figure 1.3***). (2,13)

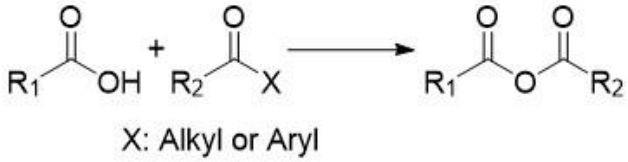


Figure 1.2: Synthesis of symmetric anhydrides from carboxylic acids treated with an acylating agent.

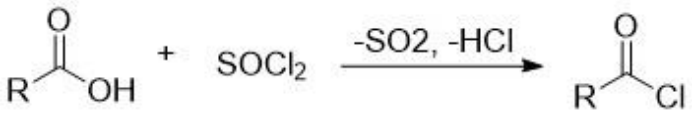


Figure 1.3: Preparation of acyl chloride.

Alternatively, anhydrides can also be obtained by combining carboxylic acids with a powerful dehydrating coupling agent, such as phosphoranes, isocyanates, phosgene, sulfonyl chloride, carbodiimides, 1,3,5-triazines and pyridazine-3(2H)-ones (***Figure 1.4***). (14) However, many of these methods struggle with a few drawbacks, including the use of expensive and/or toxic reagents, low yields, instability of the products, need of high temperature and/or harsh conditions, need of catalyst and tedious work-up procedures, which can limit their applications and have led to attempts to develop new approaches. (15)

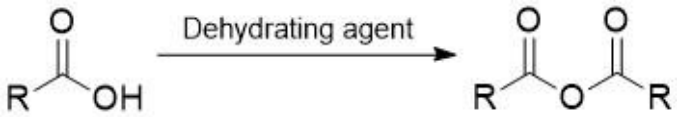


Figure 1.4: Synthesis of symmetric anhydrides from carboxylic acids treated with a dehydrating agent.

To overcome these limitations, different and ground-breaking strategies have been developed for the synthesis of anhydrides. These approaches include metal-catalysed reactions, such as Pd-catalysed and nano CuO-catalysed reactions, and the

conversion of carboxylic acids to symmetrical anhydrides catalysed by a photoredox reaction with visible light. (16)

1.4 Obtaining anhydrides from aldehydes and alcohols

Many new methods lean towards the replacement of carboxylic acids and their derivatives with aldehydes and alcohols as starting reagents, due to their high availability. Patel *et al.* have proposed the first example for the synthesis of carboxylic anhydrides from aromatic aldehydes, using *tert*-butylhydroperoxide (TBHP) as an oxidant and nano CuO as catalyst, at 120 ºC for 5h. (17) In recent years, other methodologies, both metal-catalysed and metal-free, have been proposed for producing anhydrides from aldehydes, using TBHP as an oxidant and occurring at high temperatures (***Figure 1.5***). (18) However, these methods suffer from major drawbacks, like their restricted reaction scope, as only a number of aromatic aldehydes are compatible with these procedures, and the low yields for the desired anhydrides. (18)

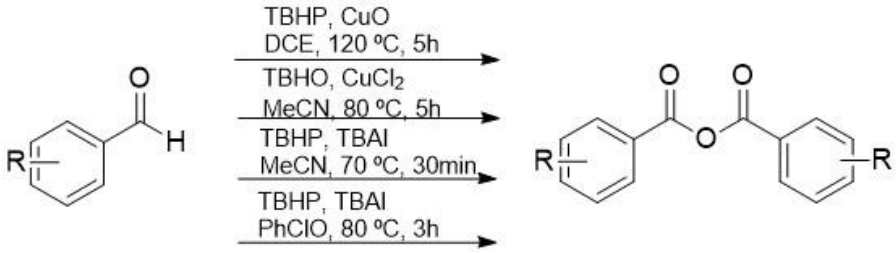


Figure 1.5: Strategies for obtaining carboxylic anhydrides from aldehydes. (18: p. 2534)

Recently, L. de Luca and co-workers have established a new process to obtain carboxylic anhydrides directly from aromatic and aliphatic aldehydes, using trichloroisocyanuric acid (TCCA) (***Figure 1.6***) as an oxidative and chlorinating agent. (19) This compound is often preferred for its safety, low toxicity and efficiency, also on large scale. All three chlorine atoms present in this structure are active, making it an economic reagent, together with its general high solubility in organic solvents that allows the reduction of the necessary volume of solvent. (20,21).

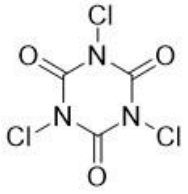


Figure 1.6: Trichloroisocyanuric Acid (TCCA)

The investigators propose a mechanism that involves the reaction of an aldehyde with TCCA in dichloromethane at room temperature, with the formation of an acyl chloride. This compound is later treated with the correspondent acid and triethylamine (Et_3N), at 0 ºC. After 1h at room temperature, the desired anhydride is formed in a good yield (***Figure 1.7***). (22)

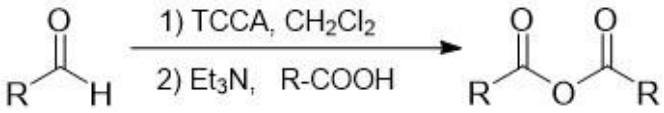


Figure 1.7: **Synthesis of carboxylic anhydrides from aromatic and aliphatic aldehydes, using TCCA as an oxidizing agent.**

As alcohols are stable compounds, with a good availability, the investigators also thought it would be interesting and efficient to be able to convert them directly into acid anhydrides. The same oxidative reagent as the previously mentioned method was used in this mechanism, in dichloromethane and at room temperature. Subsequently, an acyl chloride was generated and treated with the correspondent acid and Et_3N, at 0 ºC, producing the desired anhydride after 1h at room temperature, in a good yield. With this methodology they found it possible to synthesise both symmetric and pure mixed anhydrides from primary benzylic alcohols with carboxylic acids. The proposed mechanism, based on previous papers, includes the reaction between the alcohol and TCCA, producing a hypochlorite that readily loses hydrogen chloride to form an aldehyde. This last compound is then converted into the acyl chloride, through a radical pathway. From this point on, the mechanism is similar to the one previously described for the reaction with aldehyde as a starting reagent (***Figure 1.8***). (22)

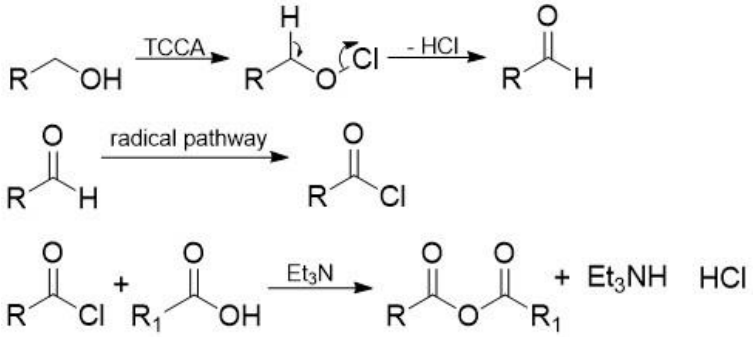


Figure 1.8: Reaction mechanism for the synthesis of anhydrides from primary alcohols.

After optimizing the conditions in which it took place, the scope of the reaction was investigated. It was possible to obtain symmetrical anhydrides from both electron-rich aromatic aldehydes and aromatic aldehydes with electron-withdrawing substituents in good yields. Aliphatic aldehydes also gave good yields for the production of the corresponding symmetric anhydrides, an unprecedent observation. The array of alcohols investigated gave the desired symmetrical anhydrides in good yields. Using this procedure, it was also possible to obtain, isolate and characterize mixed anhydrides, despite their instability. (22)

Although this new methodology makes it possible to produce anhydrides from readily available and green reagents, while using mild reaction conditions, previous studies have shown that the first step of the reaction can be extensive, taking up to 5 days to give the desired product in a good yield. Consequently, the reaction needed to occur under an Argon atmosphere, to avoid product degradation. (23) (18)

1.5 Objectives

Following the work of L. de Luca (19), in this study we aimed to optimize the previously proposed methodology to prepare anhydrides from aldehydes and alcohols, via generation *in situ* of an acyl chloride. Using the same reagents as the previous method, this pathway includes a photochemical activation of the substrate to shorten the total reaction time. TCCA was the chosen chlorinating and oxidative agent, due to the abovementioned characteristics. Based on previous studies, Et_3N was selected as base for the second step of the reaction, as this was the reagent that has given the best result. (19) In these conditions, we disregarded the need to use an Argon atmosphere to avoid product degradation, achieving a more efficient and feasible methodology.

2 Methodology

2.1 General experimental chemistry

Flash chromatography was generally performed on silica gel (pore size 60 Å, 32-63 nm particle size).

Thin-layer chromatography (TLC) analysis was performed with Merck Kieselgel 60 F254 plates. Results were visualized using UV light at 254 nm, cerium ammonium molybdate (CAM) and 2,4-dinitrophenylhydrazine (2,4-DNP) staining.

^{1}H NMR spectra were measured on a Bruker Avance III 400 spectrometer 400 MHz, using $CDCl_3$ solutions and TMS as an internal standard. Chemical shifts are reported in parts per million (ppm, d) relative to internal tetramethylsilane standard (TMS, d 0.00). The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; q, quartet; dd, doublet of doublets; br, broad. The coupling constants, J, were determined using MestreNova and are reported in Hertz (Hz).

^{13}C NMR were measured on a Bruker Avance III 100 MHz, using $CDCl_3$ solutions and TMS as an internal standard. Chemical shifts are reported in parts per million (ppm, d) relative to internal tetramethylsilane standard (TMS, d 0.00).

Melting points were determined in open capillary tubes and are uncorrected.

2.2 Equipment

- Abet tech sun 2000 simulator (under 100 mW/cm2 simulated AM 1.5G irradiance);
- Vilber Lourmat VL-208.G lamp (2 tubes, 8W each, 254 nm);
- Rotavapor BUCHI;
- Leitz Laborlux S for melting point;
- IKA Stirrer Magnetic Color IKAMAG;
- Kern analytical balance

2.3 Reagents and Solutions

All reagents and solvents were obtained by commercial source. All solvents were dried by usual methods and distilled under Argon. Aldehydes were fresh distilled before use.

- 2,4-dinitrophenylhydrazine for TLC staining: 2,4-DNP (sigma-aldrich, 97%), sulfuric acid (sigma-aldrich, 99.999%) and ethanol (sigma-aldrich, 95%);
- Cerium ammonium molybdate for TLC staining: ammonium molybdate (sigma-aldrich, 99.98%), ceric ammonium sulfate (sigma-aldrich) and sulfuric acid (sigma-aldrich, 99.999%);
- $CDCl_3$ (Sigma-Aldrich, 99.96 atom % D, ≥99%) as a solvent for ^{1}H NMR and ^{13}C NMR spectra;
- Tetramethylsilane (TMS) (Sigma-Aldrich, ≥ 99.5%) as internal standard for ^{1}H NMR and ^{13}C NMR spectra;
- TCCA (Sigma-Aldrich, ≥ 95%);
- Et_3N (Sigma-Aldrich, ≥ 99.5%);
- Hexane (sigma-aldrich, solvent grade);
- Ethyl acetate (EtOAc) (sigma-aldrich, solvent grade);
- Water;
- HCl (Sigma-Aldrich, 37%);
- $NaHCO_3$ (Sigma-Aldrich, ≥ 99.7%);
- Na_2SO_4 (Sigma-Aldrich, 99%);
- Aldehydes: benzaldehyde (Sigma-Aldrich, ≥ 99%); 4-chlorobenzaldehyde (Sigma-Aldrich, 97%); 4-nitrobenzahdehyde (Sigma-Aldrich, ≥ 98%); pivalaldehyde (Sigma-Aldrich, ≥ 96%); hydrocinnamaldehyde (Sigma-Aldrich, ≥ 95%); cyclohexanecarboxaldehyde (Sigma-Aldrich, 97%); 4-fluorbenzaldehyde (Sigma-Aldrich, 98%); 2,4-dichlorobenzaldehyde (Sigma-Aldrich, ≥ 99%); 4-(trifluoromethyl)benzaldehyde (Sigma-Aldrich, ≥ 98%); 4-cyanobenzaldehyde (Sigma-Aldrich, ≥ 98%);
- Carboxylic acids: benzoic acid (Sigma-Aldrich, ≥ 99.5%); 4-chlorobenzoic acid (Sigma-Aldrich, 99%); 4-nitrobenzoic acid (Sigma-Aldrich, 98%); pivalic acid (Sigma-Aldrich, 99%); hydrocinnamic acid (Sigma-Aldrich, 99%); cyclohexanecarboxylic acid (Sigma-Aldrich, ≥ 98%); 4-fluorbenzoic acid (Sigma-Aldrich, 98%); 2,4-dichlorobenzoic acid (Sigma-Aldrich, 98%);
- Alcohols: benzyl alcohol (Sigma-Aldrich, 99.8%); 4-chlorobenzyl alcohol (Sigma-Aldrich, 99%).

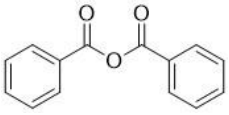
2.4 Experimental Procedure

2.4.1 General method for aldehydes

TCCA (256 mg; 1.1 mmol) was portionwise added to a solution of an aldehyde (1.1 mmol), at room temperature. In case the starting aldehyde was a solid, 1 mL of DCM was added to the mixture. The resulting suspension was sealed from the external conditions with Parafilm and stirred in the solar simulator for 1.5 hours. After this time, the reaction was monitored by TLC and when deemed necessary, the TLC plates were stained with 2,4-DNP or CAM. Next, the second step was performed. The reaction mixture was cooled to 0 ºC in an ice bath and stirred and the carboxylic acid (122 mg; 1 mmol) was then added to the mixture, followed by the addition of Et_3N (202 mg; 2 mmol) at a dropwise rate. 2 mL of DCM were added as solvent. Next to the addition of all reagents, the reaction was stirred at room temperature and monitored by TLC. The reaction was complete after 2 hours. For the products R1, R2, R3, R6, R8 and R9 the solvent was evaporated under vacuum and the residue was purified by flash chromatography.

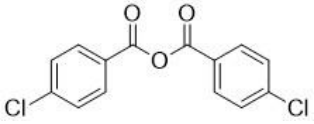
For the products R4, R5 and R7 the reaction mixture was washed three times with a solution of 5% HCl and then three times with a solution of 5% $NaHCO_3$. The organic phase was dried over anhydrous Na_2SO_4 and the solvent was then evaporated under vacuum, providing the desired anhydride.

Benzoic anhydride R1



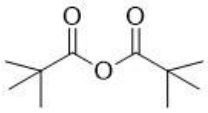
Purified by flash chromatography (Hexane/EtOAc, 4.5:0.5). Obtained as colourless oil (180 mg, 0.79 mmol, 80%): R_f 0.33 (Hexane/EtOAc, 4.5:0.5); ^{1}H NMR (400 MHz, CDCl3) δ: 8.16 (d, J = 7.6 Hz, 4H, Ar-*H*), 7.67 (t, J = 7.4 Hz, 2H, Ar-*H*), 7.52 (t, J = 7.5 Hz, 4H, Ar-*H*) (22); ^{13}C NMR (100 MHz, CDCl3) δ: 162.2 (*C*=O), 134.4 (Ar(*C*4)-C), 130.4 (Ar(*C*2,6)-C), 128.8 (Ar(*C*3,5)-C), 128.7 (Ar(*C*1)-C) (22).

4-Chlorobenzoic anhydride R2



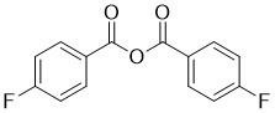
Purified by flash chromatography (Hexane/EtOAc, 4:1). Obtained as white solid (quantitative): R_f 0.32 (Hexane/EtOAc, 4:1); mp 193-194 ºC; ^{1}H NMR (400 MHz, CDCl3) δ: 8.16 (d, J = 7.6 Hz, 4H, Ar-*H*), 7.67 (t, J = 7.4 Hz, 2H, Ar-*H*), 7.52 (t, J = 7.5 Hz, 4H, Ar-*H*) (22); ^{13}C NMR (100 MHz, CDCl3) δ: 161.3 (C=O), 141.4 (Ar(*C*4)-Cl), 131.9 (Ar(*C*2,6)-C), 129.4 (Ar(*C*3,5)-C), 127.1 (Ar(*C*1)-C) (22).

Pivalic anhydride R4



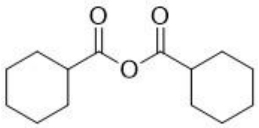
Purified by flash chromatography (Hexane/EtOAc, 4:1). Obtained as yellow oil (179 mg, 0.96 mmol, 96%): R_f 0.58 (Hexane/EtOAc, 4.5:0.); ^{1}H NMR (400 MHz, CDCl3) δ: 1.19 (s, 18H, C(C*H*$_3$)$_3$); ^{13}C NMR (100 MHz, CDCl3) δ: 173.7 (*C*=O), 39.9 (*C*(CH$_3$)$_3$), 26.3 (C(*C*H$_3$)$_3$). (22)

4-fluorobenzoic anhydride R6



Purified by flash chromatography (Hexane/EtOAc, 4:1). Obtained as white solid (quantitative) R_f 0.43 (Hexane/EtOAc, 4.5:0.5); mp 113-115 ºC; ^{1}H NMR (400 MHz, CDCl3) δ: 8.20 – 8.14 (m, 4H, Ar-*H*), 7.24 – 7.18 (m, 4H, Ar-*H)*; ^{13}C NMR (100 MHz, CDCl3) δ: 166.7 (*C*=O), 161.2 (Ar(*C*4)-F), 133.3 (Ar(*C*2,6)-C), 125.0 (Ar(*C*1)-C), 116.5 (Ar(*C*3,5)-C) (22)

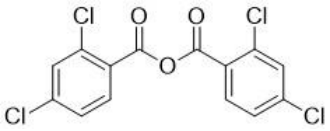
Cyclohexanecarboxylic anhydride R7



Reaction mixture washed three times with a solution of 5 % HCl and then three times with a solution of 5 % NaHCO3; the organic phase was dried over anhydrous Na2SO4 and the solvent was evaporated under reduced pressure providing the desired anhydride. Obtained as colourless oil (217 mg, 0.91 mmol, 91%); ^{1}H NMR (400 MHz, CDCl3) δ: 2.39 (tt, J = 11.1, 3.6 Hz, 2H, *H*-CHx)), 1.97 – 1.91 (m, 4H, *H*-

CHx)), 1.80 – 1.73 (m, 4H, *H*-CHx)), 1.66 – 1.60 (m, 2H, *H*-CHx)), 1.53 – 1.41 (m, 4H, *H*-CHx)), 1.34 – 1.19 (m, 6H, *H*-CHx)); ^{13}C NMR (100 MHz, CDCl3) δ: 171.8 (*C*=O), 43.9 (CHx-*C*1), 28.4 (CHx-*C*2, *C*6), 25.5 (CHx-*C*4), 25.1 (CHx-*C*3, *C*5). (22)

2,4-dichlorobenzoic anhydride R8

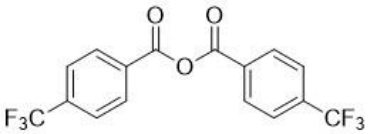


Purified by flash chromatography (Hexane/EtOAc, 4.5:0.5). Obtained as white solid (186 mg, 0.51 mmol, 51%) R_f 0.4 (Hexane/EtOAc, 4.5:0.5); mp 102-106 ºC; ^{1}H NMR (400 MHz, CDCl3) 7.97 (d, J = 8.5 Hz, 2H, Ar-*H*), 7.54 (d, J = 1.9 Hz, 2H, Ar-*H*), 7.38 (dd, J = 8.5, 1.9 Hz, 2H, Ar-*H*).; ^{13}C NMR (300 MHz, TMS) δ: 159.4 (*C*=O), 136.3 (Ar(*C*2)-C), 133.6 (Ar(*C*6)-C), 131.5 (Ar(*C*4)-Cl), 130.2 (Ar(*C*1)-C), 127.5 (Ar(*C*3)-C), 126.2 (Ar(*C*5)-C). (24)

2.4.1.1 Exceptions

TCCA (256 mg; 1.2 mmol) was portionwise added to a solution of an aldehyde (1.1 mmol), at room temperature. In case the starting aldehyde was a solid, 1 mL of DCM was added to the mixture. The resulting suspension was sealed from the external conditions with Parafilm and stirred in the solar simulator for 1.5 hours. After this time, the reaction was monitored by TLC and then the second step was performed. The reaction mixture was cooled to 0 ºC in an ice bath and stirred and the water (18 mg; 1 mmol) was then added to the mixture, followed by the addition of Et_3N (202 mg; 2 mmol) at a dropwise rate. 2 mL of DCM were added as solvent. Next to the addition of all reagents, the reaction was stirred at room temperature and monitored by TLC. The reaction was complete after 2 hours. Then, the solvent was evaporated under vacuum and the residue was purified by flash chromatography. This methodology was applied to reactions 9 and 10 (R9 and R10).

4-Trifluoromethylbenzoic anhydride R9

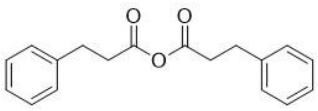


Purified by flash chromatography (Hexane/EtOAc, 4:1). Obtained as white solid (41 mg, 0.011 mmol, 22%) R_f 0.34 (Hexane/EtOAc, 4.0:1); mp 131-133 ºC; ^{1}H NMR (400 MHz, CDCl3) δ: 8.28 (d, J = 8.2 Hz, 4H, Ar-*H*), 7.82 (d, J =

8.3 Hz, 4H, Ar-*H*); ^{13}C NMR (125 MHz, CDCl3) δ 123.30 (J 1 = 271.3 Hz) (*C*F_3), 126.05 (J 3 = 3.8 Hz) (Ar(*C*3,5)-C), 130.96 (Ar(*C*2,3)-C), 131.68 (Ar(*C*1)-C), 136.11 (J 2 = 32.5 Hz) (Ar(*C*4)-CF_3), 160.77 (*C*=O). (25)

For the reaction using hydrocinnamaldehyde (R5), TCCA (256 mg; 1.1 mmol) was portionwise added to the liquid aldehyde (1.1 mmol), at room temperature, and 1 mL of DCM was added to the mixture. The resulting suspension was sealed from the external conditions with Parafilm and stirred in the solar simulator for 1.5 hour. After this time, the reaction was monitored by TLC and then the second step was performed. The reaction mixture was cooled to 0 ºC in an ice bath and stirred and the water (18 mg; 1 mmol) was then added to the mixture, followed by the addition of Et_3N (202 mg; 2 mmol) at a dropwise rate. 2 mL of DCM were added as solvent. Next to the addition of all reagents, the reaction was stirred at room temperature and monitored by TLC. The reaction was complete after 2 hours. Then, the solvent was evaporated under vacuum and the residue washed three times with a solution of 5% HCl and then three times with a solution of 5% $NaHCO_3$. The organic phase was dried over anhydrous Na_2SO_4 and the solvent was then evaporated under vacuum, providing the desired anhydride.

Hydrocinnamic anhydride R5



Purified by flash chromatography (Hexane/EtOAc, 4:1). Obtained as colourless oil (223 mg, 0.79 mmol, 79%): R_f 0.57 (Hexane/EtOAc, 4.5:0.5) (18); ^{1}H NMR (400 MHz, CDCl3) δ: 7.37 – 7.29 (m, 4H, C*H*$_2$-COOR), 7.27 – 7.08 (m, 6H, Ar-*H*), 2.99 (t, J = 7.6 Hz, 4H, C*H*$_2$-Ar), 2.77 (t, J = 7.6 Hz, 4H, Ar-*H*); ^{13}C NMR (100 MHz, CDCl3) δ: 168.4 (*C*=O), 139.4 (Ar(*C*1)-C), 128.5 (Ar(*C*3,5)-C), 128.2 (Ar(*C*2,6)-C), 126.4 (Ar(*C*4)-C), 36.6 (*C*H_2-COOR), 30.0 (*C*H_2-Ar) (22)

2.4.2 Optimization of the time of the reaction conditions for alcohols

TCCA (255.7 mg; 1.1 mmol) was added to benzylic alcohol (119 mg; 1.1 mmol) in 1 mL of DCM, at room temperature. The resulting suspension was sealed from the external conditions with Parafilm and stirred in the solar simulator. The reaction was monitored by TLC (Hex:EtOAc, 4:1) until the disappearance of the alcohol, staining the TLC plates with 2,4-DNP. The reaction was complete after 1.5 hours. Then, the

reaction mixture was cooled to 0 ºC in an ice bath and stirred. The benzoic acid (122 mg; 1 mmol) was then added to the mixture, followed by the addition of Et_3N (202 mg; 2 mmol) at a dropwise rate. 2 mL of DCM were added as solvent. Next to the addition of all reagents, the reaction was stirred at room temperature and monitored by TLC (Hex:EtOAc, 4:1) until the disappearance of the carboxylic acid. Then the solvent was evaporated under vacuum and the residue was purified by flash chromatography.

In order to find the optimal amount of TCCA as starting reagent for the first step, a second reaction was performed. TCCA (302 mg; 1.3 mmol) was added to the benzylic alcohol (119 mg; 1.1 mmol) in 1 mL of DCM, at room temperature. The resulting suspension was sealed from the external conditions with Parafilm and stirred in the solar simulator. The reaction was monitored by TLC (Hex:EtOAc, 4:1) until the disappearance of the alcohol staining the TLC plates with 2,4-DNP. The reaction was complete after 1.5 hours. Then, the reaction mixture was cooled to 0 ºC in an ice bath and stirred. The benzoic acid (122 mg; 1 mmol) was then added to the mixture, followed by the addition of Et_3N (202 mg; 2 mmol) at a dropwise rate. 2 mL of DCM were added as solvent. Next to the addition of all reagents, the reaction was stirred at room temperature and monitored by TLC (Hex:EtOAc, 4:1) until the disappearance of the carboxylic acid. Then the solvent was evaporated under vacuum and the residue was purified by flash chromatography.

Afterwards, a third reaction was carried out to test the use of a different reagent in the second step. TCCA (255.7 mg; 1.1 mmol) was added to benzylic alcohol (119 mg; 1.1 mmol) in 1 mL of DCM, at room temperature. The resulting suspension was sealed from the external conditions with Parafilm and stirred in the solar simulator. The reaction was monitored by TLC (Hex:EtOAc, 4:1) until the disappearance of the alcohol, staining the TLC plates with 2,4-DNP. The reaction was complete after 1.5 hours. Then, the reaction mixture was cooled to 0 ºC in an ice bath and stirred. Water (18 mg; 1 mmol) was then added to the mixture, followed by the addition of Et_3N (134 mg; 1.1 mmol) at a dropwise rate. Next to the addition of all reagents, the reaction was stirred at room temperature and monitored by TLC (Hex:EtOAc, 4:1) until the disappearance of the benzoyl chloride. Then the solvent was evaporated under vacuum and the residue was purified by flash chromatography.

With the aim of testing the results of a longer first step, a fourth reaction was performed. TCCA (255.7 mg; 1.1 mmol) was added to benzylic alcohol (119 mg; 1.1 mmol) in 1 mL of DCM, at room temperature. The resulting suspension was sealed from the external conditions with Parafilm and stirred in the solar simulator for 2 hours. The reaction was monitored by TLC (Hex:EtOAc, 4:1), staining the TLC plates with

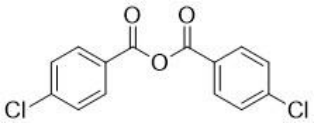
2,4-DNP. Then, the reaction mixture was cooled to 0 ºC in an ice bath and stirred. The benzoic acid (122 mg; 1 mmol) was then added to the mixture, followed by the addition of Et_3N (202 mg; 2 mmol) at a dropwise rate. 2 mL of DCM were added as solvent. Next to the addition of all reagents, the reaction was stirred at room temperature and monitored by TLC (Hex:EtOAc, 4:1) until the disappearance of the carboxylic acid. Then the solvent was evaporated under vacuum and the residue was purified by flash chromatography.

Finally, to test the influence of the amount of Et_3N used in the second step together with water, a fifth reaction was carried out. TCCA (255.7 mg; 1.1 mmol) was added to benzylic alcohol (119 mg; 1.1 mmol) in 1 mL of DCM, at room temperature. The resulting suspension was sealed from the external conditions with Parafilm and stirred in the solar simulator. The reaction was monitored by TLC (Hex:EtOAc, 4:1) until the disappearance of the alcohol, staining the TLC plates with 2,4-DNP. The reaction was complete after 1.5 hours. Then, the reaction mixture was cooled to 0 ºC in an ice bath and stirred. Water (18 mg; 1 mmol) was then added to the mixture, followed by the addition of Et_3N (134 mg; 1.1 mmol) at a dropwise rate. 2 mL of DCM were added as solvent. Next to the addition of all reagents, the reaction was stirred at room temperature and monitored by TLC (Hex:EtOAc, 4:1) until the disappearance of the benzoyl chloride. Then the solvent was evaporated under vacuum and the residue was purified by flash chromatography.

2.4.3 General method for alcohols

TCCA (302 mg; 1.3 mmol) was portionwise added to a solution of an alcohol (1.1 mmol) in 2 mL of DCM, at room temperature. The resulting suspension was sealed from the external conditions with Parafilm and stirred in the solar simulator for 1.5 hours. After this time, the reaction was monitored by TLC and when deemed necessary, the TLC plates were stained with 2,4-DNP or CAM. Next, the second step was performed. The reaction mixture was cooled to 0 ºC in an ice bath and stirred and the carboxylic acid (122 mg; 1 mmol) was then added to the mixture, followed by the addition of Et_3N (202 mg; 2 mmol) at a dropwise rate. 2 mL of DCM were added as solvent. Next to the addition of all reagents, the reaction was stirred at room temperature and monitored by TLC. The reaction was complete after 2 hours. Then, the solvent was evaporated under vacuum and the residue was purified by flash chromatography.

4-Chlorobenzoic anhydride R16



Purified by flash chromatography (Hexane/EtOAc, 4:1). Obtained as colourless oil (202 mg, 0.68 mmol, 68%): R_f 0.32 (Hexane/EtOAc, 4:1); mp 193-194 ºC; ^{1}H NMR (400 MHz, CDCl3) δ: 8.16 (d, J = 7.6 Hz, 4H, Ar-*H*), 7.67 (t, J = 7.4 Hz, 2H, Ar-*H*), 7.52 (t, J = 7.5 Hz, 4H, Ar-*H*) (22); ^{13}C NMR (100 MHz, CDCl3) δ: 161.3 (C=O), 141.4 (Ar(*C*4)-Cl), 131.9 (Ar(*C*2,6)-C), 129.4 (Ar(*C*3,5)-C), 127.1 (Ar(*C*1)-C) (22).

3 Results and Discussion

3.1 Chemistry

3.1.1 Aldehydes

Previous studies (22) have tried to establish an accurate mechanism for this reaction. However, so far, none has been fully determined. A possible mechanism is presented in **Figure 3.1**. The reaction begins with the conversion of an aldehyde to an acyl chloride, via oxidation with TCCA, following a radical pathway catalysed by sunlight. The second step of the reaction proceeds by reacting the acyl chloride with the carboxylic acid, in presence of Et_3N. The nucleophilic attack of the acyl chloride by the carboxylate readily gives the corresponding anhydride

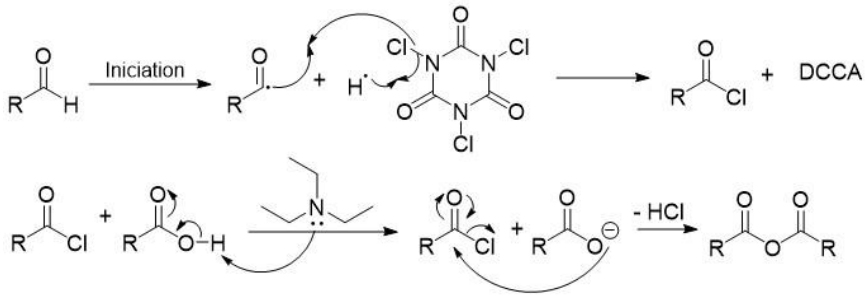


Figure 3.1: Proposed reaction mechanism.

For some reactions, it was not possible to perform the second step of the reaction with the direct use of the corresponding carboxylic acid, due to these not being available. In these cases, these reagents were generated *in situ*. A proposed mechanism for this step of the reaction is presented in **Figure 3.2**. The mechanism differs from the previous one in the second step of the reaction, where Et_3N converts water into a good nucleophile, capable of attacking the carbonyl group of the acyl chloride and generating the corresponding carboxylic acid. From this point on, the reaction follows the same mechanism as the one previously described.

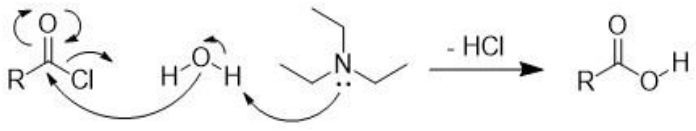


Figure 3.2: Proposed reaction mechanism, using water in the second step.

3.1.2 Alcohols

Also regarding the use of alcohols to obtain an acyl chloride, the mechanism of this reaction is not yet completely understood. A possible mechanism is presented in **Figure 3.3**, based on previous studies (22). In the first step of the reaction a series of radical pathways are catalysed by the sunlight. Firstly, the alcohol reacts with TCCA by a radical pathway and generates a hypochlorite, which easily loses HCl to form an aldehyde. From this point, the reaction follows the same mechanism proposed for aldehydes.

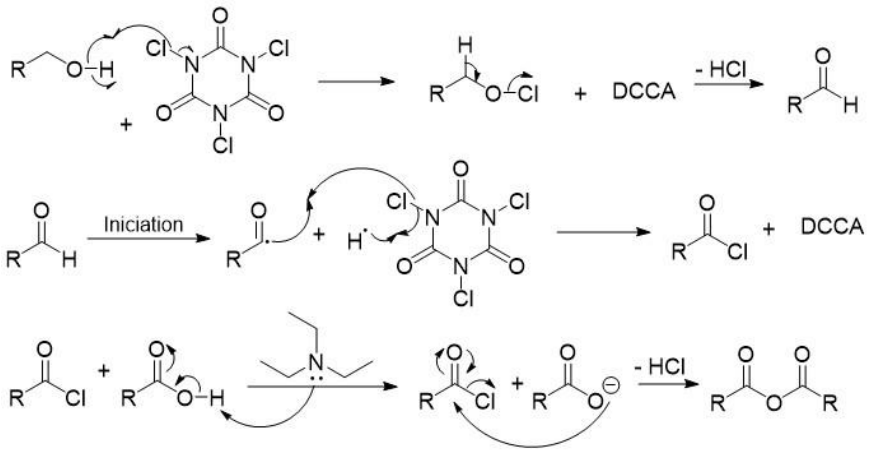


Figure 3.3: Proposed reaction mechanism.

3.2 Using aldehydes as starting reagents

3.2.1 Optimal reaction conditions

For the reactions using aldehydes as starting reagents, the optimal conditions had been determined in a simultaneous study and are presented in **Figure 3.4** and **Figure 3.5**. The aforementioned conditions were applied to all reactions, with the exception of reactions 5, 9 and 10.

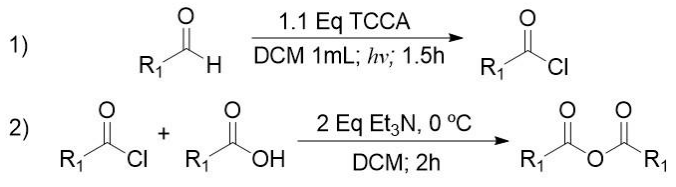


Figure 3.4: General reaction for solid aldehydes.

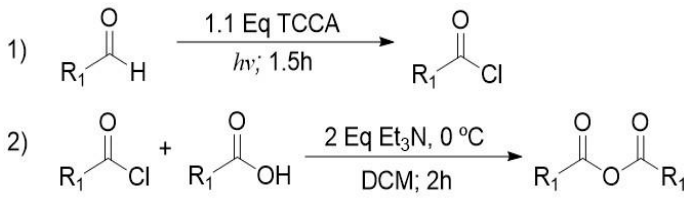


Figure 3.5: General reaction for liquid aldehydes.

In reaction 5, using hydrocinnamaldehyde, it was necessary to add 1 mL of solvent to the reaction mixture, although this is a liquid aldehyde. The methodology without DCM was applied at first but the reaction turned to a dark colour and started to release white smoke, which can be associated with the compound reactivity to highly oxidizing agents.

For reactions 9 and 10, using 4-trifluoromethylbenzoic aldehyde and 4-cyanobenzoic aldehyde as starting reagents, respectively, the carboxylic acid in the second step of the reaction was replaced by water. This alteration to the procedure was due to the fact that the corresponding carboxylic acids were not available as reagents. This issue was resolved by originating the carboxylic acids *in situ*, as demonstrated in **Figure 3.2**.

3.2.2 Evaluation of aromatic aldehydes substrate scope

The study started by investigating the reactivity of aryl aldehydes with aryl benzoic acids, to provide symmetrical anhydrides.

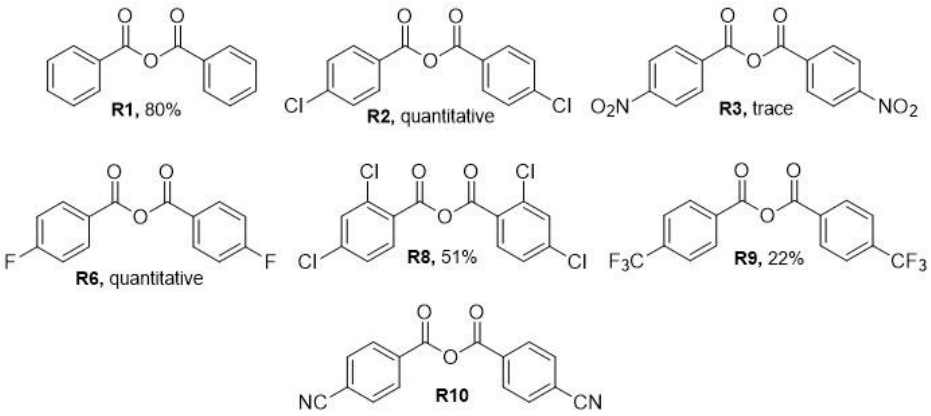


Figure 3.6: Evaluation of aromatic aldehydes scope.

3.2.2.1 Electron-rich aromatic aldehydes

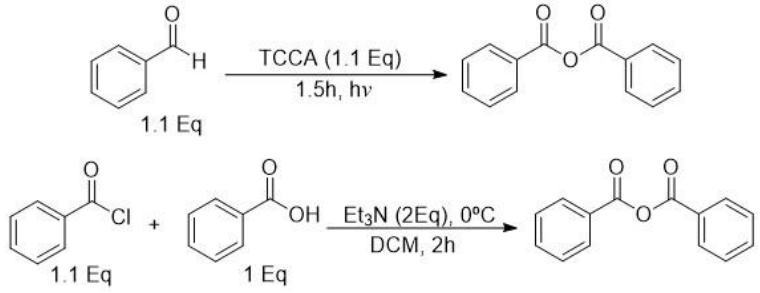


Figure 3.7: Step 1 and 2 of R1

The benzaldehyde, an electron-rich aromatic aldehyde, gave the best result, furnishing the corresponding anhydride in 80% yield (**Figure 3.7, R1**).

3.2.2.1 Electron-withdrawing aromatic aldehydes

The next group of compounds to be investigated was the aromatic aldehydes with electron-withdrawing substituents, namely fluorine, chlorine, nitro and cyanide. The 4-chlorobenzaldehyde and 4-fluorobenzaldehyde were converted to the corresponding anhydrides in good yields (**Figure 3.6, R2 and R6**).

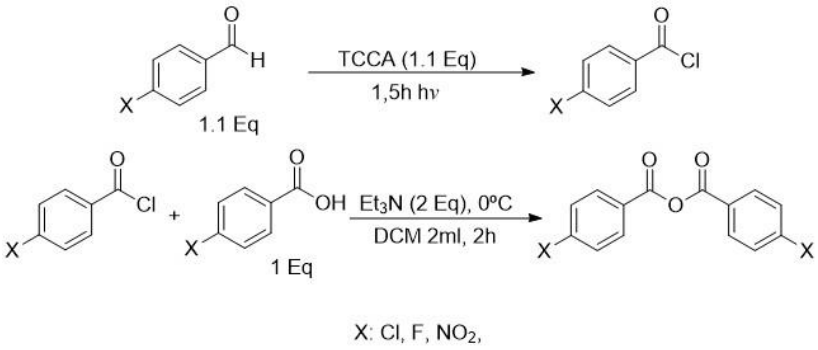


Figure 3.8: Step 1 and 2 of R2, R3 and R6.

The 4-nitrobenzaldehyde was subjected to the same optimal reaction conditions but the corresponding 4-nitrobenzoic anhydride (**Figure 3.6, R3**) was originated only in trace amounts. The TLC for the second step of the reaction showed a considerable amount of 4-nitrobenzoyl chloride. Thus, the reaction was left overnight and was monitored after 24h by TLC, using a mix of Hex:EtOAc (4:1). It was treated with 2,4-dinitrophenylhydrazine and molybdate to confirm the compounds observed were indeed the 4-nitrobenzoyl chloride, observing there was no product in significant amounts. This may be related to the poor reactivity of the corresponding carboxylate ion, which may require a longer reaction time or a different catalyst base to reach better yields. (14)

The 2,4-dichlorobenzoic and 4-tifluoromethylbenzoic anhydrides were also obtained in good yields (**Figure 3.6, R8 and R9**). The lower yields of these reactions are normal, since it was necessary to perform a second flash chromatography to purify the desired anhydride, which may have led to the loss of some product.

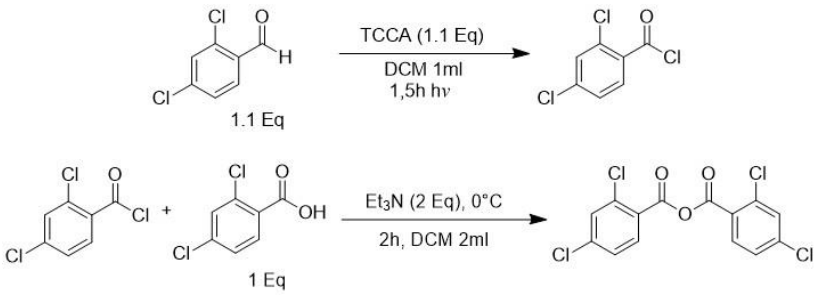


Figure 3.9: Step 1 and 2 of R8.

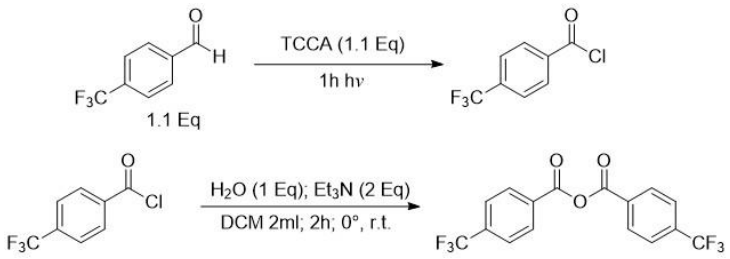


Figure 3.10: Step 1 and 2 of R9.

The reaction to furnish 4-cyanobenzoic anhydride (**Figure 3.6, R10**) was performed under the same optimal conditions and one product was isolated and purified. However, upon the analysis of the ^{1}H-NMR spectrum, it was observed that the desired anhydride had not been synthesized and there were considerable amounts of the carboxylic acid present in the product. A possible explanation for this fact may be that the cyano group considerably weakens the nucleophilicity of the carboxylic acid, leading to a decreased ability to attack the acyl chloride.

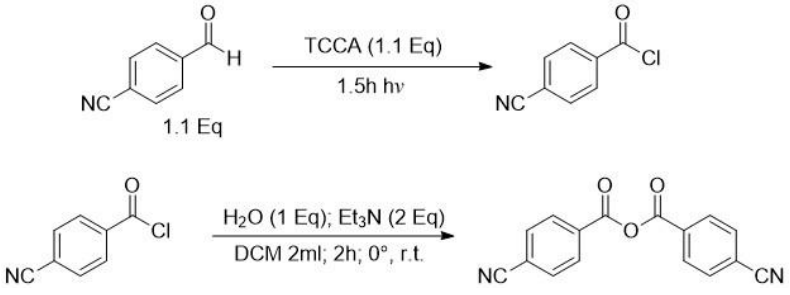


Figure 3.11: Step 1 and 2 of R10.

3.2.3 Evaluation of aliphatic aldehydes substrate scope

After analysing the scope for aromatic aldehydes, the same conditions were applied to aliphatic aldehydes. Although these compounds cannot typically survive under strong oxidative conditions (22), the corresponding anhydrides were furnished in good yields (**Figure 3.12**)

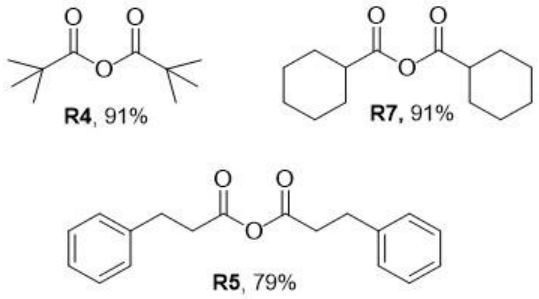


Figure 3.12: Evaluation of aliphatic aldehydes scope.

The reaction with pivalaldehyde gave the best result, with a 91% yield, even under strong oxidative conditions, without any solvent.

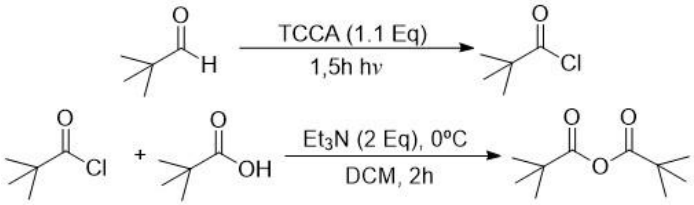


Figure 3.13: Step 1 and 2 of R4.

Regarding R5 and R7, after the addition of the TCCA to the aldehyde, the reaction mixture turned brown and released a lot of smoke, due to the high reactivity of these substrates under strong oxidative conditions. For this reason, the same reaction was performed with the addition of DCM as solvent.

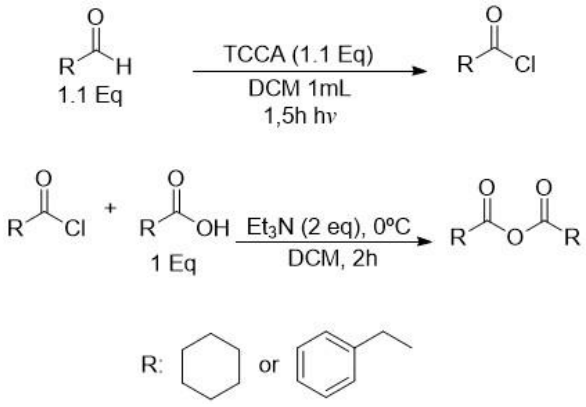


Figure 3.14: Step 1 and 2 of R5 and R7.

An analysis to the ^{1}H-NMR spectra for these reactions confirms the desired products were attained, including the pivalic anhydride that could have a worst result due to the sterically hindered substrate. However, although the products were purified, it was not possible to obtain the desired anhydrides in a pure state, which can be observed from the ^{1}H-NMR spectra.

3.3 Using alcohols as starting reagents

3.3.1 Optimal reaction conditions

In order to determine the optimal reaction conditions for the production of anhydrides from alcohols, the same compound was synthesised under different conditions and the results were compared. The various reactions performed are summarized in **Table 3.1**.

Table 3.1: Determining the optimal reaction conditions.

REACTION	FIRST STEP			SECOND STEP			YIELD
	DCM	**TCCA**	**Time**	**Carboxylic Acid**	**Water**	**Et_3N**	
R11	1 mL	1.1 Eq	1.5 h	1 Eq	---	2 Eq	50%
R12	1 mL	1.3 Eq	1.5 h	1 Eq	---	2 Eq	80%
R13	1 mL	1.1 Eq	1.5 h	---	1 Eq	2 Eq	34%
R14	1 mL	1.1 Eq	2 h	1 Eq	---	2 Eq	49%
R15	1 mL	1.1 Eq	1.5 h	---	1 Eq	1.1 Eq	48%

The investigation started by treating benzaldehyde (1.1 mmol) with TCCA (1.1 mmol), at room temperature. We observed the first step of the reaction didn't work under these conditions so we repeated it with the addition of 1 mL of DCM as solvent to the reaction mixture. Following the procedure described in the experimental section, the benzoic anhydride was generated in 50% yield.

Afterwards, we tested the possibility that increasing the amount of TCCA in the first step of the reaction would give a better yield. Treating the benzaldehyde (1.1 mmol) with 1.3 mmol of TCCA proved to be a more efficient methodology, giving an 80% yield, maintaining all the other conditions.

The next step was to analyse the effect of using water in the second step, to generate the corresponding carboxylic acid *in situ*. The desired anhydride was

obtained in 34% yield, proving to be less effective then the direct use of a carboxylic acid.

In attempt to make the method using water more efficient, the same reaction was performed, reducing the amount of Et_3N in the second step (1.1 mmol). All the other conditions were maintained and the desired anhydride was generated in 48% yield. Facing this result, it was observed that it is more effective to use a lower amount of Et_3N with water. However, this methodology is still not as efficient as the previous one, using the carboxylic acid directly (48% vs. 80%).

The next variable to be investigated was the duration of the first step of the reaction, which was prolonged for 30 minutes, to a total of 2 hours. Maintaining all the other parameters, the desired anhydride was obtained in a 49% yield.

An interpretation of all the above mentioned results determines the optimal reaction conditions as stated in **Figure 3.15**.

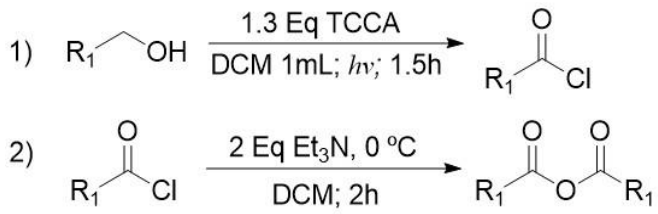


Figure 3.15: General reaction for alcohols.

3.3.2 Producing aromatic anhydrides

The optimal reaction conditions previously determined were applied to 4-chlorobenzilic alcohol, originating the 4-chlorobenzoic anhydride in a 68% yield.

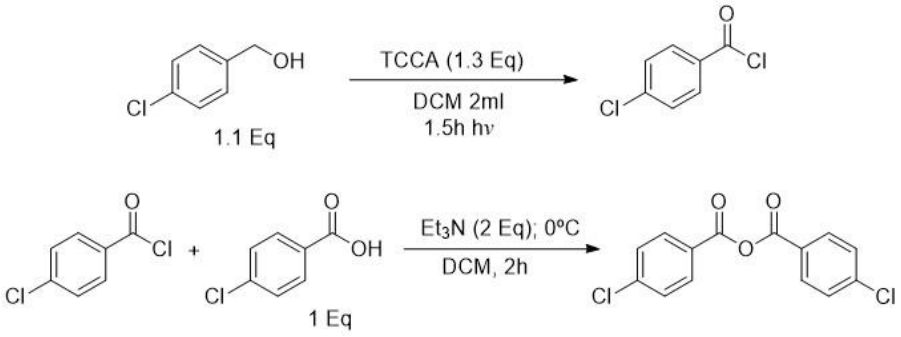


Figure 3.16: Step 1 and 2 of R16.

4 Conclusions

In order to develop a new metal free methodology for the production of carboxylic anhydrides from aromatic and aliphatic aldehydes and primary benzylic alcohols, using TCCA as chlorinating reagent and sunlight as catalyst, a number of anhydrides were synthesised under optimal reaction conditions.

The study was divided in two parts, according to the molecule used as starting reagent. For the generation of anhydrides from aldehydes, it was possible to obtain nine symmetrical anhydrides, both aromatic and aliphatic, although one of these was only present in trace amounts. The optimal reaction conditions had already been determined in a simultaneous study and were applied to all the reactions. According to the yields obtained with aromatic aldehydes, it seems that the reaction works best with electron-rich reagents, such as benzaldehyde. The results for the reaction with pivalaldehyde also appear to indicate that the reaction is not affected by sterically hindered substrates. Nevertheless, it would be prudent to perform supplementary studies that can attest to this theory, using additional electron-rich and sterically hindered reagents. All generated anhydrides were pure, as the ^{1}H-NMR didn't show the presence of any other molecules, apart from some solvents. However, not all products were subjected to ^{1}H-NMR analysis, due to a malfunction in the equipment that prevented its use for a period of time. Thus, future studies should include a complete characterization of all products. In addition to this, it would also be interesting to understand the scope of this reaction, in regard to the production of mixed anhydrides.

Among the tested products, the worst results were observed with 4-nitrobenzoic anhydride (R3), 4-trifluoromethylbenzoic anhydride (R9) and 4-cyanobenzoic anhydride (R10). In R3, the product was only obtained in trace amounts, which can be related to the poor reactivity of the substrate. The nitro group as substituent in the benzylic ring decreases the reactivity of the corresponding carboxylate ion and makes it more difficult to achieve the best results. The low yield attained with 4-trifluoromethylbenzoic anhydride may be related to the second flash chromatography that was required to purify the product.

Regarding the synthesis of anhydrides from alcohols, due to the limited amount of time, this study focused on determining the optimal reaction conditions. Afterwards, these conditions were used to test the production of different anhydrides. To define the optimal reaction conditions, specific factors of the reaction, were altered, individually, and the results were interpreted. The settings under evaluation were the

amount of solvent and TCCA used in the first step of the reaction, the use of water to generate the carboxylic acid *in situ* during the second step of the reaction, the amount of Et_3N utilized in conjunction with water and the duration of the first step of the reaction. After analysing all the results, the best conditions were fixed as stated in Erro! A origem da referência não foi encontrada..

After determining the optimal reaction conditions, these were applied to synthesize 4-chlorobenzoic anhydride from 4-chlorobenzilic alcohol. The desired anhydride was produced in a good yield. However, due to the limited time available, it was not possible to extend this study to a bigger number of reagents. Further studies should include a set of aromatic and aliphatic alcohols as starting reagents, in order to determine the scope of this reaction, both for symmetrical and mixed anhydrides.

Overall, this method presents itself as an efficient and green alternative to the already established ones for the production of anhydrides, using TCCA as chlorinating agent and solar radiation as an activator. Using cheap and readily available reagents in a stoichiometric ratio, the products were selectively obtained, without any side-products detected.

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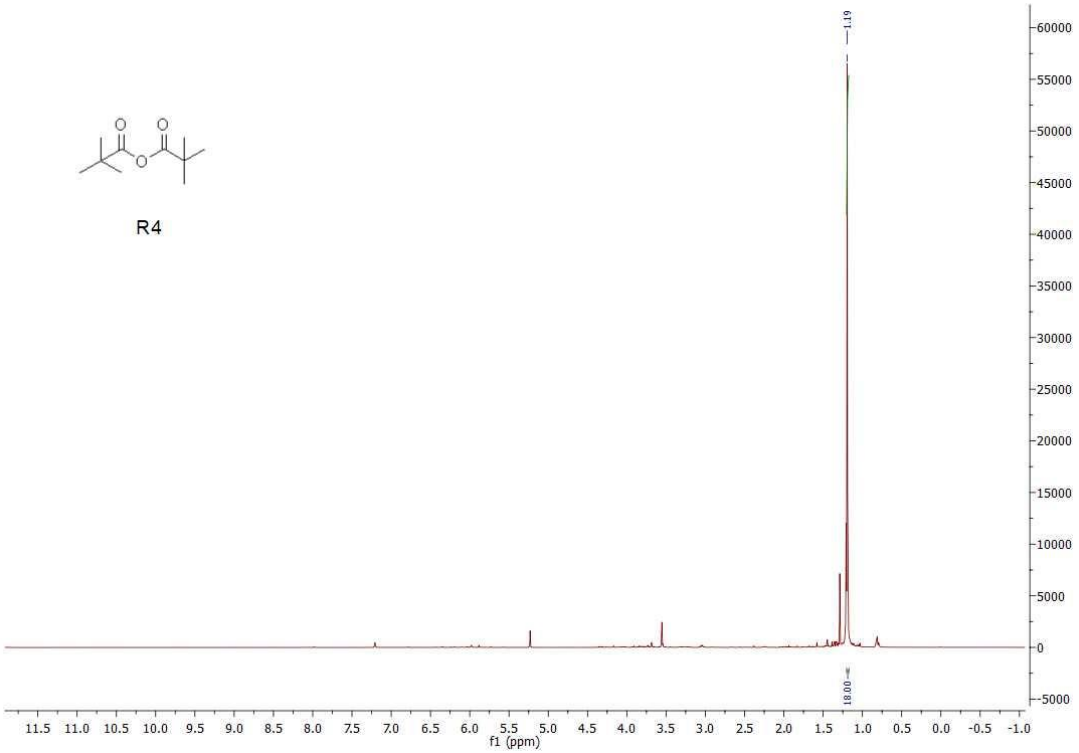
6 Appendix 1 – NMR Spectra

Reaction 4 ^{1}H-NMR



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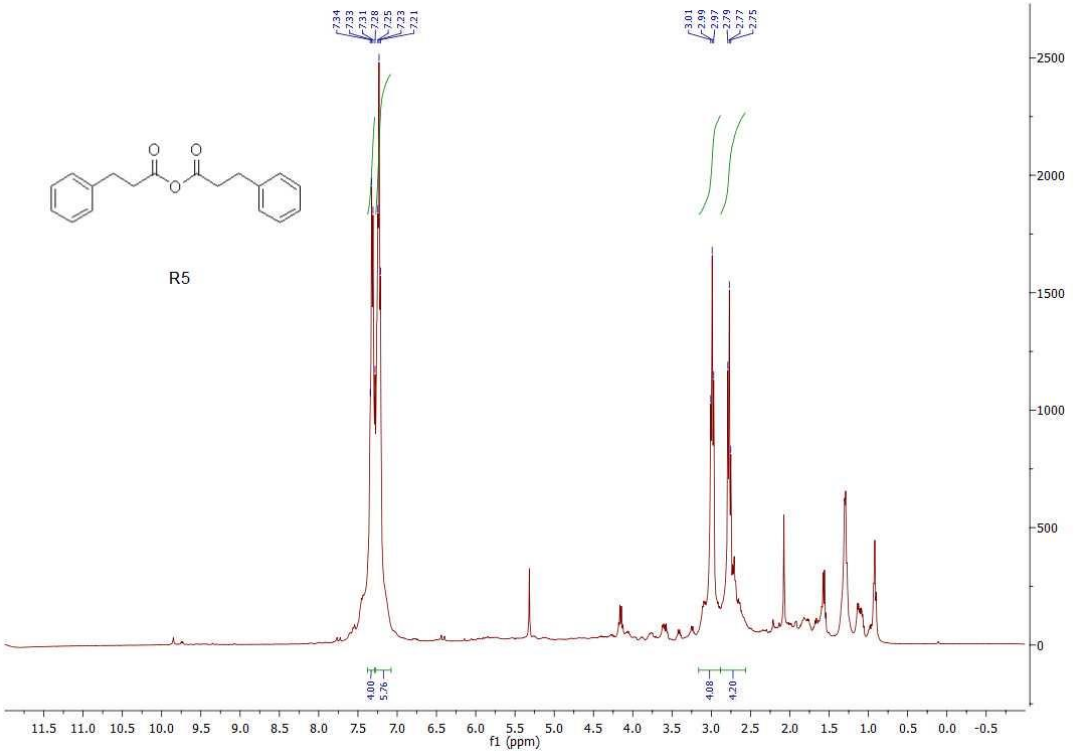

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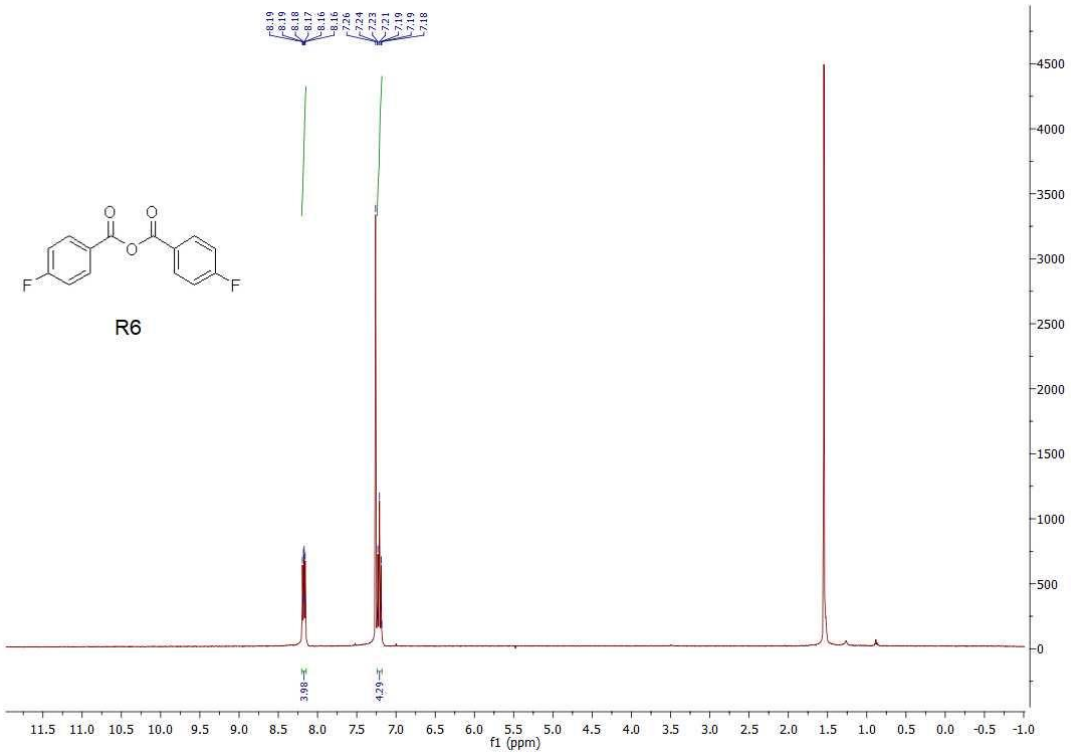

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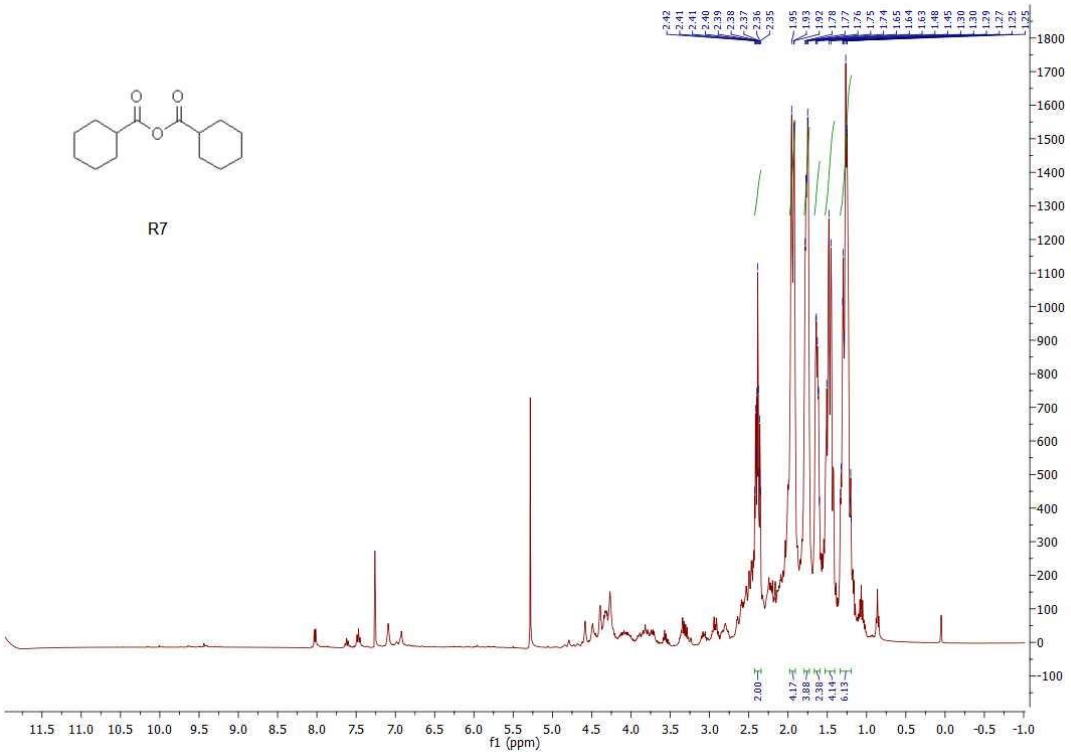
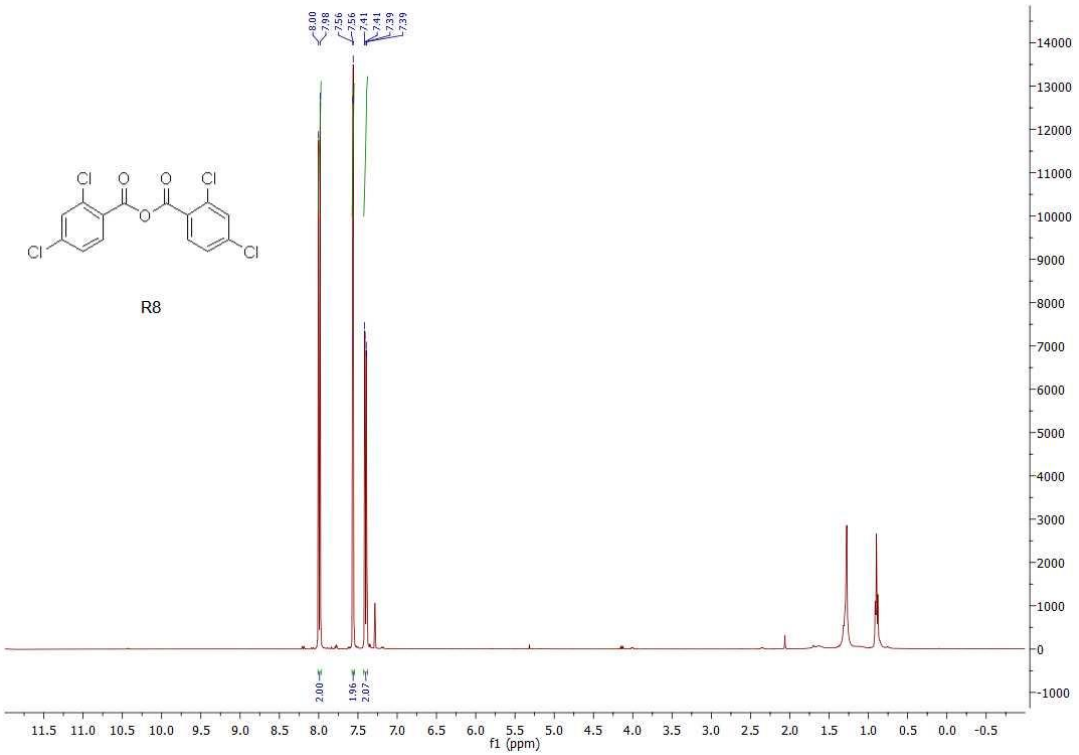
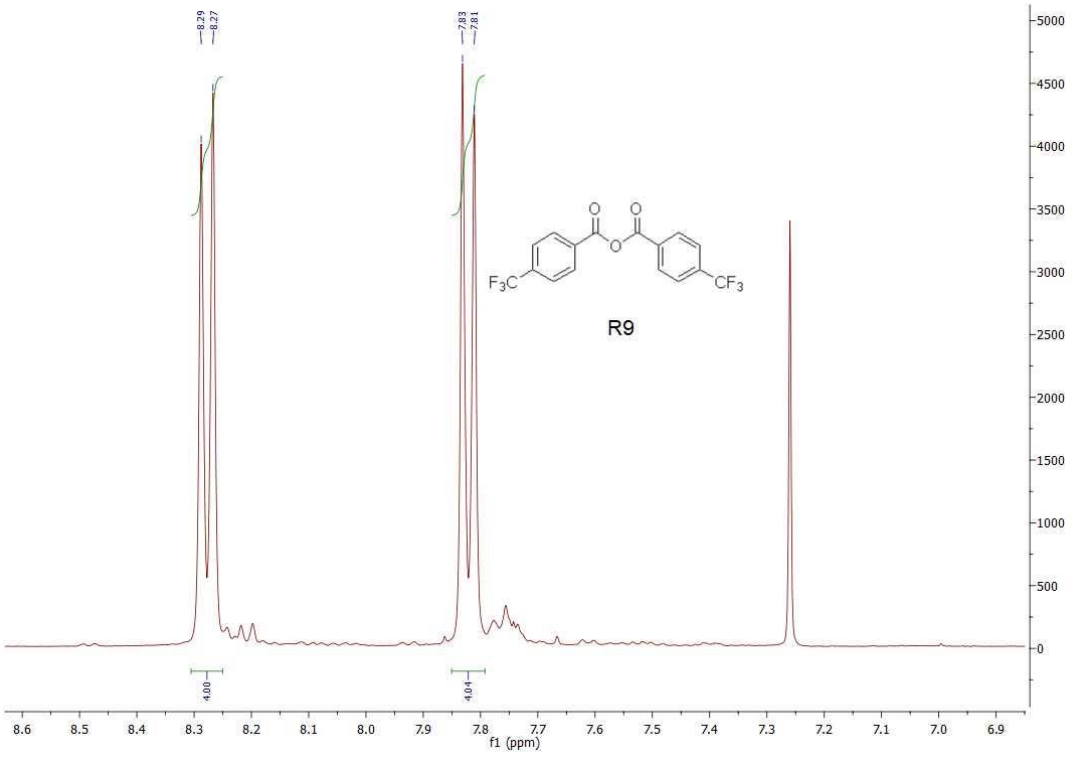


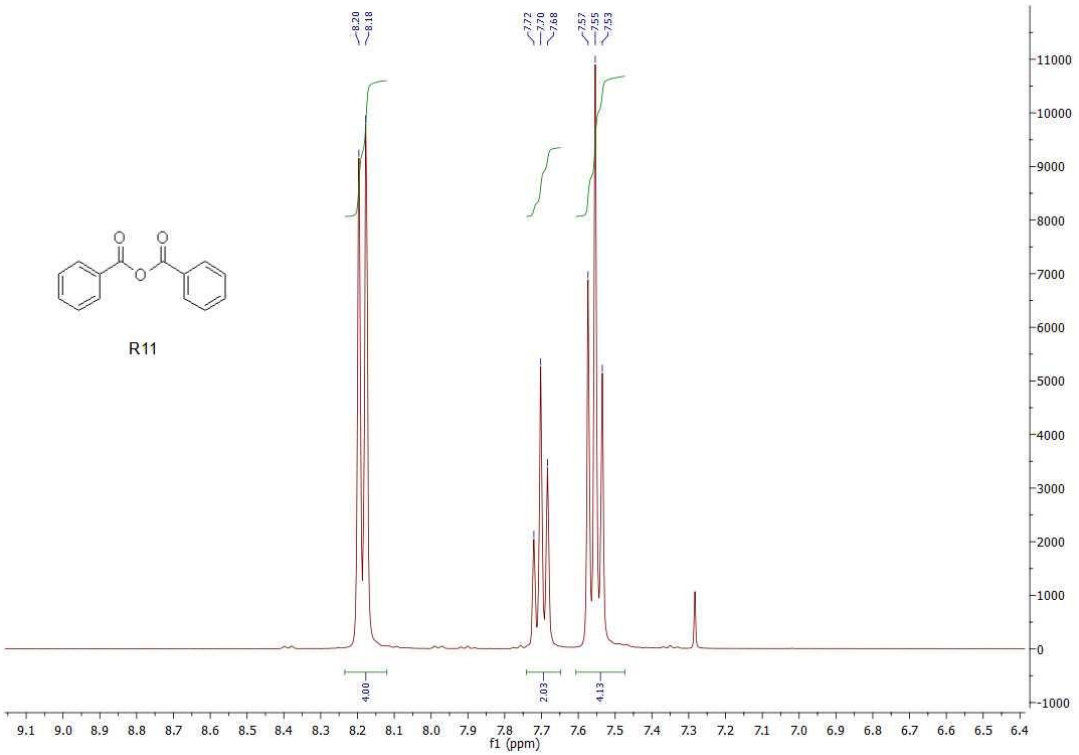
Reaction 8 ^{1}H-NMR



Reaction 9 ^{1}H-NMR



Reaction 11 ^{1}H-NMR



Reaction 15 ^{1}H-NMR